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α,β-Unsaturated acyl cyanide synthesis via triethylamine catalyzed redox cyanation

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ABSTRACT

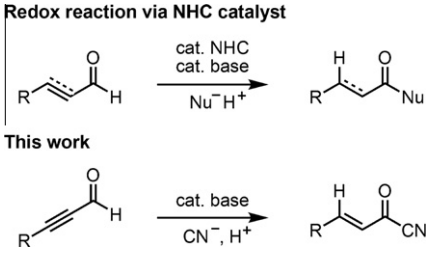
Stereoselective redox cyanation of alkynyl aldehydes was explored, furnishing (*E*)-α,β-unsaturated acyl cyanides. This reaction was catalyzed by mild TEA base, as a dual role of Lewis base and Brönsted base. TMSCN treated with TEA was an effective reagent for generating umpolung intermediates from alkynyl aldehydes, and this nucleophilic intermediate can be protonated by equimolar amount of EtOH, promoting the efficient conversion into α,β-unsaturated acyl cyanides. The synthesized acyl cyanides were successfully applied as the synthetic precursors in the iron-catalyzed arylation reactions.

The discovery of new reaction manifolds via reversal of normal reactivity of organic functional groups, known as umpolung, has become the focus of increased attention, thereby expanding the opportunities of new bond formation and functional group transformation.[1] *N*-Heterocyclic carbenes (NHCs), typically researched for their role of nucleophilic organocatalysts[2] and ligands, have been shown to catalytically convert aldehydes into acyl anion equivalents under mild conditions during transformations such as traditional benzoin and Stetter reactions. Rovis, Zeitler, Scheidt, and Bode demonstrated that α-reducible aldehyde leads to a novel redox reaction pathway under NHC catalysis in the presence of alcohols as nucleophiles, resulting in either halide elimination,[3] cyclopropane, epoxide and aziridine opening,[4] or homoenolate and homoynolate protonation.[5,6] Although the development of these carbonyl or vinylogous carbonyl anion reactions has received significant attention, a related strategy featuring catalytic acetylenic carbonyl anions has received considerably less attention.

Regarding the initiation of benzoin condensation,[7] cyanide ion from KCN or NaCN acts as a very specific catalyst that generates acyl anion equivalent. During the key step of this process, deprotonation of the aldehyde proton occurs due to increased acidity of the C-H bond caused by the electron-withdrawing effect of the CN group. As part of an ongoing study aimed at developing umpolung reactions, this study examined the reaction mode of CN reagent in an efficient redox process with mild base catalyst (Scheme 1).[8]

The classical methods for synthesis of acyl cyanides[9] from acyl halides usually require metal cyanides (potassium, copper, silver or highly toxic mercury) at a high reaction temperature while alternative approaches mostly involve several steps, including cyanosilylation, cyanohydrin formation, and oxidation. Moreover, there have been few cases of the synthetic methods for α,β-unsaturated acyl cyanides,[10] only with chemical data of cinnamoyl cyanide. In this context, atom economical, catalytic methods for the direct synthesis of acyl cyanides are presented as a way to achieve sustainable, environmentally benign redox processes as well as stereoselective preparation of α,β-unsaturated acyl cyanides using propargylic aldehydes as synthetic precursors.

Based on our hypothesis regarding the formation of α,β-unsaturated acyl cyanides, we began our investigation by examining a suitable base catalyst. Under the reaction conditions described in Table 1, cyanide nucleophile was generated from trimethylsilyl cyanide, and the alcohol additive presumably served as the electrophile (proton) source. Whereas morpholine, a relatively weak base proved to be insufficient to complete the reaction, (dimethylamino)pyridine, triethylamine and diisopropylethylamine gave



Scheme 1. General umpolung strategy.

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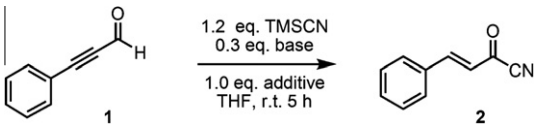
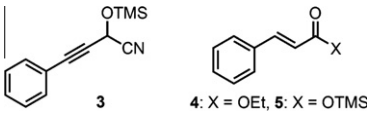
Table 1
Optimization of conditions for redox cyanation[a]



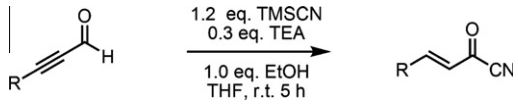
Entry	Base	Additive	Yield[b] (%)	Note[c]
1	Morpholine	EtOH	––	**3** (28)
2	DABCO	EtOH	11	
3	DMAP	EtOH	40	
4	TEA	EtOH	76	
5	DIPEA	EtOH	25	
6	KO^{t}Bu	EtOH	<10	
7	TEA	EtOH[d]	––	**4** (17)
8	TEA	^{t}BuOH	13	
9	TEA	H_2O	––	**5** (10)
10	TEA	di-^{t}Bu cresol	10	

[a] Reactions and conditions: aldehyde (**1**; 0.4 mmol), TMSCN (0.48 mmol), base catalyst (0.12 mmol), additive (0.4 mmol), THF (0.4 M), room temperature, under N_2.
[b] Determined by ^{1}H NMR spectra using internal standard after silica pad filtration.
[c] Byproducts obtained with yields in parenthesis as follows:



[d] 10 equiv of EtOH used

Table 2
Catalytic redox cyanation of alkynals: substrate scope[a]



Entry	R	Product	Yield[b] (%)
1	Ph	**2**	76 (70)
2	1-Naphthyl	**6**	77 (68)
3	2-Naphthyl	**7**	57
4	2-Thienyl	**8**	61 (59)
5	4-MeC_6H_4	**9**	54
6	4-MeOC_6H_4	**10**	67
7	4-FC_6H_4	**11**	61
8	4-BrC_6H_4	**12**	76
9	4-(CN)C_6H_4	**13**	19
10	4-(CH_3CO)C_6H_4	**14**	35
11	4-$NO_2C_6H_4$	**15**	36

[a] Reactions and conditions: aldehyde (0.4 mmol), TMSCN (0.48 mmol), base catalyst (0.12 mmol), additive (0.4 mmol), THF (0.4 M), room temperature, under N_2.
[b] Determined by ^{1}H NMR spectra using internal standard after silica pad filtration. Isolated yields are given in parenthesis.

the desired product with moderate to good yields. The use of a strong base KO^{t}Bu proved not to be productive in terms of the yield of the reaction. We assume that the strong base completely and irreversibly deprotonated the aldehyde protons and prevented the process of proton shuttling. Remarkably, this reaction resulted in the exclusive formation of the (*E*)-configured isomer, and ^{1}H NMR experiments did not show any trace of the (*Z*)-isomer. While all of the reactions showed full conversion of propargylic aldehydes by TLC analysis, ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard after short silica pad filtration indicated lower yields, suggesting the possible loss of material according to the highly reactive acyl cyanide functional group. Additionally, high purities of acyl cyanides were obtained after flash column chromatography or recrystallization of crude product mixture, with 5∼10% lower than the ^{1}H NMR yield.

Encouraged by these interesting results, we proceeded to examine the ability of other alcohols to act as a proton source. An excess amount of alcohol provided unsaturated ester **4** via attack of subsequent alkoxide nucleophile. Not surprisingly, the use of less acidic *tert*-butyl alcohol only showed the lower yield, indicating that ^{t}BuOH was an ineffective proton source. When water was used, acyl cyanide was transformed further into the corresponding acid followed by TMS-ester formation. Di-^{t}Bu cresol, which was proven to be a good proton source having nonnucleophilic phenoxide, provided acyl cyanide **2** with low yield. The use of diethyl ether and dioxane as solvents produced **2** with similar yields (70 and 69%), but other solvents such as acetonitrile, dichloromethane, and toluene gave **2** with lower yields (<5%).

A diverse range of substrates was evaluated by employing a suitable set of reaction conditions using TMSCN (1.2 equiv), TEA (0.3 equiv), and EtOH (1.0 equiv) in THF solvent (Table 2). Preparation of the required propargylic aldehydes was straightforward. They were conveniently prepared either by oxidation of propargylic alcohols, easily accessed through Sonogashira coupling with unprotected propargylic alcohol, or alternatively via formylation of deprotonated acetylene derivatives. Phenyl, naphthyl, and heteroaryl propargylic aldehydes were good substrates for the reaction, and electron-rich aryl propargylic aldehydes also readily underwent the transformation to give the desired products. Electron-poor aldehydes showed lower yields, which is identical to the results of the redox reactions catalyzed by *N*-heterocyclic carbenes.[5c] The alkynals having sterically-hindered alkyl or silyl substituents only afforded the trimethylsilyl ethers of the corresponding cyanohydrins.

As for the mechanistic view of this redox cyanation, the reaction was initiated by trimethysilylcyanation of aldehydes catalyzed by triethylamine as a Lewis base,[11] affording trimethylsilyl ether of cyanohydrins **I** (Fig. 1). Triethylamine as a Brönsted base deprotonated the acidic aldehyde protons, which subsequently underwent H-migration to provide α-trimethylsiloxy allenyl cyanides **III**. These allene intermediates were hydrolyzed and tautomerized to α,β-unsaturated acyl cyanides with the aid of triethylamine. To gain some insight into the reaction mechanism, redox reaction was carried out with EtOD, providing *deuterio*-**2** with 14% and 50% content of deuterated vinyl group (Scheme 2). Deuterated β-protons indicate that the β-protonation did not occur by a concerted hydride shift, and the deuterated ratio of less than 100% implies that the formation of intermediate **II** was relatively rapid to release protons but all the intermediate **II** cannot afford the complete conversion to the desired product **2**.

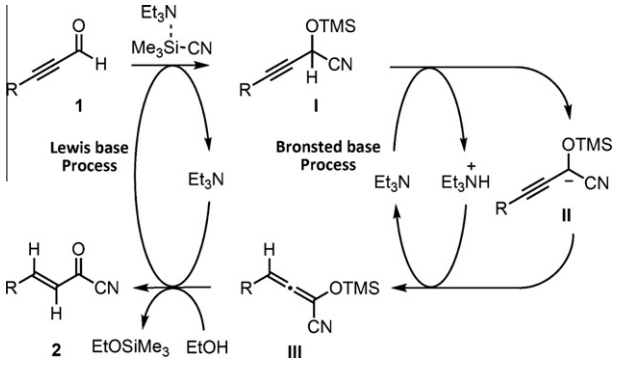
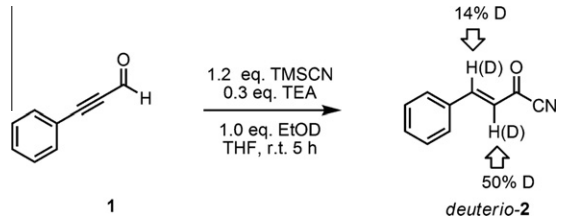
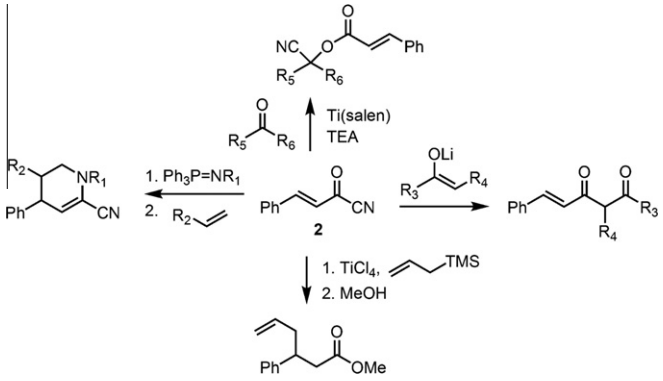


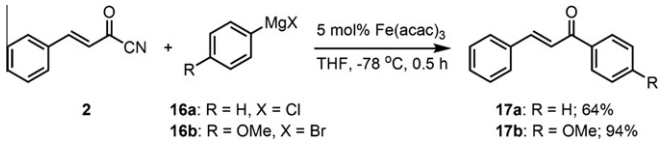
Figure 1. Plausible catalytic cycles.



Scheme 2. Deuterium experiment.



Scheme 3. α,β-Unsaturated acyl cyanides as synthetic precursors.



Scheme 4. $Fe(acac)_3$ catalyzed arylation of acyl cyanides.

The synthesized α,β-unsaturated acyl cyanide would acted as synthetic precursors in the further transformation reactions,[9a] featuring α,β-unsaturated carbonyl group or acyl cyanide group (Scheme 3). A variety of reactions, such as Hetero–Diels–Alder reaction affording tetrahydropyridine rings,[12] Michael reaction with $TiCl_4$ and allyl silanes affording enones,[13] acylation reaction with lithium enolate affording 1,3-diketones,[14] and cyanoacylation reaction to ketones affording *O*-acyl cyanohydrin esters,[15] have already been explored and show a great selectivity and efficiency.

In synthetic applications, acyl cyanides are proved to be more powerful acylating agents than acid chlorides, since the cyano group enhances the reactivity of the adjacent carbonyl group.[16] Moreover, the acylation of organometallic intermediates with acid derivatives is an important method for the preparation of polyfunctional ketones. Therefore, using the synthesized α,β-unsaturated acyl cyanide, we examined the use of acyl cyanide **2** as an acylating reagent in the reactions of aromatic organomagnesium compounds (Scheme 4). The use of catalytic amounts of $Fe(acac)_3$ (5 mol%) was beneficial[16c] for the reaction of phenylmagnesium chloride with a yield of 64% and 4-methoxyphenylmagnesium bromide reacted as well, furnishing a new polyfunctional aryl ketone **17b** with 94% yield. To the best of our knowledge, this iron catalyzed arylation reaction with α,β-unsaturated acyl cyanide was more efficient and economic than any other palladium catalyzed reaction[17a–d] with boronic acid or triarylbismuths and gallium mediated coupling reaction.[17e]

In summary, stereoselective redox cyanation for synthesis of α,β-unsaturated acyl cyanides was explored. This reaction proceeded under mild TEA base catalyst and TMSCN and EtOH were used as a cyanide nucleophile and proton electrophile source, respectively. Various types of acyl cyanides were prepared with moderate to good yields after filtration through a plunge of silica or recrystallization, although these compounds were relatively reactive. Based on the plausible mechanism, TEA catalyzed this redox reaction as a Lewis base in the cyanosilylation step and a Brönsted base in the umpolung generation step. The synthesized α,β-unsaturated acyl cyanide was successfully applied as a synthetic precursor in the transformation reactions, especially in the iron catalyzed arylation reactions. The knowledge gained from the TEA-catalyzed redox reactions is expected to contribute to the design and development of various electrophiles for use in new bond formation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.063.

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