A Convenient Triphosgene-Mediated Synthesis of Symmetric Carboxylic Acid Anhydrides

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Triphosgene [bis(trichloromethyl) carbonate] has been known since 1880,[1] but its synthetic utility had not been exploited until recently. This reagent is a versatile surrogate for phosgene gas and has been shown to mediate a number of reactions such as carbonylation (formation of oxazoles, quinazolidinediones, carbonates, urea analogues, and isocyanates),[2,3] chloroformylation,[2] chlorination,[2,4] oxidation of alcohols,[5] dehydration of formamides to isonitriles,[2] and formation of *N*-carboxyamino acid anhydrides from both unprotected[6] and *N*-BOC-amino acids.[7] We report herein a new reaction for triphosgene, namely formation of symmetric anhydrides from the corresponding carboxylic acids.

The triethylammonium salt of a carboxylic acid, prepared by the reaction of triethylamine and a carboxylic acid (1), undergoes reaction with one-sixth equivalent of
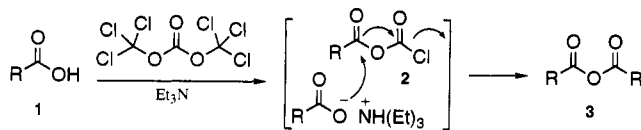
triphosgene to give an equimolar mixture of the carboxylate and the intermediary chloroformate 2. Nucleophilic displacement of the chloroformate function by the carboxylate affords the desired anhydride (3), concomitant with the formation of triethylammonium chloride as a precipitate and the carbon dioxide gas. The reaction reaches completion in minutes. The solvents of choice in our hands have been benzene, THF, or ethyl acetate, but in principle, other solvents should be equally useful. In addition, we have no evidence for the formation of diacyl carbonates as a potential biproduct of the reaction. Other organic bases may substitute for triethylamine in this reaction, however, we decided in favor of triethylamine because of the ease of isolation of its hydrochloride salt from organic solvents; triethylammonium hydrochloride precipitates completely from most organic solvents. This reaction was used to prepare the anhydrides 4–14; the method is applicable to the preparation of anhydrides from

both electon-rich and electron-deficient carboxylic acids. The spectoscopic characterization of these compounds is tabulated in Table 1.
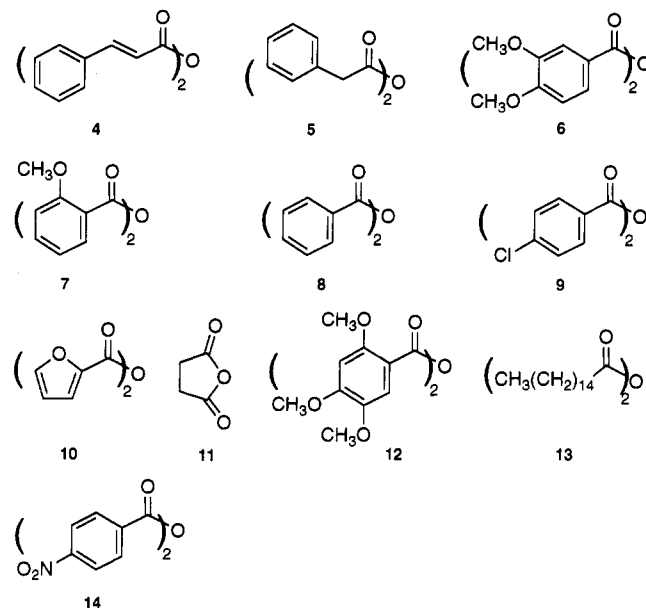
Anhydrides are typically made by the reaction of an acyl halide and a carboxylate salt[8] or the reaction of a carboxylic acid with P_2O_5,[9] methoxyacetylene,[10] or a carbodiimide.[11] A report of the synthesis of acid anhydrides by phosgene gas has also appeared in the literature.[12] This method has not received much synthetic utility in part due to the high toxicity of phosgene gas and the necessary and complicated experimental set up associated with it.[12b] The triphosgene-mediated reaction for the synthesis of anhydrides outlined here enjoys a number of advantages over the existing methods, in that the reaction is carried out under neutral conditions and does not use highly toxic or allergenic (as with carbodiimides) reagents. Furthermore, no elaborate apparatus is needed for this one-pot reaction which proceeds conveniently to completion at ice–water temperature in minutes.

Experimental Section

Proton NMR spectra were obtained at 300 MHz using a Nicolet QE-300 spectrometer. Chemical shift values (δ) are given in ppm. Infrared and mass spectra were recorded on a Nicolet DX and a Kratos MS 80RFA spectrometer, respectively. Melting points were taken on a Hoover UniMelt apparatus and are uncorrected. All other reagents, including triphosgene, were purchased from the Aldrich Chemical Co. All of the anhydrides reported in Table 1, with the exception of succinic anhydride, were prepared as described below for *o*-anisic anhydride.

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Table 1. Carboxylic Acid Anhydrides Prepared

compds	¹H NMR,[a] δ	IR,[b] cm⁻¹	MS,[c] m/z	mp, °C	yield,[d] %
4	6.55 (d, 2H, J = 16.8 Hz), 7.44 (m, 6H), 7.85 (m, 4H), 7.87 (d, 2H, J = 16.8 Hz)	1765, 1695, 1624	exptl 278.0935 (calcd 278.0943)	134–135 (lit. 138)[13]	73
5	3.73 (s, 4H), 7.28 (m, 4H), 7.32 (m, 6H)	1809, 1731	254 (M + 1)[e]	71–72 (lit. 71–72)[14]	62
6	3.95 (s, 6H), 3.97 (s, 6H), 6.94 (d, 2H, J = 8.4 Hz), 7.61 (s, 2H), 7.78 (d, 2H, J = 8.4 Hz)	1770, 1704	exptl 346.1058 (calcd 346.1052)	124–126 (lit. 124–125)[14]	79
7	3.86 (s, 6H), 7.02 (m, 4H), 7.55 (m, 2H), 8.01 (dd, 2H, J = 1.8, 7.8 Hz)	1735, 1596, 1574	exptl 286.0836 (calcd 286.0841)	71–73	65
8	7.59 (m, 4H), 7.76 (m, 2H), 8.10 (dd, 4H, J = 0.6, 8.7 Hz)	1786, 1727	exptl 226.0633 (calcd 226.0630)		98
9	7.51 (d, 4H, J = 8.4 Hz), 8.07 (d, 4H, J = 8.4 Hz)	1781, 1714, 1586	exptl 293.9844 (calcd 293.9850)	192–193 (lit. 192–193)[13]	64
10	6.62 (dd, 2H, J = 1.5, 3.4 Hz), 7.43 (d, 2H, J = 3.4 Hz), 7.72 (d, 2H, J = 1.5 Hz)	1802, 1725	exptl 206.0223 (calcd 206.0215)	71–72 (lit. 71–73)[13]	89
11	2.85 (s, 4H)	1856, 1778	exptl 100.0166 (calcd 100.0160)	117–118 (lit. 119)[15]	88
12	3.83 (s, 6H), 3.90 (s, 6H), 4.00 (s, 6H), 6.49 (s, 2H), 7.55 (s, 2H)	1718, 1690	406[f]	125–131	72
13	0.88 (t, 6H, J = 6.6 Hz), 1.26 (br s, 48 H), 1.67 (quint., 4H, J = 7.3 Hz), 2.45 (t, 4H, J = 7.3 Hz)	1795, 1739	exptl 494.4715 (calcd 494.4699)	62–63 (lit. 63.9)[13]	85
14	8.71 (d, 2H, J = 8.7 Hz), 8.87 (d, 2H, J = 8.7 Hz)	1788, 1724	exptl 316.0328 (calcd 316.0331)	194–196 (lit. 195)[15]	95

[a] 300 MHz, δ in ppm, downfield from tetramethylsilane, in $CDCl_3$, with the exception of benzoic anhydride which was measured in DMSO-d_6. [b] KBr pellet, carbonyl stretches, with the exception of benzoic anhydride which was measured neat. [c] Electron impact (EI) or chemical ionization (CI). [d] The reported yields for the known compounds from the literature range between 56 and 99%. [e] Exact mass for this compound could not be determined by either EI or CI mass spectrometry. [f] The parent-ion peak was noted only by FAB⁺ MS.

o-Anisic Anhydride (7). A solution of o-anisic acid (500 mg, 1.8 mmol), and distilled triethylamine (0.25 mL, 1.8 mmol) in 35 mL of ethyl acetate was stirred in an ice bath. Triphosgene (90 mg, 0.3 mmol) was added in one portion, upon which the formation of an immediate precipitate of Et₃N·HCl was observed. The reaction was allowed to mix in the ice bath for 10 min, followed by 15 additional min of stirring at room temperature. The solid (Et₃N·HCl) was filtered and washed with a small portion (10 mL) of ethyl acetate. The filtrate was evaporated to dryness, and the resulting residue was crystallized from ethyl acetate and hexane at room temperature to give the title compound as clear crystals (330 mg, 65%).

Succinic Anhydride (11). A solution of succinic acid (500 mg, 42 mmol) and triethylamine (1.23 mL, 42 mmol) in 120 mL of anhydrous THF was allowed to react with triphosgene (42 mg,

7 mmol) at ice–water temperature for 10 min. The reaction was subsequently stirred for 15 additional min at room temperature. The solution was filtered, and the filtrate was evaporated to dryness. The residue was crystallized from ethyl acetate to afford the desired product as white crystals (370 mg, 88%).

Supplementary Material Available: ¹H-NMR spectra of benzoic anhydride, 2,4,5-trimethoxybenzoic anhydride, and o-anisic anhydride (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Additions and Corrections

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Donald C. Dittmer,* Robert P. Discordia, Yanzhi Zhang, Christopher K. Murphy, Archana Kumar, Aurora S. Pepito, and Yuesheng Wang. A Tellurium Transposition Route to Allylic Alcohols: Overcoming Some Limitations of the Sharpless–Katsuki Asymmetric Epoxidation.

Page 723, column 1, line 25. Li(MeOH)₃BH should read Na(MeO)₃BH.

Ari M. P. Koskinen* and Heikki Hassila. Asymmetric Catalysis in Intramolecular Cyclopropanation.

Page 4480 column 1, line 7. Sentence should read as follows: The sense of absolute stereochemistry is based on optical rotation ([α]D = 41.5°) and the reported literature value for the enantiomer of **3b** ([α]D = −105.5°]).[11]

Reference 11 should read as follows: (a) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992,** *57,* 5931–5936. After the submission of the paper, a revised value ([α]D = −135.1°

(c = 1.3, CHCI₃) for the rotation of the antipode of **3b** has been reported in (b) Burgess, K.; Ho, K.-K.; Ke, C.-Y. *J. Org. Chem.* **1993,** *58,* 3767–3768.

Albert J. Fry* and U. Nilantha Sirisoma. Electrocatalytic Reduction of Benzal Chloride by Cobalt(I)(salen). A Mechanistic Investigation.

Page 4922, column 1. The 11th line from the bottom should read "path C. The distinction between paths A and B is harder".

Peter Wipf* and Hongyong Kim. Total Synthesis of Cyclotheonamide A.

Page 5592. Reference 6 should read as follows: (c) Maryanoff, B. E.; Greco, M. N.; Andrade-Gordon, P.; Nicolaou, K. C.; Liu, A.; Brungs, P. H.; Tulinsky, A. *Book of Abstracts,* 205th National Meeting of the American Chemical Society: Denver, CO, March 28–April 2, 1993; American Chemical Society: Washington, DC, 1993; ORGN 0311.