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A NEW SYNTHESIS OF CARBOXYLIC AND CARBONIC ACID ANHYDRIDES USING PHASE TRANSFER REACTIONS

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ABSTRACT - *Acyl chlorides and alkylchloroformates smoothly reacted with one molar equivalent of sodium hydroxide, using liquid-liquid phase transfer conditions to afford high yields of the corresponding symmetrical carboxylic and carbonic hemiester anhydrides. Unstable anhydrides such as 4-nitrobenzoïc, 2-furoïc and methacrylic anhydrides, which are otherwise difficult to obtain, were easily prepared by this method. The reaction mechanism does not seem to involve intermediate hydrolysis of half the acid chloride into the corresponding sodium carboxylate.*

Carboxylic acid anhydrides are very important reagents in organic chemistry. Less reactive than acyl chlorides, they are the usual intermediates for the synthesis of esters, amides and peptides. Such anhydrides can be obtained in different ways. A method extensively used is based on the reaction between a carboxylic acid and a dehydrating agent [1] such as DCC, acetic, trifluoroacetic or phosphoric anhydrides. This method was recently improved by KIKA and coworkers[2] who used trimethylsilylethoxyacetylene as a dehydrating agent in the synthesis of acid labile anhydrides.

The reaction of an acyl chloride with a metal carboxylate is another method which leads to either symmetrical or unsymmetrical anhydrides. Sodium, potassium and especially thallium salts are most often used in this case.[3] However, it has been shown recently that using insoluble basic reagents, such as polyvinylpyridine, makes the preliminary preparation of carboxylic acid salts unnecessary and moreover, gives better results.[4]

It is also possible to obtain anhydrides according to more complex methods ; [5] for example, particularly by treating a carboxylic acid salt with sulphur and bromine, [5a] by treating the free acid with a N-trihaloacetylimidazole, [5b] or with carbon tetrachloride and tris-(dimethylamino)phosphine.[5c]

Finally, GIESE[6] recently described a new synthesis based on the reaction between an acyl chloride and hydrated 1,1,1-trichloro-3,3-trifluoroacetone, which often gives excellent yields, although this method does not apply to the preparation of hindered acid anhydrides such as pivalic anhydride.

In our case, we have described in a preliminary communication[7] a rapid and very simple method for the preparation of symmetrical anhydrides from the corresponding acyl chlorides, by means of phase transfer catalysis. In the present work, we have generalized this method and we have shown that it also applies to the syntheses of symmetrical anhydrides which are difficult to obtain by other methods.

RESULTS

We used a biphasic system comprising a 20 % aqueous sodium hydroxide solution, and an organic solvent in which the acyl chloride **1** and a phase transfer catalyst (PTC) (0.1 equ.) were dissolved. The reaction was carried out at -10°C for 0.25-3 hours under vigorous stirring. At the end of the reaction, the organic phase was separated, diluted with ether, washed with water, dried and evaporated. The anhydrides **2** thus obtained were sufficiently pure for further use. The overall reaction can be represented as follows (Fig. 1).

$$\underset{\mathbf{1a}\,-\,\mathbf{p}}{2\,\mathrm{RCOCl}} + 2\,\mathrm{NaOH} \longrightarrow \underset{\mathbf{2a}\,-\,\mathbf{p}}{(\mathrm{RCO})_2\mathrm{O}} + \mathrm{H_2O} + 2\,\mathrm{NaCl}$$

Fig. 1 - Synthesis of symmetrical anhydrides of carboxylic acids (**2a**-**l**) and carbonic hemiesters (**2m**-**p**)

Our main results are summarized in the Table. A systematic study concerning the catalyst was not undertaken. However, we obtained palmitic anhydride **2b** in 90 % yield when using tetra-*n*-butylammonium chloride as a catalyst (entry 3), whereas the yield fell to 65 % when using tri-*n*-capryl methylammonium chloride ("Aliquat") (entry 2). Therefore tetra-*n*-butylammonium chloride or bromide were subsequently used as catalysts.

When the acyl chlorides **1** and the anhydrides **2** produced from them are insoluble in aqueous caustic soda, an excess of the later was not found to be critical. In these conditions, indeed, we observed high yields for the anhydrides **2a**-**c**, **e**, **f**, **h**, **j**. In the case of more water-soluble anhydrides however, it is important to use the exact quantity of sodium hydroxide necessary for the reaction to reach completion, that is, one equivalent of base for one equivalent of acyl chloride **1**. For instance, methacrylic anhydride **2i** (entry 12) was obtained in 80 % yield from the chloride **1i** when operating in the presence of one equivalent of 20 % sodium hydroxide solution, whereas the yield was 7 % only when using an excess of base (entry 11). Additionally, the preparations of readily hydrolyzable carboxylic acid anhydrides (**2g**, **k**) and carbonic hemiester anhydrides (**2m**-**p**) required precise monitoring of the quantity of sodium hydroxide used.

In most cases, we used toluene as the organic phase solvent. However, when the desired anhydride has a low boiling point, it is more advisable to use diethyl ether or even better dichloromethane.

DISCUSSION

The present reaction is a general one and may be applied to the preparation of anhydrides unlikely or difficult to obtain by other known methods. For instance, pivalic anhydride **2d** (entry 6) was obtained in 58 % with our method, whereas the method of GIESE failed in this case.[6] We have also prepared *p*-nitrobenzoic anhydride **2g** in 87 % yield, although the classical methods were found to be unsuccessful. Up to now, the anhydride **2q** was obtained by treatment of triethylammonium *p*-nitrobenzoate with phosgene.[8] Similarly, the carbonic hemiester anhydrides **2m**-**p**, which are most generally prepared by treatment of the sodium or potassium salts of appropriate carbonic hemiesters with phosgene,[9] were easily obtained in the present case and in good yields, starting from commercially available alkyl chloroformates. These carbonic

TABLE - PREPARATION OF SYMMETRIC CARBOXYLIC AND CARBONIC ANHYDRIDES

$$\underset{\underline{1}\ (18\ \text{mmol})}{2\ \text{RCOCl}} \xrightarrow[\text{20 \% aqueous NaOH}]{\text{P.T. catalyst/solvent}} \underset{\underline{2}}{(\text{RCO})_2\text{O}}$$

Entry	R	Reaction conditions				Anhydrides	Yield(%)		mp (°C) (solvent)
		solvent	catalyst	time (min)	NaOH 20 % (ml)		found	litt.	[bp (°C) (mmHg)]
1	Me-$(CH_2)_{12}$-(a)	toluene	n-Bu_4NCl	180	7,5	2a	92	87(4a)	54(Me_2CO)
2	Me-$(CH_2)_{14}$-(b)	-id-	$[Me-(CH_2)_7]_3$NMeCl	-id-	100	2b	65	75(3c)	64(AcOEt)
3	-id-	-id-	n-Bu_4NCl	-id-	-id-	-id-	90		
4	Me-$(CH_2)_{16}$-(c)	-id-	-id-	-id-	-id-	2c	81	50(1f)	70-72 (AcOEt)
5	Me_3C - (d)	Et_2O	-id-	-id-	-id-	2d	54	-	[106 (50 mm)]
6	-id-	CH_2Cl_2	-id-	-id-	7,5	-id-	58	-	
7	Me-CH_2-CH-Ph-(e)	toluene	-id-	-id-	100	2e	80	-	[144 (0,2 mm)]
8	Ph(f)	-id-	-id-	-id-	7,5	2f	95	97(3c)	43-44(Petroleum ether)
9	p-NO_2-C_6H_4-(g)	CH_2Cl_2	n-Bu_4NBr	120	-id-	2g	87	70(8)	185($CHCl_3$)
10	Ph-CH = CH (h)	toluene	n-Bu_4NCl	180	100	2h	80	91(6)	137-138 (toluene)
11	H_2C = C Me-(i)	toluene	n-Bu_4NCl	180	100	2i	7	93(6)	[197-205(760 mm)]
12	-id-	CH_2Cl_2	n-Bu_4NBr	-id-	7,5	-id-	80		
13	 (j)	toluene	n-Bu_4NCl	-id-	100	2j	60	-	140-142 (Hexane)
14	 (k)	-id-	-id-	-id-	-id-	2k	0	64(3a)	71-73($CHCl_3$-Et2O)
15	-id-	CH_2Cl_2	n-Bu_4NBr	-id-	7,5	-id-	60		
16	-$(CH_2)_3$- (l)	-id-	-id-	30	-id-	2l	76	(12)	56 ($CHCl_3$)
17	Et-O-CO- (m)	toluene	-id-	15	-id-	2m	87	-	[78 (10 mm)]
18	Ph-CH_2-O-(n)	Et_2O	n-Bu_4NCl	30	-id-	2n	82(a)	-	
19	Me_2CH-CH_2-O(o)	CH_2Cl_2	n-Bu_4NBr	180	-id-	2o	79(b)	-	[94 (2 mm)]
20	EtO-(p)	-id-	-id-	60	-id-	2p	93(b)	53(13)	[62-64 (2 mm)]

(a) Compound 2n decomposed within 2 hours at 0-4°C and could not be purified by distillation.

(b) Compounds 2o and 2p decomposed partially on distillation under N_2 ; the yields given in the table correspond to crude products.

hemiester anhydrides are not very stable and must be purified rapidly by distillation under inert atmosphere. Dibenzyl dicarbonate 2n entirely decomposed in less than two hours in the refrigerator and could not be distilled.

In order to make our synthesis more economical, we considered replacing half the amount of the starting acyl chloride by the corresponding carboxylic acid. Thus we added a toluene solution containing palmitoyl chloride 1b and tetra-n-butylammonium chloride to a suspension of palmitic acid in 20 % sodium hydroxide solution. Under these conditions, the yield of palmitic anhydride 2b was only 40 % with respect to the total amount of palmitoyl groups present in the medium. In another experiment, we added a toluene solution containing the same catalyst as above and equimolecular amounts of palmitic acid and palmitoyl chloride 1b, to 20 % aqueous caustic soda solution. In this case, the yield of palmitic anhydride 2b, calculated as above, was about 44 %. Comparison of both these yields, with the much higher yield (90 %) observed when using palmitoyl chloride 1b alone (entry 3), implies that the sodium palmitate in the aqueous solution did not react with the acid chloride in the organic solvent, and that the transformation of part of the acide chloride into the corresponding carboxylate is not an intermediate step in our present synthesis of acid anhydrides.

Therefore, it is not surprising that we could not obtain the mixed benzoyl palmitoyl anhydride by treating an alkaline aqueous solution of sodium benzoate with a toluene solution of palmitoyl chloride 1b.

We tentatively propose the following mechanism to account for the above facts (Fig.2).

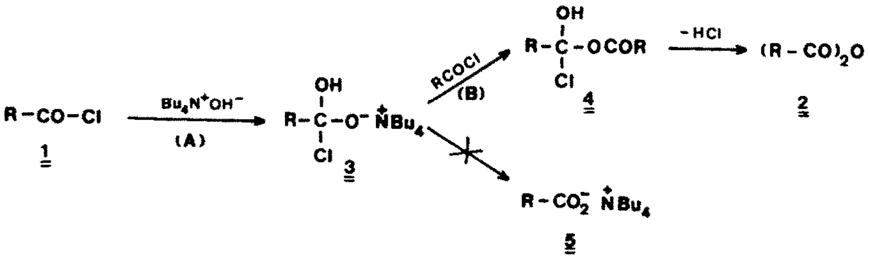

Fig. 2 - Mechanism of anhydride formation from acid chlorides

The first step (A) of this mechanism is identical with the one generally accepted for the alkaline hydrolysis of acid chlorides [10] with the catalyst being used exclusively for the transfer of hydroxide ions from the water solution into the organic phase. According to HERRIOTT, [11] tetra-n-butylammonium salts are more efficient than "Aliquat" among others, for transferring hydroxide ions into the organic phase. Presumably the ionic species 3 thus formed in step (A) rapidly reacts with a second molecule of acid chloride 1 (step B), and leads to the intermediate 4 rather than to the ammonium carboxylate 5.

CONCLUSION

We have developed a simple, rapid and general method for the synthesis of symmetrical carboxylic anhydrides from the corresponding acid chlorides. The reaction takes place under very mild conditions and makes it possible to synthesize anhydrides which are otherwise difficult to obtain.

EXPERIMENTAL SECTION

IR spectra were recorded on a Pye-Unicam SP 200 spectrophotometer. ^{1}H-NMR spectra were run with a Jeol MH 100 (100 MHz) spectrometer ; chemical shifts are expressed in δ values (ppm), using tetramethylsilane as an internal standard. Melting points were determined with a Reichert melting point apparatus, and are reported uncorrected. Elemental analyses were made by the "Service de microanalyse de l'E.N.S.C.R.". Thin layer chromatography was performed on Merck 60 F 254 silica gel plates. All the starting carboxylic acid chlorides and alkyl chloroformates are commercially available.

GENERAL PROCEDURE FOR THE PREPARATIONS OF CARBOXYLIC AND CARBONIC HEMIESTER ANHYDRIDES

Typically, a solution of n-$Bu_4N^+X^-$ (1.8 mmol) in the appropriate organic solvent (10 ml) (see Table), was added to 20 % aqueous caustic soda solution. The mixture was cooled to -10°C and vigorously stirred. A solution of the carboxylic acid chloride (1a-m) (18 mmol), or of the alkyl chloroformate (1n-p) (18 mmol) in the same solvent (50 ml), was then added over a period of 15-20 min. The mixture was stirred at - 10°C for a period of 15-180 min (see Table) and if necessary neutralized with acetic acid. The organic layer was extracted twice with sodium bicarbonate solution, washed with water and then dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded a nearly pure product, which could be purified further by the usual techniques, except for unstable carbonate 2n.

Myristic anhydride (2a) : IR(nujol) (cm^{-1}) : 1810 and 1750 (C=O) ; ^{1}H-NMR ($CDCl_3$) (ppm) : 0.88(t, CH_3), 1.30(m, CH_3-$(CH_2)_{10}$), 1.65(m, CH_2-CH_2-CO), 2.44(t, CH_2-CO).

Palmitic anhydride (2b) : IR(nujol) (cm^{-1}) : 1805 and 1745 (C=O) ; ^{1}H-NMR($CDCl_3$) (ppm) : 0.92(t, CH_3), 1.34(m, CH_3-$(CH_2)_{12}$), 1.70(m, CH_2-CH_2-CO), 2.48(t, CH_2-CO).

Stearic anhydride (2c) : IR(nujol) (cm^{-1}) : 1810 and 1745 (C=O) ; ^{1}H-NMR($CDCl_3$) (ppm) : 0.88(t, CH_3), 1.28(m, CH_3-$(CH_2)_{14}$), 1.65(m, CH_2-CH_2-CO), 2.44(t, CH_2-CO).

Pivalic anhydride (2d) : IR(neat) (cm^{-1}) : 1740 and 1810 (C=O) ; ^{1}H-NMR($CDCl_3$) (ppm) : 1.27(s, CH_3) ; Anal. Calcd. for $C_{10}H_{18}O_3$: C 64.48, H 9.74 ; Found C 63.97, H 9.93 %.

2-Phenylbutyric anhydride (2e) : IR(neat) (cm^{-1}) : 1728 and 1810 (C=O), 1600 (arom.) ; ^{1}H-NMR ($CDCl_3$) (ppm) : 0,82(t, CH_3), 1.4-2.2(m, CH_2), 3.41(t, CH), 7.0-7.4(m, C_6H_5) ; Anal. Calcd. for $C_{20}H_{22}O_3$: C 77.39, H 7.15 ; Found C 77.22, H 7.23 %.

Benzoic anhydride (2f) : IR(nujol) (cm^{-1}) : 1780 and 1720 (C=O) ; ^{1}H-NMR($CDCl_3$) (ppm) : 7.26-7.70(m, C_6H_5), 8.10(dd, C_6H_5).

4-Nitrobenzoic anhydride (2g) : IR(nujol) (cm^{-1}) : 1802 and 1735 (C=O), 1615 (C=C) ; ^{1}H-NMR ($CDCl_3$) (ppm) : 8.40(s, C_6H_4).

(E)-Cinnamic anhydride (2h) : IR(nujol) (cm^{-1}) : 1770 and 1710 (C=O), 1625 and 1580 (C=C) ; ^{1}H-NMR($CDCl_3$) (ppm) : 6.50(d,CH-CO, J = 16 Hz), 7.10-7.60(m, C_6H_5), 7.80(d, C_6H_5-CH).

Methacrylic anhydride (2i) : IR(neat)) (cm^{-1}) : 1885 and 1725 (C=O), 1630 (C=C) ; ^{1}H-NMR($CDCl_3$) (ppm) : 2.02(s, CH_3), 5.86 and 6.28(CH_2).

1-Adamatanecarboxylic anhydride (2j) : IR(nujol) (cm^{-1}) : 1810 and 1735 (C=O) ; ^{1}H-NMR($CDCl_3$) (ppm) : 1.74(t, H_4, H_6 and H_{10}), 1.96(d, H_2, H_8, H_9), 2.04(m, H_3, H_5, H_7) ; Anal. Calcd for $C_{22}H_{30}O_3$: C 77.15, H 8.83 ; Found C 77.30, H 8.91 %.

2-Furoic anhydride (2k) : IR(nujol) (cm^{-1}) : 1785 and 1740 (C=O), 1560 (C=C) ; ^{1}H-NMR($CDCl_3$) (ppm) : 6.60(m, H_4), 7.43(dd, H_3), 7.71(d, H_2).

Glutaric anhydride (2l) : IR(neat) (cm^{-1}) : 1810 and 1765 ; ^{1}H-NMR($CDCl_3$ + DMSOd6) (ppm) : 1.70-2.30(m, CH_2-CH_2-CH_2-), 2.80(t, CH_2-CO).

Ethyloxalyl anhydride (2m) : IR(neat) (cm^{-1}) : 1770 and 1745 (C=O) ; ^{1}H NMR($CDCl_3$) (ppm) : 1.40(t, CH_3), 4.38(q, CH_2).

Dibenzyldicarbonate (2n) : IR(neat) (cm^{-1}) : 1822 and 1755 (C=O), 1590 (aro.) ; ^{1}H-NMR($CDCl_3$) (ppm) : 5.23(s, CH_2), 7.40(s, Ph).

Diisobutyldicarbonate (2o) : IR(neat) (cm^{-1}) : 1825 and 1765 (C=O) : ^{1}H-NMR($CDCl_3$) (ppm) : 0.99(d, CH_3), 2.00(m, CH), 4.12(d, CH_2).

Diethyldicarbonate (**2p**) : IR(neat) (cm^{-1}) : 1820 and 1760 (C=O) ; ^1H-NMR($CDCl_3$) (ppm) : 1.38(t, CH_3), 4.37(q, CH_2).

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