JOC Notes

Product-Catalyzed Addition of Alkyl Nitriles to Unactivated Imines Promoted by Sodium Aryloxide/Ethyl(trimethylsilyl)acetate (ETSA) Combination

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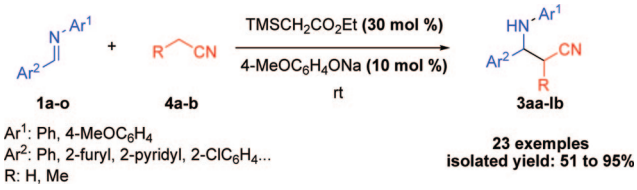
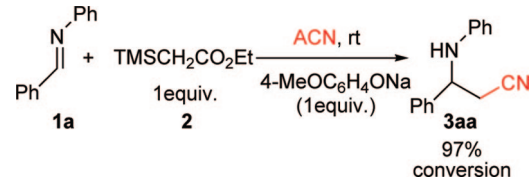


The first transition-metal-free addition of alkyl nitriles to unactivated imines was developed using a catalytic combination of 4-$MeOC_6H_4ONa$ and $TMSCH_2CO_2Et$ to promote the reaction. The corresponding β-amino nitriles are obtained in good to almost quantitative isolated yields under mild conditions. A mechanism involving an autocatalytic pathway is proposed on the basis of experimental observations.

β-Amino nitriles and hydroxy nitriles are important synthetic intermediates for the preparation of β-amino acids or γ-amino alcohols and β-hydroxy acids, respectively.[1]

Among the various methodologies reported, the cyanomethylation of imines and aldehydes is probably the most straightforward and efficient available strategy to have access to β-amino (or β-hydroxy) nitriles. While addition of nitrile compounds to aldehydes has been widely reported in the literature,[2] only a few reports deal with cyanomethylation of imines. We can mention catalytic addition of $TMSCH_2CN$ to activated imines mediated by Lewis bases such as phosphines,[2f] alkali acetate,[3] or ammonium phenoxide[4] to produce β-amino nitriles in good yields. Although rarer, direct catalytic activation of acetonitrile (ACN) by means of Lewis acidic transition-metal complexes such as Cu,[5] Pd,[6] or Ru[2k,l] complexes should also be mentioned. As a result of the coordination of ACN to the transition metal, the acidity of proton α to the nitrile group is enhanced, thereby making their deprotonation by a weak base such as DBU possible. Although these catalytic approaches are quite efficient, they are complicated to implement and remain limited to aldehydes or activated imines. Moreover, to date, no environmentally friendly catalytic methods have been reported for acetonitrile activation.

SCHEME 1. Addition of Acetonitrile to *N*-Benzylideneaniline Promoted by $TMSCH_2CO_2Et$/Sodium Aryloxide Combination



During our survey on the reactivity of $TMSCH_2CO_2Et$ (ETSA), we undertook to develop a catalytic addition of ETSA to unactivated aldimines. We first investigated Mukaiyama's reaction conditions[4] previously developed during the addition of $TMSCH_2CN$ to *N*-(*tert*-butylsulfinyl)imines. We thus chose 4-$MeOC_6H_4ONa$[7] (1 M in THF) as Lewis base, *N*-benzylideneaniline **1a** as unactivated aldimine, and ETSA **2** as carbon nucleophile precursor. Surprisingly, when the reaction was conducted in ACN, no ETSA addition product was observed and the cyanomethylated product **3aa** was found to be the only product of the reaction (Scheme 1).

We could notice that the reaction did not proceed in the absence of either $TMSCH_2CO_2Et$ or 4-$MeOC_6H_4ONa$. In a first attempt to rationalize these results, one could explain the formation of **3aa** through the deprotonation of acetonitrile by ethyl acetate anion generated in situ from ETSA and 4-$MeOC_6H_4ONa$. Interestingly, in attempting to conduct the reaction in the presence of catalytic amount of ETSA and 4-$MeOC_6H_4ONa$, we were pleased to find that the reaction proceeded

(1) Ma, D.-Y.; Wang, D.-X.; Pan, J.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2008**, *73*, 4087–4091.

(2) For examples of addition of alkyl nitriles to aldehydes, see: (a) Lal, K.; Ghosh, S.; Salomon, R. G. *J. Org. Chem.* **1987**, *52*, 1072–1078. (b) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021–2027. (c) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339–1342. (d) Ko, E. Y.; Lim, C. H.; Chung, K.-H. *Bull. Korean Chem. Soc.* **2006**, *27*, 432–434. (e) Sun, P.; Zhang, Y. *Synth. Commun.* **1997**, *27*, 3175–3180. (f) Matsukawa, S.; Kitazaki, E. *Tetrahedron Lett.* **2008**, *49*, 2982–2984. (g) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 1508–1509. (h) Suto, Y.; Kumagai, N.; L.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147–3150. (i) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757–3760. (j) Fan, L.; Ozerov, O. V. *Chem. Commun.* **2005**, 4450–4452. (k) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632–13633. (l) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 8598–8608. (m) Goto, A.; Endo, K.; Ukai, Y.; Irle, Y.; Saito, S. *Chem. Commun.* **2008**, 2212–2214.

(3) Kawano, Y.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 1134–1135.

(4) Michida, M.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 1244–1245.

(5) Yazaki, R.; Nitabaru, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 14477–14479.

(6) Aydin, J.; Conrad, C. S.; Szabü, K. J. *Org. Lett.* **2008**, *10*, 5175–5178.

(7) Although this reaction could be carried out with sodium phenoxide, we chose 4-$MeOC_6H_4ONa$ as Lewis base (1 M in THF) freshly prepared before use by treatment of 4-methoxyphenol (less hygroscopic than phenol) with NaH 95%.

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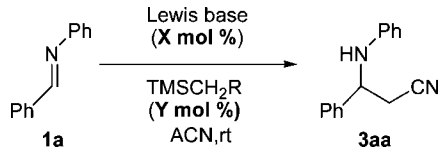
TABLE 1. Screening of Lewis Bases and Trimethylsilyl Sources



entry	Lewis base	*X* (mol %)	*Y* (mol %)	R	conv[a] (%)
1	4-$MeOC_6H_4ONa$	100	100	CO_2Et	97
2		100	20		97
3		10	20		97
4		10	10		87
5		5	10		97
6		2	4		67
7		10	20	CN	93
8				Cl	0
9				Ph	0
10	4-$MeOC_6H_4OLi$	10	20	CO_2Et	0
11	MeONa	10	20		0
12	AcONa	10	20		0
13	AcOK	10	20		0
14	DBU	10	20		0
15	DMAP	10	20		0
16	PBu_3	10	20		0
17	HMPA	10	20		0
18		100	100		0
19	Me_4NF	100	0		57[b]
20		10	0		30[b]
21		10	20		70[b]
22	LDA	10	0		67[c]
23	NaH	10	0		20[d]
24		30	0		95[e]
25		50	0		96[f]

[a] Determined by GC and/or ^1H NMR after 15 min. [b] Reaction time: 3 h. [c] Maximum conversion reached after 2 h of reaction. [d] Maximum conversion reached after 4 days of reaction. [e] Reaction time: 16 h. [f] Reaction time: 8 h.

smoothly, affording product **3aa** in almost quantitative yield. The monitoring of the reaction by ^1H NMR experiments in CD_3CN revealed that ETSA is consumed, arguing in favor of the previous mechanism that involves the formation of an acetate anion. Thus, the resulting acetonitrile anion would react with imine **1a** to furnish the **3aa**−sodium amide salt intermediate. To account for the catalytic nature of the process, it was envisioned that **3aa**−sodium amide salt intermediate could deprotonate acetonitrile to promote an autocatalytic pathway. This mechanistic scenario prompted us to develop a new autocatalytic process for the addition of ACN to imines.

We thus decided to examine different combinations of Lewis bases and silylated compounds (Table 1). We first planned to investigate the molar ratio of 4-$MeOC_6H_4ONa$ and ETSA. We found that a 1:2 ratio between 4-$MeOC_6H_4ONa$ and ETSA is optimum for obtaining a quantitative conversion within 15 min (Table 1, entries 3−5). Furthermore, catalytic amounts as low as 5 mol % of 4-$MeOC_6H_4ONa$ and 10 mol % of $TMSCH_2CO_2$-Et ensured complete conversion (Table 1, entry 5), whereas lower amounts resulted in a significant drop of the conversion (Table 1, entry 6). With these new conditions in hand, we examined various sources of silylated compounds (Table 1, entries 7−9). The presence of a strong electron-withdrawing group in the silylated compound seems to be crucial for maintaining catalytic activity. Indeed, the use of $TMSCH_2CN$ furnished the desired addition product in high conversion (Table 1, entry 7), whereas trimethylsilyl compounds containing chlorine or phenyl (Table 1, entries 8 and 9) were inactive under these catalytic conditions.

Then, we considered a wide range of Lewis bases. First, changing the counterion of the phenoxide from sodium to lithium resulted in the complete inhibition of the reaction (Table 1, entry 10). All other screened Lewis bases, i.e., alkali alkoxides or acetates and nitrogen or phosphorus derivatives, failed to promote the reaction (Table 1, entries 11−18). It is worth noting that when an excess of Me_4NF in ACN was used the β-amino nitrile **3aa** was obtained in only 57% conversion along with several byproducts (Table 1, entry 19), whereas when similar reaction conditions were used, clean and high-yielding reactions were reported by Chung et al.[2d] during the addition of ACN to various aldehydes. Interestingly, we found that with the catalytic use of Me_4NF (10 mol %) in the presence of ETSA (20 mol %) a 70% conversion was reached in 3 h and without any byproduct (Table 1, entry 21). The use of catalytic amounts of LDA or NaH allowed a maximum 67% conversion and 96% conversion, respectively (Table 1, entries 22−25), to be reached, along with longer reaction time and some problems with reproducibility. These results clearly indicate that the reaction proceeds via an autocatalytic mechanism. In an attempt to reduce the amount of ACN, 85% conversion was obtained in 45 min by conducting the reaction in THF in the presence of 10 equiv of ACN. On the basis of this screening, ETSA (30 mol %) and 4-$MeOC_6H_4ONa$ (10 mol %) were finally selected as the best candidates to explore the scope and limitations of this new autocatalytic process (Table 2).

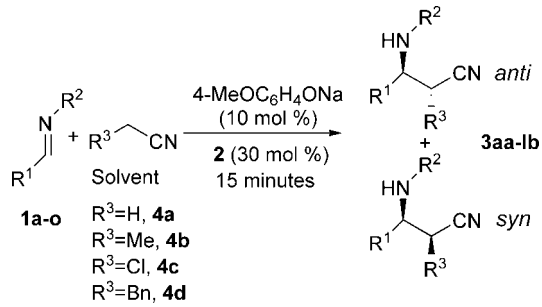
At this stage, it is worth noting that the catalytic use of mild reagents such as phenoxide salts and ETSA results in the production of ethyl acetate and ArOTMS as the sole nonreactive byproduct in catalytic amounts. In addition, such unprecedented mild reaction conditions offer the advantage of being compatible with a wider range of functional groups than conventional stronger bases such as NaH or LDA.

We first examined different nitrile derivatives **4a**−**d**. Acetonitrile **4a** and propionitrile **4b** gave almost quantitative conversion with excellent isolated yields (Table 2, entries 1 and 2). Unfortunately, chloroacetonitrile **4c** and benzyl cyanide **4d** remained totally inactive under our conditions. In all cases, the reaction was completed within 15 min except for imines **1f**,**g** (Table 2, entries 13−16). Additional strong support for an autocatalytic pathway is given by the nonreactivity observed with the activated imine **1o**, which probably arises from the too low basicity of the putative **3oa**−sodium amide salt intermediate unable to deprotonate ACN. Addition of acetonitrile **4a** furnished the β-amino nitrile **3** in moderate to good yields (51−85%), whereas the use of propionitrile **4b** resulted in somewhat higher isolated yields (89−99%). Despite those excellent yields, the *syn*/*anti* ratio of the addition product **3** was rather low and in all cases in favor of the *anti* isomer.[8] Interestingly, the *p*-anisidine imine of benzaldehyde gave good yields with acetonitrile **4a** and propionitrile **4b** (Table 2, entries 5 and 6). The resulting addition products **3ba** and **3bb**, respectively, may be easily deprotected by treatment with CAN,[9] making this methodology useful for further applications in multistep synthesis. The general trend regarding the influence of R^1 on the reaction yield reveals that imines **1** bearing an electron-donating group (Table 2, entries 7−18) furnished

(8) *Syn* and *anti* isomers of cyanomethylated products **3** were identified by comparaison of ^1H chemical shifts of the H-2 proton with literature data: Viteva, L.; Gosspodova, Tz.; Stefanovsky, Y.; Simona, S. *Tetrahedron* **2005**, *61*, 5855–5865.

(9) Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, *7*, 637–640.

TABLE 2. Substrate Generality



entry	1	R^1	R^2	4	*anti*/*syn* ratio[a]	3: yield[b] (%)
1	**1a**	Ph	Ph	**4a**		**3aa**: 85
2				**4b**	55/45	**3ab**: 98
3				**4c**		
4				**4d**		
5	**1b**	Ph	4-MeOC$_6$H$_4$	**4a**		**3ba**: 82
6				**4b**	55/45	**3bb**: 99
7	**1c**	4-Cl-C$_6$H$_4$	Ph	**4a**		**3ca**: 62[c]
8				**4b**	50/50	**3cb**: 93[c]
9	**1d**	2-ClC$_6$H$_4$		**4a**		**3da**: 65[c]
10				**4b**	61/39	**3db**: 89[c]
11	**1e**	2-MeOC$_6$H$_4$		**4a**		**3ea**: 87
12				**4b**	53/47	**3eb**: 92
13	**1f**	3-BnOC$_6$H$_4$		**4a**		**3fa**: 73[d]
14				**4b**	55/45	**3fb**: 89[e]
15	**1g**	3,4-OCH$_2$OC$_6$H$_3$		**4a**		**3ga**: 75[d]
16				**4b**	55/45	**3gb**: 95[e]
17	**1h**	2-Br-4,5-(MeO)$_2$C$_6$H$_2$		**4a**		**3ha**: 67
18				**4b**	57/43	**3hb**: 89
19	**1i**	4-CNC$_6$H$_4$		**4a**		**3ia**: 51[f]
20				**4b**	52/48	**3ib**: 91
21	**1j**	4-CF$_3$C$_6$H$_4$		**4a**		**3ja**: 64[f]
22				**4b**	50/50	**3jb**: 88
23	**1k**	2-furyl		**4a**		**3ka**: 63[g]
24	**1l**	3-pyridyl		**4a**		**3la**: 54[f,g]
25				**4b**	53/47	**3lb**: 94
26	**1m**	*i*-Pr	4-MeOC$_6$H$_4$	**4a**		
27	**1n**	4-(CH$_3$)$_2$NC$_6$H$_4$	Ph	**4a**		
28	**1o**	Ph	SO_2Ph	**4a**		

[a] Determined by ^{1}H NMR. [b] Isolated yield; in all cases conversion was found to be up to 95% determined by GC and/or ^{1}H NMR. [c] 50 mol % of ETSA. [d] Reaction time: 18 h. [e] Reaction time: 4 h. [f] 20 mol % of 4-MeOC$_6$H$_4$ONa. [g] 100 mol % of ETSA.

somewhat better yields than those possessing an electron-withdrawing groups (Table 2, entries 19−22). The reaction could also be conducted with imine **1k**,**l** derived from heterocyclic aldehydes with satisfactory to good yields, provided that a stoichiometric amount of ETSA is employed (Table 2, entries 23−25). It should be noted that when benzaldehyde was used as electrophilic species in standard conditions, no cyanomethylation product was observed. The only product of the reaction was found to be the addition product of ETSA to benzaldehyde as already observed by Mukaiyama during addition of trimethylsilyl ketene acetals to carbonyl compounds catalyzed by Lewis base.[10]

By taking account of the previous experimental results, a plausible catalytic mechanism is presented in Figure 1.

The first step would involve the reaction between ETSA and sodium aryloxide to form the sodium ketene acetal **A**, which would deprotonate the alkyl nitrile **4**. The alkyl nitrile anion **B** then reacts with the electrophilic imine **1** to form the autocatalytic species **C** as a sodium amide. The latter would be sufficiently basic to deprotonate a new molecule of alkyl nitrile **4**, thus providing the β-amino nitrile **3** and regenerating the alkyl nitrile anion **B** which is involved in a new catalytic cycle. Such a mechanism may account for the difference of reactivity between imines **1** and benzaldehyde. Indeed, it may be argued that benzaldehyde, more electrophilic than imines **1**, reacts easier with the sodium ketene acetal intermediate **A**, thus preventing deprotonation of alkyl nitrile **4**. Furthermore, the sodium alkoxide intermediate resulting from the addition of ETSA to benzaldehyde is not basic enough to promote an autocatalytic process by deprotonation of alkyl nitrile.[11]

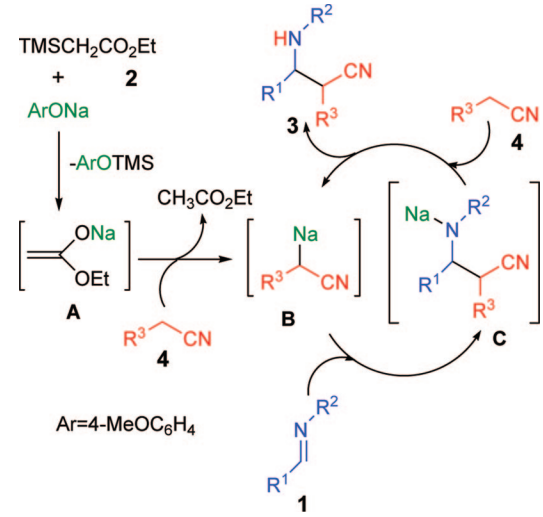


FIGURE 1. Proposed mechanism for autocatalytic cyanomethylation promoted by ETSA/sodium aryloxide combination.

In summary, we have reported the first transition-metal-free autocatalytic cyanomethylation of unactivated imines promoted by ETSA and sodium aryloxide combination with good to excellent yields. This clean and high-yielding autocatalytic approach provides an interesting alternative to the use of transition metals and to the conventional addition of α-cyano carbanion to imines for the preparation of β-amino nitriles under mild conditions. Further investigations of this catalytic approach, including an asymmetric version[12] and expanded substrate scope, are underway.

Experimental Section

Typical Procedure for the Cyanomethylation of Imines. Synthesis of 3aa. To a solution of imine **1a** (0.5 mmol) and 4-MeOC$_6$H$_4$ONa (1 M in THF, 0.05 mL, 0.05 mmol) in dry acetonitrile **4a** (2 mL) was added TMSCH$_2$COOEt **2** (0.027 mL, 0.15 mmol), and the solution was stirred at room temperature until complete disappearance of the starting material (monitored by GC and TLC). The solution was quenched with brine (5 mL) and diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and dried over MgSO$_4$. The combined organic layers

(10) Fujisawa, H.; Nakagawa, T.; Mukaiyama, T. *Adv. Synth. Catal.* **2004**, *346*, 1241–1246.

(11) Michida, M.; Mukaiyama, T. *Chem. Asian J.* **2008**, *3*, 1592–1600.

(12) The most straightforward approach to develop an asymmetric version of this autocatalytic process would consist in evaluating the performance of chiral ion pairs α-cyano carbanion/chiral quaternary ammonium initially generated from a chiral quaternary ammonium phenoxide in the presence of an alkyl nitrile and ETSA. For leading references using chiral quaternary ammonium phenoxides in organocatalysis, see: Tozawa, T.; Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Asian J.* **2007**, *2*, 123–134. Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666–667. Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 8–9. Nagao, H.; Yamane, Y.; Mukaiyama, T. *Heterocycles* **2007**, *72*, 553–565. Mukaiyama, T.; Nagao, H.; Yamane, Y. *Chem. Lett.* **2006**, *35*, 916–917.

were concentrated, and the residue was purified by flash chromatography (Et_2O/petroleum ether= 3/7 v/v) to afford the corresponding β-amino nitrile **3aa** as a pale yellow solid (85% yield). Mp = 80−82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.90 (dd, 2H, J = 6.1 Hz J = 2.6 Hz), 4.24 (brs, 1H), 4.78 (t, 1H, J = 5.9 Hz), 6.62 (d, 2H, J = 8.5 Hz), 6.77 (t, 1H, J = 8.1 Hz), 7.17 (t, 2H, J = 7.5 Hz), 7.32−7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 26.2, 54.3, 113.9, 115.1, 117.3, 118.7, 126.2, 128.4, 129.2, 129.3, 129.4, 139.9, 145.8. IR (KBr, cm^{-1}): 3408, 2244, 1602, 1505, 1451, 1311, 1271, 750, 690. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.25; N, 12.60. Found: C, 81.07; H, 6.38; N, 12.55.

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Supporting Information Available: Experimental procedures, full characterization data, and copies of NMR spectra for compounds **3aa**−**3lb**. This material is available free of charge via the Internet at http://pubs.acs.org.

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