Copper(I)-Catalyzed 1,3-Dipolar Cycloaddition of Ketonitrones to Dialkylcyanamides: A Step toward Sustainable Generation of 2,3-Dihydro-1,2,4-oxadiazoles

Anna A. Melekhova, Andrey S. Smirnov, Alexander S. Novikov, Taras L. Panikorovskii, Nadezhda A. Bokach, and Vadim Yu. Kukushkin

Saint Petersburg State University, 7/9 Universitetskaya Nab., 199034 Saint Petersburg, Russian Federation

ABSTRACT: Cu(I)-catalyzed cycloaddition (CA) of the ketonitrone, Ph₂C=N=N'(R')O⁻ (R' = Me, CH₂Ph), to the disubstituted cyanamides, NCNR₂ (R = Me₂, Et₂, (CH₂)₄, (CH₂)₅O, C₉H₁₀, (CH₂Ph)₂, Ph( Ме)), gives the corresponding 5-amino-substituted 2,3-dihydro-1,2,4-oxadiazoles (15 examples) in good to moderate yields. The reaction proceeds under mild conditions (CH₂Cl₂, RT or 45 °C) and requires 10 mol % of [Cu(NCMe)₄](BF₄) as the catalyst. The somewhat reduced yields are due to the individual properties of 2,3-dihydro-1,2,4-oxadiazoles, which easily undergo ring opening via N—O bond splitting. Results of density functional theory calculations reveal that the CA of ketonitrone to Cu(I)-bound cyanamides is a concerted process, and the copper-catalyzed reaction is controlled by the predominant contribution of the HOMO_dipole−LUMO_dipolarophile interaction (group I by Sustman’s classification). The metal-involving process is much more asynchronous and profitable from both kinetic and thermodynamic viewpoints than the hypothetical metal-free reaction.

INTRODUCTION

Although 2,3-dihydro-1,2,4-oxadiazoles¹ (DHODs; Scheme 1) are relevant to 1,2,4-oxadiazoles with broad application of the latter in material and medicinal chemistry,² it is still an almost unexplored class of heterocyclic systems because synthetic routes to DHODs are poorly elaborated. In the context of known DHOD properties, platinum(II) species featuring ligated DHODs are of biological importance, exhibiting antitumor properties.³ In addition, NR₂ substituents in 5-amino-substituted 2,3-dihydro-1,2,4-oxadiazoles could be potentially considered as a useful tool for design of bioisosteres (e.g., carboxylic acid, amino-substituted DHODs) and this reaction proceeds under harsh conditions.¹b,c,5 Although this atom-economic method is perhaps the simplest among some metals act as efficient activators of RCN dipolarophiles in the CA (D).⁶ The preparation of metal-free DHODs via routes (D)—(E) requires an additional step (E) of ligand liberation.¹d,8a This method (D—E), despite its generality, employs rather expensive platinum and palladium species.

Recently, we have demonstrated (F) that disubstituted cyanamides, N≡CNRR’, being coordinated to a Zn¹⁰ center, can be employed in the CA with acyclic N-alkyl ketonitrone Ph₂C=N=N'(O⁻)R’ (R’ = Me, CH₂Ph), and this reaction proceeds easily achieving the respective metal-free heterocycles.¹⁰ We succeeded in replacing platinum and palladium in the CA with more favorable zinc(II), but the developed method employs stoichiometric rather than catalytic amounts of Zn(OTf)₂.

Metal-mediated processes gradually lose their initial popularity because metals serve as a potential toxic waste source. However, in many instances, metal-involving syntheses (particularly metal-catalyzed) are still preferred over relevant metal-free routes because metal centers could strongly activate reactants and/or substantially reduce the number of steps leading to target compounds. These metal-involving methods were applied for generation of DHODs, and it appeared that some metals act as efficient activators of RCN dipolarophiles in the CA (D).⁶ The preparation of metal-free DHODs via routes (D)—(E) requires an additional step (E) of ligand liberation.¹d,8a This method (D—E), despite its generality, employs rather expensive platinum and palladium species.

Although CA with stoichiometric amounts of cheap zinc is an obvious development in the generation of DHODs, our goal is to demonstrate the feasibility of metal-free routes to DHODs, which are widely used in material and medicinal chemistry, and use the discovered method as a more sustainable approach to DHODs.
was to find a catalytic system for the CA and synthesis of these heterocycles. At first glance, this task may seem simple, but it proves surprisingly challenging as the dominant part of useful catalytic systems utilizes Pearson’s “hard” metal centers.

These centers, in turn, preferably coordinate with the hard oxygen center of nitrones, thus blocking these dipoles toward the CA, and also promote nitrone hydrolytic and/or deoxygenation decomposition (Scheme 2).8d,11

Taking into account our general interest in metal-mediated reactions of substrates bearing a CN triple bond (for our reviews, see refs 9c and 12) and, in particular, in their metal-catalyzed organic transformations (for recent works, see ref 13), we focused our efforts on the search for a practically useful catalytic system for generation of DHODs. After many unsuccessful attempts, we found that copper(I) exhibits catalytic properties in the CAs of ketonitrones to push–pull nitriles, such as cyanamides, giving 5-amino-substituted DHODs, and all our results disclosing the first catalytic system for generation of DHODs are consistently disclosed in sections that follow.

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**RESULTS AND DISCUSSION**

**Copper(I)-Catalyzed CA of Ketonitrones to Cyanamides. Optimization of the Catalytic System and Reaction Conditions.** Initially, dimethylcyanamide and N-(diphenylmethylene)methanamine oxide, Ph₂C=N'(Me)O⁻, were addressed as model substrates for optimization of the reaction conditions. Our variations included choice of copper species, load of catalyst, solvents, time, and reaction temperatures. The results are summarized in Table S1 (see the Supporting Information).

We tested copper(I and II) species, namely, [Cu(NCMe)₄]−(BF₄) and Cu(OTf)₂ (Table S1, entry 15), which are soluble in the used organic solvents. The complex [Cu(NCMe)₄](BF₄) was found to be the best choice, and no reaction occurred without copper species (Table S1, entries 1, 2, and 14).

Variation of load of catalyst (Table S1, entries 3−6) revealed that the highest yield was obtained when 10 mol % of [Cu(NCMe)₄](BF₄) was employed. The lowering of the yield of 1 upon decreasing the load of catalyst is probably due to decreased concentration of activated substrates. More unusual is the yield reduction upon increasing the load of catalyst above 10 mol %. This phenomenon can be rationalized by the occurrence of some side reactions at a higher catalyst concentration, for instance, CuI-mediated reduction of the ketonitrone. The reaction proceeds in the temperature range from 20 to 80 °C (Table S1, entries 7−11 and 17, in CH₂Cl₂ or toluene), and increasing the temperature leads to an enhancement of the reaction rate. Effects of concentration (Table S1, entry 12) and microwave irradiation (Table S1, entries 13 and 14) were also studied, but they only slightly affected the reaction rate. The yield was decreased when dimethylcyanamide was taken in 10-fold excess compared with the nitrone (Table S1, entry 16), and the optimal molar ratio between these substrates is 1:1. We believe that a large excess of NCNMe₂ could lead to transformation of the copper catalyst to its less active form. Solvent variation was studied for the system Ph₂C=N'(Me)O⁻:NCNMe₂ in the presence of 10 mol % of [Cu(NCMe)₄](BF₄) was employed. The lowering of the yield of 1 upon decreasing the load of catalyst is probably due to decreased concentration of activated substrates. More unusual is the yield reduction upon increasing the load of catalyst above 10 mol %. This phenomenon can be rationalized by the occurrence of some side reactions at a higher catalyst concentration, for instance, CuI-mediated reduction of the ketonitrone. The reaction proceeds in the temperature range from 20 to 80 °C (Table S1, entries 7−11 and 17, in CH₂Cl₂ or toluene), and increasing the temperature leads to an enhancement of the reaction rate. Effects of concentration (Table S1, entry 12) and microwave irradiation (Table S1, entries 13 and 14) were also studied, but they only slightly affected the reaction rate. The yield was decreased when dimethylcyanamide was taken in 10-fold excess compared with the nitrone (Table S1, entry 16), and the optimal molar ratio between these substrates is 1:1. We believe that a large excess of NCNMe₂ could lead to transformation of the copper catalyst to its less active form. Solvent variation was studied for the system Ph₂C=N'(Me)O⁻:NCNMe₂ in the presence of 10 mol % of the copper(I) catalyst (Table S1, entries 4 and 18−22). The yields of 1 are based on NMR integration with 1,4-dimethoxybenzene taken as an internal standard. Only a small increase in the yield of 1 (from 60 to 68%) upon increasing the reaction time from 2 to 24 h (Table S1, entries 4 and 8−11) is probably explained by the consumption of the catalyst in the reaction. In summary, the results of these preliminary tests demonstrate that the optimal conditions for the model reaction include [Cu(NCMe)₄](BF₄) (10 mol %), molar ratio between the reactants 1:1, temperature 45 °C and application of CH₂Cl₂ as the solvent. The order of addition of the reactants is important, and the highest yield (68%; 45 °C, 24 h) of 1 was achieved when NCNMe₂ was added to a solution of...
[Cu(NCMe)4](BF4) followed by addition of Ph2C=N′(Me)O−. If the ketonitrone was added to a solution of the catalyst followed by addition of dimethylcyanamide, the yield of the target heterocycle was substantially lower (ca. 10%). This behavior could be explained taking into account the competition of the ketonitrone and NCNMe2 for the copper(I) coordination site. We studied the reaction of ketonitrone with CuI in a separate experiment and found that their interaction leads to oxidation of copper(I) and coordination of the nitrone O atom followed by decomposition of the complexes thus formed (see later). Hence, a combination of coordinated dimethylcyanamide and free dipole leads to the CA;1a,14 therefore, the order of reactant addition indicated above is preferable. Our theoretical calculations (see later) agree with the experimental data and they support group I by Sustmann’s classification15 of CA.

**Substrate Variation.** As the next step, we extended the scope of the substrate to various disubstituted cyanamides and two aryl ketonitrone (Scheme 3), and the obtained results are summarized in Table 1.

**Scheme 3. Copper(I)-Catalyzed CA of Ketonitrone to Cyanamides**

For most combinations of cyanamides and ketonitrone, the corresponding 2,3-dihydro-1,2,4-oxadiazoles were obtained and isolated in 28–73% yields. In all reaction mixtures, unreacted ketonitrone was identified, and this reflects an incomplete conversion of substrates. The target product was not isolated for the NCNR2/Ph2C=O− (R = Me, Et) systems, whereas signals corresponding to 4 were determined by HRESI+-MS monitoring of the reaction mixtures. Product 4 was not obtained, probably due to steric restriction of the NEt2 group that prevents cyanamide–nitrone CA.

When the reaction with conventional nitriles RCN (R = Me, Ph, 4-Cl-C6H4, 4-CF3C6H4) was attempted under the same conditions (Ph2C=N′(Me)O−, 10 mol % [Cu(NCMe)4]4/[BF4]2, CH2Cl2, 45 °C, 2 days), which additionally confirmed the previously established greater reactivity of C,C-diaryl ketonitrone than that of C-aryl aldonitrone.8d The higher reactivity of ketonitrone is related to the different electronic effect of phenyl groups in aldo- and ketonitrone. In aldonitrone, the aromatic substituent at the C atom is involved in the conjugation and acts as an electron-acceptor substituent, decreasing the reactivity of the 1,3-dipoles. In C,C-diaryl ketonitrone, both aromatic substituents are out of the CON plane and are not involved in the conjugation and therefore, could not act as electron acceptors.

2,3-Dihydro-1,2,4-oxadiazoles are unstable in the presence of copper(I), and heating of 1 with [Cu(NCMe)4]4/[BF4]2 (50 mol %; nitromethane, 70 °C, 2 h) leads to almost complete decomposition of the heterocycle and formation of a mixture of benzophenone (isolated yield 25%) and 3-(diphenylmethylen)-1,1-dimethylurea (isolated yield 56%) (Scheme 4); these species are probably derived from the known10 2,3-dihydro-1,2,4-oxadiazole ring opening. Heterocycle 1 remains intact under the same conditions in the absence of the copper(I) complex.

The observed metal-mediated ring opening of 2,3-dihydro-1,2,4-oxadiazoles explains the moderate isolated yields of these heterocycles.

**Characterization of 6 and 8–16.** Heterocycles 1–3, 5, and 7 were identified by comparison of their 1H NMR and high-resolution ESIMS spectra with those known from the reaction mixture after 2 days. This observation additionally demonstrates the greater reactivity of cyanamides toward CA as compared to that of conventional nitriles; this trend was highlighted previously in our review.16 Aldonitrone, 4-MeC6H4CH=O=N′(Me)O−, did not react with NCNMe2 under the reaction conditions (10 mol % [Cu(NCMe)4]4/[BF4]2, CH2Cl2, 45 °C, 2 days), which additionally confirmed the previously established greater reactivity of C,C-diaryl ketonitrone than that of C-aryl aldonitrone.8d The higher reactivity of ketonitrone is related to the different electronic effect of phenyl groups in aldo- and ketonitrone. In aldonitrone, the aromatic substituent at the C atom is involved in the conjugation and acts as an electron-acceptor substituent, decreasing the reactivity of the 1,3-dipoles. In C,C-diaryl ketonitrone, both aromatic substituents are out of the CON plane and are not involved in the conjugation and therefore, could not act as electron acceptors.

**Scheme 4. Copper(I)-Mediated Decomposition of the Heterocycle**

| Table 1. Compound Numbering Scheme and Isolated Yields (%) of Heterocycles |
|-----------------------------------|--------|--------|--------|
| R′ of nitrone/reaction conditions | R′ of nitrone/reaction conditions | R′ of nitrone/reaction conditions |
| R′ of nitrone/reaction conditions | R′ of nitrone/reaction conditions | R′ of nitrone/reaction conditions |
|                                  | R′ of nitrone/reaction conditions | R′ of nitrone/reaction conditions |
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|                                  | R′ of nitrone/reaction conditions | R′ of nitrone/reaction conditions |

"We were unable to isolate the cycloadduct when the reaction was carried out under standard conditions (2 h, 45 °C); upon prolonged treatment (24 h, 45 °C) under harsh conditions (MW irradiation, 100 °C, 30 min), we only observed peaks corresponding to the cycloadduct in HRESI+-MS of the reaction mixture."
New heterocycles 6, 8–16 were characterized by elemental analyses (C, H, N), HRESI’-MS, $^1$H and $^{13}$C($^1$H) NMR, Fourier transform infrared (FTIR), and also by X-ray diffraction (for 9, 12, and 16). Heterocycle 4 was not isolated from the reaction mixture due to low yield and was identified by HRESI’-MS in the reaction mixtures ($m/z$: 386.2246 [M + H]$^+$, calcd 386.2227). Compounds 6 and 8–16 give satisfactory C, H, and N elemental analyses for the proposed formulas. The HRESI’-MS of these species exhibit peaks corresponding to [M + H]$^+$. The FTIR spectra of all complexes display the $\nu$(C≡N) bands in the range 1655–1660 cm$^{-1}$, which is specific for relevant DHODs.$^{8c,16}$ The protons of the N-methyl group of 9, 11, 13, and 15 appeared as a singlet in the interval 2.33–2.49 ppm; the methylene protons (NCH$_2$Ph) of 6, 8, 10, 12, 14, and
appear as a singlet located between 3.37 and 3.64 ppm. The \(^{13}\text{C}({}^1\text{H})\) NMR spectra display resonances in the interval 94.7–96.0 ppm corresponding to the quaternary C\(^3\) atoms of the heterocycles and signals at 158.0–160.6 ppm attributed to the C\(^5\) atom from the C=N moiety. In the \(^{13}\text{C}({}^1\text{H})\) NMR spectra, the peaks from the CPh\(_2\) moiety emerge as one broad singlet due to a dynamic process.

Heterocycles 9, 12, and 16 were characterized by X-ray crystallography (Figures 1, S1, and S2, see the Supporting Information). Bond distances and angles for these structures are close to those in the previously reported structures of DHODs (Table S2).

Generation of Nitrone Complexes \([\text{Cu}(\text{ON}(\text{R''})\text{CPh}_2)_4]^{-(\text{BF}_4)^2}\) (17). If the reaction of copper(I) centers with nitriles are well known, those of nitrones are poorly studied. Copper(II) nitrone complexes documented in the literature feature bidentately coordinated ligands with the nitrone moiety and the monodentate 2,5,5-trimethyl-1-pyrroline-N-oxide. For a deeper understanding of the copper(I)-catalyzed CA, we studied the reaction between the nitrone dipoles Ph\(_2\)C=N+(O\(^-\))R'' (R'' = Me, CH\(_2\)Ph) and [Cu(NCMe)],(BF\(_4\))\(_2\). Four equivalents of any one of the nitrones were added to [Cu(NCMe)],(BF\(_4\)) in CH\(_2\)Cl\(_2\) and the reaction mixture was stirred at RT. HRESI+-MS monitoring of the reaction mixture after 24 h allows the identification of peaks corresponding to the fragment ions, namely, [MCl(nitrone)\(_2\)]\(^+\), [MC1-(nitrone)]\(^+\), and [M(nitrone)],\(^+\). IR monitoring of the reaction mixture allowed the observation of the C==N stretching bands of the (nitrone)Cu\(^+\) complexes at ca. 1660 cm\(^{-1}\) (R'' = Me, Ph), whereas the uncomplexed nitrones Ph\(_2\)C=N(O\(^-\))R'' (R = Me, Ph) exhibit a medium-to-weak band at ca. 1530–1520 cm\(^{-1}\). The resulting mixture was diluted with hexane and concentrated in vacuo at RT giving a dark greenish oily residue that, on the next day, solidified furnishing a few black needle-like crystals (R'' = Me) that were studied by X-ray diffraction (17; Figure 2; for description of the X-ray structure, see the SI).

Moreover, we also found that the nitrones are unstable in the presence of a catalytic amount of the copper(I) complex. The heating of Ph\(_2\)C=N(O\(^-\))Me with [Cu(NCMe)],(BF\(_4\)) (10 mol %) under optimized conditions (45 °C, 2 h) leads to a partial hydrolytic decomposition of the dipole giving benzophenone Ph\(_2\)C==O (preparative yield 22%).

Thus, upon treatment of ketonitrones with Cu\(^+\) we observed that the reactant interplay leads to oxidation of copper(I) and a broad spectrum of products. In the context of the copper(I)-catalyzed CA, these synthetic experiments give an idea that the generation of 2,3-dihydro-1,2,4-oxadiazoles is likely to proceed via ligation of the nitriles to the Cu\(^+\) center, followed by the reaction of the metal-bound dipolarophiles with the nitrones. This assumption is fully supported by theoretical calculations whose results are presented below.

Theoretical Study of the Cu\(^+\)-Catalyzed CA of Ketonitrones to Cyanamides. To understand the mechanism of the copper-catalyzed CA of ketonitrones to cyanamides we have carried out quantum-chemical calculations at the density functional theory (DFT) level of theory of model CA of Me\(_2\)C=N(O\(^-\))Me to uncomplexed and copper-bound NCNMe\(_2\). We have successfully used this approach in studies of similar metal-assisted and metal-free 1,3-dipolar CA reactions of nitrones to isocyanides and nitriles, and metal-assisted coupling of oximes and nitriles.

We proposed three types of mechanisms for CA of Me\(_2\)C=N(O\(^-\))Me to NCNMe\(_2\), two of them are stepwise (Scheme 5 A,C) and the third is concerted (B). CA is initiated by the endothermic formation of the orientation complex OC (+4.2 and +2.3 kcal/mol for metal-free and Cu\(^+\)-catalyzed reactions, respectively). Stepwise pathways involve the formation of acyclic zwiterionic intermediates INTa or INTb (via TSs1a or TSs1b), which then undergo the cyclization (via TSs2a or TSs2b, respectively) giving the cyclic product P, whereas the

\[16\]
concerted CA proceeds via a cyclic transition state (TSc). For both metal-free and metal-involving processes no minima for structures corresponding to any acyclic intermediates were located upon a detailed search for the potential energy surface. Despite numerous attempts, in all cases, optimization led to the formation of initial species, which are separated from each other, or to product P. Thus, stepwise pathways have been excluded from consideration. On the other hand, the TSc structures, corresponding to concerted CA, were successfully found for both metal-free and metal-involving reactions (TScfree and TScCu, respectively). The cyclic nature of these transition states (Ts) has been confirmed by the topological analysis of the electron density distribution within the formalism of the quantum theory of atoms in molecules (QTAIM) method23 (we successfully used this approach in studies of noncovalent interactions and properties of coordination bonds in various transition metal complexes20,24).

The Poincaré–Hopf relation in both cases is satisfied, thus all critical points have been found. The contour line diagrams of the Laplacian distribution \( \nabla^2 \rho(r) \), bond paths, and selected zero-flux surfaces are shown in Figure S48. The ring critical point (3, +1) for the 2,3-dihydro-1,2,4-oxadiazole cycle and five suitable bond critical points (3, −1; BCPs) were determined. For TScCu, the electron density value \( \rho(r) \) at the O····C \(_\text{cyanoamde} \) BCP is significantly higher than that at the C \(_\text{nitrone}····\text{N \(_\text{cyanoamde} \) BCP, but for TScfree, these parameters at both BCPs are comparable (Table S4). The energy density \( \Delta \rho \) at the O····C \(_\text{cyanoamde} \) and C \(_\text{nitrone}····\text{N \(_\text{cyanoamde} \) BCPs in TScfree and at O····C \(_\text{cyanoamde} \) BCP in TScCu is clearly negative demonstrating some covalent contribution in these interactions, whereas \( \Delta \rho \) at the C \(_\text{nitrone}····\text{N \(_\text{cyanoamde} \) BCP in TScCu is virtually zero and hence, no covalent contribution in this contact was detected. These observations reveal that the concerted metal-involving CA reaction is significantly more asynchronous as compared to the metal-free process, which is consistent with the general trend: coordination of a Lewis acid to any reactant leads to substantial decreasing of the reaction synchronicity [CA of nitrones to the \( \text{C} \equiv \text{N} \) bond: refs 1a, 20, 21, 24d, 25; CA of nitrones to the \( \equiv \text{C} \equiv \text{C} \) bond: ref 26]. Indeed, appropriate \( S_p \) parameters (quantitative measure of the synchronicity of concerted CAs proposed by Moyano et al.27) are 0.68 for metal-involving CA versus 0.93 for metal-free CA. Inspection of the calculated activation and reaction energies (Figure 3, Table S6) indicates, first, that the activation barrier for the Cu-catalyzed CA is significantly lower than that for the metal-free coupling (by 5.4 kcal/mol in terms of Gibbs free energy in solution). Second, metal-involving process is more preferably from a thermodynamic viewpoint.

An interaction between the frontier MOs of the reactants is the driving force of CA reactions. Our calculations indicate that the CA reaction of \( \text{Me}_2\text{C} \equiv \text{N}^+\text{(Me)}\text{O}^- \) to free NCNMe\(_2\) belongs to group II processes in the Sustman classification (energy gaps between HOMO\(_\text{dipole} \)−LUMO\(_\text{dipolarophile} \), and HOMO\(_\text{dipolarophile} \)−LUMO\(_\text{dipole} \) are 0.26 and 0.25 au, respectively, see Figure 4).

The coordination of NCNMe\(_2\) to the copper(I) metal center results in a decrease of both HOMO\(_\text{Cu} \)\(_{\text{Cu}^+} \) and LUMO\(_\text{Cu} \)\(_{\text{Cu}^+} \) energies and leads to significant contraction of the HOMO\(_\text{dipole} \)−LUMO\(_\text{dipolarophile} \) energy gap and expansion of the HOMO\(_\text{dipolarophile} \)−LUMO\(_\text{dipole} \) energy gap. Thus, the simple qualitative MO consideration suggests that (i) the coordination of NCNMe\(_2\) should accelerate the nitrone CA and (ii) the metal-involving CA belongs to normal electron demand processes (group I by Sustmann’s classification).

Literature data confirm our observations and, indeed, CAs of nitrones often belong to group II reactions,36 but it is easily possible to change the type of reaction by the variation of substituents in the reactants or its coordination to the metal center. Thus, CA of nitrones to electron-deficient dipolarophiles (namely, acrylonitrile,29 acrolein,30 methyl propiolate,31 methyl acrylate,32 nitroalkenes,33 fluoroalkenes, and fluoroalkynes34) as well as metal-involving processes35 is determined by the interaction of HOMO\(_\text{dipole} \)−LUMO\(_\text{dipolarophile} \) (group I, normal electron demand reactions), whereas usage of dipolarophiles with electron-donating substituents (e.g., methyl vinyl ether)26a leads to switching of the type of reaction to inverse electron demand (HOMO\(_\text{dipolarophile} \)−LUMO\(_\text{dipole} \) group III by Sustmann’s classification).

CONCLUDING REMARKS

We found a novel synthetic approach to 2,3-dihydro-1,2,4-oxadiazoles that includes Cu\(^{\text{II}}\)-catalyzed CA of ketonitrones to disubstituted cyanamides and gives 5-amino-substituted ring systems. The reaction proceeds under mild conditions (RT or 45 °C) and requires 10 mol % of [Cu(NCMe)\(_4\)]\((\text{BF}_4)\) as the catalyst. The application of the developed method furnishes the heterocycles in good to moderate yields. The somewhat reduced yields are due to the individual properties of 2,3-dihydro-1,2,4-oxadiazoles, which easily undergo ring opening via the N—O bond splitting.

All previous approaches to 2,3-dihydro-1,2,4-oxadiazoles bearing donor substituents at the fifth position of the ring were based on the usage of stoichiometric amounts of activating metal centers (Zn\(^{\text{II}}\), Pt\(^{\text{II}}\), Pd\(^{\text{II}}\), or Pd\(^{\text{IV}}\)) and these methods included a two-step procedure followed by (for platinum and palladium) conventional recycling of these expensive metals. The discovery of a simple catalytic system for generation of 2,3-dihydro-1,2,4-oxadiazoles is certainly a step toward sustainable synthesis of this yet unexplored class of heterocycles.

Inspection of our experimental data indicates that the combination of coordinated cyanamide dipolarophile and uncomplexed nitrone dipole, not vice versa, leads to the CA. Theoretical calculations are agreeable with this conclusion. Results of the DFT calculations reveal that the CA of ketonitrones to Cu\(^{\text{II}}\)-bound cyanamides is a concerted process...
and the copper-catalyzed reaction is controlled by the predominant contribution of the HOMO_dipole−LUMO_dipolarophile interaction (group I by Sustmann’s classification). The metal-involving process is much more asynchronous and favorable from both kinetic and thermodynamic viewpoints than the hypothetical metal-free reaction.

### EXPERIMENTAL SECTION

**Materials and Instrumentation.** The dialkylcyanamides, NCNR₂ (R = Me, Et, 1/2(CH₂)₅, 1/2(CH₂)₄O, 1/2(CH₂)₄; Aldrich), and solvents were obtained from a commercial source and used as received. The dialkylcyanamides NCN(CH₂Ph)₂, NCN(Me)Ph, and NCNC₉H₁₀,₃₆ the copper(I) complex [Cu(NCMe)₄](BF₄),₃₇ and the nitrones₃₈ were synthesized in accord with the published recipes. The HRESI mass spectra were obtained on a Bruker micrOTOF spectrometer equipped with an electrospray ionization source, and MeOH was employed as the solvent. The instrument was operated in positive ion mode using an m/z range of 50−3000. The capillary voltage of the ion source was set at −4500 V (ESI+ MS) and the capillary exit was set at ±(70−150) V. In the isotopic pattern, the most intensive peak is reported. Infrared spectra were recorded using a Bruker FTIR TENSOR 27 instrument in KBr pellets.¹H and ¹³C{¹H} NMR spectra were measured using a Bruker Avance III 400/100 MHz spectrometer at ambient temperature.

**X-ray Structure Determinations.** Crystals of 9, 12, 16, and 17 were measured on an Agilent Technologies SuperNova diffractometer at a temperature of 100 K using monochromated Cu Kα radiation. All structures were solved by direct methods by means of the SHELX program₃⁹ incorporated into the OLEX2 program package.₄₀ For crystallographic data and refinement parameters, see Table S3. The carbon-bound H atoms were placed in calculated positions and were included in the refinement in the “riding” model approximation, with Uiso(H) set to 1.5Ueq(C) and C−H 0.98 Å for CH₃ groups, with Uiso(H) set to 1.2Ueq(C) and C−H 0.99 Å for CH₂ groups, and with Uiso(H) set to 1.2Ueq(C) and C−H 0.95 Å for CH groups. Empirical absorption correction was applied in the CrysAlisPro program complex using spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm. Supporting crystallographic data for this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC 1456546, 1456547, 1470262, 1468157) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

**Computational Details.** The full geometry optimization of all structures and TSs has been carried out at the DFT level of theory using the M06 functional with the help of the Gaussian-09 program package. No symmetry operations have been applied. The calculations were carried out using the multielectron fit fully relativistic energy-consistent pseudopotential MDF10 of the Stuttgart/Cologne group that described 10 core electrons and the appropriate contracted basis set for the copper atom and the 6-31G(d) basis set for other atoms. The Hessian matrix was calculated analytically for the optimized structures to prove the location of correct minima (no imaginary frequencies) or saddle points (only one imaginary frequency) and to estimate the thermodynamic parameters, the latter being calculated at 25 °C. The nature of all TSs was studied by the analysis of vectors associated with the imaginary frequency and by calculations of the intrinsic reaction coordinates using the Gonzalez−Schlegel method.₄₅

The total energies corrected for solvent effects (Eₛ) were estimated by single-point calculations on the basis of equilibrium gas-phase geometries at the same level of theory using the SMD continuum solvation model by Truhlar and co-workers with CH₂Cl₂ as the solvent. The entropic term in CH₂Cl₂ solution (Sₛ) was calculated according to the procedure described by Wertz and Cooper and Ziegler using eqs 1−4.

\[
\Delta S_1 = R \ln \frac{V_m^{s,\text{liq}}}{V_m^{s,\text{gas}}} \\
\Delta S_2 = R \ln \frac{V_m^{s,\text{liq}}}{V_m^{s,\text{gas}}} \\
\alpha = \frac{S_0,\text{liq} - (S_0,\text{gas} + R \ln V_m^{s,\text{liq}}/V_m^{s,\text{gas}})}{(S_0,\text{gas} + R \ln V_m^{s,\text{liq}}/V_m^{s,\text{gas}})} \\
\]

Figure 4. Energies of the interacting frontier MOs of Me₃C≡N(Me)O⁻ and uncomplexed or Cu-bound NCNMe₂.
\[ S_s = S_g + \Delta S_{sol} \]
\[ = S_g + [\Delta S + \alpha(S_g + \Delta S_g) + \Delta S_T] \]
\[ = S_g + [(−11.80 \text{ cal/mol K}) − 0.21(S_g − 11.80 \text{ cal/mol K})] + 5.45 \text{ cal/mol K} \]

where \( S_s \) is the gas-phase entropy of the solute, \( \Delta S_{sol} \) is the solvation entropy, \( S^0_{olv} \) and \( S^0_{gas} \) are the standard entropies and molar volume of the solvent in liquid or gas phases (173.84 and 270.28 J/mol K and 64.15 mL/mol, respectively, for CHCl₃). \( V_{olv} \) is the molar volume of ideal gas at 25 °C (24 450 mL/mol). \( V_m^0 \) is the molar volume of the standard conditions (1000 mL/mol).

The enthalpies and Gibbs free energies in solution (\( H_s \) and \( G_s \)) were estimated by using expressions 5 and 6

\[ H_s = E_s − E_{gs} + H_g \]
\[ G_s = H_s − TS_s \]

where \( E_s, E_{gs} \) and \( H_g \) are the total energies in solution and in the gas phase and gas-phase enthalpy, respectively.

A topological analysis of the electron density distribution with the help of the QTAIM formalism developed by Bader has been performed using the Multiwfn program (version 3.3.4). The Wiberg bond indices were computed using the natural bond orbital partitioning scheme.

The synchronicity of concerted CAs (\( S_s \)) was calculated using eqs 7–9

\[ S_s = 1 − (2n − 2)^{−1} \sum_{i=1}^{n} \delta B_i \]

where \( n \) is the number of bonds directly involved in the reaction (\( n = 5 \) for 1,3-dipolar CAs) and \( \delta B_i \) is the relative variation of a given Wiberg bond index \( B_i \) at the TS relative to reactants (R) and products (P), and it is calculated as

\[ \delta B_i = \frac{B_i^R − B_i^P}{B_i^R − B_i^S} \]

If the \( \delta B_i \) value is negative, it is assumed to be zero. The average value of \( \delta B_i \) (\( \delta B_{av} \)) is defined as

\[ \delta B_{av} = −n \sum_{i=1}^{n} \delta B_i \]

\( S_s \) is 0 for stepwise CAs and is 1 for the fully concerted reactions.

The Cartesian atomic coordinates of the calculated equilibrium structures are presented in the Table S7.

**Synthetic Work.** Cu-Catalyzed Synthesis of 2,3-Dihydro-1,2,4-oxadiazoles. A solution of any of NCNR₁ (0.473 mmol) in CH₂Cl₂ (2 mL) was added to solid [Cu(NCMe)₄]- (BF₄⁻) (15 mg, 0.047 mmol), and the mixture was stirred for 5 min for homogenization, whereupon Ph₂C−N(°O)−C(R).0473 mmol; R = Me, 100 mg; CH₂Ph 0.135 mg) was added, and the formed reaction mixture was stirred under conditions given in Table S1. The reaction mixture was subjected to chromatographic separation on silica gel. Heterocycles 1–16 were isolated from the first fraction (the fractions were identified by TLC on Merck 60 F254 plates under UV light; hexane/EtOAc 10:1, ν/v); unreacted nitrore was isolated from further fractions eluted by EtOAc/hexane 1:2 → pure EtOAc (5–15% recovered). Previously reported heterocycles 1–3, 5, and 7 were identified by comparison of their ¹H NMR, HRESI-MS, and TLCs with those of the known species. Full characterization of novel 2,3-dihydro-1,2,4-oxadiazoles is given below.

2-Benzyl-3,3-diphenyl-5-(piperidin-1-yl)-2,3-dihydro-1,2,4-oxadiazole (6). Yield 50%. Mp 128–132 °C. Anal. Calc. for C₂₆H₂₇N₃O (%): C, 78.56; H, 6.85; N, 10.57. Found (%): C, 78.74; H, 6.90; N 10.61. HRESI-MS, m/z: 398.2212 ([M + H]⁺, calc 398.2227). IR spectrum, selected bands, cm⁻¹: 3428 (−OH), 3100 (OH), 2925 (–CH₂, CH₂), 2855 (–CH₃, CH₃), 1635 (–C=O, –C=O). ¹H NMR in CDCl₃: δ: 1.26 (2H, CH₂, piperidine), 3.34 (2H, CH₂, piperidine), 3.48 (2H, CH₂, benzyl), 7.26–7.38 (8H, Ph, 7.69 (4H, Ph). ¹³C{¹H} NMR in CDCl₃: δ: 24.3 (CH₂-CH₂), 25.4 (CH₃-CH₃, 47.5 (CH₃-NCH₃), 58.6 (CH₂ benzyl), 95.34 (C₁), 127.1, 128.9, 130.8 (Ph), 140.1 (C=CH₂).

4-(2-Benzyl-3,3-diphenyl-2,3-dihydro-1,2,4-oxadiazol-5-yl)morpholine (8). Yield 55%. Mp 137–140 °C. Anal. Calc. for C₂₆H₂₉N₄O (%): C, 75.16; H, 6.31; N, 10.52. Found (%): C, 75.14; H, 6.32, N 10.48. HRESI-MS, m/z: 420.2033 ([M + H]⁺, calc 420.2000). IR spectrum in KBr, selected bands, cm⁻¹: 3428 (–OH), 3400 (–CH₂, –C=O, –C=O). ¹H NMR in CDCl₃: δ: 3.67 (4H, morpholine), 3.74 (2H, benzyl), 3.65 (2H, CH₂, morpholine), 7.24–7.36 (8H, Ph, 7.65 (4H, Ph). ¹H NMR in DMSO-d₆: δ: 2.34 (6H, morpholine), 3.37 (br, 2H, benzyl), 3.57 (4H, CH₂, morpholine), 7.25 (11H, Ph), 7.56, 7.58 (two br, s, 4H, Ph). ¹³C{¹H} NMR in DMSO-d₆: δ: 46.1 (CH₃-NCH₃), 57.7 (CH₂), 65.3 (CH₂-OCH₂), 94.7 (C₁), 127.1, 127.3, br, 128.0, 128.2, 130.9, 137.6 (Ph), 159.4 (C=CH₂).
**13C[1H] NMR in CDCl₃: δ: 28.7 (NCH₂CH₃), 42.4 (Me), 43.6 (NCH₂CH₃), 47.8 (NCH₃), 95.7 (C), 126.4, 126.5, 126.6, 127.4 (br), 128.0, 128.9, 133.1, 134.3 (Ph), 159.4 (C≡N).**

**2-Benzyl-5-(3,4-dihydroisoquinolin-2(1H)-yl)-3,3-diphenyl-2,3-dihydro-1,2,4-oxadiazol-1(2H)-one (12).** Yield 82%. Mp 119−121 °C. Anal. Calcd for C₃₀H₂₇N₃O (%): C, 80.34; H, 6.16; N, 12.24. Found (%): C, 82.41; H, 6.32; N, 12.61. HRESI+-MS, m/z: 420.2072 ([M + H]+, calcd 420.2071). IR spectrum in KBr, selected bands, cm⁻¹: 3080, 3060, 3025, 2925, 2895, 2845 ν(C−H), 1660 s v(N−C−N). His NMR in CDCl₃, δ: 2.37 (s, 3H, Me), 3.44 (s, 3H, Me), 7.09−7.32 (m, 13H, Ph), 7.39−7.43 (m, 4H, Ph). His C{1H} NMR in CDCl₃, δ: 39.7 (Me), 42.2 (Me), 95.8 (C), 123.9, 125.1, 127.4 br, 128.9, 143.7 (Ph), 158.7 (C≡N).

**2-Benzyl-N,N,N,3,3-triphenyl-2,3-dihydro-1,2,4-oxadiazol-5-amine (16).** Yield 50%. Mp 150−152 °C. Anal. Calcd for C₃₀H₂₇N₃O (%): C, 80.16; H, 6.01; N, 10.02. Found (%): C, 80.43; H, 6.25; N, 10.41. HRESI+-MS, m/z: 420.2072 ([M + H]+, calcd 420.2071). IR spectrum in KBr, selected bands, cm⁻¹: 3060, 3025, 2920, 2850 ν(C−H), 1665 s ν(N−C−N). His NMR in CDCl₃, δ: 2.37 (s, 3H, Me), 3.44 (s, 3H, Me), 7.09−7.32 (m, 13H, Ph), 7.39−7.43 (m, 4H, Ph). His C{1H} NMR in CDCl₃, δ: 39.7 (Me), 42.2 (Me), 95.8 (C), 123.9, 125.1, 127.4 br, 128.9, 143.7 (Ph), 158.7 (C≡N).

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