One-pot Synthesis of Acid Anhydrides from Acids Using *N,N,N′,N′*-Tetramethylchloroformamidinium Chloride under Mild Conditions

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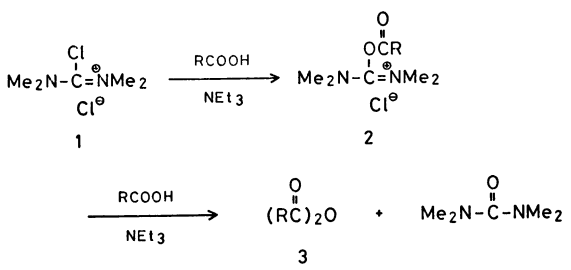
(Received May 9, 1983)

Synopsis. *N,N,N′,N′*-Tetramethylchloroformamidinium chloride reacted smoothly with a variety of carboxylic and phosphoric acids in the presence of a tertiary amine to give the corresponding acid anhydrides in high yields.

Acid anhydrides play an important role in organic syntheses as reactive intermediates, and they react with various nucleophiles such as alcohols,[1] amines,[2] aromatics,[3] and Grignard reagents[4] to give acylated compounds. On the other hand, pyrophosphates, anhydrides of phosphoric acid, are very important in biological activities as an energy source. Although many representative methods for the preparation of acid anhydrides reported so far are performed by the condensation of acids with acid chlorides,[5] one-step synthesis of acid anhydrides from acids requires a long reaction time and an elevated temperature[6] even if condensation reagents were used.[7] We now wish to report that *N,N,N′,N′*-tetramethylchloroformamidinium chloride (**1**) reacted smoothly with various kinds of acids in the presence of a tertiary amine under mild conditions to give the corresponding acid anhydrides in high yields.

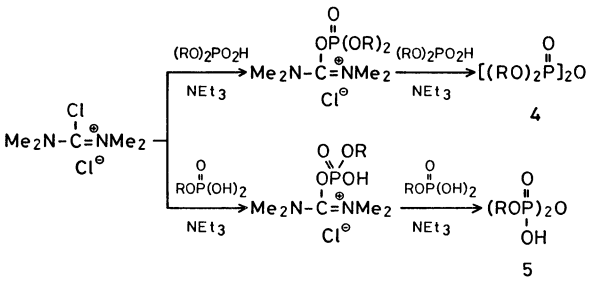
The condensation reagent, *N,N,N′,N′*-tetramethylchloroformamidinium chloride (**1**) is easily available by the reaction of *N,N,N′,N′*-tetramethylurea and oxalyl dichloride.[8] The reaction of the reagent with benzoic acid in dichloromethane was performed at −30 °C in the presence of triethylamine for 3 h, and then the reaction mixture was allowed to warm to 0 °C resulting in the formation of benzoic anhydride in 88% yield. The effect of some bases and solvents was examined in the preparation of benzoic anhydride. The use of triethylamine, tributylamine, and pyridine as a base in dichloromethane gave the anhydride in 88, 85, and 74% yields, respectively. When dichloromethane, chloroform, 1,2-dichloroethane, and acetonitrile were employed as a solvent in the presence of triethylamine, the yields of the anhydride were 88, 89, 87, and 74%, respectively. The reaction can be explained by the nucleophilic attack of the carboxylate anion to the acyloxyformamidium chloride (**2**) initially formed.



Scheme 1.

As shown in Table, aromatic carboxylic acids as well as aliphatic carboxylic acids were easily converted to the corresponding acid anhydrides (**3**) in high yields (runs 1—6), however bulky carboxylic acid and olefinic carboxylic acids required longer reaction time (runs 7—9).

Moreover, the present method was applied to the synthesis of pyrophosphate from mono- or disubstituted phosphates. Although these phosphorus compounds are dissolved well in tertiary amines such as triethylamine, such amines generally decrease the reaction rate in the phosphorylation using dicyclohexylcarbodiimide[9] or 1-imidazoylphosphonate.[10] On the contrary, the present method using *N,N,N′,N′*-tetramethylchloroformamidinium chloride in the presence of triethylamine gave tetraalkyl or tetraaryl pyrophosphates (**4**) in high yields from dialkyl or diaryl hydrogenphosphates under mild conditions and



Scheme 2.

Table 1. Synthesis of acid anhydrides from the corresponding acids

Run	Acid	Reaction temp/°C	Reaction time/h	Product	Yield %
1	Benzoic acid	−30→0	3	**3a**	88
2	4-Methoxybenzoic acid	−30→0	6	**3b**	86
3	1-Naphthoic acid	−30→0	5	**3c**	91
4	2-Furoic acid	−30→0	3	**3d**	84
5	Hexanoic acid	−30→0	5	**3e**	83
6	Cyclohexanecarboxylic acid	−30→0	7	**3f**	81
7	Pivalic acid	−30→rt	18	**3g**	84[a]
8	Cinnamic acid	−30→rt	18	**3h**	83
9	Crotonic acid	−30→rt	18	**3i**	83
10	Diphenyl hydrogenphosphate	0→rt	2	**4a**	92
11	Diethyl hydrogenphosphate	0→rt	2	**4b**	90
12	Dibutyl hydrogenphosphate	0→rt	2	**4c**	96
13	Phenyl dihydrogenphosphate	0→rt	18	**5**	61[b]

a) Determined by GLC. b) Isolated as the bis(cyclohexylammonium) salt.

in a short reaction time (runs 10—12). Further, application of the method to the synthesis of diphenyl dihydrogenpyrophosphate (**5**) from phenyl dihydrogenphosphate gave the desired compound, which was isolated as its bis(cyclohexylammonium) salt[11] in a moderate yield (run 13).

In conclusion, *N,N,N′,N′*-tetramethylchloroformamidinium chloride (**1**), which can be easily prepared from readily available tetramethylurea and oxalyl dichloride, is an effective condensation reagent for the one-pot synthesis of acid anhydrides from the corresponding acids in high yields under mild conditions.

Experimental

The ^{1}H NMR and IR spectra were taken with a Varian A-60D spectrometer and a Hitachi EPI-G2 spectrometer, respectively. Gas chromatography was carried out with a Yanaco G-180 chromatographic apparatus, using a ϕ 3 mm × 1 m, 15% SE-30 column. Acid anhydrides and pyrophosphates obtained were identified by comparison of their IR and ^{1}H NMR spectra with those of the respective authentic samples. Authentic samples of **3a**, **3e**, and **3i** were obtained from Nakarai Chem. Ltd., and other chemicals were prepared by reported methods: **3b**,[11] **3c**,[12] **3d**,[13] **3f**,[14] **3g**,[15] **3h**,[16] **4a**,[17] **4b**,[18] **4c**,[18] and **5**.[19]

*N,N,N′,N′-Tetramethylchloroformamidinium Chloride (**1**).* Oxalyl dichloride (0.30 ml, 3.5 mmol) was added into a solution of *N,N,N′,N′*-tetramethylurea (244 mg, 2.1 mmol) in 3 ml of 1,2-dichloroethane at room temperature. The reaction mixture was then stirred for 2 h at 60 °C. After removal of the solvent under a reduced pressure, the faint yellow solid residue was used in the following experiments without further purification.

*General Procedure for the Synthesis of Acid Anhydrides (**3a—c**, **h**).* *N,N,N′,N′*-Tetramethylchloroformamidinium chloride (2.1 mmol), a carboxylic acid (4.0 mmol), and triethylamine (4.0 mmol) were stirred in 6 ml of dichloromethane at −30 °C for 1 h. This reaction mixture was allowed to warm to 0 °C or room temperature for 2 h and stirred at the same temperature until the reaction completed. This mixture was washed with two 10 ml portions of saturated sodium hydrogencarbonate, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure. The residue was chromatographed on silica gel to give acid anhydride (**3a—c, h**).

*General Procedure for the Synthesis of Acid Anhydrides (**3d—f**, **i**).* *N,N,N′,N′*-Tetramethylchloroformamidinium chloride (2.1 mmol), a carboxylic acid (4.0 mmol), and triethylamine (4.0 mmol) were stirred in 6 ml of dichloromethane at −30 °C for 1 h. This reaction mixture was allowed to warm to 0 °C or room temperature for 2 h and stirred at the same temperature until the reaction completed. After removal of the solvent under a reduced pressure, a 5 ml portion of ether was added to the residue, and the mixture was filtered under argon. The residue was washed with three 3 ml portions of ether, and the combined filtrate was distilled under a reduced pressure (Kugelrohr apparatus). Bp: **3d**; 200 °C/20 mmHg, **3e**; 200 °C/20 mmHg, **3f**; 200 °C/0.3 mmHg, **3g**; 150 °C/20 mmHg, and **3i**; 200 °C/20 mmHg.

*General Procedure for the Synthesis of Pyrophosphate (**4a—c**).* *N,N,N′,N′*-Tetramethylchloroformamidinium chloride (2.1 mmol), a phosphate (4.0 mmol), and triethylamine (4.0 mmol) were stirred in 6 ml of dichloromethane at 0 °C for 1 h and further at room temperature for 2 h. After removal of the solvent under a reduced pressure, a 5 ml portion of ether was added to the residue and the mixture was filtered under argon. The residue was washed with three 3 ml portions of ether, and the combined filtrate was distilled under a reduced pressure (Kugelrohr apparatus). Bp: **4a**; 250 °C/0.3 mmHg, **4b**; 200 °C/0.3 mmHg, and **4c**; 250 °C/0.4 mmHg.

*Synthesis of Diphenyl Dihydrogenpyrophosphate (**5**) Isolated as the Bis(cyclohexylammonium) Salt.* *N,N,N′,N′*-Tetramethylchloroformamidinium chloride (2.1 mmol), phenyl dihydrogenphosphate (696 mg, 4.0 mmol), and triethylamine (409 mg, 4.0 mmol) were stirred in 6 ml of dichloromethane at 0 °C for 1 h and stirred at room temperature for 12 h. After removal of the solvent, 30 ml of water and a sufficient amount of sodium hydrogencarbonate were added to the residue to neutralize the acidic solution. To the solution was added aqueous cyclohexylamine (812 mg, 8.2 mmol) and the solution set aside at 0 °C. Bis(cyclohexylammonium) diphenyl pyrophosphate was separated and recrystallized from water as colorless needles (640 mg, 61%); mp 250—254 °C (lit,[19] mp 250—255 °C).

Partial financial support of this research by the Asahi Glass Foundation is greatly acknowledged.

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