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Synthesis of 1,2,4-Triazol-3-imines via Selective Stepwise Cycloaddition of Nitrile Imines with Organo-cyanamides

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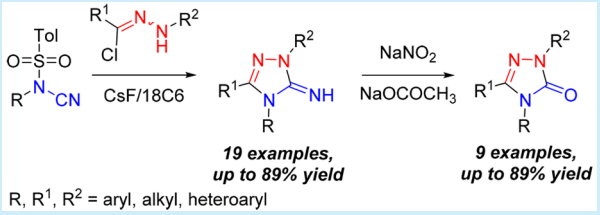
Supporting Information

ABSTRACT: A convenient method for the synthesis of 1,2,4-triazol-3-imines through a selective, formal, 1,3-dipolar cycloaddition of organo-cyanamide ions with nitrile imine dipoles is reported. Hydrolysis of the 1,2,4-triazol-3-imines yields the corresponding 1,2,4-triazol-5-ones. A stepwise mechanism, supported by DFT calculations, is invoked to explain the reaction selectivity.



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Nitrogen-rich heterocycles are an important class of compounds with broad applications and functions.[1] Nitrogen-containing rings, for example, are prevalent in many of the most successful medicines developed to date.[2] Owing to their significance and success, nitrogen heterocycles are key targets for synthesis, and there is a demand for the development of new methods that allow access to novel and/or underdeveloped nitrogen-rich cores.

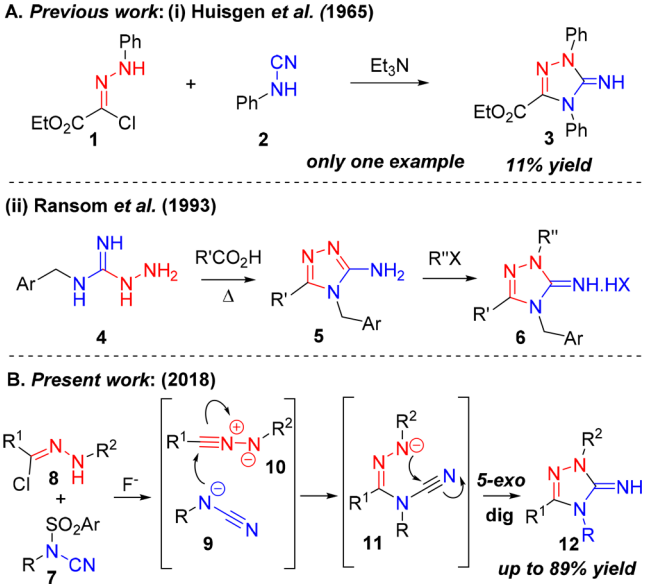
In the course of our work on the synthesis of *"rare"* nitrogen-rich scaffolds,[3] the 1,2,4-triazol-3-imine core caught our attention as an attractive, yet underdeveloped class of nitrogen-rich heterocycle with much scope for development. For example, the 1,2,4-triazol-3-imine core offers a number of important features that are attractive in drug discovery applications, including: (i) a densely functionalized heterocyclic scaffold; (ii) multiple sites to allow fine-tuning of the physicochemical properties and diversification, with defined spatial projections; and (iii) physical and thermal stability.[4]

However, despite these interesting structural features and potential, the 1,2,4-triazol-3-imine core has been somewhat overlooked, with very few syntheses or applications reported to date.

Huisgen and Aufderhaar were the first to describe the synthesis of a triazol-3-imine (**3**), in their seminal 1965 report on nitrile imine dipoles.[5] The researchers employed a 1,3-dipolar cycloaddition of ethoxycarbonyl-*N*-phenyl-nitrile imine (**1**) with phenyl cyanamide (**2**) in the presence of Et_3N, which gave the 4,5-dihydro triazole cycloadduct **3** in a modest 11% yield.[6] To the best of our knowledge, the synthesis of **3** is the only reported example of the formal cycloaddition of a nitrile imine with a cyanamide (Scheme 1A(i)).

A report by Ransom and co-workers in the early 1990s patent literature[7] described the synthesis of the neurotensin antagonist, 1,2,4-triazol-3-imine·HCl salt (**6**), through the isomerization−alkylation of amine **5**; the latter could be obtained from aminoguanidines **4**, or the corresponding acyl aminoguanidine (Scheme 1A(ii)).[8]

Scheme 1. Synthetic Approaches to 1,2,4-Triazol-3-imines: (A(i)) Huisgen's Work with PhNHCN; (A(ii)) Ransom's Linear Approach; (B) Present Work Utilizing the Cyanamide Anion



Here, we describe the first general and direct method for the synthesis of 1,2,4-triazol-3-imines by the selective reaction of organo-cyanamides[9] with nitrile imines (Scheme 1B).[10]

Given our interest in the synthesis of aromatic heterocycles by 1,3-dipolar cycloaddition chemistry,[11] we elected to revisit

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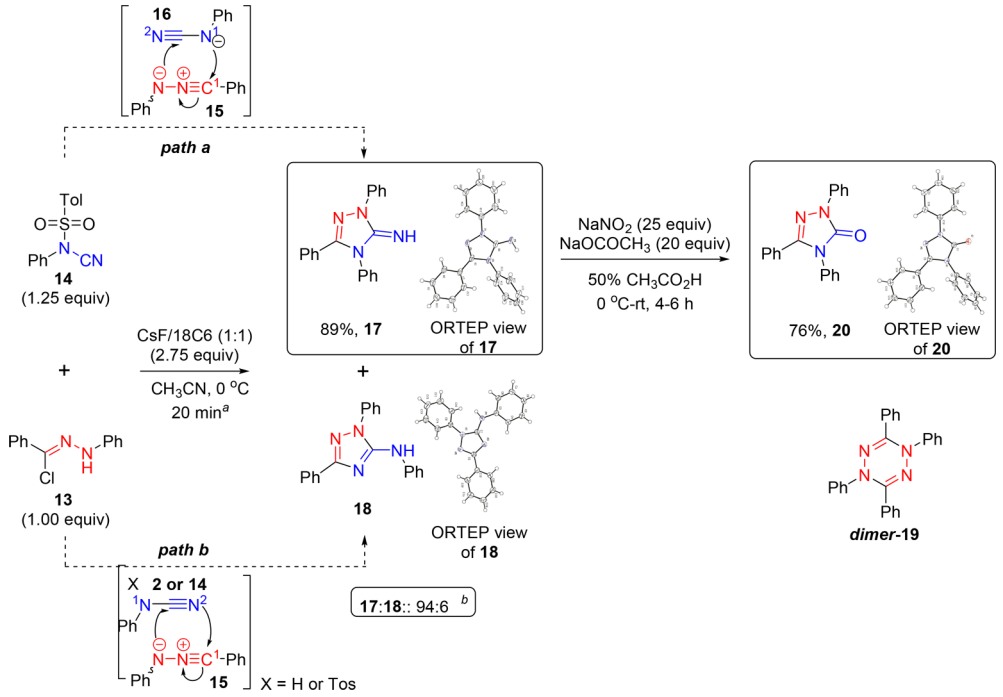
Scheme 2. Synthesis of 1,2,4-Triazol-3-imine and 1,2,4-Triazol-5-one Cores under Optimized Conditions[a]



[a]**13** added after 10 min to the reaction mixture. [b]Calculated from the ^{1}H NMR of the crude reaction mixture.

Huisgen's convergent strategy as a potentially general method for the synthesis of 1,2,4-triazol-3-imines. We have previously described how organo-cyanamide anions **9**, themselves formed by fluoride-promoted desulfonylation of *N*-tosyl *N*-phenyl cyanamide (NCTS),[12] react with increased reaction rates and improved yields in the cycloaddition with nitrile oxides to give oxadiazol-5-imine cores.[3] Given this knowledge, we elected to explore analogous conditions in the reaction with nitrile imines. Our studies began with the phenylbenzenecarbohydrazonoyl chloride (**13**) as the choice of nitrile imine precursor, and NCTS (**14**) as the source of the cyanamide anion, using tetrabutylammonium fluoride as the activating agent.[3] Under these conditions, the target triazol-3-imine **17** was isolated in 15% yield, along with the isomeric *N*-substituted 1,2,4-triazole-5-amine[13] (**18**, 11% isolated yield) product [ratio 55:45::**17**:**18** determined by integration of the ^{1}H NMR of the crude reaction mixture]. The origin of **18** can be attributed to cycloaddition of the nitrile imine dipole to the nitrile unit of the cyanamide (*path b*, Scheme 2). The structures of the isomeric triazole products **17** and **18** were both characterized by extensive spectroscopic analyses and corroborated by single crystal X-ray crystallography (Scheme 2). In addition to the triazole products **17** and **18**, the corresponding dimer 1,3,4,6-tetraphenyl-1,4-dihydro-(1,2,4,5)-tetrazine (**19**),[11] and the *N*-phenyl cyanamide (**2**) were formed as predominant side products.

Optimization studies were next performed to identify conditions for the selective formation of the target *exo*-imines (see Supporting Information (SI), Tables S1, S2, S3). The study revealed that the rate of cyanamide ion formation was slower relative to the nitrile imine dipole formation; hence a 10 min delayed addition of the hydrazonoyl chloride **13** to a prestirred mixture of **14** and CsF/18-crown-6 (18C6) in acetonitrile at 0 °C was found to be optimum, rendering the target product in an excellent 89% yield and with impressive selectivity 94:6::**17**:**18** (Scheme 2). The formation of **18** was suppressed by conducting the reaction at 0 °C, and while additives including Na_2SO_4 and molecular sieves improve the ratio of the required imine to amine products, they result in the predominant formation of the dimer **19** (see SI, Table S2).

Molecular modeling calculations performed at the M06-2X/def2-TZVP (SMD, MeCN)//B3LYP-D3(BJ)/6-311++G(d,p) (SMD, MeCN) level of theory were used to help rationalize the formation of **17** over **18** (Scheme 2). A representative model system with phenyl substituents (**15**, **16**; Scheme 2) was utilized to explore the reaction pathways. Initial adduct formation between the carbon (C^1) of the nitrile imine (**15**) and either the amine nitrogen (N^1) or nitrile (N^2) subunits of the cyanamide anion (**16**) via the reaction *path a* and *b*, respectively, was investigated (**21** and **22**, Figure 1). No transition states for a concerted one-step cycloaddition were located.

The free energy (ΔG) of product formation for both **17** and **18** is calculated to be favorable overall. The results indicate that **18** is the thermodynamic product because it is more stable than **17** by 35.4 kcal mol^{-1}. The computed energetic barriers reveal that the initial adduct formation associated with TS1 is both rate and product determining. The TS1 barrier for *path b* (**22**, 25.7 kcal mol^{-1}), to produce **18**, is slightly higher than for *path a* (**21**, 23.7 kcal mol^{-1}), which yields **17**. These calculations support our experimental observation that the formation of **18** is inhibited at reduced temperature.

Both reaction pathways exhibit the stable intermediates **23** and **24**, although they are not isolated or detected experimentally. The subsequent barrier for cyclization (TS2; **25** and **26**) was found to be readily accessible for both *paths a* and *b*. The formation of **18** proceeds through a higher barrier at 13.8 kcal mol^{-1} (**26**), while the barrier for **17** is calculated to be 6.1 kcal mol^{-1} (**25**). The difference in energy at TS2 can be rationalized by steric effects with the phenyl groups of the nitrile imine and the cyanamide unit producing a steric congestion in **26**, which is relieved by the subsequent formation of product **18**

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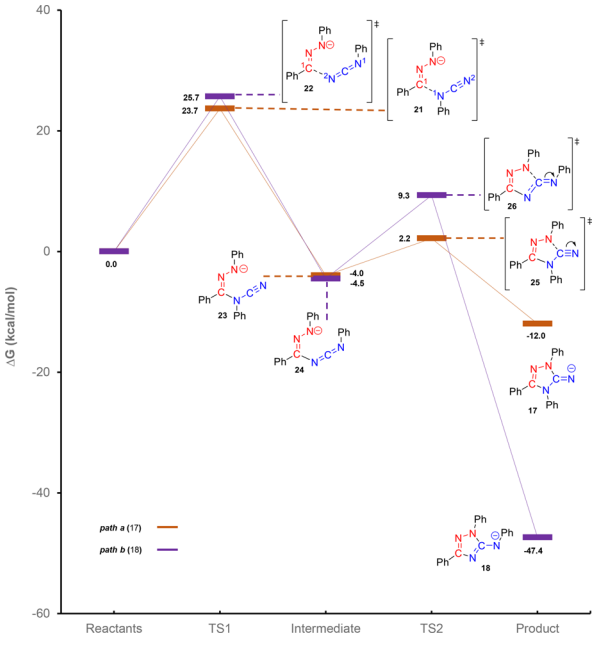


Figure 1. Calculated free energy profile (ΔG, kcal mol^{-1}) for the formation of **17** and **18** at the M06-2X/def2-TZVP (SMD, MeCN)//B3LYP-D3(BJ)/6-311++G(d,p) (SMD, MeCN) level of theory.

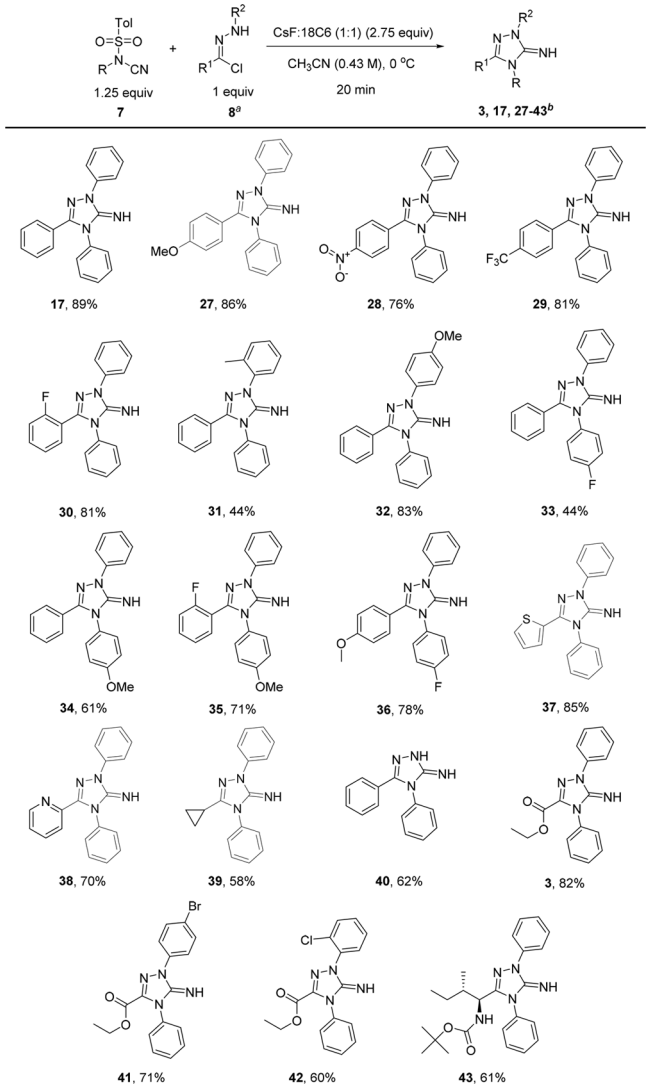
through rotation about the exocyclic C−N bond. No such steric clash is present in transition state **25**, which is consistent with the lower TS2 barrier in *path a*. Overall, the reaction is predicted to involve a two-step process and is consistent with experimental observations with formation of **17** achieved through kinetic control.

With the optimized conditions in hand, the scope of the reaction was explored with a range of substituted hydrazonoyl chlorides (both at R^1 and R^2). Both hydrazonoyl chlorides bearing electron-donating (EDG) and/or electron-withdrawing (EWG) aryl groups on R^1 were well tolerated, with products isolated in 76−86% yields (**27**−**30**, Scheme 3).

Introducing an EDG on R^2 had a profound effect on the reaction outcome; for example, *p*-methoxy substituents on the aryl group gave excellent yields (**32**, 83%). This is consistent with the findings of Qing Lin et al. on the role of electron-donating groups on R^2 in increasing the HOMO energy of the dipole.[14] Furthermore, the sterically hindered nitrile imines gave the target imines in moderate yields (**31**, 44%).

The reaction of 4-fluoro substituted cyanamide with the model substrate **13** afforded **33** in only 44% yield, whereas the corresponding *p*-methoxy substituted cyanamides yielded cyclized product in moderate yields (**34**, 61%). Furthermore, the reaction of 4-fluoro substituted cyanamides with an electron-rich nitrile imine (R^2 = EDG) yielded the imine product with much improved yields (**36**, 78%). The same was true when a combination of electron-rich cyanamide was reacted with electron-poor nitrile imine (R^2 = EWG) (**35**, 71%). Heterocyclic hydrazonoyl chlorides, such as thiophene and pyridine, were also well tolerated, giving **37** and **38** in 85% and 70% yields, respectively. Other hydrazonoyl chlorides such as cyclopropyl, alkyl esters, and an *N*H-Boc protected substrate gave good product yields (**3**, **39**−**43**, 58−82%). Noteworthy is the formation of compound **3** in 82% yield, which compares favorably to the 11% yield first reported by Huisgen [Scheme 1A(i) vs Scheme 3].

Scheme 3. Synthesis of 1,2,4-Triazol-3-imines Using Optimized Reaction Conditions[a]



[a]Ten min delayed addition of **8** (total reaction time 20 min). [b]Isolated yield of **3**, **17**, **27**−**43**; see SI for detailed information.

Having successfully achieved the synthesis of a variety of triazol-imines, we next investigated their direct conversion into 1,2,4-triazol-5-ones (**20**). Triazol-5-ones are important heterocyclic cores with a broad spectrum of biological activities[15] (e.g., Ganetepsib **44** (Scheme 4)[16] is a small-molecule heat shock protein 90 (Hsp90) inhibitor that is being developed to treat multiple solid tumor and hematologic cancers).

Treating **17** with sodium nitrite and sodium acetate in 50% acetic acid gave the desired product **20** in good yield (76%).[5b] The structure of product **20** was confirmed by spectroscopic analyses and unambiguously corroborated by single crystal X-ray crystallography. A number of other triazol-5-one products were subsequently synthesized in good to excellent yields following the same method (Scheme 4).

In conclusion, we have developed a robust one-pot method for the selective synthesis of 1,2,4-triazol-3-imine heterocyclic cores from nitrile imines and cyanamide ions in excellent yields. High-level DFT calculations support a two-step mechanistic pathway, with the target imine product produced under kinetic control. The imine products were further converted to 1,2,4-

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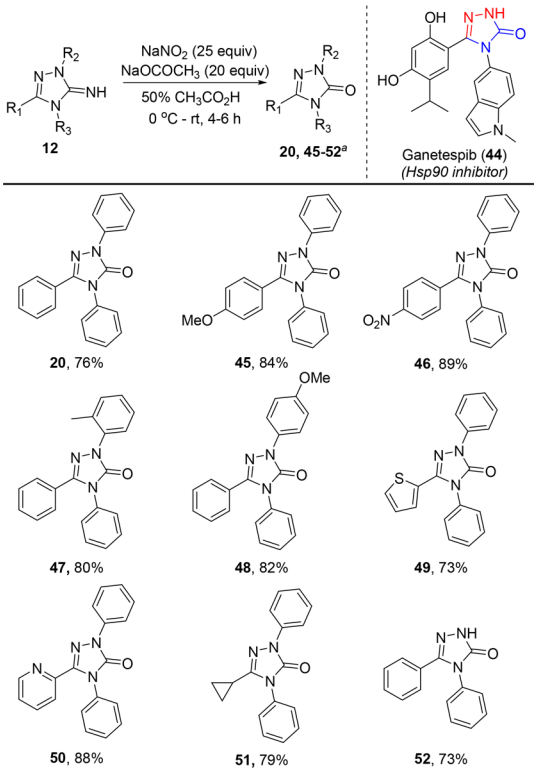
Scheme 4. Synthesis of 1,2,4-Triazol-5-one[a]



[a]Isolated yield.

triazol-5-one in excellent yield. The present method offers unique entry to rare and important nitrogen heterocycles, which will further enrich the library of available drug scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01673.

Complete experimental details and analytical data of all new compounds; H NMR, C NMR, and Cartesian coordinates and electronic energies of all species calculated (PDF)

Accession Codes

CCDC 1831602−1831604 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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