

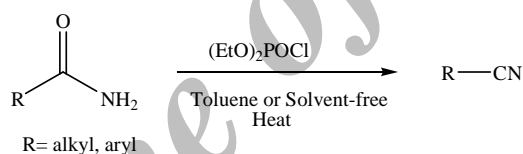
Diethyl Chlorophosphate: A New Alternative Reagent for Dehydration of Primary Amides to Nitriles in Solvent and Solvent-Free Conditions

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An efficient method for synthesis of nitriles has been developed using diethyl chlorophosphate in solvent and solvent-free conditions. Primary alkyl and aryl amides, efficiently are converted to the corresponding nitriles by heating in the presence of diethyl chlorophosphate in excellent yields. This method works under mild conditions with shorter reaction times.



Keywords: Primary amides, Dehydration, Diethyl chlorophosphate, Nitriles, Solvent-free

INTRODUCTION

The importance of nitriles as intermediates in organic synthesis is well established. The discovery of nitriles which are reversible inhibitors of thiol protease enzymes [1] has attracted our attention to developing a general and mild method for their preparation. The synthesis of nitriles from their corresponding alkyl or aryl amides is an important functional group transformation in organic synthesis [2]. Conversion of primary amides to nitriles in the presence of phosphorus pentoxide [3], titanium tetrachloride [4], thionyl chloride [5], trifluoroacetic anhydride/pyridine [6] and triphenylphosphine/carbontetrachloride [7], has been documented in the literature. Alternative reaction conditions and dehydrating reagents affording higher yields, such as diphosgene [8], (methoxycarbonylsulfamoyl) triethylammonium hydroxide (Burgess reagent) [9], ethyl iodide/

silver oxide [10], acetic anhydride/pyridine [11], refluxing acetonitrile with formic acid [12], $(\text{COCl})_2$ -DMSO/ Et_3N [13], organotin oxides [14], $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}/\text{KI}/\text{H}_2\text{O}/\text{CH}_3\text{CN}$ [15], pivaloyl chloride/pyridine [16], PdCl_2 [17], $\text{Ph}_3\text{P}/\text{I}_2$ [18], dichlorophosphate/DBU [19] and $\text{TTPX}_2/\text{Et}_3\text{N}$ [20] have been reported.

Accordingly, we report herein a simple new method for effecting this transformation by using diethyl chlorophosphate in solvent and solvent-free conditions, in which the molar ratio of diethyl chlorophosphate and primary amide is 1:1. The method is simple and applicable to both alkyl and aryl amides, isolation of the product from reaction mixtures is easy and the yields are high.

EXPERIMENTAL

Chemicals

All starting materials were used as purchased from Fluka or Merck and progress of the reactions was monitored by TLC on silica gel PolyGram SILG/UV 254 plates.

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General Procedure for the Reaction in Solvent (Method A)

For each reaction, the amide (1 mmol) and toluene (1 ml) was charged into a 5 ml double-necked round-bottom flask equipped with a magnetic stirrer and condenser. The mixture was heated to reflux and diethyl chlorophosphate (1 mmol) was added. The reaction was heated for 5-20 min and then the reaction mixture was cooled to room temperature. The crude mixture was neutralized by 10 ml aqueous solution of sodium hydroxide (5%) and was extracted by diethyl ether (2×10 ml). Drying the combined ethereal layer by anhydrous sodium sulphate and then filtration and evaporation of the solvent gave the crude product, which was purified by short column of silica gel with *n*-hexane and ethyl acetate (9:1-1:1) to give the pure product.

General Procedure for the Solvent-Free Condition (Method B)

For each reaction, the amide (1 mmol) was charged into a 5 ml double-necked round-bottom flask equipped with a magnetic stirrer and condenser. Then the mixture was heated at 120 °C and diethyl chlorophosphate (1 mmol) was added. The reaction was heated for 5-25 min and then the reaction mixture was cooled to room temperature. The mixture was extracted by diethyl ether (2×10 ml). The combined ethereal layer was allowed to dry by anhydrous sodium sulphate and then filtration and evaporation of the solvent gave the crude product, which was purified by short column of silica gel with *n*-hexane and ethyl acetate (9:1-1:1) to give the pure product.

RESULTS AND DISCUSSION

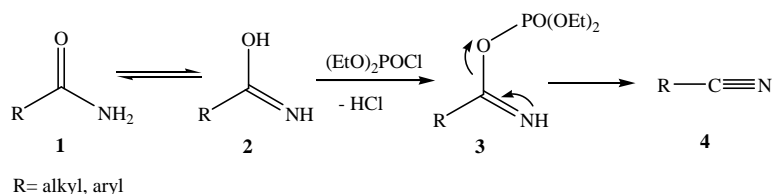
Dehydration of a series of aryl and alkyl amides to the

corresponding nitriles was conducted in toluene as solvent and in solvent-free conditions (Scheme 1).

According to the mechanism proposed in Scheme 1, primary amide (1) is in equilibrium with imidic acid (2) which could react with diethyl chlorophosphate to form the corresponding diethyl phosphate (3). Then the intermediate releases diethyl hydrogen phosphoric acid to produce nitriles subsequently. As it is shown in Table 1, good to excellent yields were obtained over dehydration of amides to nitriles in toluene as solvent (method A); however, the yields of alkyl amides were lower than those of aryl amides. All the nitriles were separated from the reaction mixture by neutralization of the produced acid, $(\text{EtO})_2\text{PO}(\text{OH})$, with aqueous solution of sodium hydroxide (5%) followed by extraction with ether. Evaporation of ether and column chromatography produced the pure nitriles. The nitriles could also be purified by a short column without neutralization of the produced acid.

Additionally, we studied the effect of solvent-free conditions (method B) on the formation of nitriles from the corresponding primary amides. The results are shown in Table 1. It appears that by omitting the solvent there is a slight improvement in the yields of the reactions; however, there is no noticeable effect on the rate of the reactions.

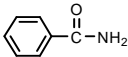

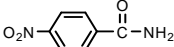
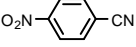
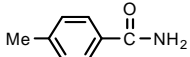

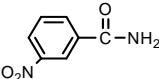
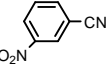
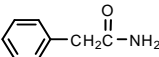
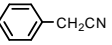
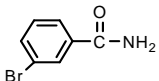
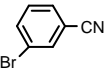
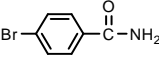

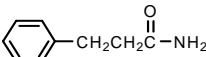
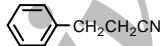
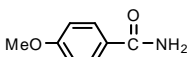

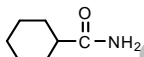

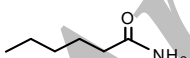
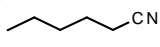
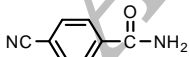

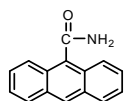
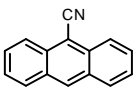
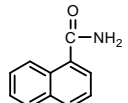
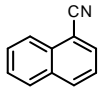
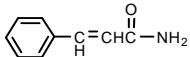
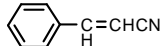
We compared our findings with a recently reported protocol [19], where ethyl dichlorophosphate was used as a dehydrating agent, whose results are shown in Table 2. According to these data, although the yields are comparable, diethyl chlorophosphate has several striking economical and environmental advantages over ethyl dichlorophosphate: a) cheaper reagent, b) less moisture sensitive, c) shorter reaction time, d) no use of toxic solvents such as CH_2Cl_2 , c) using just stoichiometric ratio of amid to dehydrating agent (1:1), and e) no need to use base.



Scheme 1

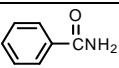
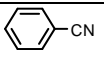
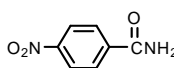
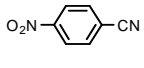
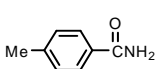
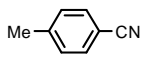
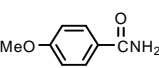
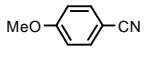
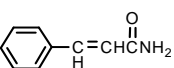
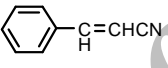
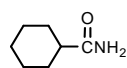
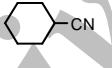
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Table 1. Dehydration of the Primary Amides to the Corresponding Nitriles in the Presence of Diethyl Chlorophosphate in Toluene (Method A) and Solvent Free Conditions (Method B)

Entry	Amide	Nitrile ^a	M.P. (°C) (Lit.) [21]	Yield (%) ^b		Reaction time (min)	
				Method A	Method B	Method A	Method B
1			192 ^c (191)	83	89	20	15
2			147-149 (147)	89	91	15	25
3			29-30 (29.5)	82	90	10	15
4			114-115 (114-17)	83	89	10	15
5			231-2 ^c (234)	86	90	10	10
6			38-9 (39.5)	80	89	10	15
7			112-13 (114)	87	87	10	15
8			260 ^c (261)	91	94	10	10
9			60-61 (61.5)	85	91	5	5
10			183 ^c (184)	72	74	10	10
11			163 ^c (163.5)	70	72	10	10
12			222-223 (224)	83	86	15	15
13			172-173 (177.5)	77	79	10	15
14			37-38 (37.5)	90	93	10	10
15			257 ^c (255)	92	94	10	10

^aAll the products are known. ^bIsolated yield. ^cBoiling point.

Table 2. Comparison Between Efficiency of Diethyl Chlorophosphate and Ethyl Dichlorophosphate in Conversion of Primary Amides to the Corresponding Nitriles

Entry	Amide	Nitrile	Diethyl chlorophosphate			Ethyl dichlorophosphate		
			Yield (%)	Mole ratio ^a	Time (min)	Yield (%)	Mole ratio ^a	Time (min)
1			89	1:1:0	15	98	1:2:3	60
2			91	1:1:0	25	93	1:2:3	120
3			90	1:1:0	15	92	1:2:3	180
4			91	1:1:0	5	94	1:2:3	180
5			94	1:1:0	10	92	1:2:3	180
6			74	1:1:0	10	80	1:2:3	180

^aMole ratio = amid: dehydrating reagent:base.

CONCLUSIONS

We reported herein the conversion of primary alkyl- and aryl amides including electron-donating and electron-withdrawing groups to their corresponding nitriles by diethyl chlorophosphate in both solvent and solvent-free conditions, which has some advantages over the previously reported methods, including: reasonably short reaction times, good to excellent yields, easy and simple work-up, no by-product formation, non-anhydrous reaction condition, non-toxic, commercially accessible reagent and solvent. Finally, the reaction could occur in solvent-free condition without losing yields.

ACKNOWLEDGEMENTS

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REFERENCES

- [1] a) J.B. Moon, R.S. Coleman, R.P. Hanzlik, *J. Am. Chem. Soc.* 108 (1986) 1750; b) S.A. Thompson, P.R. Andrews, R.P. Hanzlik, *J. Med. Chem.* 29 (1986) 104.
- [2] S.R. Sandler, W. Karo, *Nitriles (Cyanides)*, In *Organic Functional Group Preparation*, Vol. 12-I of *Organic Chemistry*, Chap. 17, Academic Press, Inc., San Diego, 1983.
- [3] a) D.B. Reisner, E.C. Coring, *Org. Synth. Coll. IV* (1963) 144; b) J.G. Humber, M.A. Davis, *Can. J. Chem.* 44 (1966) 2113.
- [4] W. Lehnert, *Tetrahedron Lett.* 12 (1971) 1501.
- [5] J.A. Krynitsy, H.W. Carhart, *Org. Synth. Coll. IV* (1963) 436.

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- [6] F. Campagna, A. Carroti, G. Casini, *Tetrahedron Lett.* 18 (1977) 1813.
- [7] E. Yamato, S. Sugasawa, *Tetrahedron Lett.* 11 (1970) 4383.
- [8] K. Mai, G. Patal, *Tetrahedron Lett.* 27 (1986) 2203.
- [9] a) D.A. Claremon, T. Phillips, *Tetrahedron Lett.* 29 (1988) 2155; b) H. Nemoto, Y. Kubota, Y. Yamamoto, *J. Org. Chem.* 55 (1990) 4515.
- [10] M.L. Sznajdman, C. Crasto, S.M. Hecht, *Tetrahedron Lett.* 34 (1993) 1581.
- [11] C.-B. Xue, W.F. Degrado, *Tetrahedron Lett.* 36 (1995) 55.
- [12] M.-P. Heck, A. Wanger, C. Mioskowski, *J. Org. Chem.* 61 (1996) 6486.
- [13] N. Nakajima, M. Ubukata, *Tetrahedron Lett.* 38 (1997) 2099.
- [14] D.S. Bose, B. Jayalakshmi, P.R. Goud, *Synthesis* 10 (1999) 1724.
- [15] M. Boruah, D. Konwar, *J. Org. Chem.* 67 (2002) 7138.
- [16] A.K. Narsaiah, K. Nagaiah, *Adv. Synth. Catal.* 346 (2004) 1271.
- [17] S.I. Maffioli, E. Marzorati, A. Marazzi, *Org. Lett.* 7 (2005) 5237.
- [18] A.V. Narsaiah, D. Sreenu, K. Nagaiah, *Synth. Commun.* 36 (2006) 137.
- [19] C.-W. Kuo, J.-L. Zhu, J.-D. Wu, C.-M. Chu, C.-F. Yao, K.-S. Shia, *Chem. Commun.* (2007) 301.
- [20] D. Vaccari, P. Davoli, M. Bucciarelli, A. Spaggiari, F. Prati, *Lett. Org. Chem.* 4 (2007) 319.
- [21] D.R. Lide (Ed.), *CRC Handbook of Chemistry and Physics*, 87th ed., CRC Press, 2006.