Journal of Fluorine Chemistry, 50 (1990) 251–255

Received June 20, 1990; accepted July 17, 1990

PRELIMINARY NOTE

A New Synthesis of 3-Fluorophthalic Anhydride

MARGHERITA PASSUDETTI, MAURIZIO PRATO, UGO QUINTILY+ AND GIANFRANCO SCORRANO*

Centro Meccanismi di Reazioni Organiche del CNR, Dipartimento di Chimica Organica dell'Universita', Via Marzolo 1, I-35131, Padua (Italy)

SUMMARY:

A high yield, one pot synthesis of 3-fluorophthalic anhydride from the easily accessible 3-nitrophthaloyl dichloride is described. The mechanistic implications of the fluorodenitration process are also discussed.

There has been considerable recent interest in the preparation of 3-fluorophthalic anhydride (4-fluoro-1,3-isobenzofurandione), a useful intermediate in industrial preparations of 3-fluoroanthranilic acid [1], fluorophthalimidines [2] and phthalamic acids [3] , oxydiphthalic anhydrides [4], fluoroisoindoline [5] and imidazolinyl derivatives [6]. Also, 3-substituted phthalic anhydrides have been extensively studied in relation to the differential reactivity of the two carbonyl groups [7].

The most obvious approach, i.e. the nucleophilic substitution of halophthalic anhydrides by means of fluoride ion, has been pursued. Thus, the 3-chloroderivative and KF, neat [8] or in benzonitrile [9], as well as in sulfolane/thionyl chloride [10], have been employed. Nucleophilic displacement of the nitro group has also been

+ Deceased on February, 5, 1990.

* Author to whom correspondence should be addressed.

0022-1139/90/$3 50

investigated. The reaction of 3-nitrophthalic anhydride with KF has been carried out neat at high temperatures (180-190 °C, with explosion at 200° [11]) or, under milder conditions, in DMF, DMSO, sulfolane, HMPA [11], as well as in benzonitrile [12]. However, in many cases, the nitro group is an intriguing leaving group. In fact, the nitrite ion, once generated, is a nucleophile strong enough to provoke undesired side reactions. Thus, the low yields encountered in the direct substitution by fluoride ion of 3-nitrophthalic anhydride have been ascribed to interference of the nitrite ion formed during the process [11,12]. The sequential treatment of 3-nitrophthalic anhydride in benzonitrile with KF, thionyl chloride, KF, thionyl chloride, and finally KF, proved to be an efficient way to the fluoro homologue [12].

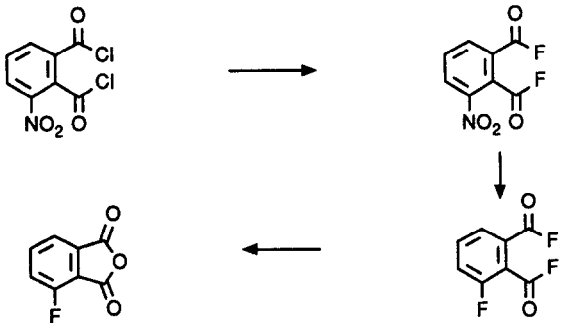
A way to solve the problem of substituting a nitro group is to use a nitrite ion trapping agent in order to avoid unwanted reactions. Several compounds are known to be efficient nitrite trappers, among them, manganese dioxide, p-toluene sulfonyl chloride, trichlorotriazine, phthaloyl dichloride, phthaloyl difluoride [13]. The use of 3-nitrophthaloyl dichloride or difluoride as starting material in the synthesis of the anhydride would have the advantage of having the nitrite trapper already in solution.

The present paper describes a high yield, fast, one pot, alternative method for the synthesis of 3-fluorophthalic anhydride starting from the readily available 3-nitrophthaloyl dichloride.

Heating 3-nitrophthaloyl dichloride (from 3-nitrophthalic acid and PCl_5 [14]) with spray-dried KF in sulfolane at 130°C for 1.5 h afforded 82% yield of isolated 3-fluorophthalic anhydride (91% gc).

By monitoring the reaction course by gc it is possible to see that the acid chloride is firstly transformed into the acid fluoride, then substitution of the nitro group and finally cyclization to the anhydride occur (Scheme 1).

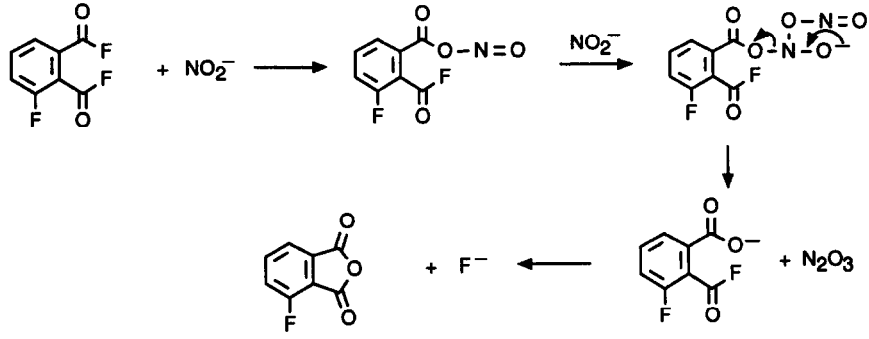
In a typical experiment, 32.5 g of spray-dried KF and 75 ml of sulfolane in a three necked round-bottomed flask equipped with mechanical



SCHEME 1.

stirrer, thermometer and distillation head, were gently heated. Under vacuum (10 mmHg) ca 10 ml of sulfolane were distilled. The heating mantle was removed and to the mixture 23.2 g of 3-nitrophthaloyl dichloride was added. The temperature was raised and kept at 130 °C for 1.5 h. After cooling, the mixture was poured into water (350 ml). The solid was collected on a Buchner funnel and taken up with 400 ml of chloroform. The solution was dried with calcium chloride and the solvent was evaporated in vacuo. A yield of 12.7 g of 3-fluorophthalic anhydride (82 %), mp 163-4 °C (lit 161.5-162.5 °C [11]) was obtained. IR (KBr, 1%): cm^{-1} 1865, 1851, 1781, 1770, 1703, 1484, 1260 [11]. Ms (EI, 70 eV), m/e 166 (M^+, 20%), 122 (100%), 94 (96%). ^{1}H-NMR ($CDCl_3$, TMS, 200 MHz) δ 7.95 (m, 1H), 7.86 (m, 1H), 7.58 (m, 1H).

A mechanistic interpretation of the trapping ability of the difluoride intermediate is proposed in Scheme 2.



SCHEME 2.

The nitrite ion formed by substitution with fluoride can react with the acid fluoride to give the nitrite ester. This, in turn, can be attacked by another nitrite ion to give, after elimination of N_2O_3, the carboxylate-fluoride which cyclizes to the anhydride. The formation of the nitrite ester and its evolution to the carboxylate ion has been invoked in other cases [12,15]. Partial evidence of this hypothesis is the blue color developed by condensing the reaction fumes at -78 °C (N_2O_3 [16]).

Experiments to validate Scheme 2 are in progress.

This work has been carried out with financial support of Miteni Srl and has been included in "Progetto Finalizzato Chimica Fine del CNR".

1 M.J. Fifolt and A.M. Foster, Eur. Pat. Appl. EP 55 629, 1982 (Chem. Abstr., *97* (1982) 197986h).

2 a.G. Hamprecht, J. Varwig and W. Rohr, Ger. Offen. DE 3 320 089, 1984 (Chem. Abstr., *102* (1985) 62079r). b. K.S Bengtsson and S.O. Thorberg, S.O. OEGREN, Eur. Pat. Appl. 26 749, 1981 (Chem. Abstr., *95* (1981) 62013b).

3 M.J. Fifolt, A.M. Foster and B.R. Cotter, Eur. Pat. Appl EP 55 630, 1982 (Chem Abstr., *97* (1982) 215784x).

4 W.T. Schwartz and J A. Pawlak, U.S. Pat. 4 697 023, 1987 (Chem. Abstr., *108* (1988) 167297n).

5 E. Cohnen, B Armah, Eur. Pat. Appl. EP 228 640, 1987 (Chem. Abstr., *108* (1987) 154338).

6 M. Los, Eur. Pat. Appl. EP 135,711, 1985 (Chem. Abstr., *103* (1985) 87875f).

7 a. M.M Kayser and O. Eisenstein, Can. J. Chem., *59* (1981) 2457. b. C. Soucy, D. Favreau and M.M Kayser, J. Org. Chem., *52* (1987) 129. c. D. W. Boykin, A. A.L. Baumstark, M.M Kayser and C.M. Saucy, Can. J. Chem., *65* (1987) 1214. d. L. Breau an M.M Kayser, Can. J. Chem., *67* (1989) 569.

8 A. Heller, J. Org. Chem., *25* (1960) 834.

9 O. Kaieda, K. Hirota, H. Ito and T. Nakamura, Jpn. Kokai Tokkyo Koho Jap. Pat. 61 47 475, 1984 (Chem. Abstr., *105* (1986) 60515t).

10 G. Hamprecht, J. Varwig and W. Rohr, Ger. Offen. DE 3 303 378, 1984 (Chem. Abstr., *102* (1985) 62069n).

11 N. Ishikawa, T. Tanabe and D. Hayashi, Bull. Chem. Soc. Jpn., *48* (1975) 39.

12 D.J. Milner, Synth. Comm., *15* (1985) 485.

13 S. Kumai, R. Seki, Y. Furukawa and M. Matsuo, Reports Res. Lab. Asahi Glass Co., Ltd, *35* (1985) 153.

14 V.J. Chambers, J. Am. Chem. Soc., *25* (1903) 607.

15 R.L. Markezich, O.S. Zamek, P.E. Donauhe and F.J. Williams, J. Org. Chem., *42* (1977) 3435.

16 A.F. Cotton and G. Wilkinson, Advanced Inorganic Chemistry, Wiley, New York, 4th edn., 1980, P. 425.