Direct Synthesis of Acyl Azides from Carboxylic Acids by the Combination of Trichloroacetonitrile, Triphenylphosphine and Sodium Azide

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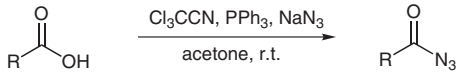
Abstract: Various carboxylic acids were converted into acyl azides in excellent yields by treating with trichloroacetonitrile, triphenylphosphine and sodium azide at room temperature. The reaction was applicable to the preparation of dipeptide without rearrangement.

Key words: carboxylic acids, azides, peptides, acylations, trichloroacetonitrile

Acyl azides have been used as valuable synthetic intermediates for the synthesis of isocyanates, ureas, amines, amides, ketenimines and carbodiimides.[1] One of important applications of these compounds is their use as activating agents for peptide bond formation, especially for the segment condensation of peptide fragments.[2] Acyl azides are usually prepared from carboxylic acid derivatives such as acyl chlorides or anhydrides with azides.[3] However, these methods have some drawbacks including low yields, rearrangement to isocyanates, and previous transformation of carboxylic acids into the corresponding acyl halides or other highly reactive carboxylic acid derivatives. To overcome these drawbacks, direct transformation of carboxylic acids or other readily available starting materials into acyl azides has been developed. It has been reported that aldehydes were converted into the corresponding acyl azides by combination of chromic anhydride and azidotrimethylsilane[4] or iodine azide.[5] The direct transformation of carboxylic acids into acyl azides was also achieved by using diphenylphosphoryl azide,[6] tetramethylfluoroformamidinium hexafluorophosphate,[7] phenyl dichlorophosphate,[8] $SOCl_2$–DMF,[9] triphosgene,[10] cyanuric chloride,[11] or NCS–Ph_3P[12] in the presence of azide ions. We herein report a mild and efficient procedure for the synthesis of acyl azides from carboxylic acids with trichloroacetonitrile, triphenylphosphine and sodium azide.

It was assumed that carboxylic acid chlorides prepared in situ from carboxylic acids with a combination of trichloroacetonitrile and triphenylphosphine might be transformed into the corresponding acyl azides by treating with azide ions (Scheme 1).[13] We chose benzoic acid as a model compound to establish the optimal reaction conditions. When benzoic acid was treated with Cl_3CCN (1.5 equiv), Ph_3P (1.5 equiv) and NaN_3 (1.2 equiv) in acetone at room temperature for one hour, the desired benzoyl azide was obtained in 74% yield along with the unreacted benzoic acid (Table 1, entry 1). However, when the amount of Cl_3CCN and Ph_3P was increased, benzoic acid was transformed to benzoyl azide completely in 30 minutes affording high yield of benzoyl azide (entry 2). The reaction could be carried out even at 0 °C without affecting the yield of benzoyl azide (entry 3). We screened organic solvents to find suitable solvents for the reaction. Acetone and acetonitrile gave excellent yields (entries 2 and 4). Other common organic solvents such as toluene, THF, diethyl ether, ethyl acetate and dichloromethane could be used although longer reaction time was required to complete the reaction (entries 5–9).



Scheme 1

Table 1 Formation of Benzoyl Azide from Benzoic Acid with Cl_3CCN, Ph_3P and NaN_3

Entry	Cl_3CCN (equiv)	PPh_3 (equiv)	Solvent	Time (h)	Yield of azide (%)
1	1.5	1.5	acetone	1	74
2	2.0	2.0	acetone	0.5	96
3	2.0	2.0	acetone	0.5	93[a]
4	2.0	2.0	MeCN	0.5	95
5	2.0	2.0	toluene	6	90
6	2.0	2.0	THF	6	90
7	2.0	2.0	Et_2O	8	86
8	2.0	2.0	EtOAc	8	91
9	2.0	2.0	CH_2Cl_2	12	87

[a] The reaction was carried out at 0 °C.

To investigate the scope and limitations of the reaction, various aryl and alkyl carboxylic acids were subjected to the reaction conditions. The results are presented in Table 2. Compared to alkyl carboxylic acids, aryl carbox-

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ylic acids afforded higher yields of acyl azides. Carboxylic acids with an electron-releasing group or electron-withdrawing group were readily converted into acyl azides in high yields. This method is found to be very mild, efficient, and general for the transformation of carboxylic acids into the corresponding acyl azides without the Curtius rearrangement.

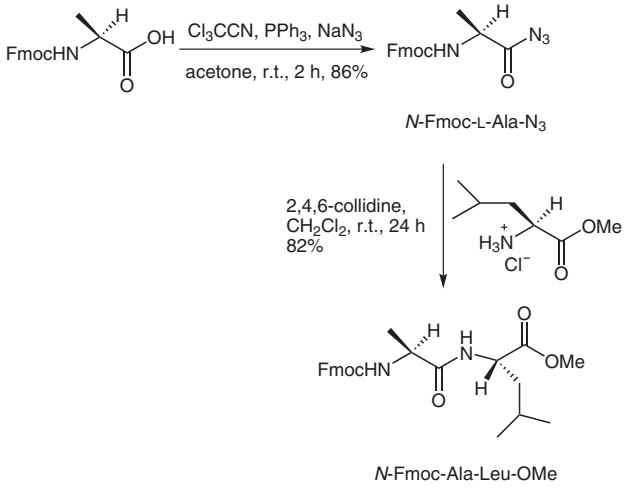
Table 2 Formation of Various Acyl Azides from Carboxylic Acids[a]

Entry	Acid	Time (h)	Yield of azide (%)
1	*p*-methylbenzoic acid	0.5	94
2	*p*-(dimethylamino)benzoic acid	0.5	93
3	*p*-chlorobenzoic acid	0.5	89
4	*p*-methoxybenzoic acid	0.5	97
5	*p*-nitrobenzoic acid	0.5	90
6	*p*-acetylbenzoic acid	0.5	91
7	salicylic acid	2.0	82
8	2-naphthoic acid	0.5	93
9	nicotinic acid	0.5	89
10	phthalimidoacetic acid	1.0	89
11	3-phenylpropionic acid	2.0	83
12	trimethylacetic acid	2.0	84
13	*n*-octanoic acid	2.0	86
14	palmitic acid	2.0	88
15	adamantane-1-carboxylic acid	2.0	87
16	*trans*-cinnamic acid	1.0	83
17	3,5-difluoro-*trans*-cinnamic acid	2.0	81
18	phenoxyacetic acid	2.0	89
19	phenylacetic acid	2.0	87

[a] See the typical experimental procedure[14] for the reaction conditions. Spectroscopic data of the products were consistent with those in the literature.

Next, we applied our present method to the synthesis of dipeptide (Scheme 2). Treatment of *N*-Fmoc-L-Ala with Cl_3CCN, Ph_3P and NaN_3 in acetone gave *N*-Fmoc-L-Ala-N_3 in 86% yield.[15] When treated with L-Leu-OMe in the presence of 2,4,6-collidine, the acyl azide was readily converted into the dipeptide, *N*-Fmoc-Ala-Leu-OMe,[16] in 82% yield without indication of deprotection or rearrangement.

In summary, we have developed a mild and convenient direct process for the synthesis of acyl azides from carboxylic acids with Cl_3CCN, Ph_3P and NaN_3. The process shows the generality for the preparation of acyl azides from various carboxylic acids. The reaction was applicable to the preparation of dipeptide without deprotection or rearrangement during the reaction.



Scheme 2

Acknowledgment

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(14) **Typical Experimental Procedure**: To a mixture of benzoic acid (122 mg, 1.0 mmol), triphenylphosphine (525 mg, 2.0 mmol) and sodium azide (78 mg, 1.2 mmol) in anhyd acetone (2 mL) under argon was added trichloroacetonitrile (0.2 mL, 2.0 mmol) dropwise at r.t. The reactants were allowed to react for 30 min. After concentration of the reaction mixture by a rotary evaporator, the residue was then diluted with CH_2Cl_2 (4 mL), and washed with H_2O (2 mL). The organic layer was dried over anhyd $MgSO_4$. After filtration, the solvent was removed and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 2:1) to give benzoyl azide (141 mg, 96%).
(15) *N*-Fmoc-L-Ala-N_3: mp 162–164 °C (lit.[17] mp 162 °C); $[\alpha]_D^{25}$ 16.3 (*c* = 1, $CHCl_3$) (lit.[17] $[\alpha]_D$ –16). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 2.2 Hz, 3 H), 3.86 (m, 1 H), 4.22 (t, *J* = 2.3 Hz, 1 H), 4.41 (d, *J* = 2.3 Hz, 2 H), 5.28 (s, 1 H), 7.22–7.84 (m, 8 H).
(16) *N*-Fmoc-Ala-Leu-OMe: mp 124–126 °C (lit.[2c] mp 123–126 °C); $[\alpha]_D^{25}$ –28.1 (*c* = 1, $CHCl_3$) (lit.[2c] $[\alpha]_D$ –25.2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 6 H), 1.42 (d, *J* = 2.2 Hz, 3 H), 1.55 (m, 1 H), 1.64 (m, 2 H), 3.71 (s, 3 H), 4.23 (t, *J* = 2.4 Hz, 1 H), 4.30 (t, *J* = 2.2 Hz, 1 H), 4.40 (d, *J* = 2.4 Hz, 2 H), 4.61 (q, *J* = 1.6 Hz, 1 H), 5.42 (s, 1 H), 6.37 (s, 1 H), 7.25–7.82 (m, 8 H).
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