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# TrocCl MEDIATED EFFICIENT SYNTHESIS OF NITRILES FROM PRIMARY AMIDES

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**Abstract:** In order to establish a rapid conversion method of primary amides to nitriles, various types of carboxamides were treated with 2,2,2-trichloroethyl chloroformate and $Et_3N$, as a dehydrating agent to obtain the desired nitriles in 82-95% yields.



The conversion of primary alkyl or aryl amides to their corresponding nitriles is an important functional group transformation in organic synthesis[1]. Recently, it demonstrated that nitriles could be converted to thiazole derivatives as inhibitors of superoxide[2], or as a starting material for synthesizing triazolo[1,5-c]pyrimidines with potential antiasthma activity[3]. A variety of reagent systems for this reaction have been documented in the literature[4]. Recently, alkylating and dehydrating methods have been introduced, permitting the reaction to proceed under mild[5], neutral conditions[6] and at lower

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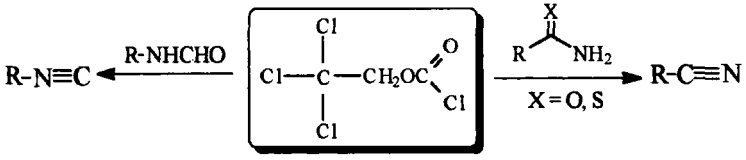
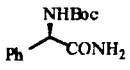
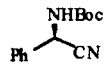
temperature[7]. Unfortunately, the reagents employed so far require special preparation, and the methods limited to only arylamides. Consequently, there is a need for the development of protocols using readily available and safer reagents which lead to high production of nitrile compounds. After surveying new reagent systems, we found that the use of 2,2,2-trichloroethyl chloroformate (TrocCl) was highly favourable for our purpose. The reaction proceeds efficiently in high yields at room temperature within a few minutes. Herein, we wish to report a new and efficient reagent for the transformation of primary amides to nitriles.

**Scheme 1**




It is well-known in the literature that TrocCl has been used for the protection of hydroxyl groups as their trichloroethyl carbonates and amines as their Troc carbamates[8]. To the best of our knowledge, however, the generality and applicability of TrocCl in the preparation of nitriles from primary amides is not known. The synthetic utility of this reagent for functional group conversion is shown in Scheme 1 and several experimental results are illustrated in Table 1. Primary aliphatic and aromatic carboxamides bearing various functional groups were cleanly converted into the corresponding nitriles.

**Table 1 : Conversion of primary amides to nitriles with TrocCl/$Et_3NH$**

| Entry | Carboxamide | Product[a] | Yield(%)[b] | mp ($^0$C)[10] | |
|---|---|---|---|---|---|
| | | | | found | reported |
| 1 | 2,4-Dichloro benzamide | 2,4-Dichlorobenzonitrile | 87 | 57-59 | 58-60 |
| 2 | 2,4-$(CH_3O)_2C_6H_3CONH_2$ | 2,4-$(CH_3O)_2C_6H_3CN$ | 93 | 91-93 | 93-94 |
| 3 | *trans*-$C_6H_5CH$=$CHCONH_2$ | *trans*-$C_6H_5CH$=$CHCN$ | 91 | - | - |
| 4 | Salicylamide | 2-Cyanophenol | 86 | 93-95 | 92-95 |
| 5 | $C_6H_5CH_2CONH_2$ | $C_6H_5CH_2CN$ | 84 | - | - |
| 6 |  |  | 75 | - | - |
| 7 | Nicotinamide | 3-Cyanopyridine | 95 | 50-52 | 50-51 |
| 8 | TBSO-$(CH2)_4CONH_2$ | TBSO-$(CH2)_4CN$ | 82 | - | - |
| 9 | 2-Ethylthioisonicotinamide | 2-Ethyl-4-cyanopyridine | 92 | - | - |
| 10 | *p*-$ClC_6H_4CSNH_2$ | *p*-$ClC_6H_4CN$ | 85 | 89-91 | 91-93 |
| 11 | 3,4,5-$(CH_3O)_3C_6H_2NHCHO$ | 3,4,5-$(CH_3O)_3C_6H_2NC$ | 83 | - | - |
| 12 | 2-Naphthalene carboxamide | 2-Cyanonaphthalene | 90 | 64-65 | 64-66 |

[a] All Products were characterized by comparison of their IR and $^1$HNMR spectra with those of authentic samples. [b]yields of pure isolated products.

Neither racemization of the α-bearing carbon[9] nor β-elimination of the nitrile groups were observed. Furthermore, the reagent was successfully utilized for the preparation of nitriles and isonitriles from thioamides and formamides respectively.

In conclusion, the short reaction period, the simple work-up, the good yield, and the mild conditions demonstrate the usefulness and the versatality of this synthetic method.

***General Procedure***: TrocCl (2.2mmol) was added dropwise to a stirred ice-cooled solution (or suspension) of the amide/formamide (2.0mmol) in dry $CH_2Cl_2$ (10ml) and dry $Et_3N$ (4.4mol). The reaction mixture was allowed to room temperature for the period of 30-60 min (monitored by TLC) and it was quenched with water (2ml). The reaction mixture was extracted with $CH_2Cl_2$ (2x15ml). The combined organic phases were washed with sat.brine, dried ($Na_2SO_4$), filtered and the solvent was removed *in vacuo* to afford the crude product which was purified by column chromatography (EtOAc/hexane, 1:9 v/v) on silica gel to afford pure nitriles/isonitrile in 75-95% yields (Table).

**Selected spectral data: 2,4-Dimethoxybenzonitrile** (entry 2)**:** IR (KBr); 2240, 1600, 1260, 830 $cm^{-1}$. $^1$HNMR (200MHz, $CDCl_3$): δ 7.42 (d, 1H), 6.52-6.39 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H). Mass (m/z): 163 ($M^+$), 138, 103, 31. **2-Ethyl-4-cyanopyridine** (entry 9)**:** IR (neat); 3050-2830, 2230, 1600, 1550, 1490, 1400 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 8.65 (d, 1H), 7.31-7.29 (m, 2H), 2.95-2.79 (q, 2H), 1.35-1.27 (t, 3H). Mass (m/z): 132 ($M^+$). **3,4,5-Trimethoxyphenylisonitrile** (entry 11)**:** IR (neat); 2160, 1600, 1250, $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 6.61 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.83(s, 3H). Mass (m/z): 193 ($M^+$), 168, 103, 31.

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9. The optical rotation of the nitrile in entry (2*S*)-**6** indicated that no racemisation occurs during the transformation process; this was confirmed by comparison with the amine hydrochloride. $[\alpha]_D$ +28.5 (*c* 1.0, $H_2O$), lit. $[\alpha]_D$ +33.0 (*c* 1.001, $H_2O$). Effenberger, F.; Kremser, A.;

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