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Cyanide-Free Synthesis of Air Stable N-Substituted Li and K Cyanamide Salts from Tetrazoles. Applications toward the Synthesis of Primary and Secondary Cyanamides as Precursors to Amidines

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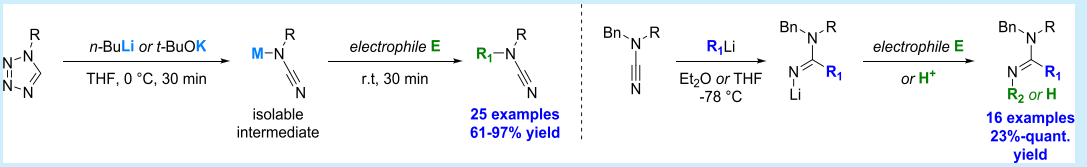
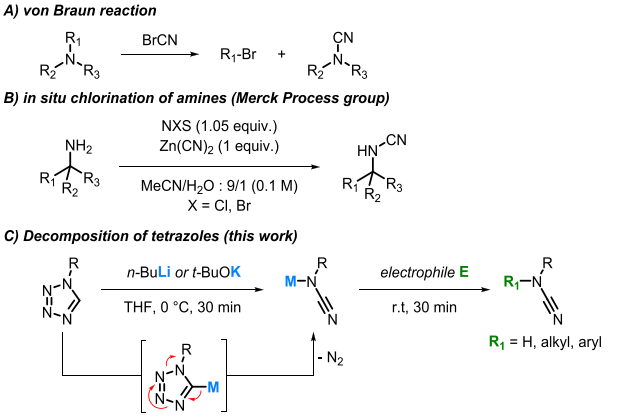


ABSTRACT: A practical two-step synthesis of N,N′-disubstituted cyanamides consists in the low-temperature metalation of N-substituted 5*H*-tetrazoles that undergo spontaneous cycloreversion at 0 °C releasing dinitrogen, and forming N-metalated cyanamides that can be reacted *in situ* with a variety of electrophiles. Remarkably, the N-substituted Li and K cyanamides are air stable white solids at room temperature. Addition of lithium organometallics to the N,N′-disubstituted cyanamides provides a new method for accessing N,N′-disubstituted amidines.

Cyanamides are versatile "value-added" organic nitrogen-containing compounds that have been known since they were first discovered in late 19th century by Cannizzaro.[1,2] The cyanamide molecule NH_2CN has been known as an inhibitor of the enzyme alcohol dehydrogenase, hence its use as a deterrent to alcohol consumption in some countries.[3] The high polarizability of the cyano group in cyanamides makes them soft electrophiles, a property that has been exploited in drug design as covalent inhibitors of cysteine-containing enzymes such as, among others, cathepsin C[4] and Janus kinase 3 (JAK3).[5,6] Because of their high N:C ratio, N-substituted cyanamides have been the mainstay of the agricultural industry for decades.[2] The cyanamide molecule, NH_2CN, is endowed with an ambident electronic character and capable of forming N salts.[2] Calcium cyanamide,[7] discovered by Frank and Caro in 1898, was used as a high-volume fertilizer and for crop protection for decades.[8] The nucleophilic character of calcium cyanamide was first demonstrated by Vliet in 1924 in its reaction with alkyl halides under strongly basic conditions in refluxing aqueous ethanol.[9] Ironically, the author was searching for a practical method for synthesizing secondary amines such as diallylamine and dibutylamine by hydrolysis of the corresponding cyanamides. Since then and to date, conventional methods of synthesis of symmetrical N,N′-disubstituted cyanamides have consisted in the electrophilic cyanation of amines using cyanogen bromide as exemplified by the von Braun reaction (Scheme 1A),[10] by Cu-mediated cyanation of amines,[11] by variations in the direct alkylation of existing cyanamide salts,[12] and by other methods.[13] In a most recent contribution from the Merck Process group, electrophilic N-cyanation was achieved by treatment of an *N*-chloroamine with

Scheme 1. Synthetic Routes to Cyanamides



zinc(II) cyanide (Scheme 1B).[14] One of the major concerns of these methods of synthesis of cyanamides relying on cyanide-containing reagents has been the potential hazards of side products such as HCN and HBr produced during the cyanation reaction. In spite of its long-standing history, the direct alkylation of commercially available cyanamide salts cannot be practically controlled to obtain N-monosubstituted

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cyanamides.[2a,c] In an isolated example, Demko and Sharpless have reported the synthesis of a monoalkylated cyanamide by displacement of a tosylate with K cyanamide in toluene at 90 °C.[15] To the best of our knowledge, a methodology study to obtain N,N′-differentiated cyanamides *without the use of cyanide-containing reagents* has not been reported.

In 1971, Raap and co-workers reported the decomposition of 1-methyl-5-lithio tetrazole into nitrogen gas and the corresponding *N*-methyl cyanamide at a temperature as low as −50 °C.[16] Related metalated tetrazoles were reacted at −98 °C in TMEDA-THF with electrophiles leading to the 1,5-disubstituted tetrazoles by Satoh and Marcopoulos.[17]

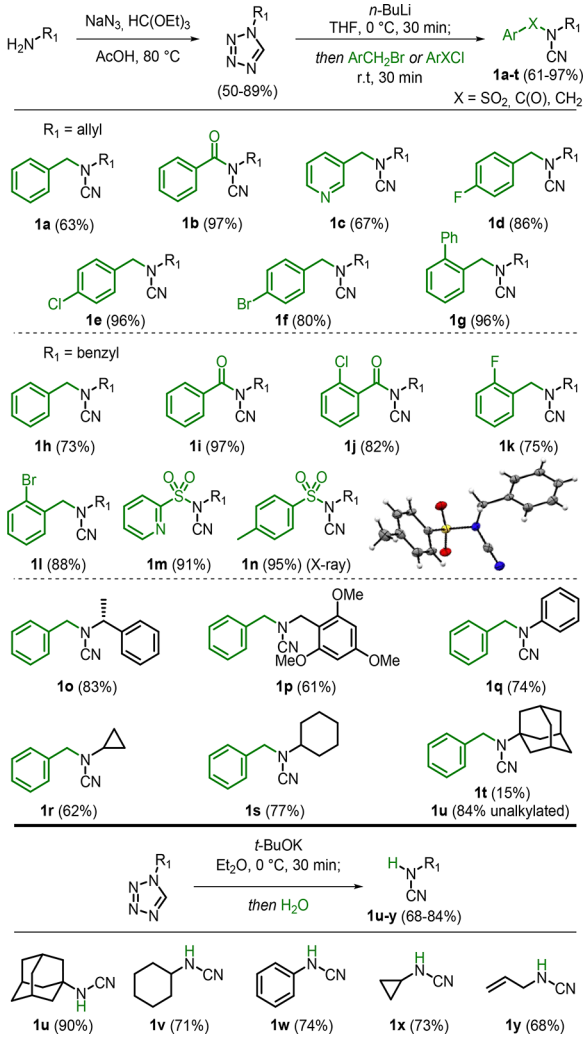
The reactivity of such C5-metalated tetrazoles remained largely unexplored until recently when Wiedemann and co-workers reported that deprotonation of *N*-benzyl-5*H*-tetrazole with *t*-BuOK in a mixture of DMAC and THF at −40 °C resulted in extensive decomposition during the metalation reaction.[18] However, they were able to engage *in situ*-generated 5-potassio tetrazoles in reactions with aldehydes and ketones to prepare 1,5-disubstituted tetrazoles. Remarkably, if not fortuitously, already in 1968, Garber and Brubaker had reported that treatment of 1-methyltetrazole with *n*-BuLi at −78 °C in THF produced a white solid that could be filtered and analyzed as the 1-methyl-5-lithio tetrazole·THF complex.[19] The competing formation of a metalo cyanamide has been considered as a disadvantage because it can interfere in subsequent reactions intended for the tetrazole core unit.[18] We surmised that this undesired side reaction can be exploited to advantage if the cyanamide salts could be isolated because the only other byproduct is dinitrogen. In that event, such N-metalo N-substituted cyanamides can be excellent coupling partners with different electrophiles under extremely mild conditions, leading to the facile and expedient formation of various symmetrical and nonsymmetrical N,N′-disubstituted cyanamides in the same flask, thereby avoiding the use of toxic cyanide reagents (Scheme 1C).

Further to our interest in the reductive fragmentation reactions of tetrazoles,[20] we became intrigued by the equally remarkable [3+2] cycloreversion reaction of N-substituted tetrazoles induced by strong bases leading to the corresponding N-substituted metalo cyanamides that have not been hitherto isolated as such. Herein, we report our results on the isolation of air stable N-substituted metalo cyanamides, their reactivities, and their conversion into diverse N-substituted cyanamides. We further report a new method for the synthesis of N,N′-disubstituted amidines from the corresponding N,N′-disubstituted cyanamides.

In preliminary studies, we used *N*-allyl tetrazole to establish reaction parameters with regard to solvent, base, temperature, and time.[21] Thus, using *n*-BuLi in THF at 0 °C followed by addition of benzyl bromide led to *N*-allyl-*N*′-benzyl cyanamide **1a** in 78% yield (NMR). The metalation and *in situ* alkylation could also be done using *t*-BuOK in ether.[18,21]

We then proceeded to evaluate the scope of the reaction by varying both the electrophiles and starting tetrazoles. The latter could be easily obtained by the condensation of a primary amine with triethylorthoformate and sodium azide in acetic acid at 80 °C as described by Gaponik and co-workers.[22] The N-substituted tetrazoles could be isolated as crude products with excellent purity. A variety of symmetrical and nonsymmetrical N,N′-substituted cyanamides could be prepared in good to excellent yields by reaction with benzylic halides, as well as aromatic acyl and sulfonyl halides (Scheme 2).

Scheme 2. Substrate Scope



Arylsulfonyl *N*-phenyl cyanamides are excellent nontoxic cyanating agents.[23] *N*-Benzyl-*N*′-alicyclic cyanamides could also be obtained in good yields. The poor yield of *N*-benzyl adamantyl cyanamide derivative **1t** was due to steric reasons because the fragmentation of the adamantyl tetrazole was successful, giving 84% of unalkylated *N*-adamantyl cyanamide **1u**.

As mentioned above, we were not aware of any efforts to isolate the metalo cyanamides in previous studies. Ca cyanamide decomposes in water and liberates ammonia.[24] Therefore, we were pleased that treatment of *N*-benzyl-5*H*-tetrazole **2** with 1.1 equiv of *n*-BuLi in THF or in ether at 0 °C for 30 min resulted in the precipitation of the corresponding *N*-benzyl Li cyanamide **3a**, which was isolated in 66% or 82% yield, respectively. Remarkably, the white air stable amorphous solid could be obtained by simple filtration and stored at room temperature for several months. The corresponding *N*-cyclohexyl **3b** and *N*-phenyl **3d** lithium salts were also isolated in the same manner on a 2 g scale (Scheme 3). Using *t*-BuOK led to the corresponding K salt of *N*-cyclohexyl cyanamide **3c**. The salts were thermally stable and melted with decomposition at temperatures above 175 °C. Alkylation of these salts with selected electrophiles led to the same products shown in Scheme 2. Treatment of the salts with acidified water led to the corresponding N-monosubstituted cyanamides exemplified by

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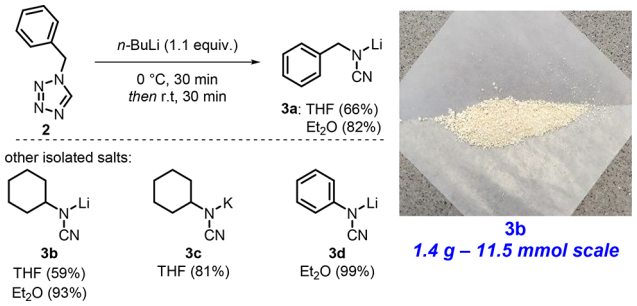
Scheme 3. Synthesis and Isolation of Cyanamide Salts

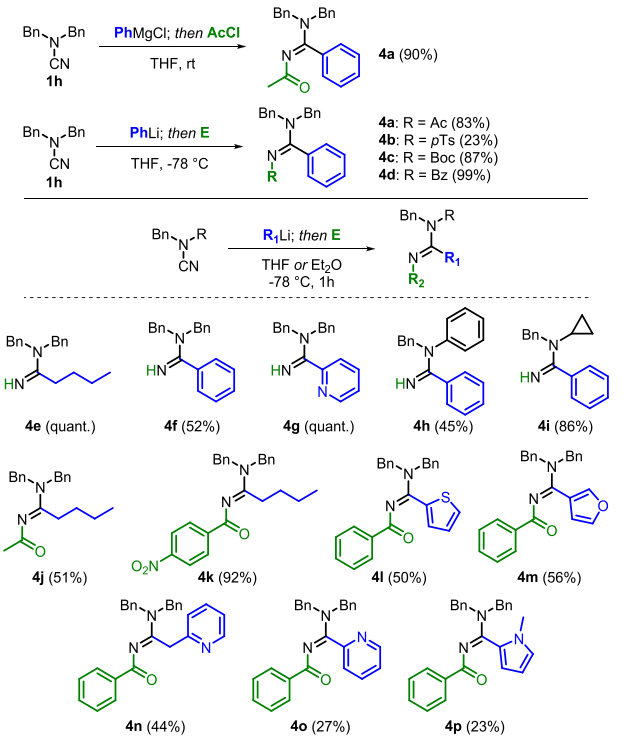


compounds **1u**−**1y**. This offers an alternative two-step cyanide-free method to the Merck protocol[14] from readily available N-substituted tetrazoles toward a variety of functionalized cyanamides. In addition to *N*-methyl cyanamide first reported by Raap,[16] *N*-aryl cyanamides have been proposed as intermediates in the decomposition of *N*-aryl tetrazole in DMSO and NaOH.[25]

The cyanamide salts could also be used in conventional S_NAr or S_N2 displacement reactions with either alkyl bromides or alkyl tosylates. Reactions took place under remarkably mild conditions at room temperature in DMSO.[21] Reaction of the salts with terminal epoxides such as styrene oxide led to the arduously accessible iminooxazolidines.[21,26]

In spite of the potential electrophilic nature of the cyano group in N,N′-disubstituted cyanamides, addition of nucleophiles has been limited to alcohols and amines requiring acid catalysis to give the corresponding ureas and guanidines, respectively.,[2227] Alternatively, strong bases such as amide salts also lead to tetrasubstituted guanidines. In principle, the analogous reaction of N,N′-disubstituted cyanamides with carbon-based nucleophiles should lead to corresponding N,N′-disubstituted amidines. However, it is expected that the electrophilicity of the cyano group will decrease due to electron donation from the *N*,*N*′-dialkyl substituents, which would require highly nucleophilic and strongly basic carbon-based reagents such as a Grignard reagent or an alkyl lithium to give the corresponding *N*,*N*′-dialkyl amidines (Scheme 4). The synthesis of N-substituted amidines usually involves indirect methods such as the reaction of thioamides or imidates with amines.[28] Considering the paramount importance of the amidine group in a plethora of medicinally important compounds,[28] we wished to explore their synthesis directly from N,N′-disubstituted cyanamides. Before embarking on what appeared to be a new method for accessing amidines, we became aware of a historically important precedent dating to 1916 when Adams and Beebe had reported the reaction of *N*,*N*′-dibenzyl cyanamide with PhMgBr to give the corresponding *N*,*N*′-dibenzyl phenyl amidine after a tedious isolation procedure.[29] They stated that amidines are "not easy substances to work with as most of them are oils or low melting, very soluble solids. Therefore, only in one case, the phenyl dibenzyl amidine, have we isolated and purified the free compound." Surprisingly, and in spite of the ready availability of N,N′-disubstituted cyanamides, this apparently simple synthetic method toward a variety of N-substituted amidines incorporating the carbon moiety of the organometallic reagent was hardly paid any attention. In a 1971 report, the addition of phenyl lithium to *N*,*N*-dimethyl cyanamide led to 28% of the desired *N*,*N*-dimethyl phenyl amidine.[30] Only recently has the synthesis of aryl amidines been reported by Larhed and co-

Scheme 4. Synthesis of Amidines



workers using a Pd(II)-catalyzed addition of aryl trifluoroborates to principally symmetrical N,N′-disubstituted cyanamides.[31] The reaction took place in MeOH as the solvent under microwave conditions and was applicable to cyanamide itself in some cases.

We were pleased that the treatment of symmetrical and nonsymmetrical N,N′-disubstituted cyanamides with Grignard and organolithium reagents under mild conditions led to the corresponding amidines, which could also be conveniently isolated as their amide derivatives (Scheme 4). Thus, the original Adams and Beebe reaction of *N*,*N*′-dibenzyl cyanamide with PhMgCl led to the corresponding *N*-acetyl amidine derivative **4a** in 90% overall yield. Simple quenching of the reaction mixture with HCl in 1,4-dioxane afforded the unsubstituted NH-amidines. With few exceptions, the yields of the reactions were good to excellent depending on the source of the organolithium reagent and the nature of the electrophilic partner. Grignard reagents failed to add at lower temperatures as opposed to their lithium counterparts that reacted at −78 °C. The control of the temperature is important as the lithio amidine intermediates were found to be unstable at room temperature, leading to the decyanation of starting cyanamide **1h** into dibenzylamine. Amidines containing a 2-pyridyl unit such as **4g** are particularly interesting especially as their free amidines due to their potential coordinating ability.[32]

In conclusion, we have developed a cyanide-free scalable method for synthesizing primary and secondary cyanamides consisting of identical or different N,N′-substituents from N-substituted 5*H*-tetrazoles in a one-flask, two-step protocol. In the presence of *n*-BuLi or *t*-BuOK, a wide range of readily available N-substituted tetrazoles undergo a cycloreversion reaction releasing dinitrogen under mild conditions. *In situ* reaction with a variety of electrophilic reagents leads to the corresponding N,N′-disubstituted cyanamides.[33] The alkali salts of several N-disubstituted cyanamides can be isolated by

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filtration and are stable to air for more than 4 months at room temperature without noticeable degradation. These Li and K salts can be used as soft nucleophiles in S_N2-type reactions with electrophilic reagents, including sulfonyl halides, alkyl halides, tosylates, and epoxides. The salts can be easily converted to the corresponding N-monosubstituted primary cyanamides. The differentially N,N′-disubstituted cyanamides readily react with Grignard and organolithium reagents to form known and novel N,N′-substituted amidines, thereby rekindling a literature precedent that has remained untested for 104 years. The cyanamide group can be involved in a plethora of reactions such as, among others, cycloadditions,[2,34] radical reactions,[2,35] and cyclotrimerizations[2,30] leading in many instances to versatile heterocyclic compounds.[2,36] The expedient method of a cyanide-free synthesis of N-mono- and N,N′-disubstituted cyanamides, combined with an alternative access to novel amidines, offers a modular protocol whereby N-substituents can be incorporated voluntarily in these historically relevant nitrogen-rich carbon compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03085.

Experimental procedures, compound characterizations, NMR spectra, and X-ray structure (PDF)

Accession Codes

CCDC 2030376 contains 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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