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In Situ Generated Magnesium Cyanide as an Efficient Reagent for Nucleophilic Cyanation of Nitrosoalkenes and Parent Nitronates

Pavel Yu. Ushakov,[a],[b] Andrey A. Tabolin,[a] Sema L. Ioffe[a] and Alexey Yu. Sukhorukov[a],[c]*

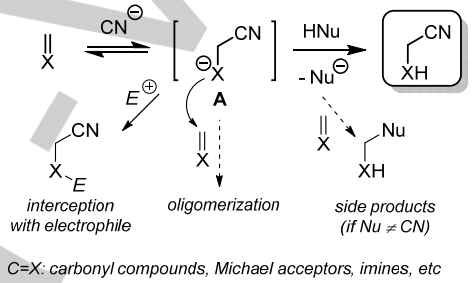
Abstract: *In situ* generated magnesium cyanide (NaCN/$Mg(ClO_4)_2$) is suggested as a convenient, readily available, non-volatile and organic-soluble reagent for hydrocyanation reactions. It was successfully used for nucleophilic cyanation of nitrosoalkenes, nitronates, as well as other typical π-electrophiles, such as imines, α,β-unsaturated ketones, alkylidenemalonates and azoalkenes.

Introduction

Addition of the cyanide anion to carbon-centered electrophiles is one of the most fundamental C,C-bond forming reactions in organic synthesis. Although being known for more than 150 years, nucleophilic cyanation is still an active area of research mainly focused on the development of enantioselective methods for 1,2- and 1,4-additions,[1] transition metal-catalyzed cyanation of aryl halides,[2] and oxidative cyanation of C–H[3] and C=C bonds.[4]

Despite of a significant progress in these areas, there is still a challenge in developing appropriate and safe reagents for nucleophilic 1,2- and 1,4-hydrocyanation reactions.[5] Nucleophilic addition of CN^- to multiple bonds is usually reversible and results in the generation of anionic species **A** (Scheme 1), which can react with the initial substrate leading to side reactions (e.g. oligomerization).[6] To shift the equilibrium and stabilize the cyanation product, it is needed to trap anion **A**, usually, either by protonation (with solvent or acid additive) or with an external electrophile (for example, a silylating agent). The nature of cyanation reagent is, thus, a key factor governing selectivity in the nucleophilic addition of the cyanide anion to π-electrophiles.

Alkali metal cyanides in water or alcohols are classical reagents for hydrocyanation reactions. However, they produce new nucleophilic species (hydroxide or alkoxide anions), which can compete with addition of CN^-.[6] Systems containing hydrogen cyanide or its surrogates (KCN/protic acid, acetone cyanohydrin) are dangerous to work with because of high toxicity. Trialkyl silyl cyanides, such as TMSCN, are easier to handle, yet these volatile reagents are toxic and easily produce HCN upon hydrolysis on air. Furthermore, desilylation of final product is required, which is not always easy.[7] Non-alkali p-metal cyanides (Et_2AlCN, $Ca(CN)_2$) are sometimes used as cyanide sources,[6, 8] however, these reagents are not generally accessible. Transition metal cyanides like CuCN, $Zn(CN)_2$ and $K_4[Fe(CN)_6]$ suffer from low solubility in organic solvents.



Scheme 1. Side processes in hydrocyanation of multiple C=X bonds.

Here, we suggest *in situ* generated magnesium cyanide (NaCN/$Mg(ClO_4)_2$) as a non-volatile, soluble in DMF and cheap reagent for 1,2- and 1,4-hydrocyanation reactions.[9] It combines a nucleophilic cyanide anion and a Lewis acid (Mg^{2+}), which covalently binds to anions **A** preventing their degradation and can be easily removed by aqueous work-up. This reagent was successfully used for nucleophilic α- and β-cyanation of nitronates **1**, which was not efficient with standard reagents such as NaCN, $Zn(CN)_2$ and silyl cyanides.

Results and Discussion

Nitronates **1** for a long time have been considered as synthetic equivalents of parent nitro compounds, which are classical α-C-nucleophiles.[10] We have demonstrated that under certain activation conditions (treatment with strong silicon-centered Lewis acids) nitronates **1** can serve as α- and β-electrophilic reagents.[10a, 11] In particular, recently we reported a TBSOTf-promoted addition of TBSCN to cyclic O-alkyl nitronates *Alk*-**1** affording corresponding α-cyano-substituted nitroso acetals **2** (Scheme 2).[12] Also, we developed β-cyanation of O-silyl nitronates *Si*-**1** through their transformation to *N*,*N*-bis(silyloxy)enamines **4** and addition of TMSCN via the intermediacy of nitrosoalkenes **NSA** (Scheme 2).[13] Upon deprotection, cyanooxime derivatives **5** cyclized into valuable 5-aminoisoxazoles **6**.[14] However, these silicon-mediated processes have drawbacks associated with the lack of efficiency

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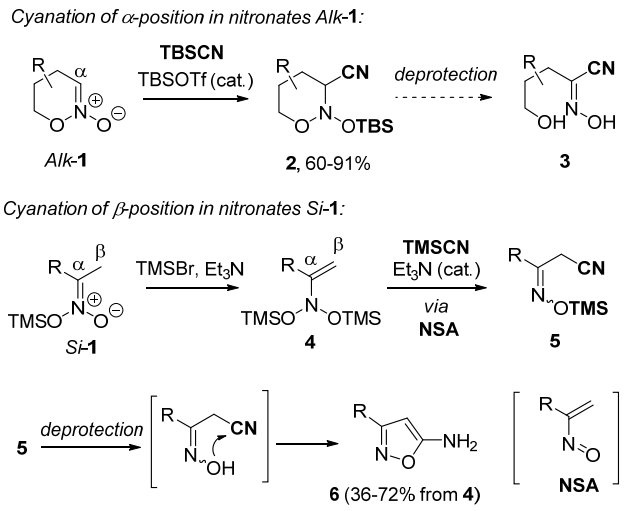
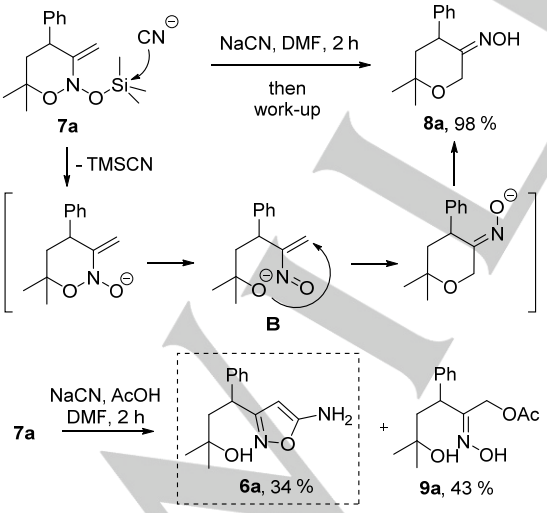
and the need of desilylation, which is not selective in the case of nitrosoacetals **2**.[12, 15] We, therefore, attempted to perform the aforementioned transformations avoiding silicon-based cyanation reagents.



Scheme 2. Umpolung α- and β-cyanations of nitronates with TMSCN

In our initial experiments aimed at preparing 5-aminoisoxazoles **6** from cyclic *N*,*N*-bis(oxy)enamines **7**, we reacted model enamine **7a** with NaCN in DMF (Scheme 3). Surprisingly, this did not result in the addition of the cyanide anion. Instead, pyranone oxime **8a** was formed as the major product, which arises from the nucleophilic attack on silicon atom and subsequent recyclization *via* anionic intermediate **B**.[16]

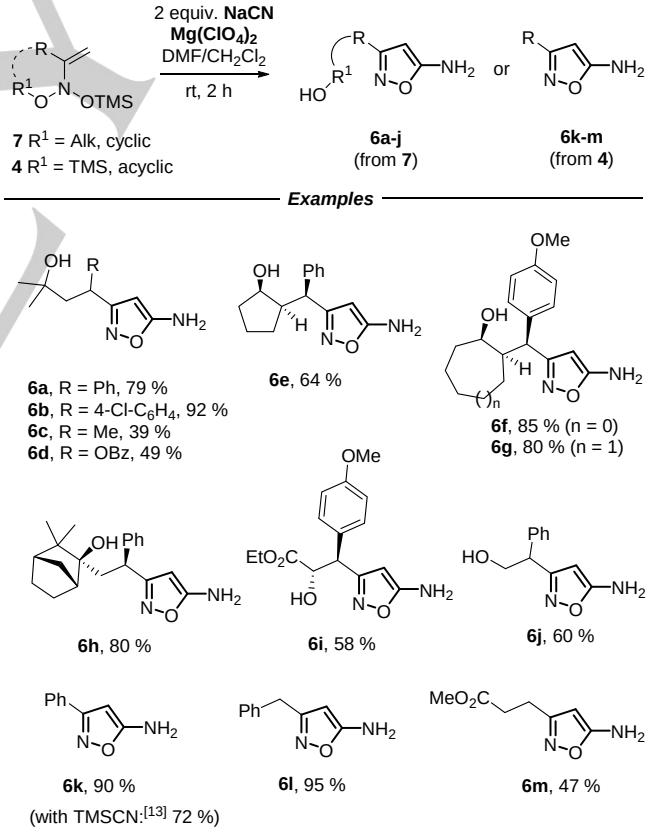


Scheme 3. Reaction of model enamine **7a** with NaCN.

When NaCN/AcOH system was used, the desired aminoisoxazole **6a** did form, however, an almost equal amount of acetate **9a** was also obtained (Scheme 3). Both products are most likely formed by a competitive 1,4-addition of HCN and AcOH to nitrosoalkene moiety of **B**.

We reasoned that the use of an oxophilic Lewis acid may prevent anionic intermediates of type **B** from cyclization thus enabling the intermolecular nucleophilic attack of CN^- on the nitrosoalkene unit. After testing some readily available metal cyanides (CuCN and $Zn(CN)_2$) and NaCN/Lewis acid systems (Lewis acid – BF_3•Et_2O, AgOTf, $Mg(OTf)_2$, $Mg(ClO_4)_2$) we found that the use of NaCN/$Mg(ClO_4)_2$ in DMF led to a smooth transformation of model enamine **7a** into the desired 5-aminoisoxazole **6a** (yield 79 %).[17] Unlike d-metal cyanides, which are poorly soluble in organic solvents, *in situ* generated magnesium cyanide gives a clear viscous solution in DMF. Reaction could be also performed in EtOH/H_2O (1 : 1) mixture, however, lower yield of product **6a** was observed (54 %).

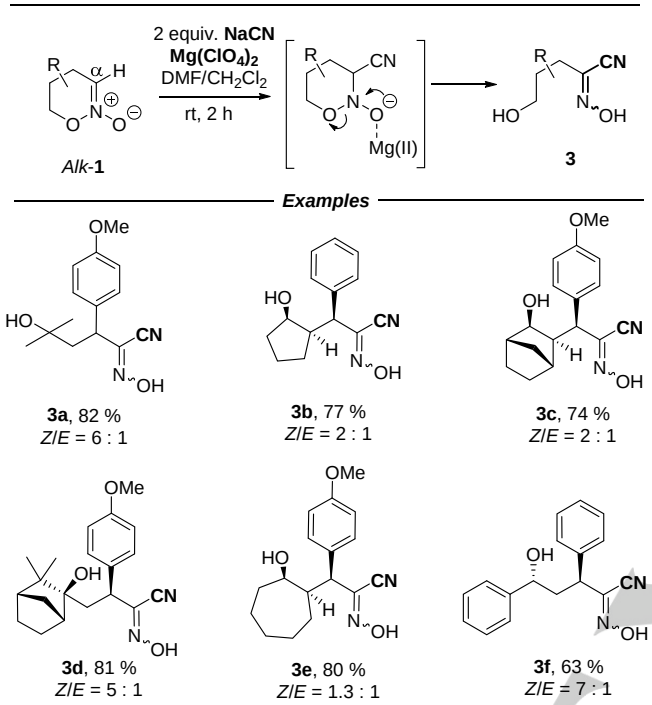
This cyanation system was successfully used to prepare 5-aminoisoxazoles **6a-m** bearing various substituents and functionalized alkyl chains at C-3 atom. Importantly, this procedure tolerated 5- and 6-membered cyclic *N*,*N*-bis(oxy)enamines **7** as well as acyclic *N*,*N*-bis(silyloxy)enamines **4** as can be seen from examples shown in Scheme 4.



Scheme 4. Synthesis of 5-aminoisoxazoles **6** using NaCN/$Mg(ClO_4)_2$ system.

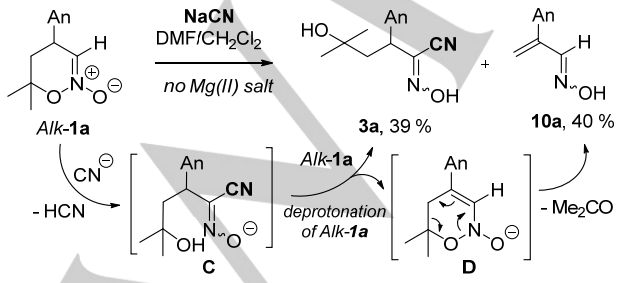
With this new reagent in hand, we attempted to achieve nucleophilic addition of the cyanide anion to the α-carbon atom

of nitronates *Alk*-**1**. Indeed treatment of *Alk*-**1** with $NaCN/Mg(ClO_4)_2$ system in DMF afforded corresponding cyanooxime derivatives **3** in good to high yields as mixtures of *E*/*Z*-isomers (Scheme 5). Products **3** are likely formed through the nucleophilic addition/ring opening mechanism.[11]



Scheme 5. Synthesis of cyanooxime derivatives **3** by α-cyanation of nitronates *Alk*-**1** using $NaCN/Mg(ClO_4)_2$ system.

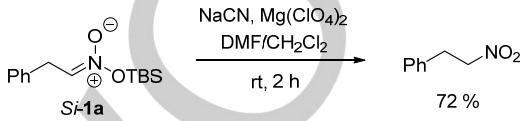
Reaction of nitronate *Alk*-**1a** with NaCN in the absence of $Mg(ClO_4)_2$ resulted in only 39 % yield of cyanooxime **3a** (Scheme 6). The second product was enoxime **10a**, which likely arises from the fragmentation of oxy-anion **D**. The latter is formed upon deprotonation of the initial nitronate *Alk*-**1a** with highly basic oximate anion **C** originating from the nucleophilic addition of CN^- to *Alk*-**1a**.[11, 18] This experiment demonstrates the importance of a Lewis acid (Mg(II) salt) for trapping reactive oxy-anions (such as **C**) in nucleophilic cyanation reactions.



Scheme 6. Reaction of nitronate *Alk*-**1a** with NaCN in the absence of $Mg(ClO)_4$. An - 4-$MeOC_6H_4$-.

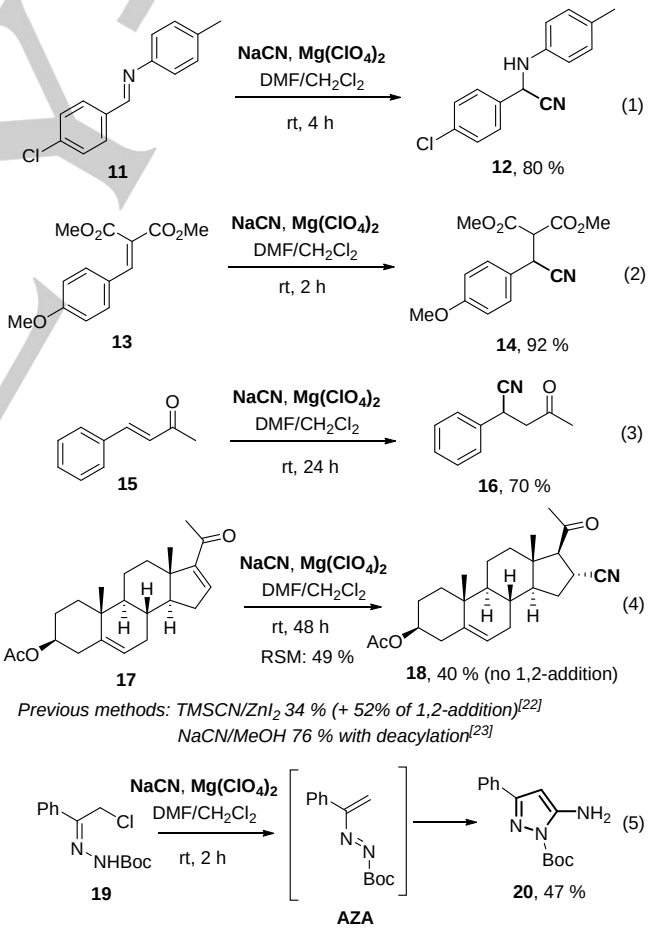
Previously reported cyanation of nitronates **1** with TBSCN used strong Lewis acids (such as silyl triflates) to activate the C=N bond through coordination with the *N*-oxide moiety.[12] Results shown in Schemes 5,6 demonstrate that the cyanide anion is nucleophilic enough to react with nitronates **1** without the need of prior activation of the nitronate moiety.

Unfortunately, we failed to achieve hydrocyanation of O-silyl nitronates *Si*-**1**, which transformed into nitroalkanes upon treatment with $NaCN/Mg(ClO_4)_2$ as exemplified in Scheme 7.



Scheme 7. Attempted α-cyanation of silyl nitronate *Si*-**1a**.

Finally, we tested $NaCN/Mg(ClO_4)_2$ system for nucleophilic cyanation of other typical electrophilic substrates (Scheme 8).



Scheme 8. Nucleophilic cyanation of various π-electrophiles with $NaCN/Mg(ClO_4)_2$ system.

We were able to perform hydrocyanation of model imine **11** as well as simple Michael acceptors such as arylidenemalonate **13** and benzylidene acetone **15** (Scheme 8, eqs. (1)-(3)). The yields of corresponding nitriles **12**,[19] **14**[20] and **16**[21] were comparable with those previously obtained employing other hydrocyanation reagents.

Hydrocyanation of a complex steroidal α,β-unsaturated ketone **17** (3β-acetoxypregna-5,16-dien-20-one) afforded exclusively 1,4-addition product **18** as a single diastereomer (82 % based on converted **17**, Scheme 8, eq. (4)). It is noteworthy, that TMSCN/ZnI_2 system afforded a mixture of 1,4- and 1,2-addition products with the latter being predominant.[22] Previously reported reaction of steroid **17** with NaCN in MeOH resulted in selective 1,4-cyanide addition, however the product underwent deacetylation under these conditions.[23]

Since NaCN/$Mg(ClO_4)_2$ system performed well in Michael addition to unstable nitrosoalkenes **NSA**, we attempted involve azoalkenes **AZA** in the same reaction (Scheme 8, eq. (5)). To the best of our knowledge, nucleophilic cyanation of **AZA** has not been reported so far.[24] As expected, reaction of chloro-substituted hydrazone **18** (the precursor of **AZA**) with NaCN/$Mg(ClO_4)_2$ delivered the desired 5-aminopyrazole, albeit in moderate yield.

We also attempted to carry out hydrocyanation of electron-rich double bond in vinyl ethers. However, no conversion was observed in the reaction of 3,4-dihydropyran with NaCN/$Mg(ClO_4)_2$ suggesting that activation of the C,C-double bond with Mg(II) Lewis acid does not occur.

Conclusions

In conclusion, we have demonstrated that *in situ* generated magnesium cyanide is a convenient reagent for nucleophilic cyanation of nitronates, conjugated nitrosoalkenes, imines, α,β-unsaturated ketones, methylenemalonates and azoalkenes. This new reagent is an alternative to silyl cyanides and has good perspectives for application in target-oriented synthesis.

Experimental section

General procedure of nucleophilic cyanation with *in situ* generated magnesium cyanide. A mixture of sodium cyanide (98 mg, 2 mmol) and magnesium perchlorate (233 mg, 1 mmol) was dissolved in DMF (4 ml) under inert atmosphere. After stirring for 1 h at r.t., a solution of electrophile (1 mmol) in 2 ml of CH_2Cl_2 was added and the mixture was stirred for additional 2 h (if not stated otherwise). Then, the mixture was diluted with water or 0.25 M solution of sodium bisulfate (50 ml) and extracted with MTBE or diethyl ether (50 ml). The organic layer was washed with water (50 ml) and brine (50 ml). Aqueous layer was saturated with NaCl and washed with MTBE or diethyl ether (50 ml). Combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by flash column chromatography. *Caution: Hydrogen cyanide (HCN) can be produced in the quenching of this reaction. Appropriate safety precautions and procedures should be employed if the reaction is performed on large scale.*

Acknowledgements

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Keywords: cyanides • nucleophilic addition • nitronates • magnesium • isoxazoles

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COMMUNICATION

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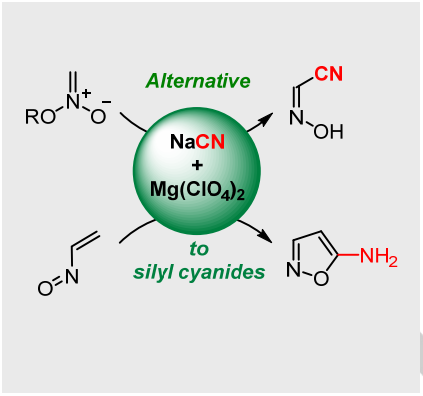

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Key topic – Hydrocyanation reactions