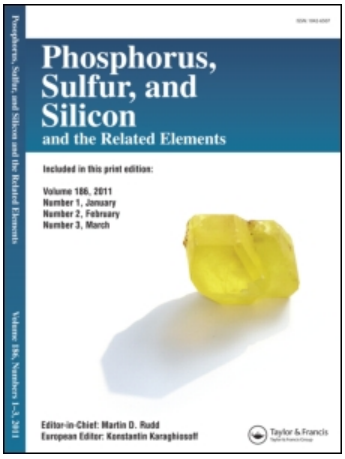

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One-Flask Synthesis of Acyl Azides from Carboxylic Acids; A Facile Route to Iminophosphoranes

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ONE-FLASK SYNTHESIS OF ACYL AZIDES FROM CARBOXYLIC ACIDS; A FACILE ROUTE TO IMINOPHOSPHORANES

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Carboxylic acids react with a mixture of N-chlorosuccinimide, triphenylphosphine and sodium azide at −30°C to form acyl azides in high yields. When two equivalents of triphenylphosphine are applied and the temperature allowed to raise, the reaction yields directly α-carbonyl stabilized iminophosphoranes via Staudinger reaction of the phosphine with the intermediate acyl azide.

Key words: Iminophosphoranes; acyl azides; one-flask synthesis.

Acyl azides are valuable synthetic intermediates, e.g., in heterocyclic chemistry and for the preparation of isocyanates (from which amines, urethanes, thiourethanes, ketenimines, carbodiimides, ureas, amides etc.) can be conveniently made.

Common methods[1] for the preparation of acyl azides include the reaction of acyl chlorides with azide ions in a mixture of water and water-miscible organic solvents such as dioxane, alcohols, acetone, acetic acid and DMF. If the reaction is performed in organic solvents without addition of water, reaction temperatures often have to be used that lead to Curtius rearrangement of the required acyl azide. Sometimes the reaction has been run under milder conditions by using "activated" sodium azide,[2] lithium azide,[3] the readily soluble, but hazardous hydrazoic acid, and, sporadically, by means of special agents like tetramethylguanidinium or other tetraalkylammonium azides.[4] On occasion, also mixed anhydrides have been used for the synthesis of acyl azides as it has been demonstrated that certain anhydrides, e.g., t-butylcarbonic diethylphosphoric anhydride, react fairly easily with azide ions. Lately, trimethylsilyl azide in the presence of pyridine or other catalysts has been shown to transform mixed anhydrides as well as acyl chlorides and reactive esters into azides. Thus the transformation of aroyl chlorides into aroyl azides has been performed at 0°C in dichloromethane in the presence of a catalytic amount of zink iodide.[5] Recent work[6] has demonstrated, however, that neither catalysts, elevated temperatures, addition of water, or reagents not readily available in the laboratory, is needed for the abovementioned transformation. Thus quantitative yields of as well aroyl as alkanoyl azides and azidoformates can be obtained from reacting commercial sodium azide with the corresponding acid chlorides or chloroformates in acetone at 0°C.[6]

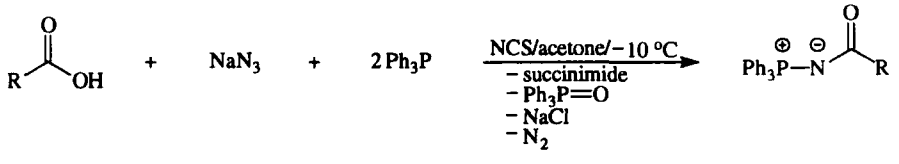
However, acid chlorides or other highly reactive carboxylic acid derivatives are not always at hand, and there is a continued interest in methods to effect a direct transformation of carboxylic acids or other readily available starting materials into acyl azides. Thus very recently aldehydes has been shown to react with azidotrimethylsilane in the presence of chromic anhydride[7] affording high yields of the

corresponding acyl azides. Also the direct transformation of carboxylic acids into azides can be effected by means of O,O-diphenylphosphoryl azide[8] or with sodium azide and phenyl dichlorophosphate in the presence of tetrabutylammonium bromide or pyridine,[9] but the latter methods have not yet found broad application.

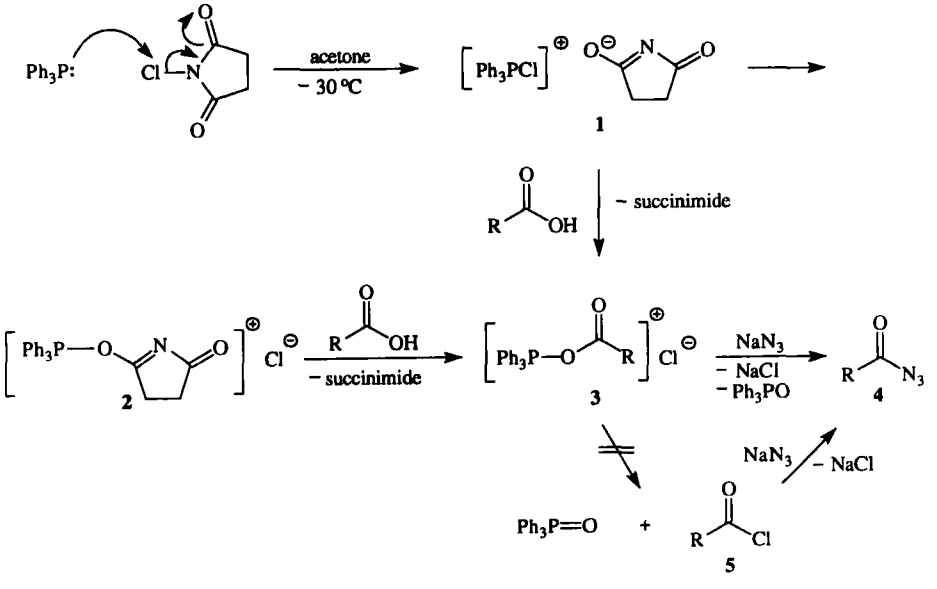
During our continued studies of iminophosphoranes we have investigated various methods with a view of finding more convenient synthetic routes for the preparation of these compounds, particularly via the reaction of organic azides with phosphines (the Staudinger reaction). Lately, in an attempt to prepare N-3,5-dinitrobenzoyliminotriphenylphosphorane **11** (Table II) in a one-flask synthesis from 3,5-dinitrobenzoic acid, triphenylphosphine, sodium azide and N-chlorosuccinimide (NCS) in acetone, we found that the reaction gave the expected iminophosphorane in excellent yield (Scheme I).

The new reaction appears to be a general one and proceeds under mild reaction conditions (−10–20°C) in acetone. Its only drawback is that the reaction mixture has to be chromatographed (a short column of silica gel was applied) in order to separate the iminophosphorane from triphenylphosphine oxide and succinimide formed in the initial step.

During further work we therefore preferred to perform the reaction in two steps by lowering the reaction temperature to −30°C and adding only one equivalent



SCHEME I



SCHEME II

of triphenylphosphine to the reaction mixture, thereby arresting the reaction at the azide stage **4** (Scheme II). The acyl azide is thereafter extracted with pentane. Evaporation of this solvent leaves the desired product (**4**), sufficiently pure for further reaction. The Staudinger reaction may preferably be performed immediately by adding the phosphine directly to the abovementioned pentane solution, wherefrom the iminophosphorane usually crystallizes in a very pure state.

As can be seen from the Table I, N-chlorosuccinimide (similar results are obtained with N-bromosuccinimide) in combination with triphenylphosphine, sodium azide and carboxylic acids provides a short and convenient route to acyl azides. We believe the reaction is initiated by a nucleophilic attack of the phosphine at the halogen atom of the N-halosuccinimide, forming a relatively stable, isolable compound **2** via the very unstable intermediate **1** supposedly formed in this first step (Scheme II). Protonation of **2**, or maybe directly of **1** by the carboxylic acid followed by nucleophilic attack at phosphorus by the carboxylate ion, then yields **3**.

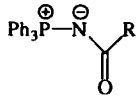
TABLE I

Preparation of alkanoyl and aroyl azides from carboxylic acids in acetone

Entry	Substrate	Product	(%) Yield
1	benzoic acid	benzoyl azide	90
2	salicylic acid	2-hydroxybenzoyl azide	81
3	2,4-dimethoxybenzoic acid	2,4-dimethoxybenzoyl azide	98
4	3,4-dimethoxybenzoic acid	3,4-dimethoxybenzoyl azide	96
5	2-naphthoic acid	2-naphthoyl azide	93
6	4-nitrobenzoic acid	4-nitrobenzoyl azide	97
7	4-chlorobenzoic acid	4-chlorobenzoyl azide	92
8	4-fluorobenzoic acid	4-fluorobenzoyl azide	90
9	4-bromobenzoic acid	4-bromobenzoyl azide	89
10	4-methylbenzoic acid	4-methylbenzoyl azide	92

TABLE II

Synthesis of iminophosphoranes



Compound	R	Yield
11	3,5-dinitrophenyl	92[a]
12	2-naphthyl	88
13	2,4-dimethoxyphenyl	90
14	3,4-dimethoxyphenyl	90

[a]Prepared in one-pot synthesis from 3,5-dinitrobenzoic acid.

Finally, the latter compound (**3**) undergoes nucleophilic attack at the carbonyl carbon by the azide ion, leading to acyl azides **4** and triphenylphosphine oxide. At first sight it would appear that the last step of the reaction might proceed via the acyl halide **5** presumably formed by nucleophilic attack at **3** by the halide ion (Cl^-, Br^-) from NCS or NBS.

A control experiment established, however, that under the abovementioned reaction conditions, acyl halides are not formed. If the reaction is performed as above, but without any sodium azide added to the reaction mixture, the reaction stops at the intermediate stage **3** (Scheme II). This points to the direct route **3** → **4** via nucleophilic attack at the carbonyl carbon of **3** by the azide ion.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken at operating frequencies of 200 and 50.3 MHz on a Varian Gemini-200 spectrometer. IR spectra were measured as films with a Perkin Elmer 1310 infrared spectrometer. Column chromatography was carried out using Merck No. 9385 silica gel 60. Melting points, determined with a Reichert Thermopan melting point microscope, are uncorrected.

One-flask preparation of iminophosphoranes from carboxylic acids. 3,5-dinitrobenzoyliminotriphenylphosphorane (**11**) was prepared from 3,5-dinitrobenzoic acid by the following one-flask procedure. To a suspension of sodium azide (0.32 g, 5 mmol) in acetone (10 ml) was added 3,5-dinitrobenzoic acid (0.53 g, 2.5 mmol) and triphenylphosphine (1.40 g, 5 mmol). The reaction mixture was vigorously stirred, cooled to about −10°C and N-chlorosuccinimide (2.5 mmol) added in small portions. The first step (azide formations) was completed in a few seconds, whereafter the Staudinger reaction started spontaneously. The cooling-bath was removed and the reaction mixture stirred for a couple of hours at ambient temperature until nitrogen evolution had ceased. When the Staudinger reaction was completed, the solvent was removed in vacuo and the remaining product stirred with dichloromethane. The salts, sodium chloride and excess sodium azide, were removed by filtration and the iminophosphorane (**11**) separated from the remaining mixture by column chomatography (silica gel, Merck No. 9385). Elution with ether/ethylacetate (5:2) yielded **11** (1.09 g, 92%).

Preparation of acyl azides. The preparation of 2,4-dimethoxybenzoyl azide (**3**) is representative. To a vigorously stirred solution of triphenylphosphine (2.62 g, 10 mmol), 2,4-dimethoxybenzoic acid (1.82 g, 10 mmol) and sodium azide (1.30 g, 20 mmol) in acetone (15 ml) at −30°C was added N-halosuccinimide (10 mmol) in small portions. The cooling bath was thereafter removed and the reaction mixture stirred for 30 min. during which time the temperature was allowed to rise to 15–20°C. The solvent was evaporated in vacuo and the remaining solid extracted with pentane. Evaporation of this solvent yielded 2,4-dimethoxybenzoyl azide (1.94 g, 98%) which after recrystallization from ether/pentane melted at 68–69°C (dec.).

Benzoyl azide (**1**). M.p. 25°C; lit.[10] 25–27°C; ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 128.9 (C_3 and C_5), 129.7 (C_2 and C_6), 131.0 (C_1), 134.5 (C_4), 172.2 (CO).

2-Hydroxybenzoyl azide (**2**). M.p. 24°C; lit.[10] 27°C; ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 113.9 (C_1), 118.4 (C_5), 119.8 (C_3), 130.3 (C_6), 137.5 (C_4), 162.1 (C_2), 176.4 (CO).

2,4-Dimethoxybenzoyl azide (**3**). M.p. 68–69°C (dec.); ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 56.3 (CH_3), 56.7 (CH_3), 99.3, 105.4, 112.8, 134.6, 162.4, 165.9, 170.1 (CO).

3,4-Dimethoxybenzoyl azide (**4**). M.p. 74–75°C (dec.); ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 56.8 (CH_3), 56.9 (CH_3), 110.8, 111.9, 123.7, 124.4, 149.2, 154.5, 171.8 (CO).

2-Naphthoyl azide (**5**). M.p. 77–79°C (dec.); lit.[11] 76°C; ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 124.9, 127.4, 128.2, 128.9, 129.4, 130.1, 131.9, 132.7, 136.5, 172.7 (CO).

4-Nitrobenzoyl azide (**6**). M.p. 69°C, lit.[10] 65°C; ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 124.1 (C_3 and C_5), 130.6 (C_2 and C_6), 135.7 (C_1), 151.3 (C_4), 170.6 (CO).

4-Chlorobenzoyl azide (**7**). M.p. 42°C, lit.[10] 45–46°C (dec.); ^{13}C NMR (50.29 MHz, acetone-d_6): δ 130.1 (C_3 and C_5), 130.4 (C_1), 131.8 (C_2 and C_5), 171.5 (CO).

4-Fluorobenzoyl azide (**8**). Oil; ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 115.5 (C_3 and C_5), 127.4 (C_1), 132.3 (C_2 and C_6), 166.3 (C_4), 171.0 (CO).

4-Bromobenzoyl azide (**9**). M.p. 46°C, lit.[12] 46°C; ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 129.3 (C_1), 129.5 (C_4), 130.5 (C_3 and C_5), 131.8 (C_2 and C_6), 171.5 (CO).

4-Methylbenzoyl azide (**10**). M.p. 33°C, lit.[13] 28°C; ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 23.0 (CH_3), 129.0 (C_1), 130.2 (C_3 and C_5), 130.3 (C_2 and C_6), 146.1 (C_4), 172.3 (CO).

3,5-Dinitrobenzoyliminotriphenylphosphorane (**11**). M.p. 190–191°C, lit.[6] 193–194°C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.45–7.70 (m, 9H, H(1,3,5)), 7.75–8.00 (m, 6H, H(2,6)), 9.09 (d, J 0.9 Hz, 1H, H(8), 9.45 (d, J 2.1 Hz, 2H, H(10,11)); ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 120.55, δ 126.39 and 128.36 (C_4), J P-C_4 99.9 Hz, 128.62, 128.70, 128.85, 128.92, δ 129.19 and 129.44 (C_3 and C_5), J P-C_3 12.3 Hz, 129.75, 132.89, 133.10, 133.15, δ 133.25 and 133.45 (C_2 and C_6), J P-C_2 10.1 Hz, 133.65, δ 142.76 and 143.20 (C_{11}), J P-C_{11} 22.4 Hz, 148.21 (C_8), 170.84 (CO).

2-Naphthoyliminotriphenylphosphorane (**12**). M.p. 187–189°C; $C_{29}H_{22}NOP$ calc. (%): C 80.72, H 5.14, N 3.25. Found: C 80.70, H 5.12, N 3.22. ^1H NMR (200 MHz, $CDCl_3$): δ 7.4–7.7 (m, 11H), 7.8–8.1 (m, 9H), 8.18 (d, 1H); ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 117.4, 118.6, 120.8, 127.25, 126.4, 128.3, 129.2, 129.4, 133.0, 133.1, 133.3, 133.5, 133.7, 161.4 (CO).

2,4-Dimethoxybenzoyliminotriphenylphosphorane (**13**). M.p. 151–154°C; $C_{27}H_{24}NO_3P$ calc. (%): C 73.46, H 5.48, N 3.17. Found: C 73.41, H 5.53, N 3.33. ^1H NMR (200 MHz, $CDCl_3$): δ 3.82 and 3.86 (6H, CH_3), 6.50 (s, 2H, $H_{aromatic}$), 7.4–7.6 (m, 9H, $H_{aromatic}$), 7.75–7.95 (m, 6H, $H_{aromatic}$), 8.20 (d, 1H, $H_{aromatic}$); ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 56.29, 56.46, 99.70, 104.40, 127.98, 128.74, 129.93, 132.25, 132.30, 133.46, 133.64, 133.96, 132.63, 134.26, 160.46, 162.19, 176.10 (CO).

3,4-Dimethoxybenzoyliminotriphenylphosphorane (**14**). M.p. 170–171°C; $C_{27}H_{24}NO_3P$ calc. (%): C 73.46, H 5.48, N 3.17. Found: C 73.51, H 5.49, N 3.22. ^1H NMR (200 MHz, $CDCl_3$): δ 3.93 and 3.94 (6H, CH_3), 6.88 and 6.92 (2H, $H_{aromatic}$), 7.4–7.6 (m, 9H, $H_{aromatic}$), 7.75–7.95 (m, 7H, $H_{aromatic}$), 8.05–8.10 (m, 1H, $H_{aromatic}$); ^{13}C NMR (50.29 MHz, $CDCl_3$): δ 56.95, 110.34, 112.60, 112.65, 123.64, 127.79, 128.87, 129.74, 132.46, 132.52, 133.31, 133.51, 148.16, 151.35, 175.71 and 175.86 (CO).

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