Mechanistic Insights into the Formation of 1-Alkylidene/Arylidene-1,2,4-triazolinium Salts: A Combined NMR/Density Functional Theory Approach

Johann Pann, Kevin Erharter, Daniel Langerreiter, Gabriel Partl, Thomas Müller, Herwig Schottenberger, Michael Hummel, Thomas S. Hofer, Christoph Kreutz,* and Lukas Fliri*

ABSTRACT: In a recent report on the synthetic approach to the novel substance class of 1-alkylidene/arylidene-1,2,4-triazolinium salts, a reaction mechanism suggesting a regioselective outcome was proposed. This hypothesis was tested via a combined NMR and density functional theory (DFT) approach. To this end, three experiments with $^{13}$C-labeled carbonyl reactants were monitored in situ by solution-state NMR. In one experiment, an intermediate as described in the former mechanistic proposal was observed. However, incorporation of $^{13}$C isotope labels into multiple sites of the heterocycle could not be reconciled with the “regioselective mechanism”. It was found that an unproductive reaction pathway can lead to $^{13}$C scrambling, along with metathetical carbonyl exchange. According to DFT calculations, the concurring reaction pathways are connected via a thermodynamically controlled cyclic 1,3-oxazetidine intermediate. The obtained insights were applied in a synthetic study including aliphatic ketones and para-substituted benzaldehydes. The mechanistic peculiarities set the potential synthetic scope of the novel reaction type.

INTRODUCTION

Thiosemicarbazide (I) and the closely related thiosemicarbazones (II) and isothiosemicarbazones (III) have been synthetically exploited over decades (Scheme 1A). After early applications in the qualitative analysis of aldehydes and ketones, the applicative focus later shifted toward their use as ligands in coordination chemistry.3-4 Compounds I–III were also soon identified as versatile starting materials in organic synthesis offering four distinct nucleophilic centers and thus allowing cascade reactions to give various heterocyclic compounds.5-8 Even after more than 100 years of research,9 unprecedented reaction outcomes of these starting materials have still been recently reported.10 In contrast, isothiosemicarbazonium salts (IV; Scheme 1A)—key intermediates for the preparation of the intensively studied isothiosemicarbazones (III)11-16—were thus far not extensively investigated for their use in cyclization reactions. Merely, their ring—chain tautomerism in solution was studied via NMR spectroscopy.17,18

In a preliminary communication, one of our research groups recently reported that these isothiosemicarbazonium salts (IV) show a distinct reactivity toward aldehydes and ketones, when subjected to slightly acidic conditions.19 Thus, the access to the substance class of 1-alkylidene/arylidene-1,2,4-triazolinium salts (V) was established, which hitherto was only obtained as a side product.20 Notably, the respective structure motif was unambiguously confirmed by X-ray crystallography.19

Although the combination of a highly reactive iminium functionality embedded in a somewhat unstable 1,2,4-triazoline ring might suggest a rapid refragmentation of the heterocycle, the six isolated substances proved to be robust and easy to handle.11,21 Even after more than one year of storage in closed, light-protected containers under ambient conditions, no signs of degradation were observable for the iodide salts.19 We were tempted to pursue further research in this area, not only because of the unprecedented structure with respect to heterocyclic chemistry. Potential applications in pharmaceutical chemistry and in materials science are known for other 1,2,4-triazoline derivatives23,24 and especially for their oxidized 1,2,4-triazole congeners.26-27 To establish a starting point for future synthetic explorations, the initially proposed reaction mechanism (Scheme 1B) for the formation of compounds of type V was tested by a combined NMR/density functional theory (DFT) approach. Furthermore, we were interested in a better understanding of the observed side reaction of educts IV leading to a metathetical carbonyl exchange, which was recently termed as transazination or transalkylidation.19,28

Received: September 22, 2021
Published: January 3, 2022
The mechanistic details of the formation of V were probed by in situ NMR spectroscopy using stable13C isotope-labeled carbonyl components: 2-13C-acetone and benzaldehyde-α-13C. Complementarily, DFT calculations were performed on the NMR-detected reaction intermediates. In the following sections, the originally proposed reaction mechanism was challenged by new findings from NMR and DFT. This illustrates that even seemingly “simple” reaction mechanisms can be more complex than originally presumed. Using a combination of in situ NMR and DFT calculations, novel insights were obtained. These methods are generally applicable to obtain a detailed picture of a reaction mechanism.

### RESULTS AND DISCUSSION

13C-Isotopic Scrambling Cannot Be Reconciled with the Originally Proposed Reaction Mechanism. Our initial efforts focused on the confirmation of the originally proposed reaction mechanism. To this end, we used in situ NMR spectroscopy and 2-13C-labeled acetone and benzaldehyde-α-13C to directly follow product formation with three different starting material compositions leading to structure motifs already determined by single-crystal X-ray spectroscopy (Figure 1A; the different starting material compositions are hereafter denoted as acetone/acetone, acetone/benzaldehyde, or benzaldehyde/benzaldehyde. The first part represents the carbonyl compound present in the isothiosemicarbazonium educt, and the second represents the carbonyl compound added for cyclization). First, isothiosemicarbazonium tetrafluoroborate (1a or 1b) was dissolved in deuterated acetonitrile. To this solution, pivalic acid/N,N-diisopropyl-N-ethylamine buffer was added. An aliquot of this solution was transferred into a standard 5 mm NMR tube. Then, the educt was characterized by 1H and 13C NMR spectroscopy at 50 °C. Subsequently, the reaction was initiated by the addition of 2-13C-acetone or benzaldehyde-α-13C (1.3 equiv with respect to 1a or 1b), and the NMR tube was again inserted into the NMR spectrometer pre-heated at 50 °C. The reaction progress was monitored via acquisition of 1D 1H and 13C for the next 5 h. It is noteworthy that in contrast to the reported reaction conditions, no molecular sieves, only a slight molar excess of the carbonyl reactants and milder temperatures were used to facilitate the in situ NMR monitoring.

Additionally, the anion was exchanged from iodide to the weakly coordinating tetrafluoroborate to avoid solubility issues in the CD3CN medium. As the reaction was readily conductible without the nucleophilic iodide, an influence of the anion on the reaction mechanism can be excluded. To our surprise, we did not observe the expected sole product formation of 2a with the incorporation of the 13C label selectively in the iminium position of the heterocycle (Figure 1B). Instead, the experimentally observed 13C labeling pattern confirms 13C-isotopic scrambling, resulting in compounds 2a and 2a’. The blue dot indicates incorporated 13C labels from 2-13C-acetone. This finding cannot be reconciled with the originally proposed reaction mechanism. 

In the following sections, we describe the newly discovered scrambling of the 13C label and how this finding provides new insights into the reaction mechanism of V. Using a combination of in situ NMR and DFT calculations, novel insights were obtained. These methods are generally applicable to obtain a detailed picture of a reaction mechanism.
Instead, we found $^{13}$C-isotopic scrambling, leading to $^{13}$C incorporation into the starting material 1a and in two positions of product 2a with an estimated distribution of almost 50:50. The positions of the $^{13}$C labels are highlighted with blue dots (Figure 1B). The same isotopic scrambling was observed in the experiment with the benzaldehyde/benzaldehyde starting material composition, leading to 2b (Figure 1A, middle). In the case of the unlabeled starting material 1a and using benzaldehyde-$\alpha^{13}$C as a reagent, however, we solely observed $^{13}$C incorporation in the exocyclic iminium position, giving product 2b (Figure 1A, middle). In addition, the carbonyl exchange side reaction was strongly suppressed, showing only a minimal amount of $^{13}$C-labeled 1b and unlabeled acetone. Under the assumption that all three experiments follow the same mechanistic details, the observations stand in contradiction to the originally presumed reaction mechanism (Scheme 1B).
Expanded Reaction Mechanism from NMR Spectroscopy and DFT Calculations. In order to develop a deeper understanding of the observed isotopic scrambling, we conducted a comprehensive in situ NMR study focusing on HSQC and HMBC experiments to track down and identify possible intermediates. For this purpose, different labeling strategies with $^{13}$C labeling of the added carbonyl compounds and the isothiosemicarbazidonium educt were applied. The experimental NMR data were complemented with in silico studies. The course of the reaction can be broken down into several distinct sequences, which will be discussed in this section in light of the experimental data and the results of the DFT calculations (Scheme 2). First, an initial nucleophilic attack of the isothiosemicarbazidonium salt on the electrophilic C-atom of the carbonyl species needs to take place. The DFT calculations of the educts 1a and 1b gave energy-optimized geometries of the modeled molecules, which showed a trigonal planar geometry of the aminic N(1). Furthermore, the almost equal bond lengths between C(2) and its neighboring atoms $^{35,36}$ suggest a delocalization of the positive charge. Therefore, iminic N(3) was identified as being the most nucleophilic position of the isothiosemicarbazidonium moiety, suggesting i as the first intermediate in the reaction sequence (Figure S2). For the subsequent steps, the originally proposed reaction mechanism was challenged by the observation of $^{13}$C isotopic scrambling (Figure 1B). We thus wanted to detect and characterize reaction intermediates by in situ NMR and using $^{13}$C-labeled starting reagents (Figure 1A). Thereby, the focus was laid on the acetone/benzaldehyde starting material composition, as it was the only one of the three investigated experiments to give a clean conversion in a reasonable conversion period under the aforementioned adjusted reaction conditions (Figure 2A). In the HSQC spectra, we were able to identify a peak with a proton resonance at 5.92 ppm and a carbon resonance at 79.3 ppm, showing an intensity build-up and a decay in accordance with a reaction intermediate (Figure 2B,C).

Using benzaldehyde-$\alpha$-$^{13}$C, the proton at 5.92 ppm was unambiguously confirmed to be attached to a $^{13}$C isotope (coupling $^{1}J_{CH} = 159$ Hz, Figure 2B). According to DFT calculations of the peak chemical shifts, the resonances were in good agreement with the cyclic carbinolamine structures (iii or iv, Table S3). This strong experimental evidence for the cyclic carbinolamine intermediate favors the initially proposed reaction mechanism for the formation of the 1-alkylidene/arylidene-1,2,4-triazolinium motifs. However, the observed $^{13}$C-scrambling for 2a and 2c and the selective synthesis of 2b cannot be explained by this simple pathway. The $^{13}$C isotopic scrambling must occur on a very fast time scale as the formation of 2a’ was observed concomitantly with the formation of 2a in the in situ NMR experiment. The simultaneous formation of 2a and 2a’ and 2c and 2c’ is in contradiction with a simple metathetical carbinyl exchange of starting materials 1a and 1b. The transazination was earlier only observed in different experiments at prolonged reaction times and refluxing temperatures, thus hinting at a presence of a higher lying activation barrier that slows down the kinetics of this reaction. $^{19}$ As we could not find any NMR experimental evidence for a key intermediate to connect pathway A and B and to introduce $^{13}$C isotope scrambling, we resorted to DFT calculations. Carbinyl exchange reactions of different N-nucleophiles are well known. $^{22}$ However, for thiosemicarbazones, the reaction was only investigated more closely in the presence of water. $^{23}$

Owing to the similarities to the extensively studied imine metathesis in the absence of water where cyclic 4-membered intermediates were proposed, we focused our DFT study on a 1,3-oxazetidine species (Scheme 2, species v). $^{37,38}$

For all three starting material compositions, calculated electronic energies ($\Delta H^e$) of isomeric intermediates ii, v, and ii‘ were compared (Figure 3). Based on the data from the theoretical calculations, no conclusions about the associated transition states and the kinetic properties of the reaction can be obtained. Nevertheless, the comparison of the electronic energies of ii, v, and ii‘ enables an estimation of the relative equilibrium constants of the respective exchange reaction steps. These estimations confirm the $^{13}$C isotopic scrambling patterns as observed in the NMR reaction monitoring, hinting toward the existence of a pre-equilibrium that leads to ii and ii‘. For the starting material compositions with active scrambling, the energy difference according to DFT calculations (for 2a, $\Delta H^e_{ii-v} = +18.9$ kJ mol$^{-1}$; for 2c, $\Delta H^e_{ii-v} = +23.6$ kJ mol$^{-1}$) was found to be significantly lower than that for the intermediates leading to 2b ($\Delta H^e_{ii-v} = +41.9$ kJ mol$^{-1}$). Investigations into the conformation of intermediates v revealed that the higher intermediate energy for 2b arises from the steric repulsion of a phenyl and methyl group. In the case of 2c, the repulsion is lower, since the phenyl groups can arrange in such a way that they are situated on the opposite sides of the ring plane. Under assumption of similar activation barriers in the three investigated starting material compositions, the thermodynamical equilibrium constants ($K_{ii-v}$) and the relative state distribution ($K_{rel} = K_{ii-v}/K_{ii-v}2a$) at the applied reaction temperature (50 °C) can be estimated using the Boltzmann distribution (Table 1).

Figure 3. Energetic landscape of the exchange mechanism, depending on the residues R1, R2, R3, and R4. The electronic energies of the intermediates were arbitrarily referenced to the lower energetic carbinolamine intermediate. The reaction is not symmetric for 2b. Investigating this landscape in terms of thermodynamic accessibility of the intermediates, these data indicate that the exchange pathway would be more accessible for the symmetric starting material compositions to give 2a and 2c than for the asymmetric starting material composition to give 2b. B3LYP/6-31+G(d,p); see the Supporting Information for computational details.
On a qualitative basis, the calculated values fairly reflect the observations of the NMR experiments. In both the acetone/acetone and benzaldehyde/benzaldehyde starting material compositions, the relative state distribution between ii and v is in an accessible range, thus leading to a superimposition of the cyclization reaction, whereas in the acetone/benzaldehyde starting material composition, the reaction pathway is thermodynamically disfavored by several orders of magnitude. In conclusion, the symmetric 1,3-oxazetidine intermediate (v) gives a very plausible explanation for the observed $^{13}$C scrambling in 2a and 2c and the regioselective formation of 2b. Further attempts to validate the proposed mechanism by DFT calculations through comparison of intermediates i–iv in the acetone/benzaldehyde and benzaldehyde/benzaldehyde starting material composition were complicated by finding a proper computational model. Thus, it was not possible to account for the reaction intermediate and solvent/buffer interactions, which very likely have a significant effect on the thermodynamic accessibility and stability of the intermediates iii and iv. Therefore, the main arguments stem from the relative intermediate energies, which in turn dictate the distribution of the pre-equilibria. The gas-phase energies showed a high-energy intermediate between cyclic structures iii and iv. However, the transition from ii to iv was in a reasonable range. Most likely, the deprotonation/protonation sequences are facilitated by concerted intramolecular reactions or intermolecular reactions with the buffer systems. A possible carbonyl exchange in the acetone/benzaldehyde starting material composition seems to be thermodynamically favored, with an energy gain of $-13.3$ kJ mol$^{-1}$ ($\Delta H_{ii-iv}^{\text{rel}}$). However, we could not find any NMR-based evidence for the scrambling product 2b', rather only minimal amounts of carbonyl exchange educt 1b. In contrast to the transition of ii to iv ($\Delta H_{ii-iv}^{\text{rel}} = +1.8$ kJ mol$^{-1}$), the cyclization in pathway B is accompanied with a higher energy path ($\Delta H_{ii-iv}^{\text{rel}} = +15.7$ kJ mol$^{-1}$). This substantiates the observed preferred dissociation of intermediate ii' to 1b over the experimentally not observed formation of 2b' (Figure S9).

Alternative pathways, which do not include cyclic carbamidine structures (iii and iv), were also considered. Especially, three-membered aziridinium structures—conceivable upon the loss of H$_2$O from a protonated form of ii—were considered as possible intermediates since such species were postulated in earlier investigations (Scheme S1). However, the calculated NMR chemical shifts differed significantly from all observed intermediate NMR resonances. Furthermore, the absence of $^1$J(ortho) coupling in the detected intermediate (Figure 2) and the calculated energy differences between the respective 3-membered ring structures and products 2a–c in the range of 240–280 kJ mol$^{-1}$ strongly disfavor this pathway (Scheme S2).

To sum up, based on the findings of the NMR/DFT study, we propose adjustments to the initially suggested reaction mechanism (Scheme 1B vs Scheme 2). Following the nucleophilic attack of the iminic isothiosemicarbazonium nitrogen on the carbonyl reagent, the formed intermediate i can diverge into two pathways. The productive pathway A

---

**Table 1. Comparison of the Thermodynamic Data Obtained by DFT Calculations**

| product | $\Delta H_{ii-iv}^{\text{rel}}$/kJ mol$^{-1}$ | $K_{ii-iv}$ | $K_{ii}$ |
|---------|---------------------------------|----------|--------|
| 2a      | +18.9                           | $1.3 \times 10^{-3}$ | 1 |
| 2b      | +41.9                           | $3.6 \times 10^{-7}$ | $2.8 \times 10^{-4}$ |
| 2c      | +23.6                           | $2.4 \times 10^{-4}$ | 0.2 |

*B3LYP/a2c-SVPAll-s; see the Supporting Information for computational details.*

---

**Figure 4.** Factors affecting stability and stereoselectivity in the formation of the 1,2,4-triazolinium salts. (A) Planar structure and electrons participating in the conjugated $\pi$-system of compound 2b (respective $\pi$-orbitals of the 1,2,4-triazolinium structure highlighted in red). The aromatic electrons of the phenyl substituent (highlighted in blue) seem to participate and further enhance the stability of 2b. (B) Preference of the Z-isomer in 2b by 39.2 kJ mol$^{-1}$ and 2c by 20.1 kJ mol$^{-1}$ due to steric interference of the residues on the iminium carbon and C(S) substituents. (C) 3D ball and stick models with van der Waals radii of the possible isomers of 2b supporting the favored formation of the Z-isomer due to steric reasons.
(Scheme 2, highlighted in red) involves—a deprotonation/protonation step giving ii—an intramolecular cyclization to iii, which further rearranges to the NMR-detectable intermediate iv. Elimination of water results in the formation of the 1-alkylidene/arylidene-1,2,4-triazolinium structure motifs 2a–c. Depending on the substitution patterns of the starting materials, a nucelophic attack of the carbonyl oxygen onto the iminic carbon in intermediate i can alternatively result in the formation of a cyclic 1,3-oxazetidine intermediate (v). This can lead to the activation of pathway B (Scheme 2, highlighted in blue) upon its dissociation to intermediate i’. In pathway B, the formed i’ either undergoes cyclization (Scheme 2, intermediates ii, iii, and iv) to a 1,2,4-triazolinium structure with scrambled substituents or dissociates following a carbonyl exchange reaction. The thermodynamic accessibility of v, which seems to be strongly dependent on the chosen educts, is thus responsible for the complex product mixtures—as evidenced by the 13C scrambling—in the acetone/acetone and benzaldehyde/benzaldehyde starting material compositions.

Considerations Regarding Stability and Factors Affecting Regio- and Stereoselectivity. Despite the potentially reactive iminium functionality in an unstable 1,2,4-triazolinium motif,21,22 the structures described herein proved to be surprisingly robust and easy to handle if protected from water. Therefore, factors contributing to the stability of products 2a–c were investigated. All three products showed a planar conformation in the obtained single-crystal X-ray structures19 and in the DFT calculations. This suggests the formation of a stabilizing expanded conjugated π-system in parts of the heterocycle and the iminium double bond. The phenyl substituents in 2b and 2c are located in the same plane as the heterocycle and also seem to participate in the conjugated system, further enhancing the thermodynamic stability through a mesomeric effect (Figure 4). On a qualitative basis, the empirically known rule in dihydro-triazole chemistry that disubstitutions at the sp3-hybridized carbon stabilize the structures also seems to apply here.40 Thus, the combination of the mesomeric effect and the C(S) dissubstitution serves as a plausible explanation for the preferred formation of 2b (Figure 4A). The enhanced stability hereby introduced is, for example, evidenced by the behavior toward water. Compared to 2c, which readily dissociates under formation of the educts when exposed to trace amounts of water (as observable in the NMR spectra recorded in DMSO-d6), the iodide congener of compound 2b could even be crystallized as a hydrate.19

In contrast to the acetone/acetone and benzaldehyde/benzaldehyde starting material compositions, the acetone/benzaldehyde reaction starting material composition led to the regioselective product formation of 2b. This outcome in the formation of 2b is presumed to be a consequence of the energetically disfavored exchange side reaction involving the 1,3-oxazetidine intermediate (v). We were further curious about the stereoselectivity as the NMR analysis and the X-ray crystal structure of 2b and 2c both revealed the Z-conformation at the iminium double bond. The results of the DFT calculations for the E/Z isomers of 2b and 2c point to a steric repulsion between the phenyl group and the substituents at C(S) in the heterocycle, resulting in a preference of the Z-isomer in 2b by 39.2 kJ mol−1 and in 2c by 20.1 kJ mol−1 (Figure 4B). Thus, in terms of molecular design for 1-alkylidene/arylidene-1,2,4-triazolinium salts, the formation of the Z isomer can be steered by the size of the substituent at the iminium double bond and at C(S) of the triazolinium heterocycle. In the case of 2c, a chiral center is introduced at C(S) of the triazolinium heterocycle. As both stereoisomers possess the same free energy, there is no thermodynamic driving factor for stereoselectivity. The geometries of the reaction intermediates, however, very likely favor one C(S) stereoisomer over the other. Owing to the difficulties in the computational treatment of the intermediate—solvent/buffer interactions, we were not able to further elucidate this issue via DFT calculations.

Consequences with Regard to the Synthetic Scope and Limitations. To further verify the findings of the presented NMR/DFT study and to explore the scope of the reaction, 13 triazolinium derivatives with aliphatic and aromatic substituents were synthesized (Scheme 3A,B; see the Supporting Information for details). Based on the results of the previous sections, we focused on two experimental starting material compositions starting from isothiosemicarbazonium salts of aliphatic ketones. First, aliphatic ketones were reacted with isothiosemicarbazonium salts 3a–c, since in this case, the scrambling reaction is active and depending on the used educts, no clean conversion can be expected (Scheme 3A). In the second starting material composition starting from 1a and 1d, para-substituted benzaldehydes were used as the carbonyl component (Scheme 3B). Here, the scrambling pathway is not
We further investigated the reactivity of benzaldehydes with different electron-donating and withdrawing para-substituents (−H, −Me, −OMe, −Cl, and −NO₂). To avoid the aforementioned solubility issues in acetonitrile, isothiosemicarbazonium tetrafluoroborates 1a and 1d were used as educts. This allowed for lower temperatures (50 °C vs 90 °C) than in the preceding work. Thus, the thermodynamically controlled, unwanted side reaction can be further suppressed, and thermosensitive educts may be used in the preparation of the triazole salts. However, these adaptations led to problems in the isolation of the products since the tetrafluoroborate salts showed similar solubility properties as the buffer. Additionally, liquid/liquid extraction procedures with aqueous solutions and chromatographic purification steps were found to be unfit since, during these steps, water-induced product degradation was observed. Upon the addition of tetrabutylammonium fluoride, the respective product fluoride salts (5a–e and 6a–e) could be obtained by applying a recently reported selective precipitation protocol from acetonitrile and diethyl ether. As predicted by the revised reaction mechanism, a regio- and stereoselective synthesis of all 1-benzylidine-1,2,4-triazolinium salts was achieved with isolated yields ranging from 40 to 60% (5a–e and 6a–e, Scheme 3B). In contrast to the 1-alkylidylenes (4a–c), a complete conversion with the aromatic aldehydes was achieved in shorter reaction times (16–72 h) and a lower molar excess (neat vs 2 equiv), which is likely ascribable to a preferred formation of products 5a–e and 6a–e through the mesomeric stabilization of the phenyl moieties. The influence of the different para-substituents was negligible on the reaction outcome, and the general reaction conditions could be applied for all compounds. There was, however, a difference in isolation behavior of methythio- (5a–e) and ethythio- (6a–e) derivatives, with the former readily precipitating from solution and the latter slowly crystallizing therefrom.

**Outlook on Possible Follow-Up Chemistry.** To give a tentative outlook on possible follow-up chemistry of the presented compounds, the behavior of 2a–c toward the strong base tetramethylguanidine (TMG) was investigated in solution NMR experiments using DMSO-d₆ as a solvent. It was expected that the proton at N(4) would be subtracted by the base, resulting in the formation of a heterocyclic betaine...
structure. Indeed, the treatment of 2b with TMG led to the disappearance of the NH peak in the 1H NMR spectrum and significant chemical shift changes in both 1H and 13C spectra were found, thus suggesting the formation of a zwitterionic species in solution (Scheme 4A, 7b and Figures S12 and S13). The deprotonation leads to a bonding situation with a charge delocalization in the conjugated π-system, which is further supported by the electron density distribution according to DFT calculations (Figure S11). However, we were not able to classify the obtained structure in the extensively researched framework of mesomeric betaines.12–14 Upon the treatment of 2c with TMG, the deprotonation of N(4) leading to 7c was also observed, which spontaneously transformed to the known 1-benzyl-1,2,4-triazole 8c (Scheme 4B and Figures S14 and S15).15 The underlying mechanism of this rearrangement would need further experiments using deuterium labeling at position C(5) in 2c, and this aspect will be covered in follow-up work. The rearrangement is supported by DFT calculations with a gain in energy of 68.5 kJ mol−1. Attempts to induce a similar alkyl shift in 7b through incubation of the NMR tube at 95 °C were not successful.

CONCLUSIONS AND OUTLOOK

Based on the outcome of the mechanistic NMR/DFT study, we were able to revise the initially proposed reaction mechanism for the formation of recently discovered 1-alkylidene/arylidene-1,2,4-triazolinium salts.15 Depending on the carbonyl components, the originally proposed regio- and stereospecific productive cyclization pathway was found to compete with a faster, unproductive side reaction. This was evidenced by the 13C isotope scrambling patterns in the NMR reaction monitoring experiments. Based on DFT calculations, a 1,3-oxazetidine species is postulated as the key intermediate connecting pathway A and B and introducing 13C isotope scrambling in the products and metathetical carbonyl exchange to the respective isothiosemicarbazonium educts (Scheme 2). This more complex behavior leads to an updated view on the reaction monitoring experiments. Based on DFT calculations, a 1,3-oxazetidine intermediate and allow for the isolation of products with unsymmetrical substitution patterns. Highlighting the mild applied reaction conditions and in many cases easily and cost effectively available starting materials, this opens new avenues in combinatoric 1,2,4-triazoline and—as shown by the deprotonation NMR experiments—1,2,4-triazole synthesis.

EXPERIMENTAL SECTION

General. All reagents and solvents were purchased from Sigma-Aldrich and used as received unless stated otherwise. The buffer solution used throughout the experiments was prepared by dissolving 0.2 mol (20.4 g) of pivalic acid and 0.1 mol (12.9 g) of N,N-dimethyl-N-ethylamine in 100 mL of CH3CN, yielding a 1.0 M stock solution with approximately pH 5. Thiosemicarbazones were prepared following published procedures.66 Synthesis and characterization of compounds 3a, 4a, and 5a were already discussed in the preceding work.19 However, we decided to include spectral characterization herein as well for clarity. NMR spectra of the isolated compounds were recorded with a Bruker Avance Neo 400 spectrometer or a Bruker NMR AV III 400 spectrometer. Owing to a reported ring–chain tautomerism in solution,18 the NMR-spectra of S-alkyl isothiosemicarbazonium salts (1a–d and 3a–c) show more peaks with different shifts and coupling patterns than expected. Only the shifts of the main isomers are given. Structural assignments were made with additional information from 1H−1H COSY, 1H−13C NOESY, 1H−13C HSQC, and 1H−13C HMBC experiments. When slightly varying the work-up procedures for 1a−d and 3a−c, the formation of different isomers can be observed, as evidenced by different appearances and melting points in hot-stage microscopy but identical NMR and MS spectra. IR spectra were obtained with a Bruker ALPHA Platinum FT-ATR instrument. HR-ESI-MS analysis was performed using a Thermo Scientific Q Exactive Orbitrap mass spectrometer (compounds 1a−c; 2a−c; 3a−c; and 4a−c; ESI positive ion mode; spray voltage 3.7 kV; solvent MeOH; and mass range from m/z 100 to 800) or with an Agilent 6530 QTOF mass spectrometer (compounds 1d; 5a−e; and 6a−e; ESI positive ion mode; spray voltage 150 V; solvent MeCN; and mass range from m/z 100 to 1100).

In Situ NMR. Reaction monitoring experiments were obtained on a 600 MHz Bruker Avance II+ spectrometer equipped with a TCI Prodigy probe or a 700 MHz Avance 4 Neo spectrometer, also equipped with a TCI Prodigy probe. Standard pulse programs from the Bruker library were used:17 1H zg30, 13C zgpg30, HSQC hscdgeddps-p3, and HMBC hmbcetgpl3nd. In order to avoid solubility issues in the CD3CN reaction medium associated with the iodide anion, NMR experiments were conducted with isothiosemicarbazonium tetrafluoroborates 1a−c. To obtain clean spectra and a reasonable signal to noise ratio, no molecular sieves and only a slight molar excess of the carbonyl reactants were used.19 To obtain reasonable spectra of the products in CD3CN for comparison, 1-alkylidene/arylidene-1,2,4-triazolinium tetrafluoroborates (2a−c) were prepared from their iodide analogues19 by anion metathesis with AgBF4. It should be noted that the iodides were used after high stability of the structure motif. The reaction was then initiated by the addition of 2-13C-acetone (1.3 equiv with respect to 1a or 1b), and the NMR tube was again inserted into the NMR spectrometer pre-heated at 50 °C. The reaction progress was monitored by the acquisition of 1H and 13C NMR spectra at 50 °C. The reaction was then initiated by the addition of 2-13C-acetone or benzaldehyde-13C (1.3 equiv with respect to 1a or 1b), and the NMR tube was again inserted into the NMR spectrometer pre-heated at 50 °C. The reaction progress was monitored by the acquisition of 1H and 13C experiments for the next 5 h. It is noteworthy that in contrast to the reported reaction conditions, no molecular sieves, only a slight molar excess of the carbonyl reactants and milder
temperatures were used to facilitate the shimmering procedure and the spectra interpretation. Owing to these adjustments, a complete conversion was not achieved in all experimental setups.

**Screening for Intermediates in the Acetone/Benzaldehyde Setup.** Isothiosemicarbazonium tetrafluoroborate (1.0 mmol; 1a or 1c) was dissolved in deuterated acetone (2000 μL). To this solution, pivalic acid/N,N-diisopropyl-N-ethylamine buffer was added (500 μL). An aliquot (600 μL, 0.3 mmol) of this solution was transferred into a standard 5 mm NMR tube. Then, the educt was dissolved in CH₃CN. After addition of Et₂O, the product iodides could be isolated. Further purification was achieved by recrystallization from MeOH/ EtOAc mixtures.

**Product Characterization.** S-Methyl-acetone Isothiosemicarbazonium Tetrafluoroborate (1b). White, crystalline solid (1.40 g; 99%). mp 111–113 °C. H NMR (400 MHz, acetone-d₆): δ 12.82 (s, 1H), 7.19–7.86 (m, 2H), 7.60–7.48 (m, 3H), 2.72 (s, 3H) ppm. ¹³C{¹H} NMR (101 MHz, acetone-d₆): δ 168.7, 154.2, 133.0 (2C), 129.90 (2C), 129.3 (2C), 13.8 ppm. IR (neat) ν: 3384 (w), 3410 (w), 3316 (w), 2989 (w), 2931 (m), 2854 (w), 1639 (s), 1613 (s), 1593 (m), 1450 (w), 1383 (m), 1335 (w), 1285 (w), 1252 (w), 1019 (w), 964 (s), 871 (w), 800 (w), 763 (m), 696 (m), 664 (m), 508 (m), 416 (w) cm⁻¹. HRMS (ESI) m/z: [M⁺] calcd for C₇H₇N₃S₃, 194.0746; found, 194.0735.

S-Methyl-benzaldehyde Isothiosemicarbazonium Tetrafluoroborate (1c). White, crystalline solid (0.47 g; 76%). mp 113–115 °C. H NMR (400 MHz, acetone-d₆): δ 9.92 (s, 1H), 7.98 (s, 2H), 2.67 (s, 3H), 2.11 (d, J = 6.9 Hz, 3H), 2.03 (d, J = 6.1 Hz, 3H) ppm. ¹³C{¹H} NMR (101 MHz, acetone-d₆): δ 169.0 (d, J = 5.8 Hz), 165.2, 25.3 (d, J = 48.1 Hz), 18.8 (d, J = 38.4 Hz), 13.9 ppm. IR (neat) ν: 3387 (w), 3299 (m), 3251 (m), 3142 (m), 3090 (m), 2977 (w), 2944 (m), 2928 (m), 2853 (w), 1628 (s), 1562 (s), 1498 (m), 1441 (s), 1380 (m), 1318 (m), 1282 (m), 1245 (m), 1221 (w), 1107 (w), 1086 (s), 1018 (vs), 995 (s), 962 (s), 857 (m), 769 (w), 729 (m), 701 (m), 666 (s), 592 (m), 523 (m), 506 (m), 444 (m), 408 (w) cm⁻¹. HRMS (ESI) m/z: [M⁺] calcd for C₇H₇N₃S₃, 147.0771; found, 147.0771.

**Synthetic Procedures and Product Characterization. General Procedures.** Detailed descriptions of the synthetic procedures are listed in the Supporting Information. Isothiosemicarbazonium Salts (1a–d and 3a–c). The respective thiosemicarbazone was reacted with trialkyloxonium tetrafluoroborates in CH₂Cl₂ through heating by means of a heating mantle at varying reaction temperatures and times. For isolation, different precipitation protocols were applied.

**1,2,4-Triazolinium Tetrafluoroborates (2a–c).** The respective iodide salt was dissolved in MeOH/CH₃CN mixtures and reacted with silver tetrafluoroborate (1.0 mmol; 1e or 1f). After removal of the resulting silver iodide residue by filtration, 1,2,4-triazolinium tetrafluoroborates (2a–c) were isolated from the filtrate by precipitation with Et₂O.

**1-Alkyliden-1,2,4-triazolinium iodides (4a–c).** The respective isothiosemicarbazone iodide (3a–c) was suspended in the aliphatic ketone (neat), before molecular sieves (3 Å) and 1.0 M pivalic acid–N,N-diisopropyl-N-ethylamine buffer solution were added. The sealed vessel was kept at elevated temperatures (50–60 °C) by means of an oil bath for 5 h without stirring. The formed colored solution was separated and mixed with a solution of tetrabutylammonium iodide dissolved in CH₂Cl₂. After addition of Et₂O, the product iodides could be isolated. Further purification was achieved by recrystallization from MeOH/EtOAc mixtures.

**Product Characterization.** 5-Methyl-acetone Isothiosemicarbazonium Tetrafluoroborate (1a). White, crystalline solid (3.4 g; 97%). mp 101–103 °C. H NMR (400 MHz, acetone-d₆): δ 9.90 (s, 1H), 8.33 (s, 1H), 7.69 (s, 1H), 2.67 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H), 1.90 (s, 6H) ppm. ¹¹B NMR (400 MHz, acetone-d₆): δ −10.95 (s, 1H), 8.67 (s, 1H), 8.45–8.39 (m, 2H), 7.81–7.66 (m, 2H), 2.75 (s, 3H), 1.87 (s, 6H) ppm. ¹³C{¹H} NMR (101 MHz, acetone-d₆): δ 172.6, 143.1, 136.1, 134.5 (2C), 130.3, 128.8 (2C), 92.1, 28.8 (2C), 14.3 ppm. ¹³C{¹H} NMR (101 MHz, DMSO-d₆): δ 170.7, 141.5, 134.8, 133.2 (2C), 129.4 (2C), 128.0, 91.0, 28.3 (2C), 13.8 ppm. IR (neat) ν: 3278 (w), 1630 (w), 1593 (w), 1484 (s), 1451 (s), 1408 (m), 1389 (m), 1328 (w), 1303 (w), 1226 (w), 1206 (w), 1103 (w), 963 (s), 944 (s), 911 (m), 876 (w), 831 (m), 764 (s), 686 (s), 606 (w), 542 (m), 524 (m), 504 (m), 484 (m), 432 (w) cm⁻¹. HRMS (ESI) m/z: [M⁺] calcd for C₇H₇N₃S₂O, 234.1059; found, 234.1045.
(Z)-1-Benzyliden-3-(methylthio)-5-phenyl-4,5-dihydro-1H-1,2,4-triazol-1-ium Tetrafluoroborate (2c). Slightly yellow crystalline solid (0.30 g; 81%). According to NMR data, the MeCN monosolvate 2c-MeCN was isolated. mp 169−171 °C. 1H NMR (400 MHz, acetonitrile-δd): δ 8.47 (s, 1H), 8.37−8.32 (m, 2H), 7.86 (d, J = 2.5 Hz, 1H), 7.79−7.74 (m, 1H), 7.68−7.59 (m, 7H), 7.04 (d, J = 2.5 Hz, 1H), 2.83 (s, 3H) ppm. 13C{1H} NMR (101 MHz, acetonitrile-δd): δ 175.4, 145.9, 136.5, 135.1, 134.7 (2C), 132.7, 130.8, 130.4 (2C), 129.1 (2C), 128.2, 118.3, 87.2, 14.5 ppm. 13C{1H} NMR (101 MHz, DMSO-δd−slight dissociation): δ 173.6, 143.8, 135.2, 135.1, 135.3 (2C), 131.5, 129.8 (2C), 129.5 (2C), 127.8 (2C), 127.5, 86.1, 13.7 ppm. IR (neat) δ: 3278 (w), 1630 (w), 1593 (s), 1484 (s), 1451 (s), 1408 (m), 1389 (s), 1328 (w), 1303 (w), 1283 (w), 1226 (w), 1200 (w), 1103 (s), 1053 (s), 994 (vs), 944 (s), 911 (s), 875 (s), 866 (s), 868 (s), 854 (m), 504 (m), 484 (m), 432 (w) cm⁻¹. HRMS (ESI) m/z [M⁺] calc’d for C16H13N5S2, 282.1059; found, 282.1042.

S-Methyl-acetoniothiosemicarbazidinium iodide (3a). White solid (20.1 g; 98%). mp 174−176 °C. 1H NMR (400 MHz, DMSO-δd): δ 11.12 (s, 1H), 9.25 (s, 3H), 2.67 (s, 3H), 2.03 (s, 3H) ppm. 13C{1H} NMR (101 MHz, DMSO-δd): δ 166.1, 164.55, 25.0, 18.9, 13.5 ppm. IR (neat): δ: 3232 (m), 3168 (m), 3078 (s), 2970 (m), 1653 (w), 1613 (vs), 1559 (vs), 1491 (m), 1432 (s), 1372 (m), 1321 (m), 1272 (s), 1225 (m), 1108 (m), 1082 (m), 1021 (m), 984 (m), 861 (m), 770 (s), 651 (vs), 593 (m), 509 (m), 417 (m) cm⁻¹. HRMS (ESI) m/z [M⁺] calc’d for C14H12N6I, 294.0674; found, 294.0673.

5,5-Dimethyl-1-(4-methylbenzylidene)-3-(methylthio)-4,5-dihydro-1H-1,2,4-triazol-1-ium iodide (5b). Yellow crystals (0.31 g; 54%). mp 198−200 °C (decomposition). 1H NMR (400 MHz, DMSO-δd): δ 10.83 (s, 1H), 8.72 (s, 1H), 8.34 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 2.74 (s, 4H), 2.45 (s, 3H), 1.88 (s, 6H) ppm. 13C{1H} NMR (101 MHz, DMSO-δd): δ 170.9, 146.0, 141.5, 134.7, 133.2 (2C), 124.8 (2C), 124.2, 107.8, 102.8 (2C), 127.5, 91.0, 28.3 (2C), 15.9 ppm. IR (neat): δ: 3012 (m), 1628 (w), 1592 (w), 1467 (w), 1198 (s), 995 (s), 782 (s), 684 (s), 504 (m) cm⁻¹. HRMS (ESI) m/z [M⁺] calc’d for C18H18N5I, 324.1059; found, 234.1064.

(4Z)-5,5-Dimethyl-1-(4-chlorobenzylidene)-3-(methylthio)-4,5-dihydro-1H-1,2,4-triazol-1-ium iodide (5d). Dark-orange crystalline solid (0.43 g; 44%). mp 182−184 °C (decomposition). 1H NMR (400 MHz, DMSO-δd): δ 11.01 (s, 1H), 8.72 (s, 1H), 8.34 (d, J = 7.9 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 2.74 (s, 4H), 1.88 (s, 6H) ppm. 13C{1H} NMR (101 MHz, DMSO-δd): δ 170.9, 140.0, 139.3, 134.7 (2C), 129.3 (2C), 126.8, 91.2, 28.3 (2C), 16.3 ppm. IR (neat): δ: 2908 (m), 2878 (m), 1580 (m), 1483 (m), 1372 (s), 1095 (m), 869 (s), 812 (s), 506 (s) cm⁻¹. HRMS (ESI) m/z [M⁺] calc’d for C18H15Cl5N5I, 526.0870; found, 526.0877.

1-(Butan-2-ylidene)-5-ethyl-5-methyl-3-(methylthio)-4,5-dihydro-1H-1,2,4-triazol-1-ium iodide-Mixture of Z- and E-isomers (4b). Yellowish, crystalline solid (0.19 g; 22%). According to NMR, a mixture of the Z- and E-isomer was isolated, which based on the ratios of approximately 80% (Z) to 20% (E), based on the integrals of the allyliden methylene peaks in the 1H NMR spectrum at 2.57 ppm (Z) and 2.45 ppm (E). mp 192−194 °C (decomposition).

1H NMR (400 MHz, DMSO-δd): only the peaks of the Z-isomer are given: δ 9.94 (s, 1H), 2.91−2.66 (m, 2H), 2.60 (s, 3H), 2.57 (s, 3H), 2.39−2.24 (m, 1H), 2.01−1.91 (m, 1H), 1.87 (s, 3H), 1.16 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H) ppm. 13C{1H} NMR (101 MHz, DMSO-δd−only the peaks of the Z-isomer are given): δ 171.3, 167.2, 93.2, 31.0, 29.5, 25.9, 19.6, 13.1, 8.9, 69.3 ppm. IR ( neat): δ: 3339 (w), 3116 (m), 2975 (m), 2936 (m), 2910 (m), 2728 (w), 1623 (w), 1505 (vs), 1481 (s), 1448 (vs), 1423 (vs), 1384 (s), 1367 (s), 1351 (m), 1289 (m), 1260 (m), 1192 (m), 1133 (m), 1003 (m), 1042 (m), 954 (s), 966 (s), 878 (m), 862 (w), 751 (w), 598 (w), 554 (w), 507 (m), 487 (m) cm⁻¹. HRMS (ESI) m/z [M⁺] calc’d for C17H17N5I, 279.0910; found, 279.0911.
\[ (Z)-1-(4-Methoxybenzylidene)-5,5-dimethyl-3-(methylthio)-4,5-dihydro-1H,1,2,4-triazol-1-ium iodide (5e) \]. Yellow, crystalline solid (0.49 g; 50%). mp 185–186 °C (decomposition). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 10.66 (s, 1H), 8.68 (s, 1H), 8.44 (d, \( J = 9.1 \) Hz, 2H), 7.26 (d, \( J = 9.1 \) Hz, 2H), 3.92 (s, 3H), 2.73 (s, 3H), 1.85 (s, 6H) ppm. \(^13\)C{\(^1\)H} NMR (101 MHz, DMSO-\(d_6\)): \( \delta \) 169.5, 164.4, 141.1, 136.0 (2C), 120.6, 115.1 (2C), 89.8, 56.0, 28.4 (2C), 13.5 ppm. IR (neat) \( \nu \): 3090 (m), 2940 (m), 1592 (s), 1442 (vs), 1200 (s), 988 (s), 756 (s), 682 (s) cm\(^{-1}\). HRMS (ESI) \( m/z \): [M]+ calcd for C\(_{14}\)H\(_{20}\)N\(_{3}\)S\(_{1}\)O\(_{1}\), 278.1322; found, 278.1328.

- **ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02327.

**Author Information**

**Corresponding Authors**

Christoph Kreutz – Institute of Organic Chemistry and Center for Molecular Bioscience Innsbruck (CMBI), Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria; orcid.org/0000-0002-7018-9326; Email: christoph.kreutz@uibk.ac.at

Lukas Fliri – Institute of General, Inorganic Chemistry and Theoretical Chemistry, Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria; Department of Bioproducts and Biosystems, Aalto University, 0076 Aalto, Finland; orcid.org/0000-0001-5555-8659; Email: lukas.fliri@aalto.fi

**Authors**

Johann Pann – Institute of General, Inorganic Chemistry and Theoretical Chemistry, Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria

Kevin Erhardt – Institute of Organic Chemistry and Center for Molecular Bioscience Innsbruck (CMBI), Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria

Daniel Langreiter – Department of Bioproducts and Biosystems, Aalto University, 0076 Aalto, Finland

Gabriel Partl – Institute of General, Inorganic Chemistry and Theoretical Chemistry, Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria

Thomas Müller – Institute of Organic Chemistry and Center for Molecular Bioscience Innsbruck (CMBI), Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria

Herwig Schottenberger – Institute of General, Inorganic Chemistry and Theoretical Chemistry, Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria

Michael Hummel – Department of Bioproducts and Biosystems, Aalto University, 0076 Aalto, Finland; orcid.org/0000-0002-6982-031X

Thomas S. Hofer – Institute of General, Inorganic Chemistry and Theoretical Chemistry, Faculty of Chemistry and Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acs.joc.1c02327

**Funding**

This work was supported by the Austrian Science Fund (FWF, projects P34370 to C and the Austrian Research Promotion Agency FFG (West Austrian BioNMR, 858017).

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

The authors are thankful to Kira Malinen for additional HRMS measurements. L.F. acknowledges helpful discussions regarding Hydride shift reactions with Prof. Thomas Magauer. The
computational results presented have been achieved using the HPC infrastructure LEO of the University of Innsbruck.

REFERENCES

(1) Sah, P. P. T.; Daniels, T. C. Thiosemicarbazide as a reagent for the identification of aldehydes, ketones, and quinones. Recl. Trav. Chim. Pays-Bas 1950, 69, 1545–1556.

(2) Almeida, J. C. L.; Amin, R. S.; Pessoa, C.; Lourenço, M. C. S.; Mendes, I. C.; Lessa, J. A. Bismuth(III) complexes with pyrazineformamidine thiosemicarbazones: Investigation on the antimicrobial and cytotoxic effects. Polyhedron 2020, 189, 114709.

(3) Liberta, A. E.; West, D. X. Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: current status. BioMetals 1992, 5, 121–126.

(4) West, D. X.; Liberta, A. E.; Padhye, S. B.; Chikate, R. C.; Sonawane, P. B.; Kumbhar, A. S.; Yerande, R. G. Thiosemicarbazone complexes of copper(II): structural and biological studies. Coord. Chem. Rev. 1993, 123, 49–71.

(5) Aly, A. A.; Hassan, A. A.; AbdEl-latief, E.-S. S. M. An Update of multicomponent reaction involving allylic bromides, carbonyl compounds and thiosemicarbazides: synthesis and reactions. J. Sulfur Chem. 2011, 32, 489–519.

(6) Wilson, F. J.; Burns, R. XCIV. Reactions of thiosemicarbazones. Part II. Action of esters of α-halogenated acids. J. Chem. Soc. Trans. 1923, 123, 799–804.

(7) Munaretto, L. S.; Ferreira, M.; Gouveia, D. P.; Bortoluzzi, A. J.; Assunção, L. S.; Inaba, J.; Creczynski-Pasa, T. B.; Sá, M. M. Synthesis of isothiosemicarbazones of potential antitumoral activity through a multicomponent reaction involving allylic bromides, carbonyl compounds and thiosemicarbazide. Tetrahedron 2020, 76, 131231.

(8) Yamazaki, C. Cyclization of Isothiosemicarbazones. I. A New Route to 2-Mercapto-imidazole Derivatives and 4-Substituted Imidazoles. Bull. Chem. Soc. Jpn. 1978, 51, 1846–1855.

(9) Yamazaki, C. Cyclization of isothiosemicarbazones. II. Preparation and structure of N-isopropenyl-1,2,4-triazoles. Tetrahedron Lett. 1978, 19, 1295–1298.

(10) Yamazaki, C. Cyclization of Isothiosemicarbazones. III. Formation of Thiazolines and Thiazoles through Potential Sulphonium Salts from N,S-Disubstituted Isothiosemicarbazones. Bull. Chem. Soc. Jpn. 1980, 53, 3289–3294.

(11) Yamazaki, C. Cyclization of isothiosemicarbazones. S. [1,2,4]-Triazolo[1,5-c]pyrimidines. J. Org. Chem. 1981, 46, 3956–3959.

(12) Yamazaki, C. Cyclization of Isothiosemicarbazones. IV. Synthesis of the [1,2,4]Triazolo[1,5-c]pyrimidine Ring System. Bull. Chem. Soc. Jpn. 1981, 54, 1767–1772.

(13) Yamazaki, C.; Takada, S.; Suzuki, K.; Ishigami, M. Cyclization of isothiosemicarbazones. 6. The formation and structures of N-alkynyl-1,2,4-triazoles and related compounds. J. Org. Chem. 1985, 50, 5513–5516.

(14) Zelenin, K. N.; Kuznetsova, O. B.; Alekseyev, V. V.; Sergutina, V. P.; Terent’ev, P. V.; Ovcharenko, V. V. Ring-chain tautomerism of 3-alkylthio-1,5-dihydro-1,2,4-triazolium salts. Chem. Heterocycl. Compd. 1991, 27, 1223–1227.

(15) Zelenin, K. N.; Alekseyev, V. V.; Pihlaja, K.; Ovcharenko, V. V. Russ. Chem. Bull. 2002, 51, 205–221.

(16) Nerdinger, S.; Fliri, L.; Partl, G.; Wurst, K.; Gelbrich, T.; Schottenberger, H. Expeditious Routes to 1,2,4-Triazolinium Salts. Heterocycles 2020, 101, 593.

(17) Al-Soud, Y. A.; Shrestha-Dawadi, P. B.; Winkler, M.; Wirsching, W.; Jochims, J. C. 1-Aza-2-azoniaallene salts: reactions with azomethines and other N-nucleophiles. J. Chem. Soc., Perkin Trans. 1 1998, 22, 3759–3766.

(18) Kadaba, P. K. 1,2,4-Triazolines. In Advances in Heterocyclic Chemistry; Katritzky, A., Ed.; Elsevier, 1989; Vol. 46, pp 169–281.

(19) Potts, K. T. The Chemistry of 1,2,4-Triazoles. Chem. Rev. 1961, 61, 87–127.

(20) Pitucha, M.; Janeczko, M.; Klimek, K.; Fornal, E.; Wos, M.; Pachuta-Stec, A.; Ginalska, G.; Kaczor, A. A. 1,2,4-Triazolin-5-thione derivatives with anticancer activity as CK1γ kinase inhibitors. Bioorg. Chem. 2020, 99, 103806.

(21) Aly, A. A.; Hassan, A.; Makhlouf, M. M.; Bräse, S. Chemistry and Biological Activities of 1,2,4-Triazolothiones-Antiviral and Antifungal Drugs. Molecules 2020, 25, 3036.

(22) Kerr, M. S.; Read de Alaniz, J.; Rivis, T. An efficient synthesis of achiral and chiral 1,2,4-triazolium salts: bench stable precursors for N-heterocyclic carbones. J. Org. Chem. 2005, 70, 5725–5728.

(23) Madilla, S.; Pagadala, R.; Jonnalagadda, S. 1,2,4-Triazoles: A Review of Synthetic Approaches and the Biological Activity. Lett. Org. Chem. 2013, 10, 693–714.

(24) Schmidt, M. B.; Zeitzler, K.; Gschwind, R. M. The elusive enamine intermediate in catalyzed aldol reactions: NMR detection, formation pathway, and stabilization trends. Angew. Chem., Int. Ed. 2010, 49, 4997–5003.

(25) Schmid, M. B.; Zeitzler, K.; Gschwind, R. M. Distinct conformational preferences of prolinol and prolinol ether enamines in solution revealed by NMR. Chem. Sci. 2011, 2, 1793.

(26) Schmidt, M. B.; Zeitzler, K.; Gschwind, R. M. Formation and stability of prolinol and prolinol ether enamines by NMR: delicate selectivity and reactivity balances and parasitic equilibria. J. Am. Chem. Soc. 2011, 133, 7065–7074.

(27) Hau, F.-L.; Habiger, C.; Wein, L. A.; Wurst, K.; Podewitz, M.; Magauer, T. Rapid Assembly of Tetrasubstituted Furans via Pummerer-Type Rearrangement. J. Am. Chem. Soc. 2021, 143, 1212–1223.

(28) Hau, F.-L.; Feichtinger, N. J.; Plangger, I.; Wein, L. A.; Müller, M.; Streit, T.-N.; Wurst, K.; Podewitz, M.; Magauer, T. Synthesis of Pyroles via Consecutive 6π-E lectrocyclization/Ring-Contraction of Sulfilimines. J. Am. Chem. Soc. 2021, 143, 9002–9008.

(29) Reed, A. E.; Weinhold, F. Natural bond orbital analysis of near-Hartree–Fock water dimer. J. Chem. Phys. 1983, 78, 4066–4073.

(30) Foster, J. P.; Weinhold, F. Natural hybrid orbitals. J. Am. Chem. Soc. 1980, 102, 7211–7218.

(31) Newkome, G. R.; Fishel, D. L. Synthesis of Simple Hydrazones of Carbonyl Compounds by an Exchange Reaction. J. Org. Chem. 1966, 31, 677–681.

(32) Ciaccia, M.; Cacciapaglia, R.; Mencarelli, P.; Mandolini, L.; Di Stefano, S. Fast transmination in organic solvents in the absence of proton and metal catalysts. A key to imine metathesis catalyzed by primary amines under mild conditions. Chem. Sci. 2013, 4, 2253.

(33) Ciaccia, M.; Di Stefano, S. Mechanisms of imine exchange reactions in organic solvents. Org. Biomol. Chem. 2015, 13, 646–654.
(42) Schmidt, A. Heterocyclic Mesomeric Betaines and Analogs in Natural Product Chemistry. Betainic Alkaloids and Nucleobases. In Advances in Heterocyclic Chemistry; Katritzky, A., Ed.; Elsevier, 2003; Vol. 85, pp 67–171.

(43) Ollis, W. D.; Rasmussen, C. A. Mes-ionic Compounds. In Advances in Heterocyclic Chemistry; Katritzky, A. R., Boulton, A. J., Eds.; Elsevier, 1976; Vol. 19, pp 1–122.

(44) Ollis, W. D.; Stanforth, S. P.; Rasmussen, C. A. Heterocyclic mesomeric betaines. Tetrahedron 1985, 41, 2239–2329.

(45) Yamazaki, C.; Ohno, M. A novel route to 1-benzyl-1,2,4-triazole derivatives through disproportionation of isothiosemicarbazones. J. Heterocycl. Chem. 1997, 34, 733–737.

(46) Liu, J.; Cao, R.; Yi, W.; Ma, C.; Wan, Y.; Zhou, B.; Ma, L.; Song, H. A class of potent tyrosinase inhibitors: alkylidenothiosemicarbazide compounds. Eur. J. Med. Chem. 2009, 44, 1773–1778.

(47) Hohenberg, P.; Kohn, W. Inhomogeneous Electron Gas. Phys. Rev. 1964, 136, B864–B871.

(48) Kohn, W.; Sham, L. J. Self-Consistent Equations Including Exchange and Correlation Effects. Phys. Rev. 1965, 140, A1133–A1138.

(49) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.;Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 16, Revision A03; Gaussian, Inc.: Wallingford CT, 2016.

(50) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys. 1993, 98, 5648–5652.

(51) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. Phys. Chem. Chem. Phys. 2005, 7, 3297–3305.

(52) Miertuš, S.; Scrocco, E.; Tomasi, J. Electrostatic interaction of a solute with a continuum. A direct utilization of AB initio molecular potentials for the prediction of solvent effects. Chem. Phys. 1981, 55, 117–129.

(53) Miertuš, S.; Tomasi, J. Approximate evaluations of the electrostatic free energy and internal energy changes in solution processes. Chem. Phys. 1982, 65, 239–245.

(54) Pascual-shirin, J. L.; Silla, E.; Tuñón, I. GEPIOL: An improved description of molecular surfaces. III. A new algorithm for the computation of a solvent-excluding surface. J. Comput. Chem. 1994, 15, 1127–1138.

(55) London, F. Théorie quantique des courants interatomiques dans les combinaisons aromatiques. J. Phys. Radium 1937, 8, 397–409.

(56) Reed, A. E.; Weinhold, F. Natural localized molecular orbitals. J. Chem. Phys. 1985, 83, 1736–1740.

(57) Reed, A. E.; Weinstock, R. B.; Weinhold, F. Natural population analysis. J. Chem. Phys. 1985, 83, 735–746.

(58) Carpenter, J. E.; Weinhold, F. Analysis of the geometry of the hydroxymethyl radical by the “different hybrids for different spins” natural bond orbital procedure. J. Mol. Struct.: THEOCHEM 1988, 169, 41–62.