Selective Synthesis of Azoloyl NH-1,2,3-Triazoles and Azolyl Diazoketones: Experimental and Computational Insights

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ABSTRACT: Here, we report that the reaction of enaminones, from a class of azole series, with sulfonyl azides leads to a difficult-to-separate mixture of two pairs of compounds: (1) 4-azoloyl-NH-1,2,3-triazoles with sulfonamides and (2) azolyl diazoketones with N-sulfonamidines, as a result of the implementation of two competing reactions. On one hand, the electron-donating methyl or methoxy group in the aryl para-position of arylsulfonyl azides favors the production of NH-1,2,3-triazoles together with sulfonamides. On the other hand, the use of highly electrophilic 4-nitrophenylsulfonyl azide promotes the formation of diazoketones and sulfonamidines. It is shown that the direction of each reaction is not only controlled by the nature of the initial enaminones and sulfonyl azides but also depends on the tested solvent. The problem of removing sulfonamides and amidines from the desired products was solved for the first time using new water-soluble enaminones. Based on the experimental and computational studies, the factors contributing to the selective course of alternative reactions were identified, and methods for the synthesis of azoloyl-NH-1,2,3-triazoles and azolyl diazoketones were developed. Density functional theory (DFT) results have shown that the 1,3-dipolar cycloaddition is totally driven toward one single regioisomer with a high asynchronous bond formation, and the introduction of an electron-deficient group in sulfonyl azides induces faster cycloaddition. Additionally, DFT calculations were used to gain further mechanistic insights on the reaction studied here.

INTRODUCTION

NH-1,2,3-Triazoles, linked to a second five-membered heterocycle through a carbonyl group, possess two active functional groups and are therefore promising building blocks for obtaining various 1,2,3-triazole derivatives. 1,2,3-Triazole is a heterocycle that has found wide applications as a privileged scaffold in the directed synthesis of substances with biological activity, in organic electronics for the synthesis of new materials, as a key fragment in the synthesis of substances capable of metal-catalyzed cycle transformations, and as a unique building block in the synthesis of various organic compounds. Among NH-1,2,3-triazoles, substances with biological activity and used as new materials with interesting optical and physical properties were also found. The primary methods of synthesis of 4-carboxyl derivatives of NH-triazoles include reactions of acylacetylenes with inorganic azides, interaction of α-diazob-γ-oxoaldehydes with aniline, ammonium, hydroxyamine, and semicarbazide, and modifications of ready NH-triazoles synthesized by other methods. All the methods mentioned above almost completely focused on the production of 4-aroyl derivatives of 1,2,3-triazole. In this aspect, another method based on the reaction of β-enaminones I with tosyl azide (2a) is an exception, which permitted to prepare three 4-heteroaroyl-triazoles (pathway A, Scheme 1). Thus, the existing synthesis methods are limited in their applicability for the production of 4-heteroaroyl-NH-triazoles.

It should be noted that changing the nature of enaminones I and the conditions of their reaction with sulfonyl azides 2 lead to switching to other products, diazoketones 5 together with amidines 7 (pathway B, Scheme 1). α-Diazoacetones are widely used in organic synthesis. They are well-known precursors of carbones and carbenoids. Being 1,3-dipoles of propargyl-allyl type, they take part in cyclopropanations, rearrangements, cycloadditions, and electrocyclic processes. They are valuable reagents for use in biological chemistry found in naturally occurring products and also included as a fragment into the structure of some anticancer drugs. Despite a large number of methods for the synthesis of diazoketones published in the literature their applicability for the synthesis of heteroaroyl diazomethanes is extremely limited. All this makes us to conclude that the search for new safe and...
effective methods for the synthesis of both NH-1,2,3-triazoles and diazomethanes of the azoloyl series is an urgent task.

To solve this dual problem at once, the reaction of enaminones of azole series \(1\) with arylsulfonyl azides \(2\), which could undergo, depending on the structure of reactants and reaction conditions, both competing reactions \(A\) and \(B\) (Scheme 1) leading to NH-1,2,3-triazoles \(4\) and diazocarbonyl compounds \(5\), respectively, is particularly promising. It should be noted that no examples have been found in the literature when products of both types \(4\) and \(5\) were obtained and identified together in one reaction. Moreover, there is no information about the factors directing the conversion of triazolines \(3\) toward the formation of a particular product \(4\) or \(5\) (Scheme 1) found by either experimental or computational methods.

The reactions of sulfonyl azides \(2\) with heterocyclic enaminones \(1\) are presented in the literature to a much lesser extent than the corresponding reactions of aromatic and alicylic enaminones. Thus, it is described\(^{16}\) that the enaminones \(1\,^{a,b}\) react with tosyl azide \((2a)\) in water to form exclusively NH-triazoles \(4\,^{a,b}\) (Scheme 2), which are the only described examples of NH-1,2,3-triazoles linked with the second heterocycle through a carbonyl group.

On the other hand, heterocyclic \(\beta\)-methylenaminones \(1\,^{c}\) react with mesyl azide \((2b)\) in water under microwave irradiation to form only the corresponding diazoketones \(5\) (Scheme 2).\(^{40}\) The method of synthesis of heteroaroyl diazo compounds \(7\) by the reaction of the corresponding chloroanhydrides \(6\) with diazomethane (Arndt–Eistert synthesis) has not found a wide application\(^{41-43}\) due to the high explosiveness and toxicity of the latter.

Here, we demonstrate a new approach that allows one to obtain both NH-1,2,3-triazoles \(4\) and diazomethanes \(5\) of heteroaroyl series based on the use of either water-soluble sulfonyl azides or enaminones containing an \(N\)-methylpiperazine residue. This approach allowed us to develop a simple and effective method for separating the desired 4-acyl-NH-1,2,3-triazoles \(4\) and diazoketones \(5\) from byproducts, sulfonamides \(6\) and amidines \(7\) (Scheme 1). A combination of experimental and computational studies of the interaction of azoloylenaminones with sulfonyl azides revealed the influence of the nature of the starting reagents and the solvents on the direction of the reaction. It was found that seemingly insignificant changes in the structure of arylsulfonyl azide, as well as a variation like the solvent, lead to drastic changes in the direction of this reaction. It is shown that the reactions of the least electrophilic tosyl azide \((2a)\) and 4-methoxyphenyl azide \((2g)\) in pyridine lead to the selective formation of NH-1,2,3-triazoles \(4\). On the contrary, the formation of diazoketones \(5\) is facilitated by the use of azide \(2e\), containing a strong electron acceptor nitro group and ethanol as a solvent. Optimal conditions were determined, and methods were developed for the selective and effective synthesis of azoloyl NH-1,2,3-triazoles \(4\) and diazoketones \(5\).
As an enaminone substrate, we initially selected the earlier synthesized^44,45 N,N-dimethylenaminones 1a−o, as well as enaminone 1p [which we first obtained in two stages via 4-acetyl-1,2,3-triazole 9 from Zidovudine (8)] (Scheme 3), where the substituent at position 1 of 1,2,3-triazole widely varied in electronic properties. In addition to 1,2,3-triazole derivatives 1a−p, one representative of the 1,2,3-thiadiazole 1q and isoxazole 1r series were chosen for the study. Selected N,N-dimethylenaminones 1a−f, g−r were reacted with several sulfonyl azides R3SO2N3 (2) (R3 = 4-MeC6H4 (2a), Me (2b), Ph (2c), 4-F3CC6H4 (2d), and 4-O2NC6H4 (2e)).

As can be seen from Scheme 3, at the end of the synthesis, the reaction mixture generally contains four products, namely, two desired ones (4 and 5) and two byproducts (6 and 7). Often, non-stoichiometric ratios of reactants were used or their conversion turned out to be incomplete, which further complicates the reaction mixture due to residual amounts of reactants. The lack of differences in the components of the reaction mixture (including unpredictable chromatographic mobility), which would allow them to be easily separated, makes this task rather difficult. Indeed, in a series of experiments that we have carried out (Scheme 3), complex combinations of chromatographic and other physico-chemical techniques had to be used to isolate the desired products of reaction 4, 5; in some cases, we could not isolate pure substances at all or only partially succeeded.

We suggested that the cardinal solution of the problem could be the use of a radically different separation principle. To do this, we decided to introduce a basic fragment into the molecule of one of the reactants 1 or 2 and, consequently, into the byproducts 6 and 7, which gives the latter solubility in acidic aqueous medium. The acidity in reactants 1 or 2 as a factor in allowing the removal of byproducts 6 and 7 was not considered because one of the desired products, monosubstituted triazoles of type 4, are also quite strong acids that form stable salts with bases, for example, triethylamine.

Initially, we decided to introduce a basic fragment into sulfonyl azide, which was achieved using the previously obtained^46 2-morpholinoethane-1-sulfonyl azide (2f) (Scheme 4).

The reactions were carried out in 1,4-dioxane and byproducts 6 and 7 were washed off after the removal of the solvent with an aqueous solution of AcOH (the use of strong acids is risky because their excess destroys diazo compounds

### RESULTS AND DISCUSSION

| compounds 1, 4, 5 | R1 | R2 |
|------------------|----|----|
| a                | Ph | H  |
| b                | 4-MeC6H4 | H  |
| c                | 2-O2NC6H4 | H  |
| d                | 4-O2NC6H4 | H  |
| e                | Me | Me |
| f                | Bu | Me |
| g                | 4-BrC6H4CH3 | Me |
| h                | Ph | Me |
| i                | 4-i-PrC6H4 | Me |
| j                | 2-Cl4-MeC6H4 | Me |
| k                | 3-ClC6H4 | Me |
| l                | 3-F3CC6H4 | Me |
| m                | 2-O2NC6H4 | Me |
| n                | 4-O2NC6H4 | Me |
| p                | 3-(3,5-dimethylpyrimidine-2(1H,3H)-dione-1-yl)-5-(hydroxymethyl)tetrahdrofuran-2-yl | Me |
The easy removal of water-soluble byproducts 6 and 7 made it possible to obtain mixtures consisting predominantly of NH-triazoles 4 and diazo compounds 5, which allowed to analyze them without preparative separation using 1H NMR spectroscopy. The separation of the mixtures in order to obtain the components was carried out using column chromatography. Doing this, to increase the difference in the chromatographic mobility of NH-triazoles 4 and diazo compounds 5, the phenomenon of a pronounced acidity of the former was used. Thus, the addition of triethylamine to the eluent at the beginning of chromatography drastically reduced the Rf of NH-triazoles 4 due to the formation of a salt, as a result of which only diazo compounds 5 were eluted. Then, a small amount of

| entry | compounds 1, 4, 5 | R¹ | R² | additive | time (h) | T (°C) | yield (%) |
|-------|------------------|----|----|----------|----------|--------|-----------|
| 1     | c                | 2-O₂NC₉H₈ | H  | –        | 72.0     | 70     | 61        |
| 2     | d                | 4-O₂NC₉H₈ | H  | AcOH     | 5.0      | 82     | 80        |
| 3     | f                | Bu    | Me | AcOH     | 2.0      | 34*    | 24*       |
| 4     | h                | Me    | Me | –        | 8.0      | 32     |           |
| 5     | h                | Me    | Me | AcOH     | 17.5     | 64     | 34        |
| 6     | h                | Me    | Me | AcOH     | 23.0     | 24     | 71        |
| 7     | i                | 4-MeC₆H₄ | Me | HCl      | 48.0     | 15*    | 62*       |
| 8     | j                | 4-i-PhC₆H₄ | Me | –        | 24.0     | 39     | 54        |
| 9     | l                | 3-CIC₆H₄ | Me | –        | 6.0      | 65     | 27        |

* Without isolation, according to 1H NMR, ** in reference to azide 2f
AcOH was added to the eluent to destroy the salt, after which NH-triazoles 4 were eluted.

However, in the majority of cases, the selective formation of one of the two types of reaction products does not take place (Scheme 4). We assumed that the addition of acetic acid to the reaction mixture would shift the reaction in favor of the formation of diazo compounds 5 due to the neutralization of the basic morpholine fragment from sulfonyl azide 2f. Though the expected effect was observed in a series of experiments (cf. entry 4, Scheme 4, with entry 5 and, especially, entry 6), the desired selectivity was not achieved. Thus, the introduction of the basic fragment into the sulfonamide component of sulfonyl azides 2 did not provide the synthesis of NH-triazoles 4 and diazo compounds 5 with satisfactory selectivity, which reduces the preparative attractiveness of the tested approach.

An approach alternative to the previous one is the use of enamiones of type 10 with the basic fragment of N-methylpiperazine, which was introduced instead of the dimethylamino group by the transamination reaction of enamiones 1. The preferred method for the synthesis of enamiones 10 was found to be heating enamiones 1 in N-methylpiperazine with letting the releasing dimethylamine to dissipate in the atmosphere (Scheme 5). The excess N-methylpiperazine can be regenerated to a great extent by distilling it from the reaction mixture after the end of the reaction. Thus, a series of new enamiones bearing a fragment of N-methylpiperazine of the 1,2,3-triazole series 10a–p was obtained, as well as one representative of the 1,2,3-thiadiazole 10q and isoxazole 10r series (Scheme 5).

In the synthesis of the o- (10c) and p-nitro derivative (10d), significant amounts of o- and p-nitroaniline were detected in the reaction mixture, respectively, presumably due to the decomposition of compounds 10c and 10d under the action of N-methylpiperazine. As a result, p-nitro enamione 10d was obtained with a yield of 82%, and the yield of o-isomer 10c was only 48% with a conversion rate of the starting compound 1c of 95%. Thus, the transamination reaction is of limited applicability for the preparation of compounds 10 that are labile to N-methylpiperazine.

The synthesized enamiones 10 have a higher melting point, are more stable during storage and are significantly more polar than initial dimethyl enamiones 1, which favor their purification by crystallization or column chromatography, and altogether make them more convenient in synthetic practice.

In syntheses using N-methylpiperazine enamiones 10 (Scheme 6), it was found possible to apply a method for isolating compounds 4 and 5, similar to the one used in the reaction of enamiones 1 with azide 2f (Scheme 4).

In order to increase the practical value of the method under development, we looked for the reaction conditions leading to the predominant formation of one of the two types of reaction products, NH-triazoles 4 or diazo compound 5. Initially, the influence of the nature of sulfonyl azide 2 on the ratio of reaction products when interacting with enamione 10h (Scheme 7) was studied. The reactions were carried out in 1,4-dioxane at room temperature.

Based on the experimental results presented in Scheme 7, it can be concluded that the electronic properties of the substituent in sulfonyl azides 2 significantly affect the direction of the reaction. Thus, the use of azides 2a and 2g containing electron-donating substituents leads to a maximum yield of NH-triazole 4h (Scheme 7, entries 1 and 6), while sulfonyl azide 2e with an electron-acceptor group affords the maximum yield of diazo compound 5h (Scheme 7, entries 1, 6). For the further optimization of the method for obtaining NH-triazoles 4 from a pair of arylsulfonyl azides 2a and 2g, which showed similar results, tosyl azide (2a) was chosen as much more available. Thus the study of the effect of the solvent nature on the yield of NH-triazoles 4 (Scheme 8) was carried out using the reaction of enamione 10h with tosyl azide (2a).

Data of Scheme 8 demonstrate that the best yields of NH-triazole 4h are provided by the use of pyridine as a solvent (entries 9–11). Further, the effect of the reaction temperature on the yield of the desired NH-triazole 4h was studied in this solvent (Scheme 8, entries 9–11). Notably, an increase in temperature to 75 °C leads to a certain decrease in the yield of the desired product 4h (Scheme 8, entry 11), while it is practically invariable in the temperature range from room to 52 °C.

It should be noted that in the studies presented in Schemes 7 and 8, an attempt to introduce into the reaction an excess of enamione 10h or sulfonyl azide 2 always led only to that after the reactant taken in deficiency completely disappeared, the reactant taken in excess was detected in the reaction mixture.
using $^1$H NMR, moreover in an amount close to that expected by balance calculation, while the yield of the desired products 4 and 5 remained practically the same.

Thus, the optimal conditions for the synthesis of NH-triazoles 4 from enamiones 10 were recognized as the use of tosyl azide (2a) as a sulfonyl azide and pyridine as a solvent at a temperature of 25–52 °C with an equimolar ratio of reactants.

Having optimal conditions in hands, we synthesized a series of compounds of the 1,2,3-triazole series 4a–p, as well as one representative of the 1,2,3-thiadiazole 4q and isoxazole 4r series; the results are given in Scheme 9.

As already noted, the highest yield of diazo compound 5h in the experiments presented in Scheme 7 is achieved using 4-nitrophenylsulfonyl azide (2e). In this respect, the optimization of the method for obtaining diazo compounds 5 was carried out using reagent 2e. Thus, the effect of the solvent on the yield of reaction products was studied by analyzing a series of experiments, where it changed in the reaction of sulfonyl azide 2e with enamione 10q. It was found that in this series (entries 1–5, Scheme 10), the use of ethanol leads to the maximum yield of diazo compound 5q. Later, we locked ethanol as a solvent and investigated the effect of the reaction temperature on the yield of diazo compound 5q (entries 5–7, Scheme 10). It was revealed that the yield of diazo compound 5q decreased in the row rt > 4 °C ≈ 70 °C.

Similar to the optimization of the synthesis of NH-triazoles 4 (Schemes 9 and 10), the use of an excess of enamione 10q or sulfonyl azide 2e in the reaction led merely to their overspending. As a result, the best conditions for the synthesis of diazo compounds 5 from enamiones 10 were formulated as follows: 4-nitrophenylsulfonyl azide (2e) as a sulfonyl azide, ethanol, or methanol as a solvent, the reaction temperature was room temperature (in the case of enamione 10o, the reaction was carried out at an elevated temperature because of its low solubility) with an equimolar ratio of reactants.

Scheme 9. Syntheses of NH-Triazoles 4a–r in Optimized Conditions

| comp. | R$^2$ | R$^3$ | time (h) | T (°C) | yield (%) |
|-------|-------|-------|----------|--------|-----------|
| 4a, 5, 10 | 4-MeC$_6$H$_4$ | Me | 4.0 | rt | 94 | 0 |
| b | 4-3MeC$_6$H$_4$ | Me | 5.0 | rt | 92 | 0 |
| c | 2-3O$_2$NC$_6$H$_4$ | Me | 12.0 | rt | 96 | 0 |
| d | 4-3O$_2$NC$_6$H$_4$ | Me | 12.0 | rt | 96 | 0 |
| e | Ph | Me | 3.0 | rt | 95 | 0 |
| f | Me | Me | 3.0 | rt | 91 | 0 |
| g | 4-BrC$_6$H$_4$CH$_2$ | Me | 3.0 | rt | 79 | 14 |
| h | Ph | Me | 67.0 | rt | 89 | 5 |
| i | 4-MeC$_6$H$_4$ | Me | 3.0 | rt | 96 | 0 |
| j | 4-tBuC$_6$H$_4$ | Me | 3.0 | rt | 80 | 14 |
| k | 2-Cl-4-tBuC$_6$H$_4$ | Me | 36.0 | rt | 85 | 9 |
| l | 3-ClC$_6$H$_4$ | Me | 4.0 | rt | 91 | 0 |
| m | 3-FC$_6$H$_4$ | Me | 3.0 | rt | 97 | 0 |
| n | 2-3O$_2$NC$_6$H$_4$ | Me | 4.0 | rt | 98 | 0 |
| o | 3-3O$_2$NC$_6$H$_4$ | Me | 1.5 | 80 | 75 | 22 |
| p | 3-(3,5-dimethylpyrimidine-2,4(1H,3H)-dione-1-y1)-5-(hydroxymethyl)tetrahydrofuran-2-yl | Me | 1.0 | rt | 96 | 0 |
In these optimal conditions, a series of diazocarbonyl compounds of 1,2,3-triazole series were synthesized, as well as one representative of 1,2,3-thiadiazole and isoxazole series, which are given in Scheme 11.

Scheme 10. Reaction of Enaminone 10q with Azide 2e in Different Solvents

| entry | solvent | T (°C) | time (h) | compound 4q yield (%) | compound 5q yield (%) |
|-------|---------|--------|----------|-----------------------|-----------------------|
| 1     | MeCN    | rt     | 24.0     | 51                    | 10                    |
| 2     | THF     | rt     | 21.5     | 50                    | 10                    |
| 3     | AcMe    | rt     | 26.0     | 49                    | 12                    |
| 4     | MeOH    | rt     | 20.0     | 2                     | 59                    |
| 5     | EtOH    | rt     | 25.0     | 2                     | 71                    |
| 6     | tBuOH   | rt     | 424.0    | 2                     | 56                    |
| 7     | EtOH    | 70      | 5.5      | 1                     | 53                    |

*Without isolation, according to 1H NMR spectra

NH-1,2,3-Triazoles are solid colorless substances with a relatively high melting point. Their structure correlates with the data of 1H and 13C NMR spectroscopy, which was also confirmed by ultra-high-performance liquid chromatography with high-resolution mass spectrometry (UHPLC-HRMS) detection, and X-ray analysis was performed for a single crystal of compound 4f (Figure 1).

Diazocompounds 5 are solid light yellow substances with a relatively low melting point (n-butyl derivative 5f could not be crystallized). Their structure correlates with the data of 1H and 13C NMR spectroscopy and UHPLC-HRMS. In the 1H NMR spectra of diazo compounds 5, broad singlets of protons from the diazoketone fragment C(==O)CHN2 are observed at 5.04—6.76 ppm. The IR spectra of compounds 5 display the characteristic bands of the valence vibrations of the diazo group in the range of 2096—2115 cm⁻¹. Additionally, the structure of diazo compounds 5 is confirmed by the X-ray analysis performed for a single crystal of compound 5c (Figure 2).

Previously, the synthesis of one of the diazo compounds, 2-diazo-1-(5-methyl-1,2,3-thiadiazol-4-yl)-methyl-1-one (5q), by an alternative method is described in ref 42. However, except for the melting point, no analytical characteristics are published in the article, which makes it unsuitable for confirmation of the structure of compound 5q synthesized by us.

The plausible mechanism for the formation of compounds 5−7 is depicted in Scheme 12. We assumed that triazoline generated by the cycloaddition reaction of enaminone 1 with sulfonyl azide 2 is a common intermediate on pathways A and B, leading to the desired products 4 and 5. Theoretically, as indicated in Scheme 12, pathway A includes the elimination of sulfonyl amide 6 and formation of triazoline 11, which is followed by the 1,3-H shift to result in final NH-triazole 5 (A1)
or via the elimination of dialkyl amine and generation of 1-aryl sulfonyl-1,2,3-triazole 12. The latter reacts with dialkyl amine to form triazole 5 accompanied by sulfonamide 4 (A2). We also assume that the formation of the second desired compound, diazo compound 5, occurs via the cycloreversion of triazoline 3. Therefore, we have performed computational simulations to gain close insights into the nature of such an important transformation using density functional theory (DFT) approaches (see below).

Computational Investigations. We next performed DFT simulations to gain further insights into the reaction mechanism. The calculations were performed at the (SMD)-M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) level of theory (see the Computational Methods). Overall, we have calculated the mechanistic pathway for the formation of the desired product 4a and its isomers in 1,4-dioxane (Figure 3). Despite the cycloaddition of enaminone 1a with sulfonyl azide 2a being approximately thermoneutral to give intermediate Int4a, the latter is kinetically favored over by a substantial barrier difference of more than 16 kcal/mol via TS3a although the other isomeric intermediate Int4a is slightly thermodynamically exergonic ($\Delta G = -2.1$ kcal/mol). This sharp preferability for the formation of intermediate Int4a is reasoned to factors indicated below.

This regioemic preferability of the formation of intermediate Int4a has shown to be important to rationalize the

Figure 1. Molecular structure of NH-triazole 4f solvate with a representation of the atoms by thermal vibration ellipsoids of 50% probability.

Figure 2. Molecular structure of compound 5c with representation of the atoms by thermal vibration ellipsoids of 50% probability.

Scheme 12. Plausible Mechanism of Formation of NH-Triazoles 4 and Diazo Compounds 5
considerable difference between TSs leading to different regioisomers. Generally, the 1,3-dipolar cycloaddition is a concerted and pericyclic process as an asynchronous addition, where both electronic and steric factors significantly contributed to the regioselectivity. The electronic effect is a dominant combination of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), and this is clearly governed by the largest coefficients of HOMO and LUMO of the reacting atoms. Although the steric effect is well known to compete with the electronic effects through favoring the opposite regioisomer exclusively, we have noticed a remarkably different behavior here that would lead to a considerable energy difference between TS3a and TS3ar. Our simulations have revealed three important observations that make TS3a considerably more favorable than TS3ar (Figure 3a).

First, the non-covalent interaction (NCI) calculations disclose a strong bonding interaction between methyl groups of enaminone and oxygen atoms of sulfonyl azide, as shown by the absolute values of charges for atom H20 with O30 and atom H23 with O31 (Figure 4a). Second, and in this regard, the NCI results manifest an electrostatic interaction between the hydrogen atom H5 of the triazole ring and the nitrogen atom N28 of the azide moiety. These two types of interactions are completely absent in the other TS, TS3ar. Third, the high asynchronous attack via \((3 + 2)\) cycloaddition is clearly evidenced (Figure 4b). The intrinsic reaction coordinate (IRC) calculations showed that while the first N–C bond forms at 1.56 Å, the other N–C bond is still away in the transition state zone at 2.37 Å, consequently resulting in a high asynchronous (3 + 2) cycloaddition due to a 0.81 Å bond difference between the first and second N–C bond formation (Figure 4b, top). However, the other regiomeric (3 + 2) addition through TS3a, is calculated to be totally concerted, as indicated by the IRC calculations, by which the formation of both N–C bonds reaches 1.56 Å simultaneously (Figure 4b, bottom).
Despite the fact that the 1,3-dipolar cycloaddition reaction was previously investigated using DFT simulations,\textsuperscript{51−53} our novel (3 + 2) cycloaddition seems to be in need for further attention. The effect of substituents on the 1,3-dipolar cycloaddition is investigated and shown in Figure 4c. In this regard, in comparison with our model investigated here, R\textsubscript{1} and R\textsubscript{2} = Me (Figure 4c, entry 1), replacing the methyl group with a phenyl group results in the formation of a five-membered ring with a slightly less barrier of ΔΔG\textsuperscript{⧧} = 0.4 kcal/mol, making it slightly more exergonic (ΔΔG\textsubscript{r} = −1.3 kcal/mol) (Figure 4c, entry 2). While R\textsubscript{2} remains a Ph group and R\textsubscript{1} is substituted with methyl at the para position, the calculated barrier increases to 25.5 kcal/mol but becomes more exergonic (ΔG\textsubscript{r} = −2.9 kcal/mol) (Figure 4c, entry 3). In contrast, the barrier dropped to 24.8 kcal/mol when a para-methyl group was replaced with a para-nitrophenyl group (Figure 4c, entry 4). Interestingly, in the presence of an electron-withdrawing group like NO\textsubscript{2} in sulfonyl azide (R\textsubscript{2}), when R\textsubscript{1} = Ph, the five-membered ring formation proceeded with a reduced barrier of 23.3 kcal/mol (Figure 4c, entry 6) compared to our model substrate used in this investigation (Figure 4c, entry 1, R\textsubscript{1}, R\textsubscript{2} = Me). Overall, from these results, the rate of cycloaddition seems to be more likely higher when the electron-deficient group is involved in the azide moiety.

To complete the pathway of NH-1,2,3-triazoles 8a formation, we assumed that favorable intermediate Int\textsubscript{4a} would undergo two separate pathways to release three different molecules (8, Int\textsubscript{11}, and 13), as shown in Figure 3. On the one hand, intermediate Int\textsubscript{4a} affords the elimination of sulfonyl amide 9 and triazoline Int\textsubscript{11}, which follows by either 1,3-H shift to form NH-triazole 13 or 1,2-H shift to form our desired product 8. However, this pathway was shown to be kinetically disallowed due to the substantial barrier of 37.8 kcal/mol that is needed to be overcome via TS\textsubscript{10} as a thermoneutral step (ΔG\textsuperscript{⧧} = −0.8 kcal/mol) to give intermediate Int\textsubscript{11}. Concurrently, in addition to the unfavorable sulfonyl amide 9 elimination, the intermediate Int\textsubscript{11} will subsequently undergo either a high activation barrier of 25.7 kcal/mol via 1,2-H shift TS\textsubscript{12} to furnish compound 13 or through a forbidden pathway 1,3-H shift TS\textsubscript{12} with a barrier of 59.3 kcal/mol to release compound 8. Therefore, regarding the mild conditions employed in our methodology, both shifts were totally ruled out.

On the other hand, the elimination of dimethyl amine and generation of 1-methylsulfonyl-1,2,3-triazole intermediate Int\textsubscript{6a} seems to be a more sensible pathway although it still required a higher barrier of 29.7 kcal/mol through the four-membered transition-state TS\textsubscript{5a} as a highly exergonic step of 16.8 kcal/mol to form intermediate Int\textsubscript{6a} (Figure 3). If latter...
intermediate Int6a is formed, it reacts with dimethylamine to form triazole 8a accompanied with sulfonyl amide 9 with a calculated exergonicity of 17.0 kcal/mol. Therefore, to overcome this high calculated barrier via TS5a and allow a smooth dimethyl amine elimination, a water molecule is needed to form a six-membered TS. Indeed, the addition of a water molecule as a catalyst lowers the barrier of HNMe2 needed to form a six-membered TS. Therefore, to overcome this high calculated barrier via the model reaction of 1-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)-3-(dimethylamino)prop-2-en-1-one (1a) with mesyl azide (2a), the dialkyl amine elimination is more preferable by more than 13 kcal/mol than sulfonyl amide elimination.

Further DFT simulations were performed to understand the formation of diazo compound 5a under these reaction conditions. We assume that the formation of the second desired compound occurs via the (3+2) cycloreversion of triazoline intermediate Int4a. Figure 5 shows an energetic comparison between the elimination and cycloreversion of intermediate Int4a calculated in 1,4-dioxane. The results presented in Figure 5 indicate that the elimination pathway is more favored than cycloreversion. Here, the cycloreversion needs a further higher barrier of 28.6 kcal/mol to release diazo compound 5a as a less exergonic pathway of 7.6 kcal/mol. Based on the experimental observations, we have seen that switching solvents from 1,4-dioxane to ethanol tunes the reaction direction in favor of diazo compound 5a formation. Accordingly, we have performed simulations in ethanol to reveal the impact of the solvent on the pathway preferability.

Table 1 presents the effect of the solvent (1,4-dioxane and ethanol) and substituents on computed free energy of activation for the elimination and cycloreversion pathways from triazoline intermediate Int4. Overall, the results point out that elimination is more likely to be favored in 1,4-dioxane despite the variety of substituents, whereas the cycloreversion comparatively becomes clearly favorable than elimination in ethanol. More importantly, our calculations reveal that 1,4-dioxane lowers the barrier needed for the elimination process, whereas ethanol increases the barrier dramatically. Conversely, 1,4-dioxane increases the barrier of cycloreversion largely, whereas ethanol decreases the barrier of cycloreversion substantially. According to our calculations, the barrier for the cycloreversion of intermediate Int4 is substantially lower in ethanol for the azide moiety with electron-withdrawing R = 4-

■ CONCLUSIONS

In conclusion, the interaction of azolyl enamiones 1 with sulfonyl azides 2 was studied. Examples of the concurrent formation of two types of products, NH-1,2,3-triazoles 4 and azolyl diazoketones 5, were discovered. The introduction of the basic fragment into the molecule of one of the reactants made it possible to significantly simplify the technology of isolating the desired products. By varying the sulfonyl azide, solvent, and reaction temperatures, factors favoring the implementation of each of the alternative pathways were found, and convenient laboratory methods for the synthesis of several hitherto unavailable azolyl-4-carbonyl-NH-1,2,3-triazoles 4 as well as azolyl diazoketones 5 were developed. DFT calculations were utilized to reveal the mechanism of the formation of NH-triazoles from enamine 1a and azide 2a. The DFT results have shown that the 1,3-dipolar cycloaddition is totally driven toward one single regioisomer with a high asynchronous bond formation with non-covalent interactions being considerably effective, by which the existence of an electron-deficient group on sulfonyl azides induces faster cycloaddition. Following the formation of the cycloadduct intermediate, namely, 4H-1,2,3-triazeole, the reaction was found to undergo smoothly within the six-membered TS elimination of dialkyl amine, facilitated by a water molecule, which undergoes an N–S bond cleavage to release the desired product 4a. In this regard, our calculations revealed that 1,4-dioxane makes the elimination process more favorable, whereas cycloreversion becomes the preferred pathway to form diazo compound 5a when ethanol is used. Finally, this work opens an avenue to the selective convenient preparation (including scale-up production) of diverse NH-1,2,3-triazoles and carbon-diazomethanes, valuable as building blocks and for the other applications.

■ EXPERIMENTAL SECTION

General. 1H, 13C, and 19F NMR spectra were recorded at 400 and 600 MHz (1H), 101 and 151 MHz (13C), and 376 MHz (19F) in DMSO-d6 or DCCl3 solutions. Unless specifically mentioned, 13C NMR spectra were recorded with proton decoupling (BB), spectra of diazo compounds were obtained in the j-mode (attached proton test, APT). For NMR spectra on 1H and 13C nuclei, the residual signals DMSO-d6 and HCCl3 were used as an internal reference. In the 19F NMR spectra, the chemical shifts of the signals are given relative to FCl3. The analysis of compounds by UHPLC-HRMS was performed using a tandem quadrupole time-of-flight accurate mass detector, chromatographic separation was achieved using an ultra-high-performance liquid chromatography-electrospray ionization-mass spectrometry (UHPLC-ESI-MS) system.
Table 1. Computed Free Energy of Activation (in kcal/mol) Showing the Effect of Substituents on the Cycloreversion Step of Intermediate Int4 through TS15a–f and Compared with Elimination through TS5H2Oa–f Calculated at the (SMD)-M06-2X/6-31+G(d,p)//M06-2X/6-31G(d) Level of Theory in Two Different Solvents 1,4-Dioxane and Ethanol at 298.15 K

| entry | R1  | R2  | elimination TS5H2Oa–f (ΔGf) | cycloreversion TS15a–f (ΔGf) |
|-------|-----|-----|-----------------------------|-----------------------------|
|       |     |     | 1,4-dioxane | ethanol | 1,4-dioxane | ethanol |
| 1     | Me  | Me  | 23.8          | 27.8 | 28.6          | 25.2 |
| 2     | Ph  | Ph  | 26.1          | 27.7 | 26.1          | 22.7 |
| 3     | 4-MeC6H4 | 4-MeC6H4 | 26.2          | 27.7 | 26.3          | 22.1 |
| 4     | 4-O2NC6H4 | 4-O2NC6H4 | 26.2          | 28.1 | 26.8          | 23.2 |
| 5     | Ph  | 4-MeC6H4 | 25.8          | 25.9 | 24.9          | 20.3 |
| 6     | Ph  | 4-O2NC6H4 | 22.1          | 24.3 | 21.8          | 16.9 |

The preliminary control of the progress of reactions and the purity of the obtained products was carried out on plates for TLC “Sorfil” UV-254, manifestation in UV light. The temperatures of the reactions are indicated in the bath. For column chromatography, KSKG silica gel of a specially indicated cases, were carried out in sealed vessels. The separation of the solid phase from the liquid was carried out by centrifugation (3000 rpm). Melting points were determined on a melting point apparatus and are uncorrected. All solvents were prepared according to standard methods, a petroleum ether (PE) fraction of 70–100 °C was used.

Starting Materials. The synthesis of N,N-dimethylenimiones 1a–q was described earlier.44 Sulfonyl azides 2a–e were prepared from the corresponding sulfonyl chlorides.54 Compound 2d was obtained according to ref 55. Water-soluble sulfonyl azide 2f was synthesized as is described in ref 46. Substance Zidovudine 8 is commercially available.

1-((2R,5S)-4-(4-Acetyl-5-methyl-1H-1,2,3-triazol-1-yl)-5-(hydr oxymethyl)tetrahydrofuran-2-yl)-3,5-dimethylpyrimidine-2,4(1H,3H)-dione (9). A solution of Zidovudine (8) (1030 mg, 3.85 mmol), acetaldehyde (1517 mg, 15.15 mmol), Et3N (780 mg, 7.71 mmol), and DBU (253 mg, 1.66 mmol) in 1,4-dioxane (2.1 g) was kept at 55 °C for 3 d. Volatiles were evaporated to dryness. The residue was treated with PE. The residue was separated with column chromatography: applied as a solution in DCM, eluted successively with DCM and DCM/EtOAc (1:1), and finally with EtOAc. Portions of the EtOAc eluate, containing the desired product, were combined, evaporated to dryness, and the residue was crystallized from EtOH, washed with Et2O, and dried. Yield 32% (722 mg), beige powder, mp 165–169 °C. 1H NMR (400 MHz, DMSO-d6): δ 1.81 (s, 3H), 2.57 (s, 6H), 2.63–2.68 (m, 1H), 2.70–2.82 (m, 1H), 3.63–3.70 (m, 2H), 4.26 (d, J = 3.6 Hz, 1H), 5.21 (t, J = 4.0 Hz, 1H), 5.31 (t, J = 4.8 Hz), 6.50 (t, J = 6.8 Hz, 1H), 7.79 (s, 1H), 11.34 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 8.7, 12.3, 27.5, 36.8, 57.4, 61.0, 61.06, 84.4, 109.8, 136.1, 137.5, 142.8, 150.5, 163.7, 193.4. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C15H19N5O5, 350.1459; found, 350.1468.

General Procedure for the Preparation of Enamiones 10. A mixture of enamine 1 (3.0 mmol) and N-methylpiperazine (4 mL) was refluxed with communication with the atmosphere for 2 min–5 h. For compounds 10a–c, 10h, 10l, and 10q, an excess of N-methylpiperazine was
distilled off. For compounds 10d, 10p, and 10s, thick suspensions were formed and distillation of excessive N-methylpiperazine was done after the removal of the solid phase. The distillate (2.0-2.6 mL or 50-65%) was recovered and used in the further syntheses. For more information about product isolation, see each specific case.

\[(E)-3-(4-Methylpiperazin-1-yl)-1-(1-phenyl-1H,1,2,3-triazol-4-yl)prop-2-en-1-one (10a)\]

Compound 10a was obtained in 80% (714 mg) yield according to the general procedure (enamine 1a: 727 mg, 5 h). The crude product was purified with column chromatography: applied as a solution in EtOAc, eluted successively with EtOAc and EtOAc/EtOH (5:1). Portions of the eluate containing enaminone 10a were combined, evaporated to dryness, and the residue was crystallized from PhH/PE. Light yellow powder, mp 174°C. 1H NMR (400 MHz, DMSO-d6): δ 2.30 (s, 3H), 2.38-2.50 (m, 4H), 3.38-3.52 (m, 4H), 6.30 (d, J = 12.5 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.73 (d, J = 7.7 Hz, 2H), 7.86 (d, J = 12.5 Hz, 1H), 8.47 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 45.4, 46.1, 53.4, 53.8, 55.0, 92.8, 120.6, 123.0, 129.1, 129.9, 136.9, 150.4, 152.6, 181.0. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C17H19N5O2, 303.1513; found, 303.1519.

\[(E)-3-(4-Methylpiperazin-1-yl)-1-(1-(p-tolyl)-1H,1,2,3-triazol-4-yl)prop-2-en-1-one (10b)\]

Compound 10b was obtained in 98% (916 mg) yield according to the general procedure (enamine 1b: 769 mg, 5 h). The crude product was purified with column chromatography: applied as a solution in EtOAc, eluted successively with EtOAc and EtOH, and finally with EtOAc/EtOH (5:1). The last portions of the eluate (EtOAc/EtOH), containing enaminone 10b were combined, evaporated to dryness, and the residue was crystallized from PE. Light yellow powder, mp >240°C. 1H NMR (400 MHz, DMSO-d6): δ 2.29 (s, 3H), 2.61 (s, 2H), 3.41 (s, 2H), 3.47-3.79 (m, 4H), 6.25 (d, J = 12.6 Hz, 1H), 7.92 (d, J = 12.6 Hz, 1H), 8.50 (d, J = 8.7 Hz, 2H), 8.55 (d, J = 8.7 Hz, 2H), 9.53 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 45.5, 54.0, 66.4, 92.0, 121.0, 124.4, 125.4, 140.7, 147.0, 150.1, 152.3, 178.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C18H19N5O2, 343.1513; found, 343.1525.

\[(E)-3-(4-Methylpiperazin-1-yl)-1-(1-(4-nitrophenyl)-1H,1,2,3-triazol-4-yl)prop-2-en-1-one (10d)\]

Compound 10d was obtained in 82% (842 mg) yield according to the general procedure (enamine 1d: 862 mg, 1 h; DMF for better solubility: 2 mL). The crude product was washed with EtOH and twice with Et3O. The residue was crystallized from 1,4-dioxane. Yellow powder, mp >240°C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ 2.23 (s, 3H), 2.61 (s, 2H), 3.41 (s, 2H), 3.47-3.79 (m, 4H), 6.25 (d, J = 12.6 Hz, 1H), 7.92 (d, J = 12.6 Hz, 1H), 8.40 (d, J = 8.7 Hz, 2H), 8.55 (d, J = 8.7 Hz, 2H), 9.53 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 45.5, 54.0, 66.4, 92.0, 121.0, 124.4, 125.4, 140.7, 147.0, 150.1, 152.3, 178.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C18H19N5O2, 343.1513; found, 343.1525.

\[(E)-1-(1,5-Dimethyl-1H-1,2,3-triazol-4-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (10e)\]

Compound 10e was obtained in 95% (711 mg) yield according to the general procedure (enamine 1e: 583 mg, 20 min). The crude product was treated with boiling n-octane. The residue was crystallized from PhH–PE to afford pure enamine 10e. Light yellow powder, mp 171–174°C. 1H NMR (400 MHz, DMSO-d6): δ 2.29 (s, 3H), 2.36-2.49 (m, 4H), 2.58 (s, 3H), 3.27-3.52 (m, 4H), 3.92 (s, 3H), 6.29 (d, J = 12.9 Hz, 1H), 7.71 (d, J = 12.9 Hz, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 9.1, 34.1, 45.3, 46.1, 53.0, 54.3, 92.7, 120.4, 122.9, 130.3, 134.5, 139.1, 150.2, 152.5, 181.0. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C17H19N5O2, 312.1819; found, 312.1833.

\[(E)-1-(1-Butyl-5-methyl-1H-1,2,3-triazol-4-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (10f)\]

Compound 10f was obtained in 90% (787 mg) yield according to the general procedure (enamine 1f: 709 mg, 5 min). The crude product was purified with column chromatography: applied as a solution in DCM and eluted successively with DCM and DCM with the addition of Et3N (5 drops per 10 mL). Portions of eluate containing enamine 10f were combined, evaporated to dryness, and crystallized from PE. Light yellow powder, mp 176–178°C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ 2.29 (s, 3H), 2.36-2.49 (m, 4H), 2.58 (s, 3H), 3.27-3.52 (m, 4H), 3.92 (s, 3H), 6.29 (d, J = 12.9 Hz, 1H), 7.71 (d, J = 12.9 Hz, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 9.1, 34.1, 45.3, 46.1, 53.0, 54.3, 93.4, 135.9, 144.5, 151.7, 183.2. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C18H23N5O2, 350.1662; found, 350.1670.
powder, mp 74–76 °C. \(^{1}\)H NMR (400 MHz, DCCl\(_3\)): \(\delta\) 0.93 (t, \(J = 7.4\) Hz, 3H), 1.32 (dd, \(J = 15.1, 7.5\) Hz, 2H), 1.67–1.92 (m, 2H), 2.28 (s, 3H), 2.42 (t, \(J = 4.0\) Hz, 4H), 2.57 (s, 3H), 3.32–3.57 (m, 4H), 4.21 (t, \(J = 7.3\) Hz, 2H), 6.30 (d, \(J = 12.9\) Hz, 1H), 7.70 (d, \(J = 12.9\) Hz, 1H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, DCCl\(_3\)): \(\delta\) 9.1, 13.5, 19.7, 31.7, 45.3, 46.1, 47.2, 52.9, 54.4, 93.5, 135.3, 144.3, 151.6, 183.3. HRMS (ESI-TOF) m/z: [M + H]\(^{+}\) calcd for C\(_{15}\)H\(_{26}\)N\(_{5}\)O, 292.2132; found, 292.2137.

(E)-1-(1-(4-Bromobenzyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (10g). Compound 10g was obtained in 98% (1189 mg) yield according to the general procedure (enaminone 1g: 1213 mg, 5 min).

To the crude product was purified with column chromatography: applied as a solution in DCM, eluted successively with DCM and EtOAc, and finally with DCM with the addition of Et\(_{2}\)N (5 drops per 10 mL). Portions of the eluate, containing enaminone 10g, were combined, evaporated to dryness, and crystallized from PhH–PE. Colorless powder. HRMS (ESI-TOF) m/z: [M + H]\(^{+}\) calcd for C\(_{18}\)H\(_{24}\)N\(_{5}\)O, 326.1975; found, 326.1981.

The structure of compound 10g favors the trapping of residual solvents, which are difficult to get rid of. For the spectral confirmation of the structure, picrate adduct 10ga was prepared.

(E)-1-(1-(4-Bromobenzyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one Picrate (10ga). To a mixture of enaminone 10g (100 mg, 0.286 mmol) in EtOH (900 mg), a solution of picric acid (66 mg, 0.286 mmol) in EtOH (400 mg) was added at vigorous stirring. A thick yellow solid phase forms immediately. After stirring for 5 min, the solid phase was separated and washed once with a small amount of EtOH and with Et\(_{2}\)O (twice). The crude product in Et\(_{2}\)O to obtain analytically pure compound 10ga was obtained in 93% (912 mg) yield according to the general procedure (enaminone 1g: 811 mg, N-methylpiperazin-2e, 5 min).

After cooling to room temperature, the solid phase was separated, washed with PE, and dried. Light gray powder, mp 170–172 °C. \(^{1}\)H NMR (400 MHz, DCCl\(_3\)): \(\delta\) 2.30–2.52 (m, 4H), 2.60 (s, 3H), 3.35–3.54 (m, 4H), 6.39 (d, \(J = 12.8\) Hz, 1H), 7.43 (d, \(J = 7.0\) Hz, 2H), 7.52 (d, \(J = 7.5\) Hz, 3H), 7.76 (d, \(J = 12.8\) Hz, 1H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, DCCl\(_3\)): \(\delta\) 10.2, 45.8, 46.1, 53.1, 93.6, 125.3, 129.5, 129.6, 135.9, 136.3, 144.5, 151.7, 183.1. HRMS (ESI-TOF) m/z: [M + H]\(^{+}\) calcd for C\(_{18}\)H\(_{23}\)BrN\(_{5}\)O, 404.1086; found, 404.1086.

(E)-1-(5-Methyl-1-(p-tolyl)-1H-1,2,3-triazol-4-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (10i). Compound 10i was obtained in 93% (912 mg) yield according to the general procedure (enaminone 1i: 811 mg, N-methylpiperazin-2e, 5 min). The reaction mixture was cooled to room temperature, the thick solid phase was separated, and washed with Et\(_{2}\)O twice. Crude enaminone 10i was crystallized from PhH–PE to afford pure compound 10i. To obtain the additional amount of enaminone 10i, the filtrate from the crystallization was evaporated to dryness. The filtrate from the reaction mixture and Et\(_{2}\)O washes were combined, excess of N-methylpiperazine was recovered by evaporation, and the solid residue was treated with PE three times. Both residues were combined and purified with column chromatography: applied as a solution in DCM, eluted successively with DCM and EtOAc, and finally with EtOAc/EtOH (1:1). Portions, containing the product 10i, were combined, evaporated to dryness, and crystallized from PhH–PE to afford the additional amount of pure enaminone 10i. Light yellow powder, mp 190–192 °C. \(^{1}\)H NMR (600 MHz, DCCl\(_3\)): \(\delta\) 2.32 (s, 3H), 2.43 (s, 3H), 2.45–2.49 (m, 4H), 2.59 (s, 3H), 3.40–3.51 (m, 4H), 6.40 (d, \(J = 12.8\) Hz, 1H), 7.29–7.35 (m, 4H), 7.77 (d, \(J = 12.8\) Hz, 1H). \(^{13}\)C\(^{1}\)H NMR (151 MHz, DCCl\(_3\)): \(\delta\) 10.3, 21.3, 45.4, 46.1, 53.1, 54.0, 54.9, 93.7, 125.2, 130.2, 133.4, 136.5, 140.0, 144.5, 151.8, 183.3. HRMS (ESI-TOF) m/z: [M + H]\(^{+}\) calcd for C\(_{20}\)H\(_{28}\)N\(_{5}\)O, 326.1975; found, 326.1981.

(E)-1-(1-(4-Isopropylphenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (10j). Compound 10j was obtained in 98% (1039 mg) yield according to the general procedure (enaminone 1j: 859 mg, 5 min). After cooling to room temperature, the solid phase was separated, washed with Et\(_{2}\)O twice, and with PE to afford pure enaminone 10j. Light yellow powder, mp 194–196 °C. \(^{1}\)H NMR (400 MHz, DCCl\(_3\)): \(\delta\) 1.28 (d, \(J = 6.9\) Hz, 6H), 2.31 (s, 3H), 2.39–2.53 (m, 4H), 2.60 (s, 3H), 3.00 (dq, \(J = 13.8, 6.8\) Hz, 1H), 3.34–3.55 (m, 4H), 6.40 (d, \(J = 12.8\) Hz, 1H), 7.36 (q, \(J = 8.4\) Hz, 4H), 7.77 (d, \(J = 12.8\) Hz, 1H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, DCCl\(_3\)): \(\delta\) 10.3, 23.9, 34.0, 45.3, 46.1, 53.1, 54.4, 93.6, 125.3, 127.5, 133.6, 134.4, 145.7, 150.7, 151.7, 183.2. HRMS (ESI-TOF) m/z: [M + H]\(^{+}\) calcd for C\(_{20}\)H\(_{28}\)N\(_{5}\)O, 354.2288; found, 354.2293.
(E)-1-(1-(3-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(4-methylyperazin-1-yl)prop-2-en-1-one (10l). Compound 10l was obtained in 97% (1006 mg) yield according to the general procedure (enaminone 1k: 914 mg, 1.5 h). The crude product was purified with column chromatography: applied as a solution in EtOAc, eluted successively with EtOAc and AcMe, and finally with EtOH. Portions of the eluate (EtOH), containing enaminone 10l, were combined, evaporated to dryness, and crystallized from n-octane. Light yellow crystals, mp 172−172 °C. ¹H NMR (400 MHz, DCCl₃): δ 2.32 (s, 3H), 2.43 (s, 3H), 2.46 (s, 3H), 2.44−2.49 (m, 4H), 3.39−3.51 (m, 4H), 6.41 (d, J = 12.9 Hz, 1H), 7.18−7.31 (m, 2H), 7.39 (s, 1H), 7.78 (d, J = 12.9 Hz, 1H). ¹³C{¹H} NMR (101 MHz, DCCl₃): δ 9.5, 21.1, 45.3, 46.0, 53.1, 54.3, 93.4, 128.6, 128.7, 130.8, 130.9, 131.3, 138.1, 142.5, 143.8, 151.7, 182.9. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₈H₂₃ClN₅O, 360.1586; found, 360.1599.

(E)-1-(1-(3-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(4-methylyperazin-1-yl)prop-2-en-1-one (10m). Compound 10m was obtained in 97% (959 mg) yield according to the general procedure (enaminone 1m: 872 mg, 1.7 h). The crude product was crystallized from PhH−PE to a final pure sample was prepared by column chromatography: applied as a solution on DCM, eluted successively with DCM and EtOAc, and finally with EtOAc/EtOH (1:1). Portions of the eluate (EtOH), containing enaminone 10m, were combined, evaporated to dryness, and crystallized from PhH−PE to afford pure enaminone 10m. Light yellow powder, mp 158−160 °C. ¹H NMR (400 MHz, DCCl₃): δ 2.32 (s, 3H), 2.42−2.50 (m, 4H), 2.52 (s, 3H), 3.38−3.55 (m, 4H), 6.37 (d, J = 12.8 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.68−7.89 (m, 3H), 8.18 (d, J = 8.0 Hz, 1H). ¹³C{¹H} NMR (101 MHz, DCCl₃): δ 9.55, 45.4, 50.3, 54.8, 93.4, 125.8, 129.0, 129.6, 131.6, 134.2, 142.5, 145.5, 151.9, 182.5. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₇H₂₁N₅O₃, 357.167; found, 357.1677.

(1R,2R,5S)-5-(Hydroxymethyl)-4-(5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)-1-((2R,5S)-5-(Hydroxymethyl)-4-(5-methyl-4-((E)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (10n). Compound 10n was obtained in 83% (887 mg) yield according to the general procedure (enaminone 1n: 904 mg, 5 min). The crude product was treated with PE twice and purified by column chromatography: applied as a solution in DCM, eluted successively with DCM and EtOAc, and finally with EtOAc/ EtOH (1:1). Portions of the eluate, containing product 10n, were combined, evaporated to dryness, and crystallized from PhH−PE to afford pure enaminone 10n. Light yellow powder, mp 158−160 °C. ¹H NMR (400 MHz, DCCl₃): δ 2.32 (s, 3H), 2.42−2.50 (m, 4H), 2.52 (s, 3H), 3.38−3.55 (m, 4H), 6.37 (d, J = 12.8 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.68−7.89 (m, 3H), 8.18 (d, J = 8.0 Hz, 1H). ¹³C{¹H} NMR (101 MHz, DCCl₃): δ 9.55, 45.4, 50.3, 54.8, 93.4, 125.8, 129.0, 129.6, 131.6, 134.2, 142.5, 145.5, 151.9, 182.5. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₇H₂₁N₆O₃, 357.167; found, 357.1677.

(E)-1-(5-Methyl-1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)-3-(4-methylyperazin-1-yl)prop-2-en-1-one (10o). Compound 10o was obtained in 89% (952 mg) yield according to the general procedure (enaminone 1o: 904 mg, 2 min). After cooling to room temperature, the solid phase was separated, washed with EtO twice, and with PE to afford pure enaminone 10o. Light yellow powder, mp 218−219 °C. ¹H NMR (400 MHz, DCCl₃): δ 2.32 (s, 3H), 2.41−2.56 (m, 4H), 2.71 (s, 3H), 3.37−3.55 (m, 4H), 6.37 (d, J = 12.7 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 12.8 Hz, 1H), 8.43 (d, J = 8.8 Hz, 2H). ¹³C{¹H} NMR (101 MHz, DCCl₃): δ 10.6, 45.6, 46.2, 53.4, 53.9, 55.0, 93.4, 125.2, 125.8, 136.3, 140.8, 145.2, 148.1, 152.2, 182.6. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₇H₂₁N₆O₃, 357.167; found, 357.1676.
treated with a small amount of PE, the residue was crystallized in 97% (734 mg) yield according to the general procedure (enaminone 1q: 592 mg, 10 min). The crude product was treated with a small amount of PE, the residue was crystallized from n-heptane. Light yellow powder, mp 125−126 °C. 1H NMR (600 MHz, DCCl3): δ 2.31 (s, 3H), 2.46 (d, J = 4.1 Hz, 4H), 2.91 (s, 3H), 3.45 (s, 4H), 6.50 (d, J = 12.7 Hz, 1H), 7.78 (d, J = 12.7 Hz, 1H). 13C{1H} NMR (151 MHz, DCCl3): δ 11.2, 45.5, 46.1, 53.5, 53.8, 55.1, 95.1, 157.8, 182.4. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C11H11N3O3, 286.0683; found, 286.0687.

(E)-1-(5-Methyl-1,2,3-thiadiazol-4-yl)-3-(4-methylpiperazin-1-yl)prop-2-en-1-one (10q). Compound 10q was obtained in 73% (757 mg) yield according to the general procedure (enaminone 1r: 872 mg, 5 min). The reaction mixture was left at room temperature for 12 h, the formed precipitate was separated, washed with PE, and crystallized from n-heptane. Light yellow powder, mp 164−166 °C. 1H NMR (400 MHz, DCCl3): δ 2.28 (br s, 3H), 2.33 (s, 4H), 2.60 (s, 3H), 3.00 (br s, 2H), 3.29 (d, J = 12.7 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 12.7 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H). 13C{1H} NMR (151 MHz, DCCl3): δ 12.8, 45.2, 46.1, 53.2, 53.5, 53.6, 55.0, 97.1, 117.7, 130.3, 135.8, 152.4, 160.3, 171.5, 183.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C11H11N5O, 241.0832; found, 241.0834.

General Procedure for the Preparation of NH-1,2,3-Triazoles 4. A solution of enaminone 10 (1.0 mmol) and TsN3 (2a, 1.0 mmol, 197 mg) in PyH (4.6 g) was kept at ambient temperature (for 4-nitro derivative 10o, at 80 °C, for 1,2,3-thiadiazole 10q and isoxazole 10r derivatives, at 52 °C) for 2−50 h. Volatiles were evaporated to dryness, the residue was treated with a mixture of H2O (6 g) and AcOH (350 mg), followed once again by the same mixture, finally with H2O (6 g), and dried. While preparing triazoles 4d and 4o, aqueous acetic washes were used for the isolation of 1-methyl-4-tosylpiperazine (6a) and 4-methyl-N-((4-methylpiperazin-1-yl)methylene)benzenesulfonamide in an oxalate form (7aa), respectively. The details are available from specific protocols of the synthesis. Content of NH-triazole 4 and diazo compound 5 in the mixture was estimated based on 1H NMR. Pure products 4 and 5 were isolated with column chromatography of the mixture: applied as a solution in DCM with an addition of Et3N (5 drops per 10 mL), eluted successively with DCM and EtOAc, and finally with EtOAc with an addition of AcOH (5 drops per 10 mL). Portions of the eluate, containing products 4 and 5, were combined, evaporated to dryness, and crystallized.

(1-Phenyl-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4a). Compound 4a was obtained in 94% (226 mg) yield according to the general procedure (enaminone 10a: 297 mg, 4 h). Colorless powder, mp 247−249 °C (i-PrOH/ Et2O). 1H NMR (400 MHz, DMSO-d6): δ 7.56 (t, J = 7.4 Hz, 1H), 7.65 (t, J = 7.7 Hz, 2H), 8.03 (d, J = 7.8 Hz, 2H), 8.99 (s, 1H), 9.67 (s, 1H), 15.96 (br s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 120.8, 127.7, 129.4, 129.9, 131.8, 136.1, 143.8, 146.1. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C11H9N6O, 241.0832, found, 241.0834.

(1-(p-Tolyl)-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4b). Compound 4b was obtained in 92% (234 mg) yield according to the general procedure (enaminone 10b: 311 mg, 5 h). Colorless powder, mp 229−230 °C (H2O). 1H NMR (400 MHz, DMSO-d6): δ 2.40 (s, 3H), 7.43 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 8.98 (s, 1H), 9.61 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 20.6, 120.6, 127.6, 130.3, 131.7, 133.8, 139.2, 144.0, 146.0, 175.8. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C11H10N5O, 228.0880; found, 228.0881.

(1-(2-Nitrophenyl)-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4c). Compound 4c was obtained in 96% (274 mg) yield according to the general procedure (enaminone 10c: 342 mg, 12 h). Light gray powder, mp 230−233 °C (EtOH, decomp.) 1H NMR (400 MHz, DMSO-d6): δ 7.86−7.97 (m, 1H), 8.02 (d, J = 3.3 Hz, 2H), 8.31 (d, J = 8.0 Hz, 1H), 8.98 (br s, 1H), 9.69 (s, 1H), 15.97 (br s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6 + Cs2CO3): δ 125.7, 128.4, 128.8, 131.5, 131.8, 132.5, 134.7, 143.9, 144.3, 145.7, 175.8. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C11H9N6O3, 286.0683; found, 286.0687.

(1-(4-Nitrophenyl)-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4d). Compound 4d was obtained in 96% (274 mg) yield according to the general procedure (enaminone 10d: 342 mg, 12 h). Gray powder, mp 252−256 °C (treated with EtOH and Et2O, decomp.). For better characterization by the 13C NMR spectrum, acetate salt 4da was prepared. 1H NMR (400 MHz, DMSO-d6): δ 8.37 (d, J =
1-Methyl-4-tosylpiperazine (6a). Aqueous acetic acid washes were combined and evaporated to dryness. The residue was treated with aqueous NH₃, washed with water, and dried. A crude product was purified with column chromatography: applied as a solution in DCM and eluted successively with DCM and DCM/EtOAc (1:1). Portions of the eluate, containing the desired product 6a, were combined, evaporated to dryness, and the residue was crystallized from PhH−PE. Yield 84% (213 mg), colorless solid, mp 144−145 °C (lit.56 143−145 °C).

(1,5-Dimethyl-1H-1,2,3-triazol-4-y1)(1H-1,2,3-triazol-5-y1)methanone (4e). Compound 4e was obtained in 95% (183 mg) yield according to the general procedure (enaminone 10e: 249 mg, 3 h). Colorless powder, mp 169−172 °C (H₂O). ¹H NMR (400 MHz, DMSO-d₆): δ 2.59 (s, 3H), 4.01 (s, 3H), 8.91 (br s, 1H). ¹³C{¹H} NMR (101 MHz, DMSO-d₆): δ 22.5, 121.5, 125.5, 128.1, 133.9, 140.6, 144.3, 147.1, 174.2, 176.2. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₃H₁₁N₆O, 269.1145; found, 269.1150.

(1-Butyl-5-methyl-1H-1,2,3-triazol-4-y1)(1H-1,2,3-triazol-4-y1)methanone (4f). Compound 4f was obtained in 91% (213 mg) yield according to the general procedure (enaminone 10f: 291 mg, 3 h). Gray powder, mp 138−140 °C (PhH−PE). ¹H NMR (600 MHz, DMSO-d₆): δ 0.90 (t, J = 7.4 Hz, 3H), 1.20 (d, J = 15.0, 7.5 Hz, 2H), 1.71−1.85 (m, 2H), 2.62 (s, 3H), 4.37 (t, J = 7.2 Hz, 2H), 8.92 (s, 1H), 15.81 (br s, 1H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 23.1, 22.5, 121.9, 125.7, 128.1, 133.1, 133.7, 140.0, 142.9, 143.4, 147.4, 177.8. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₆H₁₄N₆O, 295.1302; found, 295.1306.

(1-(4-Bromobenzyl)-5-methyl-1H-1,2,3-triazol-4-y1)(1H-1,2,3-triazol-4-y1)methanone (4g). Compound 4g was obtained in 79% (274 mg) yield together with diazo compound 5g in 13% yield (42 mg) according to the general procedure (enaminone 10g: 404 mg, 3 h). Colorless powder, mp 162−164 °C (PhH−PE). ¹H NMR (600 MHz, DMSO-d₆): δ 2.58 (s, 3H), 5.69 (s, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 8.94 (s, 1H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆): δ 9.5, 50.5, 121.9, 130.3, 132.3, 133.2, 134.9, 140.0, 142.9, 143.2, 177.8. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₁H₁₂BrN₆O, 347.0250; found, 347.0263.

(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-y1)(1H-1,2,3-triazol-4-y1)methanone (4h). Compound 4h was obtained in 89% (226 mg) yield together with diazo compound 5h in 5% yield (11 mg) according to the general procedure (enaminone 10h: 311 mg, 67 h). Colorless powder, mp 200−202 °C (EtOH). ¹H NMR (600 MHz, DMSO-d₆): δ 2.60 (s, 3H), 7.54−7.72 (m, 5H), 9.03 (br s, 1H), 15.87 (br s, 1H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆ + C₆H₅CO₂H): δ 10.11, 125.6, 129.8, 130.3, 133.1, 135.0, 139.9, 142.4, 143.0, 177.5. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₂H₁₁N₆O, 255.0989; found, 255.0994.

(5-Methyl-1-(4-methylphenyl)-1H-1,2,3-triazol-4-y1)(1H-1,2,3-triazol-4-y1)methanone (4i). Compound 4i was obtained in 96% (258 mg) yield according to the general procedure (enaminone 10i: 325 mg, 3 h). Gray powder, mp 148−151 °C (i-PrOH−H₂O). ¹H NMR (600 MHz, DMSO-d₆): δ 2.43 (s, 3H), 2.58 (s, 3H), 7.47 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 8.96 (s, 1H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆ + C₆H₅CO₂H): δ 10.5, 21.2, 125.8, 130.6, 133.0, 133.7, 140.2, 140.6, 142.9, 143.4, 178.0. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₃H₁₃N₆O, 269.1145; found, 269.1150.

(1-(4-Isopropylphenyl)-5-methyl-1H-1,2,3-triazol-4-y1)(1H-1,2,3-triazol-4-y1)methanone (4j). Compound 4j was obtained in 80% (215 mg) yield together with diazo compound 5j in 14% yield (38 mg) according to the general procedure (enaminone 10j: 354 mg, 3 h). Gray powder, mp 217−220 °C (EtOH). ¹H NMR (400 MHz, DMSO-d₆): δ 1.27 (d, J = 6.9 Hz, 6H), 2.60 (s, 3H), 3.03 (dt, J = 13.7, 6.9 Hz, 1H), 7.56 (dd, J = 22.3, 8.5 Hz, 4H), 9.01 (s, 1H), 15.84 (br s, 1H).
(1-(2-Chloro-4-methylphenyl)-5-methyl-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4k). Compound 4k was obtained in 85% (257 mg) yield together with diazo compound 5k in 9% yield (25 mg) according to the general procedure (enaminone 10k: 360 mg, 36 h). Colorless powder, mp 211–213 °C (EtOH–H2O, decomp.). 1H NMR (600 MHz, DMSO-d6): δ 2.45 (s, 3H), 2.46 (s, 3H), 7.46 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.69 (s, 1H), 9.04 (s, 1H). 13C{1H} NMR (151 MHz, DMSO-d6): δ 9.9, 21.0, 129.7, 129.8, 130.0, 130.4, 131.2, 133.0, 141.9, 142.2, 143.4, 144.0, 177.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C15H17N6O, 297.1458; found, 297.1460.

(1-(3-Chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone 4l. Compound 4l was obtained in 91% (263 mg) yield according to the general procedure (enaminone 10l: 346 mg, 4 h). Colorless needles, mp 195–196 °C. 1H NMR (400 MHz, DMSO-d6 + Cs2CO3): δ 2.62 (s, 3H), 7.72 (dd, J = 13.4, 4.3 Hz, 3H), 7.87 (s, 1H), 9.01 (br s, 1H), 15.88 (br s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6 + Cs2CO3): δ 10.0, 124.5, 125.6, 130.3, 131.4, 133.0, 134.0, 136.1, 140.2, 143.0, 177.5. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C15H16ClN6O, 289.0895; found, 289.0897.

(1-(3-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4m). Gray powder, mp 180–181 °C. Compound 4m was obtained in 97% (264 mg) yield according to the general procedure (enaminone 10m: 329 mg, 3 h). 1H NMR (400 MHz, DMSO-d6): δ 2.63 (d, J = 1.6 Hz, 2H), 7.47–7.64 (m, 2H), 7.64–7.80 (m, 2H), 15.90 (br s, 1H), 9.01 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 10.0, 113.2 (d, J = 25.1 Hz), 117.3 (d, J = 20.9 Hz), 121.8 (d, J = 3.2 Hz), 128.2, 131.6 (d, J = 9.1 Hz), 132.7, 136.1 (d, J = 10.4 Hz), 141.2 (d, J = 19.1 Hz), 142.8, 162.0 (d, J = 246.5 Hz), 177.3. 19F{1H} NMR (376 MHz, DMSO-d6): δ −110.47. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C15H10F3N6O, 273.0895; found, 273.0897.

(5-Methyl-1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4p). Compound 4p was obtained in 98% (356 mg) yield according to the general procedure (enaminone 10p: 474 mg, 1 h).

(5-Methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4o). Compound 4o was obtained in 75% (224 mg) yield according to the general procedure at 80 °C (enaminone 10o: 356 mg, 1.5 h). Gray powder, mp 274–278 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ 2.68 (s, 3H), 8.03 (d, J = 8.5 Hz, 2H), 8.50 (d, J = 8.5 Hz, 2H), 9.02 (s, 1H), 15.90 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6 + Cs2CO3): δ 10.1, 125.1, 126.7, 133.1, 139.8, 140.3, 142.7, 143.0, 148.0, 177.4. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C21H15N6O3, 300.0840; found, 300.0833.

4-Methyl-N-(4-methylpiperazin-1-yl)methylenebenzenesulfonamide Oxalate (7aa). Aqueous acetic acid washes were combined and evaporated to dryness. The residue was purified with column chromatography: applied as a solution in DCM with the addition of Et3N (5 drops per 10 mL), eluted successively with DCM and EtOAc, and EtOAc/EtOH (1:1). Portions of the eluate, containing the desired product 7aa, were combined and evaporated to dryness. The oily residue was dissolved in EtOH (1700 mg) and warmed to 45 °C. To this solution, oxalic acid (35 mg, 0.39 mmol) was added at once. The solution was left to cool to room temperature and kept for 2 h, while the solid phase forms gradually. It was separated, washed with Et3O twice, and dried. Yield 18% (67 mg), beige powder, mp 189–191 °C (EtOH). 1H NMR (400 MHz, DMSO-d6): δ 2.36 (s, 3H), 2.53 (s, 3H), 2.84 (t, J = 5.0 Hz, 2H), 2.89–2.96 (m, 2H), 3.66 (d, J = 4.8 Hz, 2H), 3.70–3.80 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 8.29 (s, 1H), 10.41 (br s, 1H). 13C{1H} NMR (151 MHz, DMSO-d6): δ 21.0, 40.9, 43.3, 47.1, 51.8, 52.9, 126.1, 129.5, 139.8, 142.2, 158.7, 163.9. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C21H10O3N2O4S, 282.1271; found, 282.1278.

1-(2R,5S)-5-(Hydroxymethyl)-4-(5-methyl-1H-1,2,3-triazole-4-carbonyl)-1,1,2,3-triazol-1-yl)tetrahydrofururan-2-yl)-3,5-dimethylpyrimidine-2,4(1H,3H)-dione (4p). Compound 4p was obtained in 96% (400 mg) yield according to the general procedure (enaminone 10p: 474 mg, 1 h).
Colorless powder, mp 172−177 °C. 1H NMR (400 MHz, DMSO-d$_6$): δ 1.88 (s, 3H), 2.67−2.73 (m, 4H), 2.86 (dd, J = 14.1, 4.7 Hz, 1H), 3.19 (s, 3H), 3.61−3.80 (m, 2H), 4.34 (d, J = 3.6 Hz, 1H), 5.23−5.34 (m, 1H), 6.59 (t, J = 6.7 Hz, 1H), 7.89 (s, 1H), 8.97 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d$_6$ + Cs$_2$CO$_3$): δ 11.5, 133.2, 144.7, 156.1, 162.0, 178.0. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C$_{10}$H$_7$N$_6$O$_3$, 259.0574; found, 259.0601.

(5-Methyl-1,2,3-thiadiazol-4-yl)(1H-1,2,3-triazol-4-yl)methanone (4q). Compound 4q was obtained in 78% (131 mg) yield according to the general procedure (enaminone 10q: 252 mg, 4 h at 52 °C). Beige powder, mp 171−173 °C (i-PrOH). 1H NMR (400 MHz, DMSO-d$_6$): δ 2.91 (s, 3H), 9.00 (br s, 1H), 15.86 (br s, 1H). 13C{1H} NMR (101 MHz, DMSO-d$_6$): δ 11.5, 133.2, 144.7, 156.1, 162.0, 178.0. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C$_{10}$H$_7$N$_6$O$_3$, 196.0288; found, 196.0294.

(3-(4-Chlorophenyl)-5-methylisoxazol-4-yl)(1,2,3-triazol-4-yl)methanone (4r). Compound 4r was obtained in 85% (245 mg) yield according to the general procedure (enaminone 10r: 346 mg, 4 h at 52 °C). Colorless powder, mp 154−155 °C (EtOH−H$_2$O). 1H NMR (400 MHz, DMSO-d$_6$): δ 2.53 (s, 3H), 7.47 (s, 4H), 8.62 (s, 1H), 15.74 (br s, 1H). 13C{1H} NMR (101 MHz, DMSO-d$_6$): δ 12.7, 115.6, 127.1, 128.6, 130.0, 131.1, 134.6, 145.6, 160.6, 173.4, 180.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C$_{11}$H$_{10}$ClN$_5$O, 289.0487; found 289.0493.

**General Procedure for the Preparation of Diazoketones 5.** A mixture of enaminone 10 (1.0 mmol) and 4-nitrophenylhydrazon azide (2e, 1.0 mmol) in EtOH (4.8 g) was stirred at room temperature (at 80 °C for enaminone 13p) for 2−49 h. The solid phase [main amount of N-((4-methylpiperazin-1-yl)methylene)-4-nitrobenzenesulfonyamide (7b)] was separated, the liquid phase was evaporated to dryness. The residue was treated with a mixture of H$_2$O (6.0 g) and AcOH (313 mg), once again with the same mixture and finally with water (6.0 g). While preparing diazo compound 5c, aqueous acetic washes were used for the isolation of 1-methyl-4-((4-nitrophenyl)sulfonyl)piperazine (6b). The details are available from a specific protocol of the synthesis. The separation of multicompont mixture thus obtained, containing diazo compounds 5 and NF-1,2,3-triazoles 4, and purification of crude products were performed similarly to the general procedure for the preparation of NH-1,2,3-triazoles 4 (see above). For diazo compounds 5e and 5f, which are well soluble in water, the modified work-up was applied (see the specific procedure).

2-Diazo-1-(1-phenyl-1H-1,2,3-triazol-4-yl)ethan-1-one (5a). Compound 5a was obtained in 85% (181 mg) yield together with compound 4a in 9% (22 mg) yield according to the general procedure (enaminone 10a: 297 mg, 23 h). Light yellow powder, mp 192−193 °C (PhH−PE, decomp.). IR (ATR, ZnSe, cm$^{-1}$): ν 2104 (N−N stretch), 1615, 1540, 1367, 861, 734. 1H NMR (400 MHz, DMSO-d$_6$): δ 6.81 (s, 1H), 7.45−7.74 (m, 3H), 7.97 (d, J = 7.6 Hz, 2H), 9.43 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d$_6$): δ 55.2, 120.5, 124.3, 129.3, 129.9, 136.1, 146.3, 178.5. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C$_{16}$H$_{12}$N$_4$O, 214.0723; found, 214.0729.

2-Diazo-1-(1-p-tolyl-1H-1,2,3-triazol-4-yl)ethan-1-one (5b). Compound 5b was obtained in 84% (191 mg) yield together with compound 4b in 9% (23 mg) yield according to the general procedure (enaminone 10b: 311 mg, 22 h). Light yellow powder, mp 168−169 °C (n-octane, decomp.). IR (ATR, ZnSe, cm$^{-1}$): ν 3058, 2104 (N−N stretch), 1617, 1541, 1368, 1027, 862, 810, 748. 1H NMR (600 MHz, DMSO-d$_6$): δ 2.39 (s, 3H), 6.76 (s, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.79−7.89 (m, 2H), 9.33 (s, 1H). 13C{1H} NMR (151 MHz, DMSO-d$_6$): δ 21.0, 55.6, 120.9, 124.6, 130.7, 134.4, 139.5, 146.7, 178.9. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C$_{17}$H$_{21}$N$_8$O$_5$, 228.0880; found, 228.0881.

2-Diazo-1-(1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)ethan-1-one (5c). Compound 5c was obtained in 80% (206 mg) yield together with compound 4c in 10% (29 mg) yield according to the general procedure (enaminone 10c: 342 mg, 48 h). Light yellow powder, mp 158−159 °C (PE, decomp.). IR (ATR, ZnSe, cm$^{-1}$): ν 2203 (N−N stretch), 1720, 1531, 1189. 1H NMR (400 MHz, DCCl$_3$): δ 6.48 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 7.2 Hz, 1H), 8.41 (s, 1H). 13C{1H} NMR (101 MHz, DCCl$_3$): δ 55.3, 126.0, 126.4, 128.1, 129.9, 131.6, 134.2, 144.6, 147.0, 178.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C$_{10}$H$_7$N$_6$O$_3$, 259.0574; found, 259.0601.

1-Methyl-4-((4-nitrophenyl)sulfonyl)piperazine (6b). Aqueous acetic acid washes were combined and evaporated to dryness. The residue was treated with aqueous NH$_4$OH washed with water, and dried. A crude product was purified with column chromatography: applied as a solution in DCM and eluted successively with DCM and DCM/EtOAc (1:1).
Portions of the eluate, containing the desired product 6b, were combined, evaporated to dryness, and the residue was crystallized from PhH–PE. Yield 13% (44 mg), light brown powder, mp 155–156 °C (PhH–PE). 1H NMR (400 MHz, DCCl3): δ 2.26 (s, 3H), 2.41–2.55 (m, 4H), 3.09 (br s, 4H), 7.94 (d, J = 8.7 Hz, 2H), 8.37 (d, J = 8.7 Hz, 2H). 13C{1H} NMR (101 MHz, DCCl3): δ 45.8, 46.0, 54.1, 124.4, 129.0, 141.9, 150.4. By 1H NMR spectrum, the product corresponds to 1-methyl-4-[(4-nitrophenyl)sulfonyl]piperazine (6b), described earlier.57

2-Diazo-1-(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)ethan-1-one 5d. Compound 5d was obtained in 79% (204 mg) yield together with compound 4d in 9% (27 mg) yield according to the general procedure (enaminone 10d: 342 mg, 46 h). Light yellow powder, 202–204 °C (n-BuOH, decomp.). IR (ATR, ZnSe, cm⁻¹): ν 3114, 2115 (N–N stretch), 1596, 1518, 1363, 1345, 859. 1H NMR (400 MHz, DMSO-d6): δ 6.82 (br s, 1H), 8.29 (d, J = 9.0 Hz, 2H), 8.45 (d, J = 9.0 Hz, 2H), 9.63 (s, 1H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 55.4, 121.3, 124.9, 125.4, 140.4, 146.6, 147.3, 178.1. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₀H₁₀N₅O₃, 259.0574; found, 259.0573.

2-Diazo-1-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)ethan-1-one 5e. Compound 5e was obtained in 89% (147 mg) yield together with compound 4e in 6% yield according to the modified general procedure (enaminone 10e: 249 mg, 3 h). Liquid phases after the removal of the main amount of amidine 7b were combined and evaporated to dryness. According to the 1H NMR spectrum, the mixture contained NH-triazole 4e in 5% (6 mg) yield. To isolate diazo compound 5e, the mixture was separated with column chromatography: applied as a solution in DCM and eluted successively with DCM and DCM/ETOAc (1:1). Portions, containing diazo compound 5e, were combined, evaporated to dryness, and the residue was crystallized from PE to afford pure diazo compound 5e. Light yellow powder, mp 129–130 °C (PE). IR (ATR, ZnSe, cm⁻¹): ν 2097 (N–N stretch), 1608, 1570, 1360, 1309, 1020, 864, 570, 516. 1H NMR (400 MHz, DCCl3): δ 2.58 (s, 3H), 3.96 (s, 3H), 6.39 (s, 1H). 13C{1H} NMR (101 MHz, DCCl3): δ 8.8, 34.2, 54.3, 136.1, 141.9, 180.9. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₀H₁₀N₅O₃, 259.0723; found, 259.0728.

N-(4-Methylpiperazin-1-yl)methylene-4-nitrobenzenesulfonamide (7b). Beige powder, mp 200–202 °C. 1H NMR (600 MHz, DMSO-d₆): δ 2.19 (s, 3H), 2.31 (t, J = 4.9 Hz, 2H), 2.37–2.42 (m, 2H), 3.50–3.57 (m, 2H), 3.57–3.63 (m, 2H), 8.03 (d, J = 8.8 Hz, 2H), 8.33 (s, 1H), 8.35 (d, J = 8.8 Hz, 2H). 13C{1H} NMR (151 MHz, DMSO-d₆): δ 43.2, 45.4, 49.6, 53.3, 54.5, 124.4, 127.52, 148.3, 149.2, 158.7. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₂H₁₇N₆O₅S, 313.0971; found, 313.0973.

1-(1-Butyl-5-methyl-1H-1,2,3-triazol-4-yl)-2-diazoethanone (5f). Compound 5f was obtained in 94% (195 mg) yield according to the same procedure as for the preparation of compound 5e (enaminone 10e: 291 mg, 3 h). Yellowish oil. IR (ATR, ZnSe, cm⁻¹): ν 2104 (N–N stretch), 1621, 1570, 1364, 1315, 864. 1H NMR (400 MHz, DCCl3): δ 0.95 (t, J = 7.4 Hz, 3H), 1.35 (dd, J = 15.0, 7.5 Hz, 2H), 1.78–1.90 (m, 2H), 2.59 (s, 3H), 4.25 (t, J = 7.3 Hz, 2H), 6.41 (br s, 1H). 13C{1H} NMR (101 MHz, DMSO-d₆): δ 8.9, 13.5, 19.8, 31.7, 47.6, 54.3, 135.5, 141.8, 181.0. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₉H₁₉N₅O₂, 288.1207; found, 288.1202.

1-(1-(4-Bromobenzyl)-5-methyl-1H-1,2,3-triazol-4-yl)-2-diazoethan-1-one (5g). Compound 5g was obtained in 82% (263 mg) yield according to the general procedure (enamine 10g: 404 mg, 4 h). Light yellow powder, mp 104–108 °C (PE, decomp.). IR (ATR, ZnSe, cm⁻¹): ν 2096 (N–N stretch), 1610, 1562, 1367, 1007. 1H NMR (400 MHz, DCCl3): δ 2.50 (s, 3H), 5.45 (s, 2H), 6.43 (br s, 1H), 7.05 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H). 13C{1H} NMR (101 MHz, DCCl3): δ 8.9, 51.1, 54.5, 122.8, 128.9, 132.3, 132.9, 135.9, 142.2, 180.7. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₉H₁₈BrN₅O₂, 320.0141; found, 320.0151.

2-Diazo-1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethan-1-one (5h). Compound 5h was obtained in 88% (200 mg) yield according to the general procedure (enamine 10h: 311 mg, 20 h). Light yellow powder, mp 97–100 °C (PE). IR (ATR, ZnSe, cm⁻¹): ν 3063, 2108 (N–N stretch), 1623, 1608, 1563, 1364, 1324, 865, 760. 1H NMR (400 MHz, DMSO-d₆): δ 2.60 (s, 3H), 6.48 (s, 1H), 7.39–7.48 (m, 2H), 7.55 (d, J = 7.0 Hz, 3H). 13C{1H} NMR (101 MHz, DCCl3): δ 8.9, 54.8, 125.4, 129.7, 130.1, 135.0, 136.7, 141.0, 180.2. HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₉H₁₆NO₂, 228.0880; found, 228.0881.

2-Diazo-1-(5-methyl-1-(4-methylphenyl)-1H-1,2,3-triazol-4-yl)ethan-1-one (5i). Compound 5i was obtained in 86% (208 mg) yield according to the general procedure (enamine 10i: 325 mg, 3 h). Light yellow powder, mp 117–120 °C (PE). IR (ATR, ZnSe, cm⁻¹): ν 2102 (N–N stretch), 1613, 1364, 822. 1H NMR (400 MHz, DCCl3): δ 2.45 (s, 3H), 2.59 (s, 3H), 6.49 (br s, 1H), 7.31 (dd, J = 6.2,
2-Diazo-1-(1-(4-isopropylphenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethan-1-one (5j). Compound 5j was obtained in 92% (248 mg) yield according to the general procedure (enaminone 10j: 354 mg, 4 h). Light yellow powder, mp 189 °C (EtOH, decomp.). IR (ATR, ZnSe, cm⁻¹): v 2106 (N–N stretch), 1620, 1384, 873, 857, 789, 518. ¹H NMR (400 MHz, DCCl₃): δ 2.63 (s, 3H), 6.47 (s, 1H), 7.28–7.20 (m, 3H), 7.61–7.47 (m, 1H). ¹³C [¹H] NMR (101 MHz, DCCl₃): δ 9.9, 54.7, 113.0 (d, J = 24.6 Hz), 117.2 (d, J = 20.9 Hz), 120.8 (d, J = 3.4 Hz), 131.1 (d, J = 8.9 Hz), 136.5 (d, J = 4.9 Hz), 136.6, 141.9, 162.7 (d, J = 248.6 Hz), 180.6. ¹⁹F [¹H] NMR (376 MHz, DCCl₃): δ −109.43. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₁H₉F₂N₂O, 246.0786; found, 246.0787.

1-(1-(2-Chloro-4-methylphenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-2-diazoethan-1-one (5k). Compound 5k was obtained in 83% (228 mg) yield according to the general procedure (enaminone 10k: 360 mg, 24 h). Light yellow powder, mp 142–146 °C (PhH–PE). IR (ATR, ZnSe, cm⁻¹): v 3075, 2103 (CH₃CN), 1612, 1529, 1306, 955, 886. ¹H NMR (400 MHz, DCCl₃): δ 2.55 (s, 3H), 6.48 (s, 1H), 7.50 (dd, J = 7.7, 1.4 Hz, 1H), 7.83 (dd, J = 24.8, 7.7, 1.5 Hz, 2H), 8.22 (dd, J = 8.0, 1.5 Hz, 1H). ¹³C [¹H] NMR (101 MHz, DCCl₃, APT mode): δ 9.3, 54.8, 126.0, 128.6, 129.6, 132.0, 134.3, 138.4, 141.5, 145.38, 180.4. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₄H₁₂N₂O₂, 270.0371; found, 270.0355.

2-Diazo-1-(1-(2-nitrophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethan-1-one (5l). Compound 5l was obtained in 92% (250 mg) yield according to the general procedure (enaminone 10l: 356 mg, 4 h). Yellow powder, mp 95–98 °C (n-octane). IR (ATR, ZnSe, cm⁻¹): v 3075, 2103 (CH₃CN), 1612, 1529, 1306, 955, 886. ¹H NMR (400 MHz, DCCl₃): δ 3.26 (s, 3H), 6.70 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 8.46 (d, J = 9.0 Hz, 2H). ¹³C [¹H] NMR (101 MHz, DMSO-d₆, APT mode): δ 9.5, 54.9, 125.0, 126.4, 137.2, 139.9, 141.5, 148.0, 179.9. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₄H₁₂N₂O₂, 270.0371; found, 273.0728.

1-(2,5-Diisopropylphenyl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,5-dimethyl-pyrimidine-2,4(1H,3H)-dione (5n). Compound 5n was obtained in 76% (207 mg) yield according to the general procedure (enaminone 10n: 356 mg, 4 h). Yellow powder, mp 140–141 °C (n-octane). IR (ATR, ZnSe, cm⁻¹): v 3075, 2103 (CH₃CN), 1612, 1529, 1306, 955, 886. ¹H NMR (400 MHz, DCCl₃): δ 3.00 (dt, J = 6.9 Hz, 6H), 2.60 (s, 3H), 6.48 (s, 1H), 7.50 (dd, J = 7.7, 1.4 Hz, 1H), 7.83 (dd, J = 24.8, 7.7, 1.5 Hz, 2H), 8.22 (dd, J = 8.0, 1.5 Hz, 1H). ¹³C [¹H] NMR (101 MHz, DCCl₃, APT mode): δ 9.3, 54.8, 126.0, 128.6, 129.6, 132.0, 134.3, 138.4, 141.5, 145.38, 180.4. HRMS (ESI-TOF) m/z: [M + H]⁺ calcd for C₁₄H₁₂N₂O₂, 270.0371; found, 273.0728.
HRMS (ESI-TOF) m/z: [M + H]+ calcd for C_{66}H_{20}N_{7}O_{5}, 390.1520; found, 390.1537.

2-Diazo-1-(5-methyl-1,2,3-thiadiazol-4-yl)ethan-1-one (5q). Compound 5q was obtained in 71% (119 mg) yield together with compound 4q in 2% (4 mg) yield according to the general procedure (enaminone 10q; 252 mg, 25 h). Light yellow needles, mp 95 °C (PE). IR (ATR, ZnSe, cm⁻¹): ν 2101 (N–N stretch), 1603, 1478, 1344, 860. ¹H NMR (600 MHz, DCCl₃): δ 2.94 (s, 3H), 6.67 (s, 1H). ¹³C{¹H} NMR (151 MHz, DCCl₃): δ 10.9, 57.2, 154.2, 157.9, 180.0. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C₅H₅N₄OS, 169.0179; found, 169.0176.

1-(3-(4-Chlorophenyl)-5-methylisoxazol-4-yl)-2-diazoethan-1-one (5r). Compound 5r was obtained in 52% (136 mg) yield together with compound 4r in 44% (127 mg) yield according to the general procedure (enaminone 10r; 346 mg, 50 h). Light yellow oil, gradually crystallizing under a layer of PE, mp 83 °C (PE). IR (ATR, ZnSe, cm⁻¹): ν 3078, 2110 (N–N stretch), 1613, 1581, 1429, 1360, 1089, 851. ¹H NMR (400 MHz, DCCl₃): δ 2.70 (s, 3H), 5.04 (s, 1H), 7.50 (dd, J = 21.6, 8.5 Hz, 4H). ¹³C{¹H} NMR (101 MHz, DCCl₃): δ 13.2, 57.8, 114.8, 126.8, 129.3, 130.6, 136.7, 159.8, 173.8, 180.0. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C₁₂H₉ClN₃O₂, 262.0378; found, 262.0376.

X-ray Structural Analysis. X-ray structural analysis of compounds 4f and 5c was performed on an Xcalibur 3 single-crystal diffractometer according to the standard method (Mo Kα radiation, graphite monochromator, 295(2) K, ω-scanning with a step of 1°). The structures were solved and refined using the SHELXTL software suite. The structures were solved by the direct method with the ShelX program, the structures were refined with the ShelXL program using a full-matrix method of least squares by F² in anisotropic approximation for nonhydrogen atoms. The hydrogen atoms were placed in the calculated positions and included in the refinement according to the riding model. The complete X-ray structural data sets for compounds 4f and 5c were deposited at the Cambridge Crystallographic Data Center (deposition numbers CCDC 2091552 and CCDC 2091548, respectively).

COMPUTATIONAL METHODS

All mechanical quantum calculations were performed using Gaussian 09. The geometries were fully optimized at the hybrid meta-generalized gradient approximation M06-2X/6-31G(d). All minima intermediates were verified by the absence of negative eigenvalues in the vibrational frequency analysis. Transition-state structures were found using the Berny algorithm and verified by vibrational analysis. The transition states were visualized by animating the negative eigenvector coordinate. Single-point energies of the optimized geometries were evaluated using the larger basis set M06-2X/6-311+G(d,p) in the presence of a solvation model based on the density (SMD) solvation model using 1,4-dioxane or ethanol as a representative solvent medium. The thermal corrections evaluated from the unscaled vibrational frequencies at the M06-2X/6-31G(d) level of theory were then added to the M06-2X/6-311+G(d,p) electronic energies to obtain the free energies. In order to determine the minimum energy path on the potential energy surface, IRC calculations, by defining the phase for the transition vector motion along the path, were performed for the identified transition states using the Hessian-based predictor-corrector integrator to confirm the reaction path proceeding in both directions (reactant and product), in which the Hessian was recomputed every three predictor steps with a step size along a reaction path of 0.05 bohr. All energies reported in this paper are Gibbs free energies at 298.15 K using unscaled frequencies. All activation free energies are quoted relative to infinitely separated reagents. Optimized structures are illustrated using CYLview.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05898.

- X-ray crystallographic data for compound 4f (CIF)
- X-ray crystallographic data for compound 5c (CIF)
- ¹H and ¹³C NMR spectra for all new compounds, X-ray diffraction study of 4f and 5c, and calculation details (PDF)

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Notes

The authors declare no competing financial interest.
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ADDITIONAL NOTE

“To record $^{13}$C NMR spectra of NH-triazoles 4, in most cases, the addition of $\text{Cs}_2\text{CO}_3$ was used to cause the deprotonation of NH and thus suppress prototropy.

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