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A High-Yielding Preparation of β-Ketonitriles

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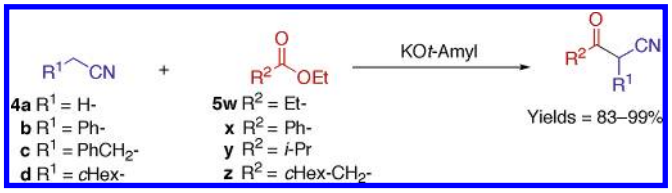
ABSTRACT

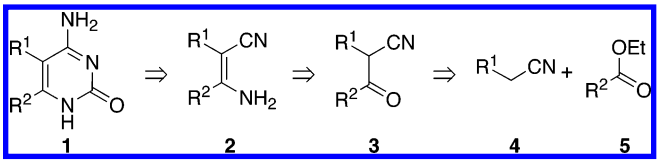


β-Ketonitriles are important precursors for a wide variety of biologically active heterocycles. A facile procedure for the high-yielding acylation of nitrile anions with unactivated esters to provide β-ketonitriles is reported. The procedure is successful with enolizable and nonenolizable esters as well as hindered nitrile anions.

β-Ketonitriles are useful synthetic intermediates.[1] They have been used as precursors for a wide variety of heterocyclic structures including, but not limited to, aminopyrazoles,[2] aminoisoxazoles,[3] 2-pyridones,[4] and imidazoles,[5] while decyanation provides ketones.[5] During our recent research into the Thorpe condensation of cyanomethyl ethers,[6] we developed an improved procedure to obtain β-ketonitriles through the base-mediated, direct acylation of nitrile anions with unactivated esters. This report describes this remarkably high-yielding and operationally facile condensation.

It was noted during our previous work that simple alkyl nitriles are unreactive under the conditions reported (KO*t*-Amyl, THF, 0 °C) for Thorpe condensation of cyanomethyl ethers en route to unnatural cytosine analogues.[6] It was recognized that our previous method is inherently limited by the Thorpe condensation for the synthesis of differentially substituted pyrimidines. To extend our annulation method to access a variety of 5- and 6-substituted cytosine analogues **1**, a cross-Thorpe condensation is needed to directly obtain the differentially substituted enaminonitriles **2**. This type of cross-condensation is unrealistic for several reasons: (1) regioselectivity and chemoselectivity of condensation is usually unselective; (2) Thorpe condensation of unactivated alkyl nitriles requires high temperature and concentration; and (3) homocoupling is competitive with cross-coupling.[7] Recognizing the inherent limitations of a dimerization approach, we envisioned obaining the desired β-enaminonitriles **2** from the corresponding β-ketonitriles **3** via simple transamination and that β-ketonitriles **3** could be prepared by coupling of nitrile **4** and ester **5** (Scheme 1).

Scheme 1. β-Ketonitriles as Precursors to Unnatural Cytosines



The condensation of nitrile anions and acylating agents has been reported by many groups in modest to excellent

(1) Elnagdi, M. H.; Elgemeie, G. E. H. *Synthesis* **1984**, 1−26.
(2) Ranatunge, R. R.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Young, D. V.; AZemetseva, I. S. *Bioorg. Med. Chem.* **2004**, *12*, 1357−1366.
(3) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Butcher, R. J.; Edafiogho, I. O.; Stables, J. P.; Cooke, N.; Goodwin, A. M.; Smith, C. A.; Scott, K. R. *Eur. J. Med. Chem.* **2002**, *37*, 635−648.
(4) Hauser, C. R.; Eby, C. J. *J. Am. Chem. Soc.* **1957**, *79*, 728−731.
(5) Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.* **2004**, *47*, 6311−6325.
(6) Barkin, J. L.; Faust, M. D.; Trenkle, W. C. *Org. Lett.* **2003**, *5*, 3333−3335.

(7) For a review of nitrile-stabilized carbanion reactivity, see: Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* (*N.Y.*) **1984**, *31*, 1−364.

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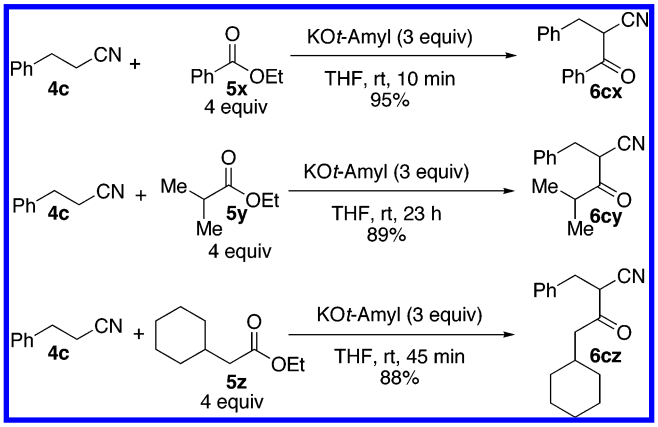
yields with nonenolizable esters but, in general, poor to moderate yields with most enolizable esters.[1,7−10] The highest yields for unactivated esters are reported by Hauser and coworkers using sodium amide as the base in liquid ammonia—a procedure with many inherent hazards.[11] Despite the poor results described in the literature, we decided to assay a modification of our previously reported condensation conditions using phenethylnitrile with ethyl esters as the trapping agent in an attempt to obtain the corresponding β-ketonitriles (Scheme 2). We were delighted to observe that our initial

Scheme 2. Initial Acylation Results



experiments provided excellent yields of the β-ketonitriles. It was particularly surprising and unprecedented that enolizable esters **5y** and **5z** would give high yields of β-ketonitriles **6cy** and **6cz**. We decided to optimize our conditions and evaluate their compatibility with a variety of substitution patterns to determine the generality of the new procedure.

The first set of optimization experiments focused on the effect of the molar ratios of respective reagents (Table 1). After screening a variety of equivalencies, we found that the fastest and cleanest reaction was observed with 4 equiv of ester and 3 equiv of base relative to nitrile with complete reaction of the limiting nitrile observed in 0.5 h for most cases. An isolated yield of 80% was obtained for the condensation of benzylnitrile and 4 equiv of ethyl cyclohexyl acetate when treated with 3 equiv of alkoxide base for 30 min at room temperature (entry 1, Table 1). Increased reaction times did not appreciably affect the observed yield in the positive direction, but decreased yields were observed for some cases with increasing time.[12] Additionally, it was found that order of addition did not appreciably affect the

(8) For a review of the chemistry of cyclic nitriles, see: Fleming, F. F.; Zhang, Z. Y. *Tetrahedron* **2005**, *61*, 747−789.

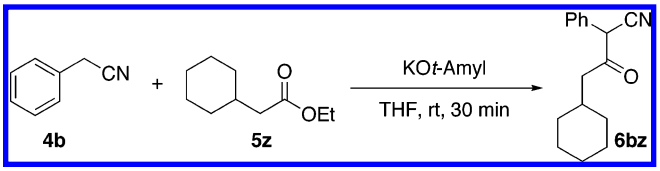
(9) For an early example of intramolecular nitrile anion acylation using an alkoxide base, see: Blake, J.; Wilson, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1964**, *86*, 5293−5299.

(10) For a recent example of nitrile carbanion acylation with an activated benztriazole ester, see: Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 4932−4934.

(11) Eby, C. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1957**, *79*, 723−725.

(12) Increased reaction time leads to the observation of increasing amounts of multiple unidentified products with aromatic signals in their ^{13}C NMR spectra.

Table 1. Optimization of Reagent Equivalents



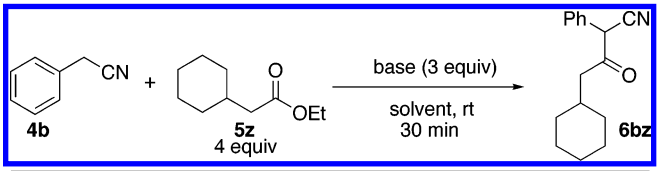
entry	base (equiv)	ester (equiv)	yield[a] (%)
1	3	4	80
2	2	4	62
3	2	3	49
4	1.5	4	61
5	1.5	3	60
6	1.5	2	42
7	1.5	1.5	46
8	1	4	28
9	1	3	34
10	1	2	54
11	1	1.5	63
12	1	1	19

[a] Isolated yield of **6bz** after silica gel chromatography.

isolated yield. For operational ease, the base was added to the nitrile followed by addition of the ester to the mixture.[13] It should be noted that 1.5 equiv of ester and 1 equiv of base provided reasonable yields (62%, entry 11, Table 1) but we chose to proceed with the conditions for entry 1 which provided the highest isolated yield of the desired β-ketonitrile.

Subsequently, we examined the combined effects of the base and solvent on the reaction (Table 2). Upon screening,

Table 2. Solvent and Base Effects on the Condensation Reaction



	KO*t*-Amyl (%) 1.7 M PhMe	LiHMDS (%) 1.0 M THF	NaHMDS 1.0 M THF	KHMDS (%) 0.5 M PhMe
THF	80	63	66	41
toluene	64 (69)[a]	66	62	31
Et_2O[b]	56	64	63	48
DME[b]	50	60	38	46
DMF[c]	25	33	23	35

[a] Isolated yield after 1 h. [b] Reactions in Et_2O and DME were run for 1 h. [c] Reactions in DMF were run for 2 h.

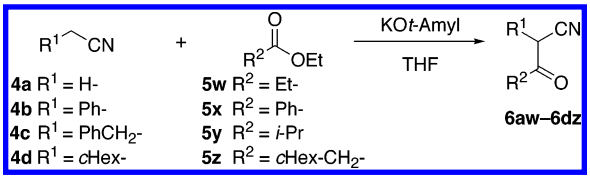
we discovered that THF provided the most rapid reactions with all bases, with complete consumption of the nitrile within 30 min. While exhibiting slower rates of reaction,

(13) Addition of the base to a mixture of the nitrile and ester gave identical yields in the cases examined.

toluene provided clean reactions with somewhat lower isolated yields. In contrast, diethyl ether and DME exhibited substantially slower reaction rates (yields reported for 1 h reactions) and the slow development of unidentified aromatic byproducts. Dimethyl formamide proved to be unsuitable for the cross-condensation as the rate of reaction was exceptionally slow and unrecognizable aromatic products were rapidly formed. In regards to base, KO*t*-Amyl provided the highest yields and fastest reactions in most solvents.

Upon completion of our solvent and base screen, we examined the scope of the acylation reaction with a variety of nitriles **4a**−**d** and esters **5w**−**z** using the optimal base and solvent combination: KO*t*-Amyl and THF (Table 3).

Table 3. Acylation of Nitrile Anions with Ethyl Esters



entry	nitrile	ester	temp (°C)	time (h)	product	yield[a] (%)
1	**4a**	**5w**	rt	11	**6aw**	99
2	**4a**	**5x**	rt	1	**6ax**	99
3	**4a**	**5y**	60	3	**6ay**	84[b]
4	**4a**	**5z**	60	3	**6az**	96
5	**4b**	**5w**	rt	0.33	**6bw**	99
6	**4b**	**5x**	rt	0.33	**6bx**	99
7	**4b**	**5y**	60	1	**6by**	98
8	**4b**	**5z**	60	0.17	**6bz**	99
9	**4c**	**5w**	rt	48	**6cw**	89
10	**4c**	**5x**	rt	0.17	**6cx**	95
11	**4c**	**5y**	rt	23	**6cy**	89
12	**4c**	**5z**	rt	0.75	**6cz**	88
13	**4d**	**5w**	140[c]	3	**6dw**	83
14	**4d**	**5x**	60	0.17	**6dx**	89
15	**4d**	**5y**	60	15	**6dy**	92
16	**4d**	**5z**	60	15	**6dz**	90

[a] Isolated yield after silica gel chromatography. [b] Isolation of β-ketonitrile **6ay** was hindered by its volatility. [c] This reaction was performed in a sealed vessel in a PersonalChemistry microwave reactor.

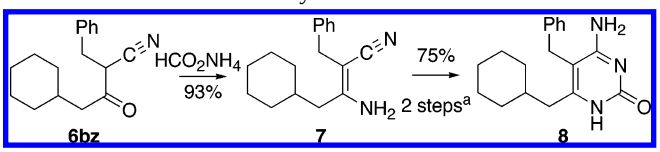
In our study of the acylation, good to excellent yields were obtained after reaction at room temperature for most cases.[14]

(14) **Representative procedure:** A solution of KO*t*-Amyl (1.33 mL, 2.61 mmol, 3.0 equiv, 1.7 M in PhMe, Fluka) was added dropwise to a stirred room temperature solution of nitrile **4b** (101.5 mg, 0.87 mmol, 1.0 equiv) in THF (3.0 mL) followed by dropwise addition of ester **5w** (0.32 mL, 3.48 mmol, 4.0 equiv). After 20 min at room temperature, the reaction mixture was diluted with 0.25 M HCl (100 mL) and EtOAc (100 mL). The layers were separated and the organic layer is washed sequentially with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), concentrated, and chromatographed (silica gel, EtOAc/Hex) to provide 149.5 mg (99%) of **6bw** as a colorless oil.

In contrast, the β-branched nitrile **4d** with various esters, and acetonitrile (**4a)** with the enolizable and branched esters, required elevated temperatures for high yields. The best conditions for these more difficult cases involved heating the reaction mixture at 60 °C for varying amounts time dependent on nitrile and ester. Higher temperatures often lead to undesired byproducts while lower temperatures resulted in incomplete reaction. The elevated temperature provided excellent yields of the desired β-ketonitriles **6ay**, **6az**, **6by**, **6bz**, **6dx**, **6dy**, and **6dz** (84%,[15] 88−99%, respectively).

Preliminary results have shown that β-ketonitriles are competent templates for unnatural cytosine analogues via the corresponding enaminonitrile (Scheme 3). This sequence

Scheme 3. β-Ketonitriles as a Template for an Unnatural Cytosine[a]



[a] Reagents and conditions: (a) BzNCO, pyridine, CH_2Cl_2, rt; (b) NaOEt, EtOH/PhH, reflux.

validates the utility of β-ketonitriles as templates for 5,6-disubstituted pyrimidines and showcases our previously reported method for pyrimidine annulation.[6] The scope of this method for pyrimidine construction will be expanded upon in future publications.

In conclusion, we have developed the reaction of nitrile anions with esters to provide β-ketonitriles in unprecedented yields. Our procedure employs operationally facile reaction conditions and provides excellent yields even with traditionally difficult substrates. Further studies are underway to examine the scope of these transformations. These studies will be reported in due course.

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Supporting Information Available: Experimental procedures for the preparation of **7** and **8** as well as characterization data and spectra of **6aw**−**6dz**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) β-Ketonitrile **6ay** is exceptionally volatile, which made isolation difficult.