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A New Method for the Synthesis of Nitriles from Amides Under Non-Acidic Conditions

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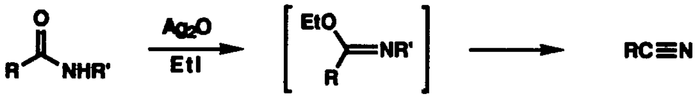
Abstract: Aryl carboxamides and other electron rich amides were converted to the respective nitriles in good yields by treatment with Ag_2O and C_2H_5I in benzene at reflux.

Although many methods have been described for the conversion of amides to nitriles,[1] most require the use of highly reactive reagents or harsh conditions in acidic media which precludes their application to acid-sensitive compounds. Several published procedures are potentially compatible with the use of carboxamides containing acid-sensitive functional groups;[2-4] however, some of these have limitations, such as the need for isolation of an unstable intermediate and subsequent treatment with strong base,[2] or tedious work up procedures.[3] Presently, we describe a simple one step procedure for the conversion of electron-rich amides to nitriles under non-acidic conditions. As shown in Scheme 1, this involves the treatment of the carboxamide with silver oxide and ethyl iodide in benzene at reflux.

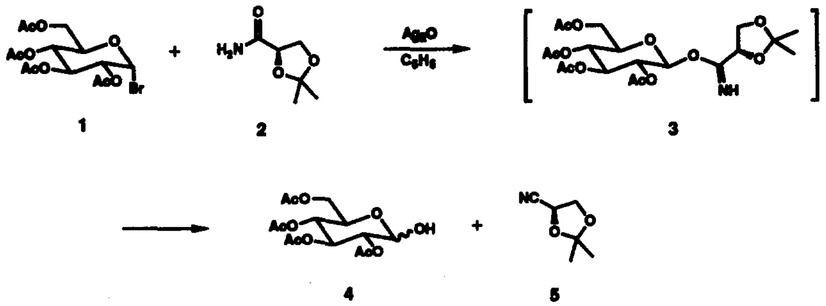
Scheme 1



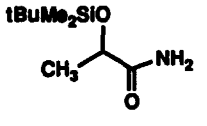
It is well known that alkyl halides react with amides in the presence of Ag_2O to form *O*-alkyl imidates (Scheme 1);[5] Sinaÿ and coworkers extended this finding for the preparation of *O*-glycosyl imidates by admixture of glycosyl halides and simple N-alkylamides.[6] In comparison, when we used unsubstituted amide 2 and bromosugar 1 we obtained a 1:1 mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose

(4) and nitrile 5 (Scheme 2), presumably via the (unstable) intermediate *O*-glycosyl imidate 3. Because 5 was formed cleanly and in good yield, we sought to exploit the observation to develop a new procedure for the conversion of carboxamides to nitriles.

Scheme 2



Accordingly, carboxamide 2 was treated with a number of alkyl iodides under a variety of conditions. The products, which varied in relative amounts according to the specific reaction conditions, included the *O*-alkyl imidate, *N*-alkylamide, *N*,*N*-dialkylamide, and the desired nitrile 5. The nitrile was produced optimally (>90% of all isolable products) in the presence of Ag_2O[7] and ethyl iodide (1.1 eq) in benzene at reflux. That the *O*-ethyl imidate was an intermediate leading to nitrile 5 (cf Scheme 1) may be appreciated from its formation as the only detectable product when the foregoing alkylation was run using the same reagents that produced 5 optimally, but at 25 °C rather than at reflux.[8] The optimal conditions determined for the conversion 2→5 were used to effect the conversions of several other carboxamides to the respective nitriles on a preparative scale (Table I).



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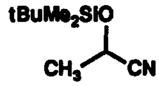

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As shown in the Table, the desired nitriles were obtained in good yields. Comparison with previous reports indicated the yields to be comparable or higher than those accessible by other methods. Aside from the straightforward work-up

Table I. Conversion of Amides to Nitriles in the Presence of Ag_2O + EtI[a].

Starting Amide	Product	Isolated Yield (%)
$C_6H_5CONH_2$	C_6H_5CN[b]	82
p-$MeC_6H_4CONH_2$	p-MeC_6H_4CN[b]	70
p-$EtOC_6H_4CONH_2$	p-$EtOC_6H_4CN$[b]	81
p-$FC_6H_4CONH_2$	p-FC_6H_4CN[b]	73
p-$ClC_6H_4CONH_2$	p-ClC_6H_4CN[b]	77
p-$BrC_6H_4CONH_2$	p-BrC_6H_4CN[b]	80
p-$NO_2C_6H_4CONH_2$	p-$NO_2C_6H_4CN$[b]	83
trans-$C_6H_5CH{=}CHCONH_2$	*trans*-$C_6H_5CH{=}CHCN$[b]	89
2[b]	**5**[c]	50
6[c]	**7**[c]	93

[a] In a typical experiment, a solution of the amide (5 mmol), silver oxide (1.8 g, 7.7 mmol) and powdered 4 Å molecular sieves (5.0 g) in dry benzene (50 ml) was stirred in the dark at 25 °C for 12 h. Ethyl iodide (0.86 g, 0.44 ml, 5.5 mmol) was then added to the solution, which was subsequently heated at reflux under argon for 17 h. The cooled solution was filtered (Celite); the filtrate was concentrated under diminished pressure. Purification was accomplished by chromatography on silica gel; elution was carried out with hexane and ethyl acetate in varying proportions. [b] Structural characterization included comparison of physical constants with those of previously described authentic samples. [c] Compounds **5**, **6** and **7** were characterized by ^{1}H-NMR and mass spectrometry.

procedure, the present method may be of substantial advantage when using acid-sensitive carboxamides, such as the last two entries in the Table. When the conversion **2** → **5** was attempted using the method of McElvain and Clarke,[3] nitrile **5** was obtained in only 38% yield.

The procedure exemplified in Table I works well only for electron-rich carboxamides. Simple aliphatic amides either gave complex mixtures, or failed to react altogether. This may reflect a lack of facility of Ag_2O-promoted *O*-alkylation of simple carboxamides,[10] the greater thermal stability of the derived *O*-alkyl imidates,[5] or both.

References

1. Larock, R.C. "Comprehensive Organic Transformations, A Guide to Functional Group Preparations"; VCH Publishers, Inc.: New York, **1989**.
2. Borch, R.F. *Tetrahedron Lett.* **1968**, 61.
3. McElvain, S.M.; Clarke, R.L. *J. Am. Chem. Soc.* **1947**, *69*, 2657.
4. (a) Liberek, B.; Baczel, Cz.; Grzonka, Z. *Tetrahedron Lett.* **1966**, *22*, 2303. (b) Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1984**, *32*, 2560. (c) Rigo, B.; Lespagnol, C.; Pauly, M. *J. Heterocycl. Chem.* **1986**, *23*, 183. (d) Claremon, D.A.; Phillips, B.T. *Tetrahedron Lett.* **1988**, *29*, 2155.
5. (a)Roger, R.; Neilson, D.G. *Chem. Rev.* **1961**, *61*, 179, and references therein. (b) Challis, B.C.; Challis, J.A. in "The Chemistry of Amides"; Zubicky, J., Ed.; Interscience Publishers: **1970**, p. 752 and references therein. (c) Neilson, D.G. in "The Chemistry of Amidines and Imidates"; Patai, S., Ed.; J. Wiley and Sons: London **1975**, p. 385-489.
6. (a) Pougny, J.-R.; Sinaÿ, P. *Tetrahedron Lett.* **1976**, 4073. (b) Jacquinet, J.C.; Sinaÿ, P. *Tetrahedron* **1979**, *35*, 365. (c) Milat, M.-L.; Zollo, P.A.; Sinaÿ, P. *Carbohyd. Res.* **1982**, *100*, 263.
7. Only *N*-alkylated products were obtained in the absence of Ag_2O, as anticipated.[5]
8. The *O*-alkyl imidates were also detected as reaction intermediates by ^{1}H-NMR. Lander and Jewson[9] have shown previously that *O*-alkyl imidates decompose thermally to afford nitriles and alcohols.
9. Lander, G.D.; Jewson, F.T. *J. Chem. Soc.* **1903**, *83*, 766.
10. In fact, few examples appear in the literature; *O*-alkyl imidates of simple caroxamides are prepared by a different route.[5]

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