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A Strategy for the Synthesis of Aryl α-Ketoamides Based upon the Acylation of Anions Derived from Cyanomethylamines Followed by Oxidative Cleavage†

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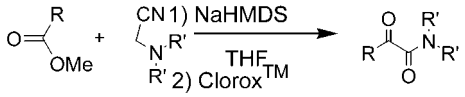
ABSTRACT

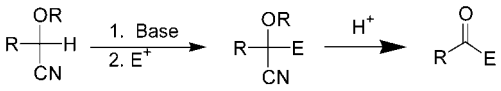


R = pyridine, pyrrole or benzene; R' = Alkyl

Cyanomethylamines, prepared by alkylation of amines with chloroacetonitrile, were deprotonated using NaHDMS in THF, reacted with heteroaryl or substitutedphenyl esters, and then oxidized by adding Clorox™ to afford aryl α-ketoamides in a single operation in good overall yields.

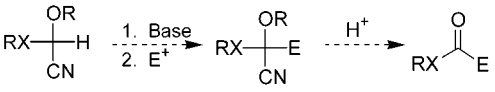
Since the introduction of protected cyanohydrins as umpolung reagents for the elaboration of carbonyl derivatives by Stork in 1971,[1] they have been extensively investigated and widely applied (Scheme 1).[2] However, the inherent reactivity of cyanohydrins limits them to the preparation of aldheydes and ketones **3** in which R = H, alkyl or aryl. To access carbonyl derivatives of a higher oxidation state, an additional oxygen atom or a nitrogen substituent attached to α-position of a cyanohydrin, as depicted in structure **4**, Scheme 2, is required. However, such novel cyanohydrin derivatives are of intrinsically lower stability, either in the native form or as the anion, providing an impediment to simple manipulation or further structural modification. As a consequence, amino-substituted cyanohydrin derivatives have not been utilized to prepare amides directly by the process summarized in Scheme 2.

Scheme 1



1 **2** **3**

Scheme 2



4 **5** **6**

X = O, NR

† Dedicated to Professor Gilbert Stork on the occasion of his 80th birthday.

(1) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *92*, 474.

(2) (a) Seoane, G. *Curr. Org. Chem.* **2000**, *4*, 283. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (c) Johnson, D. V.; Griengl, H. *Chim. Oggi.* **1997**, *15*, 9. (d) Effenberger, F. *Enantiomer* **1996**, *1*, 359.

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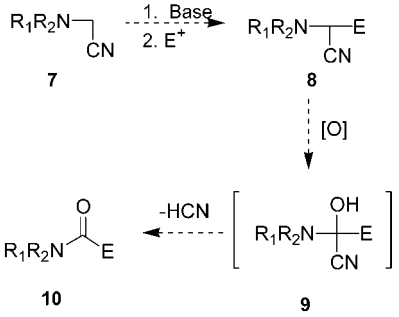
Scheme 3



A conceptually new strategy for the generation and utilization of cyanohydrins is depicted in Scheme 3 and comprises reaction of the anion[3] of a cyanomethylamine (**7**) with an electrophile to afford a substituted cyanomethylamine **8** in situ. Oxidation to the corresponding cyanohydrin accompanied by the spontaneous release of HCN[4] would provide the amide **10**, an α-keto-amide if the electrophile E is an ester.

The targets of initial interest in exploring and developing this strategy were α-keto-amides of the general type depicted in Figure 1, a consequence of their synthetic utility and

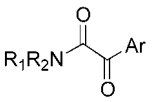


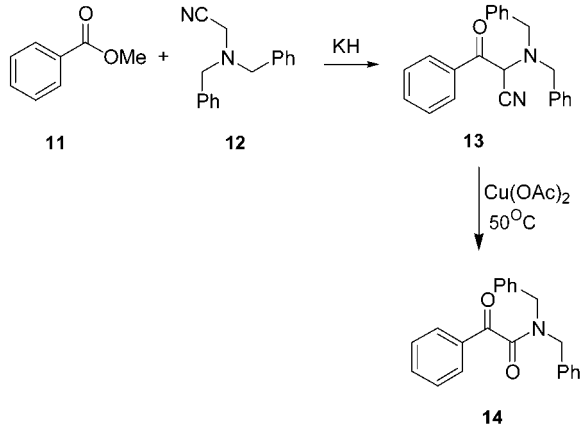
Figure 1.

potential application to drug discovery.[5] α-Keto-amide derivatives have been reported to exhibit a range of biological properties, including antimicrobial[5a] and antipsychotic activity.[5b]

Precedent for this approach was provided in 1983 by Takahashi and co-workers,[6] who showed that phenylated α-keto-amides **14** were formed by reacting benzoic ester **11** and cyanomethylamine **12** using KH as the base, followed by oxidation with Cu(II)$(OAc)_2$, as summarized in Scheme 4. However, the process described by Takahashi requires two individual reaction steps with purification of the intermediate **13**, and the oxidation procedure requires elevated temperatures.

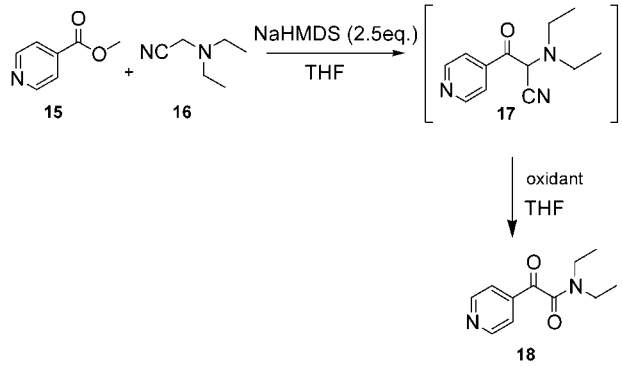
In the course of optimizing this strategy to provide a reaction procedure of broader scope and application, NaH-

Scheme 4



MDS was found to be a suitable and convenient base that offered practical advantage over KH. Treatment of **16** with 2.5 equiv of NaHMDS followed by the addition of ester **15** would be expected to afford a more acidic product that would immediately be deprotonated by the excess NaHMDS. Reaction of the anion generated in this fashion with a variety of common oxidants was examined, as summarized in Table 1. The cheap and simple oxidant sodium hypochlorite

Table 1. Oxidation of Intermediate **17**



oxidation conditions	% yield[a] of **18** after 20 mins (8 h)	% yield[a] of **17** after 20 mins (8 h)
*m*CPBA (1 equiv)	8 (8)	65 (61)
*m*CPBA (1.5 equiv)	22 (28)	50 (43)
*m*CPBA (2 equiv)	26 (35)	26 (25)
oxone (2 equiv, with H_2O)	51 (62)	0 (0)
H_2O_2 (2 equiv, 30% in H_2O)	3 (19)	97 (0)
H_2O_2-urea (2 equiv)	0 (0)	100 (100)
AcOOH (2 equiv, 32% in AcOH)	24 (34)	22 (9)
Clorox (2 equiv, 5.25% NaOCl)	64 (76)	0 (0)

[a] LC-MS yields determined by using 4-*tert*-butylpyridine as an internal standard.

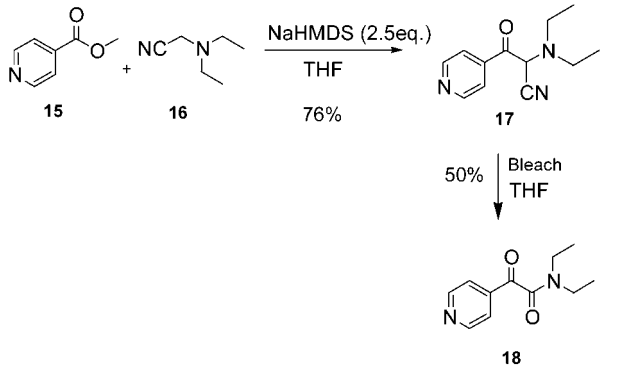
solution (common bleach) proved to be optimal and provided product **18** in 64% yield after a 20 min exposure and in 76% yield after stirring overnight.

(3) (a) Stork, G.; Ozorio, A. A.; Leong, A. Y. W. *Tetrahedron Lett*. **1978**, 5175. (b) Wakamatsu, T.; Kondo, J.; Hobara, S.; Ban, Y. *Heterocycles* **1982**, *19*, 481. (c) Besson, L.; Le Bail, M.; Aitken, D. J.; Husson, H.-P.; Rose-Munch, F.; Rose, E. *Tetrahedron Lett*. **1996**, *37*, 3307. (d) Marco, J. L.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 6345. (e) Amrollah-Madjdabadi, A.; Stella, L. *Bull. Soc. Chim. Fr*. **1987**, 350.

(4) (a) Chuang, T.-H.; Yang, C.-C.: Chang, C.-J.; Fang, J.-M. *Synlett* **1990**, 733. (b) Oriegel, A. E.; Yusta, F.; Brena, L. J. *Synthesis* **1983**, 109. (c) Onda, M.; Harigaya, Y.; Horie, J. *Chem. Pharm. Bull*. **1978**, *26*, 3330. (d) Yang, C. C.; Tai, H. M.; Sun, P. J. *Synlett* **1997**, 812.

A stepwise analysis of the reaction was performed in order to investigate the individual reaction processes, as summarized in Scheme 5. The initial acylation reaction proceeded

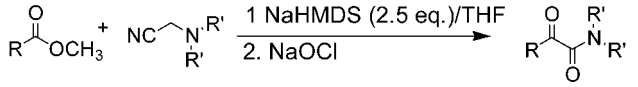
Scheme 5



efficiently, and **17** was isolated in 76% yield. However, oxidation of pure α-cyano ketone **17** delivered compound **18** with an isolated yield of 50%. Apparently the excess base or other reagents present in the one-pot procedure enhanced the yields of the oxidation. The identical figures of the overall yield (76%) of compound **18** in Table 1 and the isolated yield (76%) of intermediate **17** in Scheme 5 implied the oxidation of the anion of compound **17** should be quantitative. Thus, the one-pot process should be the method of choice.

The optimized one-pot process[7] was then utilized in liquid phase to generate a library of 12 heteroaryl α-keto-amide derivatives using an input of four esters and three cyanomethylamines.[8] As shown in Table 2, this procedure afforded products in good overall yields, as determined by LC-MS. Confirmation of the LC-MS yields was obtained for one product from each ester series by standard purification and isolation methods. A good result from compound **12e-1** further confirmed this method could be applied to hydrocarbon aromatics as well.

Table 2. One-Pot Preparation of Aryl α-Ketoamide from Aryl Esters and Aminoacetonitriles



19 **20** **21**

product	R	R	% yield
21a-1	2-pyridine	Et	73[a], 79[b]
21a-2	2-pyridine	*n*-Pr	67[b]
21a-3	2-pyridine	$-(CH_2)_6-$	61[b]
21b-1	3-pyridine	Et	61[a], 81[b]
21b-2	3-pyridine	*n*-Pr	57[b]
21b-3	3-pyridine	$-(CH_2)_6-$	81[b]
21c-1	4-pyridine	Et	71[a], 76[b]
21c-2	4-pyridine	*n*-Pr	72[b]
21c-3	4-pyridine	$-(CH_2)_6-$	92[b]
21d-1	*N*-Me-2-pyrrole	Et	59[a], 67[b]
21d-2	*N*-Me-2-pyrrole	*n*-Pr	59[b]
21d-3	*N*-Me-2-pyrrole	$-(CH_2)_6-$	40[b]
21e-1	4-*t*-Bu-benzene	Et	66[a]

[a] Isolated yields. [b] LC-MS yields calculated by using 4-*tert*-butylpyridine or 1-methylpyrrole.

In summary, a general method has been devised for the construction of heteroaryl or phenyl α-keto-amides that proceeds with high efficiency in a procedurally simple operation. The success of this process broadens the synthetic utility of cyanohydrins and further application of this methodology as a general amide synthon is under active investigation.

Acknowledgment. The authors are very grateful to Ms. Marie D'Andrea for assistance in obtaining exact MS spectra.

Supporting Information Available: ^1H and ^{13}C spectra and HRMS or MS data of compounds **17**, **21a-1**, **21b-1**, **21c-1**, **21d-1**, **and 21e-1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Takahashi, K.; Shibasaki, K.; Ogura, K.; Iida, H. *Chem. Lett.* **1983**, 859.

(7) **General Procedure for the Preparation of Oxoacetyl Amides.** NaHMDS (20 mL, 1.0 M in THF, 20 mmol) was added into a solution of 2-(diethylamino)acetonitrile (1 mL, 7.7 mmol) and methyl isonicotinate (1 mL, 7.3 mmol) in dry THF (100 mL). After 10 h of stirring at room temperature, Clorox (22 mL) was added, and the mixture was stirred a further 30 min at room temperature. The reaction mixture was quenched with saturated Na_2SO_3 solution, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layer was dried over $MgSO_4$. Concentration in vacuo afforded a residue that was purified by silica gel chromatography to provide *N*,*N*-diethyl 2-oxo-(4-pyridyl)-acetamide (1.07 g, 71%).

(8) The library was achieved in 100 mg scale for each reaction.