Base-Catalyzed Autoxidation of α-Aminonitriles. An Efficient Method for Conversion of Aldehydes to Amides and 2-Amino-2-sulfenylacetonitrile to Carbamates

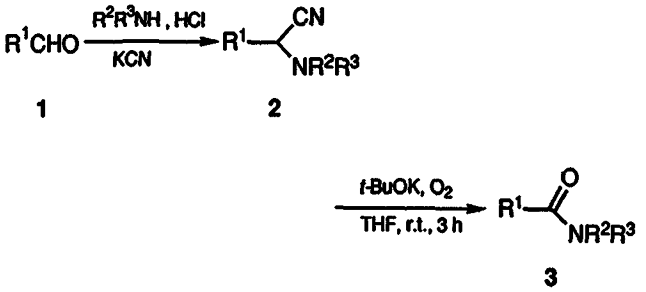
Tsung-Hsun Chuang, Chau-Chen Yang, Chih-Jung Chang, Jim-Min Fang*

Department of Chemistry, National Taiwan University, Taipei, 10764, Taiwan, Republic of China

Received 15 October 1990

Abstract: The α-aminonitriles **2**, prepared from aromatic, aliphatic, and α,β-unsaturated aldehydes, undergo autoxidation in the presence of potassium *tert*-butoxide to give the corresponding amides **3** in high yield. The α-sulfenyl-α-aminonitrile **4** (methylphenylamino(phenylthio)acetonitrile) is converted to the alkyl *N*-methyl-*N*-phenylcarbamates **6** by concurrent autoxidation and substitution with alkoxide ions.

α-Aminonitriles are very useful synthons. They are readily hydrolyzed by base or mineral acid to give α-amino acids and carbonyl compounds.[1] The cyano group of α-aminonitriles is removed by reduction with Na, $NaBH_4$ or $LiAlH_4$.[2] The cyano group is replaced by alkyl groups on treatment with Grignard reagent or allylzinc bromide to give products of amines.[2] Although these isohypsic and reductive methods are extensively studied, the oxidative process for conversion of α-aminonitriles to carboxylic amides is rarely explored. A report by Stella has mentioned the facile autoxidation of 2-amino benzyl cyanide in a base medium to produce the corresponding benzamide.[3] It is considered the α-aminonitrile is easily deprotonated to give a reactive anion, which readily loses a single electron leading to a captodative radical accessible to oxidation by the air.[3] We thus use this approach to prepare various amides (**3**) and carbamates (**6**) from aldehydes (**1**) and 2-amino-2-sulfenylacetonitrile (**4**).

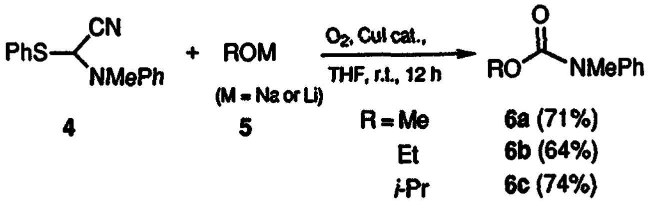


(Eq. 1)

As shown in Table 1, aromatic, aliphatic and α,β-unsaturated aldehydes are condensed with KCN and amines (the Strecker reaction) to give high yields of α-aminonitriles **2**.[4] Various amines including aniline, *N*-methylaniline, morpholine, *l*-ephederine and its methyl ether are used, and they do not interfere with the subsequent base-catalyzed autoxidation. A typical procedure is described as following. To a solution of *t*-BuOK (1 mmol) in anhydrous THF (5 mL), cooled to -78 °C, was added dropwise a THF solution (2 mL) of the aminonitrile **2** (1 mmol). After 10 min, a stream of oxygen was bubbled into the solution. The cooling bath was removed and the mixture was kept stirring for additional hours at room temperature. The reaction was quenched by addition of aqueous KI, the mixture was concentrated and taken up with EtOAc. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated to give the carboxylic amide **3**.

Table 1. Conversion of aldehydes **1** to amides **3** via aminonitriles **2**.

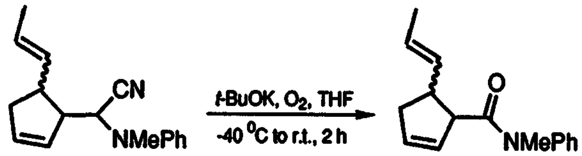
R^1CHO R^1 =	R^2R^3NH R^2, R^3 =	Aminonitrile (yield, %)	Amide (yield, %)
Ph	H, Ph	**2a** (95)	**3a** (80)
Ph	Me, Ph	**2b** (91)	**3b** (90)
Ph	$(CH_2)_2O(CH_2)_2$	**2c** (89)	**3c** (91)
Ph	Me, CHMeCH(OMe)Ph	**2d** (92)	**3d** (97)
Et	Me, Ph	**2e** (78)	**3e** (89)
n-Pr	Me, Ph	**2f** (71)	**3f** (93)
i-Pr	Me, Ph	**2g** (90)	**3g** (92)
PhCH=CH	$(CH_2)_2O(CH_2)_2$	**2h** (81)	**3h** (75)
PhCH=CH	Me, CHMeCH(OH)Ph	**2i** (81)	**3i** (82)



(Eq. 2)

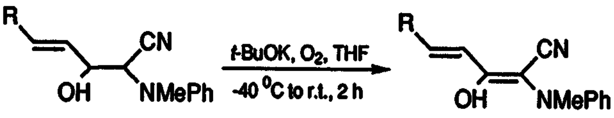
We found the crude aminonitriles **2**, obtained from the Strecker reaction of aldehydes, are transformed to the amides equally efficiently by the above method. Thus, a broad range of carboxylic amides are prepared from aldehydes in high overall yields without purification of the intermediate α-aminonitriles. Gilman has reported a method to prepare amides by oxidizing aldehydes with MnO_2 in the presence of sodium cyanide and an amine.[5] This oxidation process is limited to aromatic or α,β-unsaturated aldehydes, but useless for aliphatic aldehydes. Cheung has demonstrated the oxidation of butyraldehyde with *N*-bromosuccimide to yield an acid bromide, which is trapped with benzylamine to form an amide.[6] This method fails to effect clean oxidation when the substrate contains olefinic double bonds. The preformed bisulfite adducts of aromatic aldehydes are also transformed into amides by oxidation with $DMSO/Ac_2O$ and subsequent quenching with amines.[7] Boche *et al.* have shown the *O*-(trimethylsilyl)aldehyde cyanohydrin undergoes electophilic amination with *N,N*-dimethyl-*O*-(diphenylphosphinyl)hydroxy amine.[8] The carboxylic amides may be obtained by subsequent hydrolysis, but they are confined to have the NMe_2 moiety.

To further illustrate the superiority of the present method, the α-sulphenyl α-aminonitrile **4** is elaborated to the carbamates **6a-d** by alkoxide ions under an oxygen atmosphere (Eq. 2).[9] The mechanism for the autoxidation of **2** and **4** is not clearly determined, although the reaction may be counted on the substitution of the α-proton with an epoxy anion as a postulated intermediate.[10] The α-aminonitrile **7** of a more delicate system[9] is also successfully oxidized to the amide **8** in the base medium (Eq. 3). However, α-aminonitriles **9** and **11** yield to the dienenitriles **10** and **12** under similar conditions of the autoxidation (Eq. 4 and 5).[9]



7 **8** (78%)

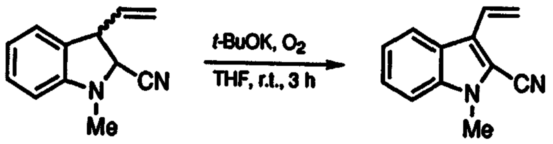
(Eq. 3)



9a R = Me **10a** (60%)

9b R = Ph **10b** (62%)

(Eq. 4)



11 **12** (82%)

(Eq. 5)

Acknowledgment. We thank the National Science Council for financial support.

References and Notes

(1) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.

(2) Bunnelle, W. H.; Shevlin, C. G. *Tetrahedron Lett.* **1989**, *30*, 4203 and the references cited therein.
Fang, J. M.; Chang, H. T. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1945 and the references cited therein.

(3) Stella, L. unpublished results, see also Viehe, H. G.; Janousek, Z.; Merenyi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.

(4) Fang, J. M.; Yang, C. C.; Wang, Y. W. *J. Org. Chem.* **1989**, *54*, 481.

(5) Gilman, N. W. *J. Chem. Soc. Chem. Commun.* **1971**, 733.

(6) Cheung, Y. F. *Tetrahedron Lett.* **1979**, 3809.

(7) Wuts, P. G. M.; Bergh, C. L. *Tetrahedron Lett.* **1986**, *27*, 3995.

(8) Boche, G.; Bosold, F.; Nießner, M. *Tetrahedron Lett.* **1982**, *23*, 3255.

(9) Compound **4** is prepared by treating the anion of 2-*N*-methylanilino acetonitrile with diphenyl disulfide. Compound **7** is prepared by an intramolecular free radical cyclization of the corresponding alkenenitrile containing a 3-bromoallyl substituent at the C-4 position, see also Fang, J. M.; Chang, H. T.; Lin, C. C. *J. Chem. Soc. Chem. Commun.* **1988**, 1385. Compound **11** is prepared by the photochemical cyclization of 2-*N*-methylanilino-2,4-pentadienenitrile, see also Schultz, A. G.; Sha, C. K. *Tetrahedron* **1980**, *36*, 1757.

(10) Aurich, H. G. *Tetrahedron Lett.* **1964**, 657.
Rabjohn, N.; Harbert, C. A. *J. Org. Chem.* **1970**, *35*, 3240.