A MILD AND EFFICIENT METHOD FOR THE SYNTHESIS OF ACYL AZIDES FROM CARBOXYLIC ACIDS UTILIZING PHOSPHONITRILIC CHLORIDE

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ABSTRACT

An efficient method has been described for the one pot synthesis of acyl azides from corresponding carboxylic acids and sodium azide utilizing phosphonitrilic chloride trimer (Cl$_6$N$_3$P$_3$) in combination with NMM under extremely mild conditions. A variety of carboxylic acids has been converted to azides in good to excellent yields. Aromatic carboxylic acids as well as aliphatic and unsaturated carboxylic acids have been smoothly converted into corresponding acyl azides without Curtius rearrangement to an isocyanate.


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INTRODUCTION

Carboxylic acids are highly desirable substrates in organic chemistry. They are effective intermediates for organic synthesis, can be easily handled and stored. They are stable but less reactive compounds. Therefore, in organic synthesis, it is essential to enhance its reactivity. In the activation of carboxylic acid the hydroxyl group has been replaced by electron withdrawing substituent which increases the polarization of carboxyl group and thus its reactivity. During the process of activation, the carboxylic moiety becomes highly reactive towards nucleophilic attack. The carboxylic acids can be activated in situ activation by coupling reagents. These coupling reagents are highly effective and easy to handle, for the activation of carboxylic acids under mild and compatible conditions. They can be coupled with various functional groups including the most commonly protecting groups.[1-4] Activation of carboxylic acids were carried out by the conversion to more reactive functional groups such as anhydride, [5-7] acyl halide [8-10] and acyl azides.[11-12] Various coupling reagents used for the activation of carboxylic acids are Sn[N(TMS)2]2,[13] N-Halo succinimide / PhP, [14] Cl3CCN / PhP,[15] ArB(OH)2, [16] DMAP/BOC–OX, [17] Me2NSO4 and N, N-Dimethylamine, [18]. 2-Mercaptopyridine-1-oxide based uranium salt, [19] Tosyl chloride, [20] Triphosgene. [21]

The peptides, isocyanates and other compounds have been synthesized from organic acid azides. [22] In organic synthesis, acyl azides are widely used as synthetic intermediates.[23-30] Organic azides have been extensively used for the synthesis of pharmacologically active substances, heterocycles and nitrogen containing compounds commonly related to natural products[31-39].

Acyl azides have been prepared by various methods. [40-44] Acyl azides have been synthesized from acid derivatives such as acid halides and acid hydrazides. [28-29, 40] A reaction of acyl chloride and azide ions in a mixture of water and water miscible organic solvents was used for preparation of acyl azides. This reaction is thermally sensitive, can undergo Curtius rearrangement of acyl azide in organic solvents, which leads moisture sensitive products-isocyanates. Acyl azides were synthesized from acyl chloride by reacting with polymer-supported azide ion reagent in high yields.[45] Acyl chlorides were converted to acyl azides by reacting with hazardous hydrazoic acid using tetramethyl guanidium or tetraalkyl ammonium azide.[43]

Aldehydes were converted directly to carboxamoyl azides / acyl azides using pyridinium chlorochromate,[46] triazidichlorosilane-manganese dioxide,[47] iodide azide,[48] t-butyl hypochlorite.[49] Acyl azides were reported to be prepared from acyl chlorides or anhydrides or mixed carboxylic acid anhydride[27] using lithium azide,[42] sodium azide,[50,51] tetraalkyl ammonium guanidium azide,[52] tetrabutyl stannyl azides,[53] phenyl dichlorophosphate.[54] Conversion of acyl chloride into acyl azide at 0°C in dichloromethane using zinc iodide as a catalyst was reported.[44] Acyl azides were also prepared from N-acyl benzotriazoles.[55,56]

Acyl azides were prepared commonly from carboxylic acids which then undergo Curtius rearrangement to form isocyanates.[1] The extensive work was reported on the conversion of carboxylic acid to acyl azide. The acid activators such as ethyl chloroformate,[57,58] SOCl2-DMF,[59] NCS-PPh3, [60] triphosgene, [61] 3,4,5-trifluorobenzene boronic acid,[62] cyanuric chloride [63] and DMF-POCI3,[64] were reported for this transformation. Various methods were developed for conversion of carboxylic acids into corresponding acyl azides using Deoxo-Fluor, [65] PPh3/Cl3CCN, [66] and BOP, [67] TBTU, [68] chlorodiphenylphosphine/iodine,[69] TPP-TCCA.[70]

Phosphonitrilic chloride (PNT) having six functional chlorine atoms is a white crystalline compound, which is thermally stable and soluble in variety of organic solvents. PNT has been used as dehydrating agent [71], reagent [72,73], catalyst [74-76] and activator [77] for various organic transformations. PNT has not yet been utilized for the activation of carboxylic acid. Therefore, in search of an efficient carboxylic acid activator and considering a great utility of acyl azides, we report the use of PNT catalyzed efficient method for the direct coupling of carboxylic acid (I) with sodium azide (II) to acyl azides (III) under mild conditions (Scheme 1)

\[
\begin{align*}
\text{R} &\quad \text{R} \\
\text{O} &\quad \text{O} \\
\text{OH} &\quad \text{NaN}_3 \\
\text{PNT, NMM} &\quad \text{CH}_2\text{Cl}_2, \text{ rt} \\
\text{R} &\quad \text{R} \\
\text{N}_3 &\quad \text{N}_3
\end{align*}
\]

\[\text{R} = \text{Aryl, alkyl}\]

\[\text{I} \quad \text{II} \quad \text{III}\]

Scheme 1
**EXPERIMENTAL PROCEDURE**

PNT (0.2 mmol) was dissolved in 10 ml dichloromethane and NMM (1.21 mmol) was added with constant stirring at temperature 0-5 °C. After 30 minutes the carboxylic acid (1mmol) was added and stirring was continued. After complete disappearance of carboxylic acid (TLC), sodium azide (1.21 mmol) was added and further stirring continued at room temperature for three hours. Then reaction mixture was taken into separating funnel along with washing of reaction flask by dichloromethane (2×10 ml). The combined layer was washed with NaHCO₃ (2×10 ml) and H₂O (2×10 ml). It was then dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure to get desired product. All the products were purified by column chromatography (pet ether: ethyl acetate, 9:1 v/v).

**RESULTS AND DISCUSSION**

One equivalent of PNT activates 6 equivalents of carboxylic acid, which merits the existing carboxylic acid activators. In the present work, PNT was activated by NMM in dichloromethane at 0-5 °C to give a morpholinium salt that has been reacted with various structurally diverse carboxylic acids (I) to form corresponding activated esters. The activated esters were then reacted with sodium azide (II) at room temperature to give desired products (III) (Scheme 2) in excellent yields. (Table 1)

![Scheme 2](image-url)

Aromatic as well as aliphatic carboxylic acids reacted with sodium azide under these conditions to afford the corresponding azides in good to excellent yields. Aromatic carboxylic acids with electron withdrawing groups (Table 1, entries 4 and 5) gave higher yields compared to electron donating groups (Table 1, entry 6). Remarkably, α, β-unsaturated carboxylic acids, for instance, cinnamic acid (Table 1, entry 8), was converted to corresponding cinnamoyl azide in good yield without giving any side products. The PNT promoted process has several advantages over the reported hazardous expensive processes that make it suitable for azidation. Transformation has been carried out under mild conditions without Curtius rearrangement leading to an isocyanate.

PNT having six reactive chlorine atoms upon treatment with six equivalent of NMM in dichloromethane at 0-5 °C forms suspension of morpholine salt. We propose structure IV for this salt.
IV

Therefore we have utilized PNT together with NMM for the activation of carboxylic acid similar to cyanuric chloride: NMM combination. PNT activates six equivalents of carboxylic acid compared to three equivalents by cyanuric chloride. The method provides a clean route for the formation of acyl azides. (Table 1)

Table 1: Synthesis of acyl azides from carboxylic acids utilizing PNT.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Acyl azides</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
<th>M.P. (°C)</th>
<th>Lit [61, 63]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzoic acid</td>
<td>Benzoyl azide</td>
<td>90</td>
<td>oil</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>p-Toluic acid</td>
<td>p-Toluoyl azide</td>
<td>89</td>
<td>88-89</td>
<td>88-90</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>p-Chlorobenzoic acid</td>
<td>p-Chlorobenzoyl azide</td>
<td>90</td>
<td>39</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>p-Nitrobenzoic acid</td>
<td>p-Nitrobenzoyl azide</td>
<td>97</td>
<td>70</td>
<td>68-69</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3,5-Dinitrobenzoic acid</td>
<td>3,5- Dinitrobenzoyl azide</td>
<td>97</td>
<td>100-103</td>
<td>100-102</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>p-Methoxybenzoic acid</td>
<td>p-Methoxybenzoyl azide</td>
<td>88</td>
<td>68</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Phenoxy acetic acid</td>
<td>Phenoxy acetyl azide</td>
<td>95</td>
<td>oil</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Cinnamic acid</td>
<td>Cinnamoyl azide</td>
<td>96</td>
<td>83</td>
<td>82-84</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Hexanoic acid</td>
<td>Hexanoyl azide</td>
<td>94</td>
<td>oil</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Octanoic acid</td>
<td>Octanoyl azide</td>
<td>96</td>
<td>oil</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Decanoic acid</td>
<td>Decanoyl azide</td>
<td>97</td>
<td>oil</td>
<td>oil</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS

The present protocol was found to be an efficient procedure for the activation and subsequently conversion of carboxylic acid into acyl azides under mild conditions. Aromatic carboxylic acids with electron withdrawing groups were converted into corresponding acyl azides in higher yields than that of electron donating groups. PNT was also found to be efficient for α, β-unsaturated carboxylic acids.

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