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One-pot synthesis of dehydrating reagent and its application in preparation of nitriles from amides

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ABSTRACT

A new efficient method for preparation of dehydrating reagent was reported. N, N-dimethylformamide (DMF) reacted with oxalyl chloride $[(\text{COCl})_2]$, then the resultant reacted with phenol in the presence of a triethylamine (Et_3N) to give the corresponding product in high yield. The reaction is fast, eco-friendly, operationally simple, and economic; the product's purification is very simple. Meanwhile this compound had been successfully used as efficient dehydrating reagent in application of synthesizing nitriles from amides. © 2012 Trade Science Inc. - INDIA

KEYWORDS

Dehydrating reagent;
DMF;
Phenol;
Eco-friendly;
Nitriles;
Amides.

INTRODUCTION

In view of nitriles' importance as intermediates in organic synthesis, especially widely used in medicine, pesticides, dye, etc. Nitriles can be converted into thiazole derivatives which can be used as inhibitors of superoxide^[1]. Also, nitriles can be converted into losartan and valsartan that have been used as antagonist of angiotensin II^[2]. Many methods for preparation of nitriles have been reported at present^[3,4], especially dehydration reactions such as aldoxime dehydration^[5-7], amide dehydration^[8], etc. At the same time many dehydrating reagents like P-ylide-dimethyl fluorenylidene-tributylphosphoranylidene-succinate^[9], $(\text{COCl})_2$ -DMSO- Et_3N ^[10], phosphorus pent-oxide^[11,12], thionyl chloride^[13], trifluoroacetic anhydride/pyridine^[14] and iron porphyrin systems^[15] have been reported. However, these above dehydrating reagents have the disadvantages of low yields, boundedness, tedious operation, high desire of experiment condition and so on.

Therefore, there still exists a need for the develop-

ment of eco-friendly, high-efficiency, widely-used and mild dehydrating reagent. We report here the dehydrating reagent which provides a practically useful method for this preparation.

RESULTS AND DISCUSSION

This method could apply into aromatic amides which possess different substituent groups such as $-\text{CH}_3$, $-\text{OH}$, $-\text{Cl}$, $-\text{NO}_2$, etc, and the results we can see in the TABLE 1 indicated that the different substituent groups on benzene ring had some effect on reaction rate. The aromatic amide whose benzene ring owned electron-donating group ($-\text{CH}_3$, and $-\text{OH}$) had higher reactivity and faster reaction rate than that whose benzene ring owned electron-drawing group ($-\text{NO}_2$ and $-\text{Cl}$), which was probably due to the electron-donating group could provide the benzene ring more electrons and then activate the benzene ring.

Compound II is a kind of composite organic salt dehydrating agent, which consist of imine cations. While

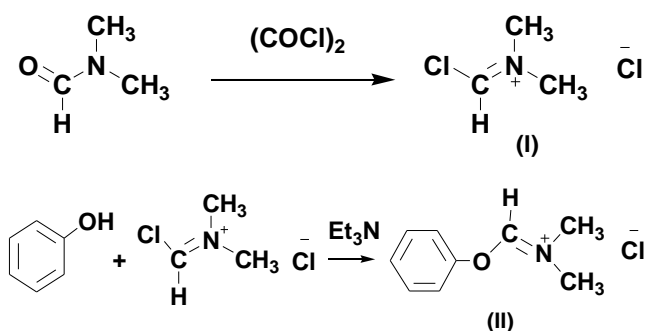
in the process of its synthesis we had try three commonly used chlorinating agents: PCl_5 , POCl_3 , and $(\text{COCl})_2$. Thereinto PCl_5 had a strong ability of chloride, however it could react with tiny amounts of water and generated POCl_3 , and POCl_3 generated inorganic phosphate that was very difficult to remove in the reaction, which influence the purity and yield of target product. What's more important was that PCl_5 and POCl_3 could produce H_3PO_4 . While the effect of using $(\text{COCl})_2$ as chlorinating agent was satisfactory: the byproduct was belong to gas and easy to isolate, and the yield could reach very high. The aim of adding Et_3N was to neutralize HCl generated in the reaction and to catalyze the reaction.

Compound II can be seen that the centre carbon atom has low electron cloud density according to the structure of the dehydrating agent. As a result, it increased the activity of the dehydrating agent, which let it easier to capture the amino group and the adjacent carbon hydrogen of amide. It can be conclude that the mechanism of this reaction was nucleophilic addition – elimination: the centre carbon atom of dehydrating agent captured amino group of the amide, the anion ion captured the adjacent carbon hydrogen, resulting in that the amide dehydrated into corresponding nitrile.

In conclusion, dehydrating reagent compound II presented in this report which has advantages of simple synthetic route and cheap raw materials is believed to be high-yield, easy to post process, and operationally simple for the conversion of amides to nitriles. The analogues of compound II and the dehydration of other functional groups such as aldoxime, carbamate, and some amides with complex structure will be reported in due course.

EXPERIMENTAL

The reaction process was monitored by Thin-Layer Chromatography (TLC) on silica gel GF254 plate using petroleum ether/ethyl acetate (3:1 v/v) as the developing solvent. All the liquid parent materials were freshly distilled and dried. Melting points were determined on a microscopy apparatus (SGW X-4) and uncorrected. The products were characterized by comparison of their melting points and boiling points with the literature values.

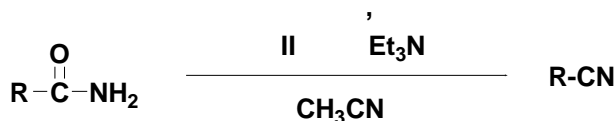


General procedure for the preparation of compound (I)

Dichloromethane (20.0ml) and DMF (1.2ml, 0.015mol) were added into a dry three-necked round bottom flask equipped gas absorption device, stirred in an ice-water bath. Later Oxalyl chloride (1.3ml, 0.015mol) was dropwise added under protection of nitrogen. A large number of white solide appeared quickly, after 5 minutes, the reaction was quenched by tetrahydrofuran, then pure white solide was got after removing the solvent, and the yield was up to 98%^[16].

General procedure for the preparation of compound (II)

DMF (15ml) was added into a 50 ml three-necked round bottom flask which was dried absolutely and equipped gas absorption device, stirred in an ice-salt bath. Later Oxalyl chloride (1.3ml, 0.015mol) was dropwise added under protection of nitrogen. A large number of white solide appeared quickly, after 10 minutes Et_3N (1.6ml, 0.012mol) and phenol (1.2g, 0.013mol) dissolved in DMF were dropwise added. 10 minutes later filter out triethylamine hydrochloride and obtain orange transparent solution. Pale yellow crystal was got by removing the DMF, dried in a vacuum tank, and the yield was 82%^[17].



General procedure for the preparation of benzonitrile (Entry 1)

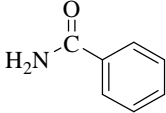
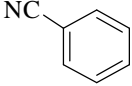
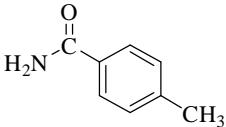
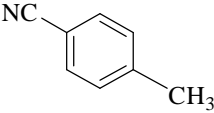
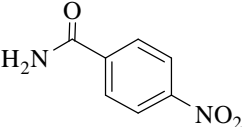
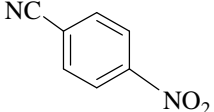
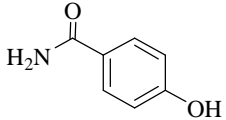
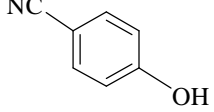
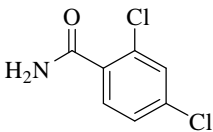
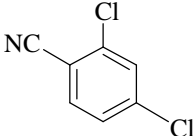
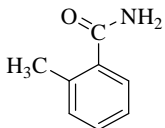
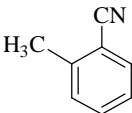
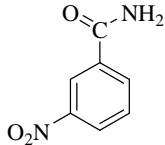
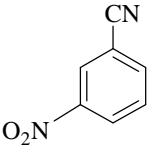
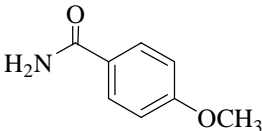
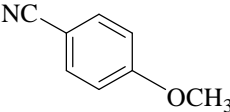
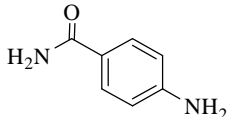
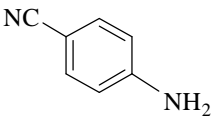
Benzamide (1.21g, 0.01mol), and CH_3CN (20ml) were added into a 50 ml three-necked round bottom flask equipped phosphorous pentoxide drying tube, stirred in an ice-salt bath (-5°C - 0°C). After 10 min com-

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pound II (2.70g, 0.011mol) was put in the flask and went on stirring 20 min. Then Et_3N (0.02mol) was added slowly by syringe, the stirring was continued at room temperature until the benzamide was disappeared

by TCL tracer. Then resultant of the reaction was filtered, rotary evaporated to remove the solvent, distilled, and collected 186-189°C cut fraction (0.95g) in 95% yield.

TABLE 1 : Conversion of amides to nitriles.

Entry	Substrate	Nitriles	Time (h.)	Yield (%)	b.p./($^{\circ}\text{C}/\text{mm Hg}$)	
					Found	Reported
1			1.4	95	186-189	188
2			1.3	98	218	218
3			1.6	91	148	149
4			1.2	93	112-113	113
5			1.5	92	128-129	129-130
6			1.2	96	204-206	205
7			1.6	92	116-118	118
8			1.1	89	53-56	54-56
9			1.2	92	86-89	88

Entry	Substrate	Nitriles	Time (h.)	Yield (%)	b.p./($^{\circ}$ C/mm Hg)	
					Found	Reported
10			1.2	88	68	67-68
11			1.1	89	74	74
12			1.6	89	78-79	79
13			1.2	93	146	147
14			1.7	90	65	66

General procedure for the preparation of 4-methylbenzonitrile (Entry 2)

4-methylbenzamide (1.21g, 0.01mol) and CH_3CN (20ml) were added into a 50 ml of three-necked round bottom flask and the mixture was stirring with a ice salt bath (-5°C - 0°C) for 10 min; Then compound II (2.7g, 0.011mol) was added into the above mixture. With stirring 20 min, Et_3N (0.02mol) was slowly injecting into the solution using a syringe then stirring at room temperature under TLC trace until the 4-methylbenzamide had disappeared. After the reaction, the compound was filtered and rotary steam in order to remove the solvent and the solid residue were dissolved into dichloromethane. The solution was filtered and washed with 20 ml deaerated water; then the organic phase was dried using anhydrous sodium sulphate. After that, the colature was obtained by removing the solvent, further purification of the above colature, 1.0 g of 4-methylbenzonitrile was obtained and the yield was 98%.

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