An Efficient Method for Preparation of Acyl Chlorides and Symmetrical Anhydrides from Carboxylic Acids with Btc/Dmf

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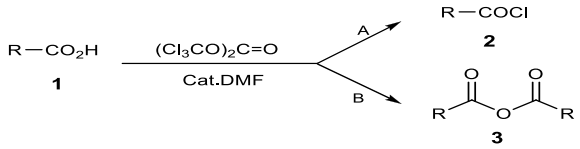
Summary: Efficient conversion of carboxylic acids to the corresponding acyl chlorides or symmetrical anhydrides can be carried out at relatively mild condition using *bis*-(trichloromethyl) carbonate and *N,N*-dimethyl formamide.

Introduction

Acyl chlorides and symmetrical acid anhydrides are very useful intermediates because of their wide used in organic synthesis.[1-5] A plethora of reagents such as thionyl chloride,[6] phosphorus trichloride [7] and phosphorus pentachloride, [8] have been utilized as such or in combination with a base. Though these transformations are routine, newer systems continue to be developed as reflected by the recent reports where trichloroacetonitrile/ triphenyl-phosphine (TPP) [9] was used for the conversion of carboxylic acids to acyl chlorides and Ph_3P/CCl_3CN, [10] TosCl /K_2CO_3, [11] Bis-(trichloromethyl) carbonate (BTC)/Et_3N [12] and $Ph_3P/COCl_2$ [13] have been utilized for the conversion of carboxylic acids to symmetrical acid anhydrides. However, there are some drawbacks such as high cost, low yield, harsh reaction conditions and contamination with by-products. Thus, the development of inexpensive, stable, mild and environmentally friendly processes is still in demand. Herein, we report an efficient method for the preparation of acyl chlorides and symmetrical acid anhydrides from carboxylic acids by using BTC with catalytic amount of N, N-dimethylformamide (DMF) in moderate to good yields (Scheme 1).



Scheme 1: Synthesis of acyl chlorides and symmetric anhydrides

Results and discussion

As is known, BTC (triphosgene) has emerged as a versatile synthetic auxiliary in the preparation of various organic compounds.[14] It is a stable solid (mp. 79-80°C, bp. 205-207 °C, only slight decomposition to phosgene occurs at its boiling point), [15] safe to handle and conveniently transport and store. Reactions with BTC usually proceed under relatively mild conditions and often afford good to excellent yields.

Initial studies were undertaken using benzoic acid and BTC in tetrahydrofuran（THF）as a model reaction to investigate the suitable ratio of DMF. The reactions were conducted in the presence of 1% mol, 2% mol, 3% mol, 5% mol, 10 %mol and no DMF. It was found that only 26% yield of corresponding product was formed even after 14 h in the absence of DMF. The best result of 93% was achieved by using 3% mol DMF as a catalyst after 6 h. 1% mol, 2% mol, 5% mol and 10% mol amount of DMF also showed catalytic activities which gave the product in yields of 85%, 89%, 82%, 76%, respectively. Solvents such as THF, dichloromethane, ethyl acetate and chlorobenzene were also tested. It appears that THF is a much better solvent (93%) than the other solvents such as ethyl acetate (84%), dichloromethane (81%), chlorobenzene (76%). Subsequently, some other acids were used to expand upon this reaction and the results are summarized in Table-1. It was found that a series of acyl chlorides were obtained as the major products in all cases with good yields and electron-donating or electron-withdrawing groups on aromatic substrates had practically no effect on the overall transformation.

The formation of symmetrical acid anhydrides was discovered serendipitiously during the preparation of benzoyl chloride at increased temperature and with lower the amount of BTC; another product was detected on TLC and identified as benzoic anhydrides by ^1H NMR, ^{13}C NMR and MS. A possible mechanism for synthesis of acyl chlorides and symmetrical acid anhydrides may be proposed as shown in Scheme 2.

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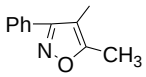
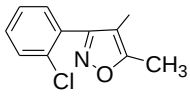
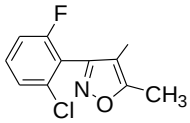
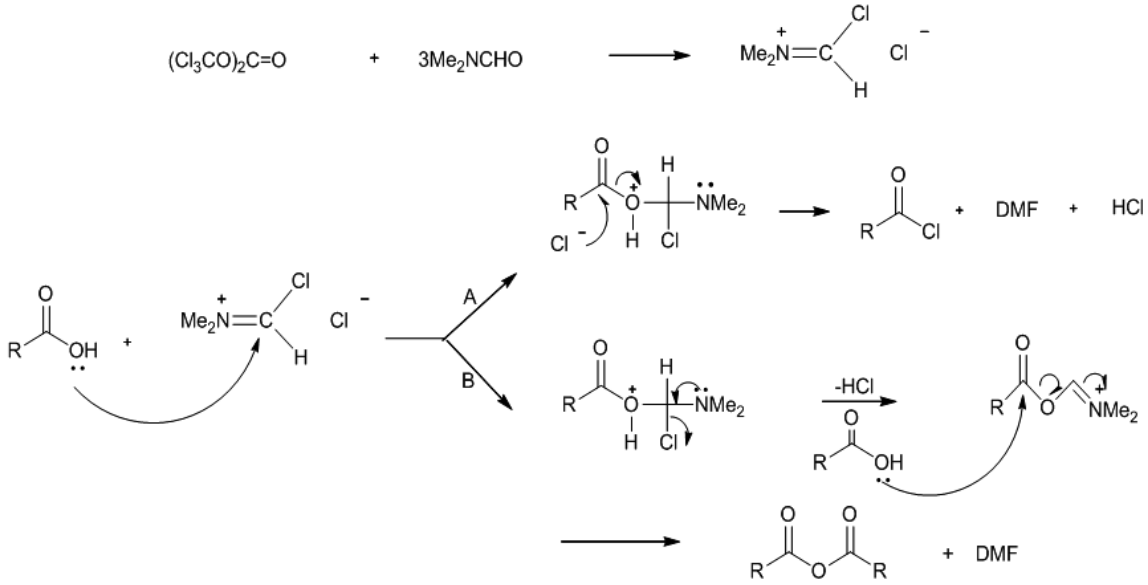
Table-1: Synthesis of Acyl Chlorides[a.]

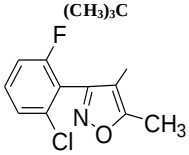
R	Product	Yield[b](%)	Time(h)	mp. (°C)	lit. mp. (°C)
CH_3COCH_2	2a	91	5	Liquid	Liquid [16]
$CH_3(CH_2)_9CH_2$	2b	95	5	Liquid	Liquid [17]
$CH_3CH_2OCO(CH_2)_3CH_2$	2c	92	5	Liquid	Liquid [18]
C_6H_5	2d	93	5	Liquid	Liquid [19]
4-$MeOC_6H_4$	2e	93	5	Liquid	Liquid [20]
2-ClC_6H_4	2f	95	5	Liquid	Liquid [21]
4-$NO_2C_6H_4$	2g	90	5	72-73	71-73 [20]
$C_6H_5CH_2$	2h	95	5	Liquid	Liquid [22]
	2i	93	5	Oil	Oil [23]
	2j	92	5	Oil	Oil [24]
	2k	93	5	Oil	Oil [25]

a) Reaction conditions: carboxylic acids (100 mmol), BTC (37 mmol), DMF (3 mmol), THF (25 mL). b) Yields based on carboxylic acids.



Scheme 2: Possible mechanism for the synthesis of acyl chlorides and symmetric anhydrides.

Table 2: Synthesis of Symmetrical Acid Anhydrides[a.]

R	Product	Yield[b](%)	Time(h)	mp. (°C)	*lit.* mp. (°C)
$CH_3(CH_2)_9CH_2$	3a	90	3	41	41-42[26]
4-BrC_6H_4	3b	96	3	222	225-226[27]
4-$MeOC_6H_4$	3c	95	3	96	97-99[28]
CH_3CH_2	3d	97	3	Liquid	Liquid[29]
C_6H_5	3e	98	3	43-44	42-43[30]
2-ClC_6H_4	3f	96	3	79-81	77-79[26]
4-$NO_2C_6H_4$	3g	93	3	195-198	194[30]
$(CH_3)_3C$	3h	82	3	Liquid	Liquid [26]
	3i	88	3	278	

a) Reaction conditions: carboxylic acids (100 mmol), BTC (17 mmol), DMF (3 mmol) , THF(25 mL), 50℃ b) Yields based on carboxylic acids.

The only report [12] of the synthesis of acid anhydrides by BTC did give good yields, and furthermore one equivalent of triethylamine was used as acid scavenger. In our experiments carboxylic acids were converted into the corresponding symmetrical acid anhydrides efficiently with BTC/DMF. By screening a variety of ratios of benzoic acid/BTC/DMF in THF, a ratio of 100:17:3 was determined to be the most suitable system to generate the benzoic anhydride with good yields at 50□. We applied the optimal protocol to a variety of carboxylic acids and the results are summarized in Table-2. This reaction proceeded smoothly and gave the corresponding products in excellent yields.

In summary, we have developed a simple and straightforward procedure for synthesis of acyl chlorides and symmetrical acid anhydrides with BTC/DMF under relatively mild conditions. Compared to previous reported methodologies, the present protocol features environmentally friendly and mild reaction conditions and good yields.

Experimental

Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. H^1 NMR spectra were measured on a Varian Mercur plus-400 spectrometer with tetramethylsilan (TMS) as an internal standard and $CDCl_3$ as the solvent. Mass (MS) spectra were obtained with a Finnigan Trace DSQ spectrometer. Elemental analysis was performed on a VarioEL-3 instrument. All chemicals are from commercial sources.

Typical Procedure for Synthesis of Acyl Chlorides (Path A)

A mixture of compound carboxylic acid (100 mmol, DMF 3 mmol) and THF (10 mL) was placed in a 100 mL three-necked flask, a solution of BTC (37 mmol) in THF (15 mL) was added dropwise over a period of 4 hours at room temperature. Then the mixture was continued to stir for 1 hour. The solvent along with the generated HCl were vaporized at normal pressure and then the residue was distilled under vacuum to give acyl chlorides or solid residue was could be purified by recrystallization form ethyl acetate. The data of acyl chlorides is shown in Table-3.

Typical Procedure for Synthesis of Symmetrical Acid anhydrides(Path B)

A mixture of compound carboxylic acid (100 mmol, DMF 3mmol) and THF (10 mL) was placed in a 100 mL three-necked flask equipped with a reflux condenser, a solution of BTC (17 mmol) in THF (15 mL) was added dropwise over a 2.5 hours at 50°C and then the mixture was continued to react about 0.5 hour at 50°C. The solvent along with the generated HCl were vaporized at normal pressure and then the residue was distilled under vacuum to give symmetrical acid anhydrides or solid residue was could be purified by recrystallization from ethyl acetate. The data of symmetrical acid anhydrides is shown in Table-3.

Table-3: Data of Acyl Chlorides and Symmetrical Acid Anhydrides.

Product	IR (cm^{-1}) (C=O)	^{1}H NMR(δ)
2a	1755	4.90 (2 H, s, CH_2), 2.18 (3 H, s, CH_3).
2b	1801	2.88 (2 H, t, J = 7.2 Hz, CH_2), 1.72-1.69 (2 H, m, CH_2), 1.36-1.21 (14 H, m, 7×CH_2), 0.88 (3 H, t, J = 7.2 Hz, CH_3).
2c	1801	4.13 (2 H, q, J = 3.6 Hz, CH_2), 2.93 (2 H, t, J = 6.8 Hz, CH_2), 2.34 (2 H, t, J = 7.2 Hz, CH_2), 1.71-1. 68 (4 H, m, 2×CH_2), 1.26 (3 H, t, J = 6.8 Hz, CH_3).
2d	1775	8.11 (1 H, d, J = 7.2 Hz, Ar H), 7.68-7.61 (3 H, m,Ar H), 7.50 (1 H, t, J = 7.2 Hz, Ar H).
2e	1758	8.06（2 H, d, J = 7.6 Hz, Ar H）, 6.98 (2 H, d, J = 7.6 Hz, Ar H), 3.90 (3 H, s, CH_3).
2f	1800	8.11 (1 H, d, J = 7.6 Hz, Ar H), 7.56-7.50 (2 H, m,Ar H), 7.42 (1 H, t, J = 7.2 Hz, Ar H).
2g	1758	8.33-8.24 (4 H, m Ar H).
2h	1081	7.45-7.19 (5 H, m, Ar H), 4.12 (2 H, s, CH_2).
2i	1763	7.54-7.45 (5 H, m, Ar H), 2.81 (3 H, s, CH_3).
2j	1764	7.56-7.45 (4 H, m, Ar H), 2.85 (3 H, s, CH_3).
2k	1763	7.46-7.42 (1 H, m, Ar H), 7.32 (1 H, d, J = 8.0 Hz, Ar H), 7.13 (1 H, t, J = 8.8 Hz, Ar H), 2.87 (3 H, s, CH_3).
3a	1793, 1711	2.44 (4 H, t, J = 1.4 Hz, CH_2), 1.70-1.62 (4 H, m, CH_2), 1.30-1.26 (32 H, m, 16×CH_2), 0.88 (6 H, t, J =1.4 Hz, CH_3).
3b	1785, 1720	8.10 (4 H, d, J = 8.4 Hz, Ar H), 7.53 (4 H, d, J = 8.4 Hz, Ar H).
3c	1785, 1711	8.11 (4 H, d, J = 8.0 Hz, Ar H), 7.82 (4 H, d, J = 8.0 Hz, Ar H), 3.84 (6 H, s, 2×CH_3).
3d	1786, 1725	1.18 (6 H, t, J = 3.6 Hz)， 2.50 (4 H, q, J = 6.8 Hz).
3e	1785, 1726	8.12 (4 H, d, J = 8.4 Hz, Ar H), 7.68-7.58 (2 H, m, Ar H), 7.54-7.48 (4 H, m, Ar H).
3f	1780, 1718	8.04 (2 H, d, J = 7.2 Hz, Ar H), 7.54-7.48 (4 H, m, Ar H), 7.42-7.26 (2 H, m, Ar H).
3g	1684, 1602	8.36 (4 H, d, J = 7.2 Hz, Ar H), 8.21 (4 H, d, J = 7.2 Hz, Ar H).
3h	1809, 1741	1.27 (18 H, s, 6×CH_3).
3i [a]	1874, 1793	7.38-7.33 (2 H, m, Ar H), 7.26 (2 H, d, J = 7.2 Hz, Ar H), 7.09 (2 H, t, J = 7.6 Hz, Ar H), 2.64 (6 H, s, 2×CH_3).

a) 13C NMR (100 MHz, CDCl3): δ = 115.0, 115.2, 118.5, 118.6, 126.0, 130.8, 130.9, 134.9, 143.8, 159.6, 162.2. MS (EI): m/z (%) = 493 (M++1, 3), 240 (13), 238 (41), 198 (35), 196 (100), 132 (10). Anal. Calcd. for C22H12Cl2F2N2O5 (493): C, 53.5%; H, 2.5%; N, 5.8%; Found: C, 53.6%; H 2.5%; N, 5.7%.

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