Direct and facile synthesis of acyl azides from carboxylic acids using the trichloroisocyanuric acid–triphenylphosphine system

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Abstract: A mild, efficient, and practical method for the one-step synthesis of acyl azides from carboxylic acids using a safe and inexpensive mixed reagent, trichloroisocyanuric acid–triphenylphosphine, is described.

Key words: carboxylic acid, acyl azide, trichloroisocyanuric acid, triphenylphosphine, sodium azide.

Résumé : On décrit une méthode de synthèse en une étape des azotures d’acyles à partir d’acides carboxyliques; la méthode est à la fois douce, efficace et pratique et elle implique l’utilisation d’un réactif sécuritaire et pas cher, soit un mélange d’acide trichloroisocyanurique et de triphénylphosphine. [Traduit par la Rédaction]

Mots-clés : acide carboxylique, azoture d’acyle, acide trichloroisocyanurique, triphénylphosphine, sodium azide.

Introduction

Acylic azides are important intermediates in organic chemistry and especially in pharmaceuticals,1–3 dyes,4 and agrochemicals.5–8 They have been extensively used in the synthesis of amides, nitriles, cycloaddition reactions, peptide bond formation,9,10 and in heterocyclic chemistry.11–13 Many single-step and multistep protocols have been developed to convert carboxylic acids to acyl azides.14–17 Acyl azides are usually prepared from acid derivatives such as acid chlorides, acyl hydrazides,18 or mixed anhydrides.19–21 Acid chlorides are not always easy to access or store. They are highly sensitive to moisture and require care in handling. Acyl hydrazides require the availability of the hydrazide.22–24 Mixed anhydrides need to be generated from a carboxylic acid and alkyl chloroformate. There are few reports on the direct conversion of carboxylic acids to acyl azides using acid activators such as SOCl2–dimethylformamide (DMF),25,26 trichloroacetonitrile–dimethylformamide,27,28 tert-butyl dicarbonate,52 and dochlorosilane activated MnO2.56,57 and Dess–Martin periodinane.58,59 Modified methods in which carbamoyl azides were formed directly from aldehydes via acyl azides in a one-pot synthesis have been also reported.60,61

In continuation of our recent work on the use of triphenylphosphine (TPP) in the synthesis of alkyl azides, cyanides, thiocyanates, isocyanates, and nitriles,62–70 and by considering the activity of trichloroisocyanuric acid (TCCA) as an electron deficient and N-halo reagent towards TPP, in this paper, we wish to report a more simplified one-step method for the conversion of carboxylic acids to acyl azides.

Results and discussion

Since carboxylic acids are more readily available commercially than acyl azides, herein we propose a more robust, mild, and highly efficient procedure for the direct conversion of carboxylic acids to acyl azides using the triphenylphosphine–trichloroisocyanuric acid–NaN3 system (Scheme 1).

At first, the reaction of p-nitrobenzoic acid was initially performed in the presence of different molar ratios of RCO2H–TPP–TCCA–NaN3 at 0 °C to room temperature. The effect of different solvents was also studied (Table 1). Employing the ratio of 1:1:0.3:3 in CH2Cl2 at room temperature gave the best results and produced p-nitrobenzoyl azide in a quantitative yield after 40 min (Table 1, entry 9). By performing the reaction at reflux, p-nitrobenzoyl azide and some byproducts were obtained at a longer reaction time (Table 1, entries 6 and 10). In refluxing CH3CN and CH2Cl2, p-nitrobenzoyl azide was converted to p-nitrobenzene isocyanate (as a Curtius rearrangement product) by losing N2.

The conversion of carboxylic acid to corresponding acyl azides exhibits high efficiency. Applying the optimized conditions, different aryl, alkyl, and heteroaryl carboxylic acids on reaction with triphenylphosphine–trichloroisocyanuric acid in the presence of sodium azide undergo smooth conversion to corresponding acyl azides with excellent yields (Table 2). The carboxylic acids were rapidly converted into their corresponding products in a very short reaction time (45–120 min) with 100% conversion.

The mechanism of these transformations is not obvious. A plausible mechanism is depicted in Scheme 2. The initial attack of carboxylic acid to corresponding acyl azides exhibits high efficiency. Applying the optimized conditions, different aryl, alkyl, and heteroaryl carboxylic acids on reaction with triphenylphosphine–trichloroisocyanuric acid in the presence of sodium azide undergo smooth conversion to corresponding acyl azides with excellent yields (Table 2). The carboxylic acids were rapidly converted into their corresponding products in a very short reaction time (45–120 min) with 100% conversion.

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Further mechanistic studies require confirming this mechanism. On the basis of the previously mentioned mechanism, triphenylphosphine plays an important role in this transformation. The reaction of p-nitrobenzoic acid with sodium azide was carried out in the absence of triphenylphosphine but after long period of time no benzoyl azide was obtained. It is noteworthy that no evidence for the formation of carboxylic acid chlorides as...
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Because of steric effects, acyl azide at a longer reaction time compared to benzoic acid phenyl moiety, the acidity of 4-methoxy benzoic acid decreases.

Electron-withdrawing groups increase the acidity of carboxylic acid, which leads to an easier formation of acyl azides without the formation of any Curtius rearrangement products.

It is important to note that triphenylphosphine-trichloroisocyanuric acid is a safe and inexpensive mixed reagent compared with the recently reported use of hazardous and expensive N-methylmorpholine and triphosphene.

**Experimental**

**General**

The products were purified by column chromatography and characterized by spectroscopic data (IR, $^1$H NMR, and $^{13}$C NMR). The purity determinations of the products were accomplished by thin-layer chromatography (TLC) on silica gel polygram STI G/UV 254 plates. Melting points were determined with an Electrothermal Type 9100 melting point apparatus. Elemental analyses were made by a Thermo Finning Flash EA1112 CHNO-S analyzer and agreed with the calculated values. The FT-IR spectra were recorded on an Avatar 370 FT-IR Thermo Nicolet spectrometer. The NMR spectra were recorded on a Bruker Avance 100 and 400 MHz instrument in CDCl$_3$. The $^1$H and $^{13}$C NMR chemical shifts ($\delta$) in ppm were downfield from tetramethylsilane (CDCl$_3$: $\delta_C = 77.0$ ppm; residual CHCl$_3$ in CDCl$_3$: $\delta_H = 7.26$ ppm). Caution: Azido compounds may represent an explosion hazard when being concentrated under vacuum or stored neat. A safety shield and appropriate handling procedures are recommended.

**Benzoyl azide (Table 2, entry 1)**

Oil (lit. report:71 oil). IR (neat, cm$^{-1}$) $\nu$: 3067, 2173 (2179),$^{59}$ 2129 (2127),$^{59}$ 1695 (1682),$^{59}$ 1598, 1582, 1450, 786, 695.

**4-Nitrobenzoyl azide (Table 2, entry 2)**

Solid; mp 64–65 °C (lit. value$^{71}$ mp 65 °C). IR (KBr, cm$^{-1}$) $\nu$: 3108, 3092, 2855 (2850),$^{59}$ 1410 (1409),$^{59}$ 1408, 1694 (1690),$^{59}$ 1600, 1535, 847. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C, ppm) $\delta$: 8.34 (d, 2H, $J = 8.4$ Hz), 8.24 (d, 2H, $J = 8.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$, 25 °C, ppm) $\delta$: 170.9 (170.9 –CON$_3$),$^{59}$ 151.2, 123.8, 135.7, 130.6.

**3-Nitrobenzoyl azide (Table 2, entry 3)**

Solid; mp 65–67 °C (lit. value$^{71}$ mp 67 °C). IR (KBr, cm$^{-1}$) $\nu$: 3092, 2203, 2154 (2137),$^{59}$ 1697 (1700),$^{59}$ 1686, 1632, 900, 730, 708. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C, ppm) $\delta$: 8.9 (s, 1H), 8.5 (ddd, 1H, $J = 8.2$ Hz, $J = 1.2$ Hz, $J = 0.8$ Hz), 8.39 (dt, 1H, $J = 8.0$ Hz, $J = 1.2$ Hz), 7.72 (t, 1H, $J = 8.0$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$, 25 °C, ppm) $\delta$: 170.6 (170.6 –CON$_3$),$^{59}$ 148.4, 134.9, 132.3, 123.0, 128.5, 124.4.

**Conclusions**

In conclusion, the present method for the preparation of acyl azides is very simple without requiring any drastic experimental conditions. Also, the trichloroisocyanuric acid-triphosphene system is a very mild and efficient general mixed reagent for the conversion of carboxylic acids to the corresponding acyl azides without the formation of any Curtius rearrangement products.
Table 2. The synthesis of acyl azides from carboxylic acids using a triphenylphosphine–trichloroisocyanuric acid–sodium azide system.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid</th>
<th>Acyl azide&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (min)</th>
<th>Molar ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzoic acid</td>
<td>Benzoyl azide</td>
<td>60</td>
<td>1:1:0.3:3</td>
<td>97</td>
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<tr>
<td>2</td>
<td>4-Nitrobenzoic acid</td>
<td>4-Nitrobenzoyl azide</td>
<td>40</td>
<td>1:1:0.3:3</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>3-Nitrobenzoic acid</td>
<td>3-Nitrobenzoyl azide</td>
<td>50</td>
<td>1:1:0.3:3</td>
<td>95</td>
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<tr>
<td>4</td>
<td>3,4-Dichlorobenzoic acid</td>
<td>3,4-Dichlorobenzoyl azide</td>
<td>120</td>
<td>0.5:1:0.3:3</td>
<td>98</td>
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<tr>
<td>5</td>
<td>4-Chlorobenzoic acid</td>
<td>4-Chlorobenzoyl azide</td>
<td>70</td>
<td>1:1:0.3:3</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>2-Chlorobenzoic acid</td>
<td>2-Chlorobenzoyl azide</td>
<td>110</td>
<td>0.5:1:0.3:3</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>4-Bromobenzoic acid</td>
<td>4-Bromobenzoyl azide</td>
<td>75</td>
<td>1:1:0.3:3</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>4-Methylbenzoic acid</td>
<td>4-Methylbenzoyl azide</td>
<td>70</td>
<td>1:1:0.3:3</td>
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<tr>
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<td>0.5:1:0.3:3</td>
<td>97</td>
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<td>10</td>
<td>4-Methoxybenzoic acid</td>
<td>4-Methoxybenzoyl azide</td>
<td>90</td>
<td>1:1:0.3:3</td>
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<tr>
<td>11</td>
<td>Cinnamic acid</td>
<td>Cinnamoyl azide</td>
<td>90</td>
<td>0.5:1:0.3:3</td>
<td>95</td>
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<tr>
<td>12</td>
<td>3-Nitrocinnamic acid</td>
<td>3-Nitrocinnamoyl azide</td>
<td>80</td>
<td>0.5:1:0.3:3</td>
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<td>13</td>
<td>4-Chlorocinnamic acid</td>
<td>4-Chlorocinnamoyl azide</td>
<td>110</td>
<td>0.5:1:0.3:3</td>
<td>94</td>
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<tr>
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<td>Phenylethanoic acid</td>
<td>Phenylethanoyl azide</td>
<td>70</td>
<td>0.5:1:0.3:3</td>
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<tr>
<td>15</td>
<td>2,2-Diphenylethanoic acid</td>
<td>2,2-Diphenylethanoyl azide</td>
<td>75</td>
<td>0.5:1:0.3:3</td>
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<tr>
<td>16</td>
<td>Hexanoic acid</td>
<td>Hexanoyl azide</td>
<td>40</td>
<td>0.5:1:0.3:3</td>
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<td>Oleic acid</td>
<td>Octadec-9(Z)-enoyl azide</td>
<td>30</td>
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<td>Stearic acid</td>
<td>Stearoyl azide</td>
<td>40</td>
<td>0.5:1:0.3:3</td>
<td>94</td>
</tr>
<tr>
<td>19</td>
<td>Thiophene-3-carboxylic acid</td>
<td>Thiophene-3-carbonyl azide</td>
<td>60</td>
<td>0.5:1:0.3:3</td>
<td>95</td>
</tr>
<tr>
<td>20</td>
<td>Pyridine-4-carboxylic acid</td>
<td>Pyridine-4-carbonyl azide</td>
<td>55</td>
<td>0.5:1:0.3:3</td>
<td>93</td>
</tr>
<tr>
<td>21</td>
<td>Pyridine-2,6-dicarboxylic acid</td>
<td>Pyridine-2,6-dicarbonyl diazide</td>
<td>60</td>
<td>1:2:0.6:4</td>
<td>95</td>
</tr>
</tbody>
</table>

Note: The products were characterized by <sup>1</sup>H nuclear magnetic resonance (NMR), <sup>13</sup>C NMR, melting points, and infrared (IR) data.

<sup>a</sup>Identified by comparison data with authentic samples.

<sup>b</sup>Molar ratio: RCO₂H–TPP–TCCA–NaN₃.

Scheme 2.

3,4-Dichlorobenzoic azide (Table 2, entry 4)
Solid; mp 56–58 °C (lit. value<sup>c2</sup> mp 58–59 °C). IR (KBr, cm⁻¹): 3091, 2194, 2152, 1698, 1585, 826, 784. <sup>1</sup>H NMR (400 MHz, CDCl₃, 25 °C, ppm) δ: 8.12 (d, 1H, J = 1.6 Hz), 7.87 (dd, 1H, J = 8.4 Hz, J = 1.6 Hz), 7.56 (d, 1H, J = 8.4 Hz). <sup>13</sup>C NMR (100 MHz, CDCl₃, 25 °C, ppm) δ: 170.6, 139.1, 133.4, 130.8, 130.4, 128.4. Anal. calcd. for C₇H₃Cl₂N₃O (%): C 38.92, H 1.40, N 19.45; found: C 39.70, H 1.46, N 19.06.

4-Chlorobenzoic azide (Table 2, entry 5)
Solid; mp 38–41 °C (lit. value<sup>c4</sup> mp 39–42 °C). IR (KBr, cm⁻¹): 3088, 2177 (2174), 1680 (1680), 1588, 1486, 849.

2-Chlorobenzoic azide (Table 2, entry 6)
Oil (lit. report: oil). IR (KBr, cm⁻¹): 3289, 2138, 1645, 757.
4-Bromobenzoyl azide (Table 2, entry 7)
Solid; mp 45–47 °C (lit. value27 mp 47 °C). IR (KBr, cm−1): 3020, 2172, 2132, 1679, 1582, 846. 1H NMR (400 MHz, CDCl3, 25 °C, ppm): δ: 7.91 (d, 2H, J = 8.2 Hz), 7.63 (d, 2H, J = 8.2 Hz). 13C NMR (100 MHz, CDCl3, 25 °C, ppm): δ: 171.9 (171.8), 49 132.1, 130.9, 129.8, 129.5.

4-Methylbenzoyl azide (Table 2, entry 8)
Solid; mp 33–35 °C (lit. value23 mp 35 °C). IR (KBr, cm−1): 3043, 2962, 2933, 2869, 2137 (2145), 77 1716 (1710), 77 1464, 1192, 722.

3,5-Dimethylbenzoyl azide (Table 2, entry 9)
Solid; mp 29–31 °C. IR (KBr, cm−1): 3050, 2930, 2921, 2905, 2861, 2169, 1607, 885, 650. 1H NMR (100 MHz, CDCl3, 25 °C, ppm): δ: 7.65 (2H), 7.25 (1H). 13C NMR (100 MHz, CDCl3, 25 °C, ppm): δ: 171.7 (171.69 – CONJ), 59 164.6, 131.7, 123.2, 113.9, 55.5.

Pyridine-2,6-dicarbonyl diazide (Table 2, entry 21)

5 Supplementary data
Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjcl-2011-0493.

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References

4-Hexanoyl azide (Table 2, entry 16)
Oil (lit. report:75 oil). IR (neat, cm−1): 2923, 2852, 2272, 2135 (2145), 77 1716 (1710), 77 1464, 1192, 722.

4-Chlorocinnamoyl azide (Table 2, entry 13)
Solid; mp 138–140 °C (lit. value28 mp 140 °C). IR (KBr, cm−1): 3068, 2914 (2915), 1680 (1685), 1629, 1588, 1498, 826. 1H NMR (400 MHz, CDCl3, 25 °C, ppm): δ: 7.72 (d, 1H, J = 16 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz), 6.41 (d, 1H, J = 16.0 Hz). 13C NMR (100 MHz, CDCl3, 25 °C, ppm): δ: 171.9, 145.2, 137.1, 132.3, 129.7, 129.4, 119.6.

Phenylenethyloxy azide (Table 2, entry 14)
Oil (lit. report:25 oil). IR (neat, cm−1): 3009, 2989, 2267, 2138 (2137), 59 1713 (1714), 59 1492, 1454, 719.

4-Phenylbutyloxy azide (Table 2, entry 15)

Hexanoyl azide (Table 2, entry 16)
Oil (lit. report:25 oil). IR (neat, cm−1): 3062, 2933, 2869, 2137 (2135), 59 1697 (1722), 59 1533, 1232.

OCTADEC-9(Z)-ENOLY AZIDE (Table 2, entry 17)

Stearoyl azide (Table 2, entry 18)
Solid; mp 37–39 °C (lit. value26 mp 38–40 °C). IR (KBr, cm−1): 2923, 2852, 2272, 2135 (2145), 77 1716 (1710), 77 1464, 1192, 722.

Thiophene-3-carboxyl azide (Table 2, entry 19)
Oil (lit. report:28 oil). IR (neat, cm−1): 3108, 2928, 2201 (2273), 2139 (2139), 1686, 1516, 728. 1H NMR (100 MHz, CDCl3, 25 °C, ppm): δ: 8.2 (dd, 1H), 7.6 (dd, 1H), 7.4 (dd, 1H).

Pyridine-4-carboxyl azide (Table 2, entry 20)
Oil (lit. report:28 oil). IR (neat, cm−1): 2928, 2853, 2190, 2140, 1705, 1564, 1407, 690.

Pyridine-2,6-dicarboxyl azide (Table 2, entry 21)