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Aryl chlorothionoformate : A new versatile reagent for the preparation of Nitriles and Isonitriles under mild conditions

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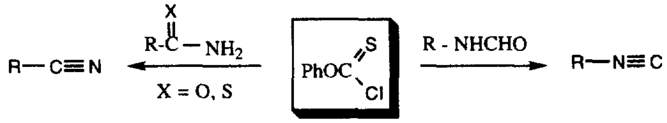
Abstract:
Aryl chlorothionoformate is a very useful reagent for the preparation of nitriles and isonitriles in high yields under essentially neutral conditions.

Keywords: Phenyl chlorothionoformate, thioamides, nitriles, isonitriles.

Developing efficient and mild protocols for functional group transformations is an important process in synthetic organic chemistry. In view of their potential utility in organic synthesis [1], several methods for preparation of nitriles by dehydration of carboxamides using phosphorous pentoxide [2], thionyl chloride [3], triphenylphosphine [4], boron trifluoride [5] and phase-transfer catalysis [6] have been documented in the literature. More recently, dehydrating and alkylating reagents have been disclosed, permitting the reaction to proceed under neutral [7], mild conditions [8] and at lower temperature [9] or in liquid triphasic systems [10]. Unfortunately, these methods have limitations, such as being limited to arylamides and that the reagents employed require special preparation or tedious work up procedures. In order to circumvent some of the problems highlighted above, a mild and efficient method is still warranted for the generation of nitriles from primary amides.

Scheme 1



Literature reports have demonstrated that aryl chlorothionoformate is widely used for the tri-n-butyltin hydride mediated deoxygenation of alcohols *via* thionocarbonates [11]. To date, however, its generality and use for the preparation of nitriles is not known, to the best of our knowledge. Herein, we wish to report a new and practically useful method for the preparation of nitriles from primary amides using aryl chlorothionoformate and pyridine in CH_2Cl_2 at room temperature. The synthetic utility of aryl chlorothionoformate for

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functional group conversions is shown in scheme 1 and several experimental results are summarized in Table 1[†]. Primary aliphatic and aromatic carboxamides bearing various functional groups were cleanly converted into the corresponding nitriles in high yields. Furthermore, the reagent was successfully utilized for the preparation of nitriles and isonitriles from thioamides and formamides respectively.

Table 1 conversion of primary amides to nitriles with aryl chlorothionoformate

Entry	Substrate	Time,h	Product[a]	yield (%)[b]
1	2,4-$(CH_3O)_2C_6H_3CONH_2$	5.0	2,4-$(CH_3O)_2C_6H_3CN$	91
2	2-$O_2NC_6H_4CONH_2$	7.0	2-$O_2NC_6H_4CN$	87
3	*trans*-$C_6H_5CH{=}CHCONH_2$	6.0	*trans*-$C_6H_5CH{=}CHCN$	80
4	$C_6H_5CH_2CONH_2$	9.0	$C_6H_5CH_2CN$	84
5	2-Naphthalenecarboxamide	6.5	2-Cyanonaphthalene	88
6	Nicotinamide	6.0	3-Cyanopyridine	92
7	TBSO-$(CH_2)_4$-$CONH_2$	8.5	TBSO-$(CH_2)_4$-CN	81
8	AcO-$(CH_2)_4$-$CONH_2$	8.0	AcO-$(CH_2)_4$-CN	83
9	2-Ethylthioisonicotinamide	5.0	2-Ethyl-4-cyanopyridine	95
10	4-$CH_3C_6H_4CSNH_2$	6.0	4-$CH_3C_6H_4CN$	90
11	$C_6H_5CH_2NHCHO$	10.0	$C_6H_5CH_2NC$	82
12	3,4,5-$(CH_3O)_3C_6H_2NHCHO$	7.5	3,4,5-$(CH_3O)_3C_6H_2NC$	85

[a] All products were characterized by comparison of their m.p, IR and ^1H NMR spectra with those of the authentic samples.
[b] Unoptimized yields of pure isolated products.

In conclusion, the good yield, simple work-up and the fairly neutral conditions of this method offers an alternative to the well documented dehydration of carboxamides.

Footnotes : [†] General procedure: Aryl chlorothionoformate (1.1 mmol) was added dropwise to a stirred ice-cooled solution (or suspension) of the amide (1.0 mmol) in dry CH_2Cl_2 (5 ml) and anhydrous pyridine (2.0 mmol) at such a rate that the temperature was kept below 5°C. The reaction mixture was then allowed to warm to room temperature for specified time (Table) and it was quenched with water (2 ml). The reaction mixture was extracted with CH_2Cl_2 (2 x 15 ml). The combined organic phases were washed with sat. brine, dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford the crude product which was purified by column chromatography on silica gel. Pure nitriles were obtained in 80-95% yields (Table).

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