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One-pot, direct synthesis of acyl azides from carboxylic acids using $Ph_2PCl/I_2/NaN_3$ reagent system

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Abstract

A mild, efficient and simple method for the preparation of acyl azides from carboxylic acids using chlorodiphenylphosphine in the presence of molecular iodine and sodium azide is described.

Keywords: Chlorodiphenylphosphine; Iodine; Acyl azides; Carboxylic acids; Sodium azide

Acyl azides have widespread utility as highly reactive reagent in organic chemistry [1]. They are extremely useful in the preparation of amides and heterocyclic chemistry [1–3]. The well known Curtius rearrangement of acyl azides under thermal condition lead to isocysnates, which in turn undergo easy conversion into amines, carbodiimides, urease, urethanes, thiourethanes and other derivatives [2a].

Acyl azides can be prepared in several different ways: (i) reaction of acid chlorides or mixed anhydrides with azide ions [1,4], (ii) treating acylhydrazines with nitrosyl precursors [1,4], (iii) using acid activator such as $SOCl_2$/DMF [5], cyanuric chloride/*N*-methylmorpholine [6], triphosgene/triethylamine [7], ethyl chloroformate [8], diphenyl-phosphoryl azide [9], NCS/Ph_3P [10], benzotriazole-1-yl-oxy-tris(dimathylamino)phosphonium hexafluoro-phosphate (BOP) [11], phenyl dichlorophosphate [12], Cl_3CCN/Ph_3P [13], $POCl_3$/DMF [14], 2-azido-1,3-dimethyl-imidazolinium chloride [15], bis(2-methoxyethyl)aminosulfur trifluoride [16] and (iv) from aldehydes using chromic anhydride/trimethyl silylazide [17], $PhI(OAc)_2$ [18], triazidochlorosilane activated MnO_2 [19], IN_3 [20], *tert*-butyl hypochlorite [21] and Dess-Martin periodinane [22]. Although these methods are available for the preparation of acyl azides, there are still drawbacks such as long reaction time [23], by-product formation, hazardous and expensive reagents [6,7], multi-step protocol [1,4,23] and tedious reaction conditions [22]. Therefore, additional methods for this conversion are still valuable.

Recently, we reported efficient methods for the synthesis of alkyl esters, phenolic and thioesters [24] and also nitro aromatic compounds [25] using Ph_2PCl/I_2 reagent system. In continuation of our works, we report here a highly efficient conversion of carboxylic acids using Ph_2PCl/I_2 and sodium azide to their acyl azides in a one-pot, direct synthesis.

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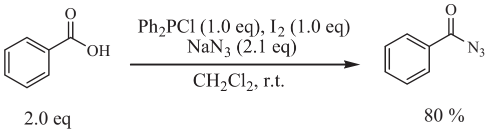
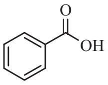
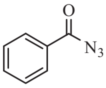
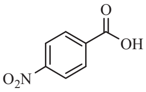
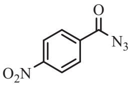
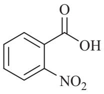
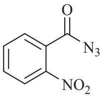
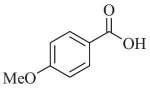
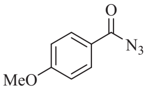
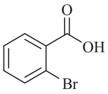
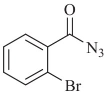
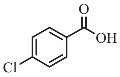
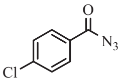
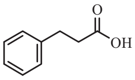
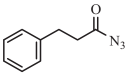
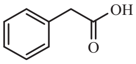
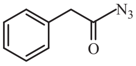
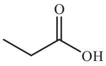
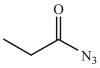
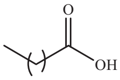
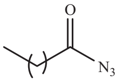


Scheme 1.

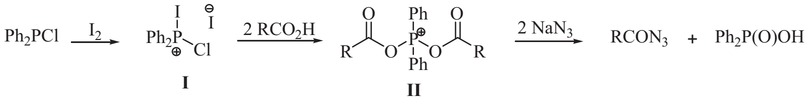
Chlorodiphenylphosphine is commercially available and inexpensive, making large-scale synthesis using this reagent system especially attractive. In this system the resulting phosphorus byproduct, diphenylphosphinic acid, can be extracted with base during product workup.

Optimization study revealed that 1.0 equiv. of both Ph_2PCl and I_2 was sufficient to complete the reaction between 2.0 equiv. of carboxylic acid and 2.1 equiv. of NaN_3 in CH_2Cl_2 at room temperature (Scheme 1). We next examined a variety of aromatic and aliphatic carboxylic acids and the optimized reaction conditions were applied to these substrates (Table 1).

Table 1
Synthesis of acyl azides from carboxylic acids using $Ph_2PCl/I_2/NaN_3$.

Entry	Carboxylic acid	Acyl azide	Time (min)	Yield %[a] (Ref.)
1			90	80 [11]
2			30	90 [11]
3			40	85 [21]
4			120	65 [21]
5			80	91 [26]
6			70	90 [21]
7			3 h	73 [21]
8			3 h	80 [21]
9			3.5 h	77 [21]
10			3 h	80 [21]

[a] Isolated yield.



Scheme 2.

As can be seen from the results in Table 1, both aromatic and aliphatic carboxylic acids converted cleanly to azides in high yields. As expected, the presence of the nitro group on aromatic ring (stronger aryl acids) is very effective in activating the carboxylic group toward reaction with azide ion (entries 2 and 3) compared to weaker acids such as benzoic and 4-methoxybenzoic acid (entries 1 and 4).

Based on the previous studies [24] and above results, the reaction may proceed *via in situ* generated acyloxyphosphonium ion (II). The attack of the azide ion at the carbonyl carbon atom of this intermediate affords the corresponding acyl azide along with diphenylphosphinic acid as shown in Scheme 2.

In conclusion, an efficient new one-pot direct method for the synthesis of various acyl azides from carboxylic acids was found. Mild reaction conditions, simplicity and ease of work-up and low toxicity of the reagents in contrast to the hazardous reagents reported in the literature are the advantages of our system.

1. Experimental

Typical procedure for the conversion of benzoic acid into benzoylazide: To a flask containing a stirring mixture of Ph_2PCl (1.0 mmol, 0.18 mL) and I_2 (1.0 mmol, 0.253 g) in dichloromethane (5 mL), was added benzoic acid (2.0 mmol, 0.244 g) at room temperature. Sodium azide (2.1 mmol, 0.136 g) was then added to the reaction mixture. After 90 min, the organic layer was washed successively with saturated aqueous sodium carbonate (3× 5 mL), aqueous sodium thiosulfate (2× 5 mL) and water (5 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated. Purification by a short silica gel column chromatography using *n*-hexane afforded the pure benzoyl azide in 80% yield. IR (KBr) 2138 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.49 (m, 2H), 7.60–7.66 (m, 1H), 8.05 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 128.7, 129.4, 130.6, 134.4, 172.6.

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