ELSEVIER

Journal of Fluorine Chemistry 115 (2002) 75–77

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Preparation of acyl fluorides with hydrogen fluoride-pyridine and 1,3-dicyclohexylcarbodiimide

Chinpiao Chen*, Chin-Tzu Chien, Chu-Hsiang Su

Department of Chemistry, National Dong Hwa University, Hualien 974, Taiwan, ROC

Received 17 September 2001; received in revised form 7 January 2002; accepted 10 January 2002

Abstract

This work presents an efficient procedure for preparing acyl fluorides by simply reacting carboxylic acid with hydrogen fluoride-pyridine and 1,3-dicyclohexylcarbodiimide (DCC) in dichloromethane. The acyl fluorides were converted in situ to the corresponding benzyl carboxylic esters by adding benzyl alcohol and triethylamine to the reaction mixture.

Keywords: Acyl fluoride; Hydrogen fluoride-pyridine; 1,3-Dicyclohexylcarbodiimide

1. Introduction

Acyl fluorides are generally prepared by halogen exchange from the corresponding acyl chlorides with potassium fluoride [1], potassium hydrogen difluoride [2], hydrogen fluoride [3], antimony trifluoride [4], zinc fluoride [5], etc. [6]. Sulfur tetrafluoride [7], selenium tetrafluoride [8], cyanuric fluoride [9], (diethylamino)sulfur trifluoride (DAST) [10], tetramethylfluoroformamidinium hexafluorophosphate [11], benzyl fluoride [12], etc. [13] have also been used for fluorination of carboxylic acids. Halogen exchange reactions with fluorides generally require a high reaction temperature and direct fluorinations are inappropriate for acid derivatives containing multifunctional groups. Cyanuric fluoride is an extremely mild reagent, particularly when used in the fluorination of amino acids to amino acid fluorides [9b,9c] for peptide synthesis. However, this reagent is too expensive.

This work presents an economical, mild and convenient synthetic method for the fluorination of carboxylic acids to acyl fluorides using hydrogen fluoride-pyridine and 1,3-dicyclohexylcarbodiimide (DCC), in situ converted to carboxylic acid esters by adding benzyl alcohol and triethylamine to the reaction mixture. The C–F bond of acyl fluorides has a greater stability than the corresponding acyl chlorides toward neutral oxygen nucleophiles such as water or methanol. However, the acyl fluorides can still not withstand the moisture for an extended period. Therefore, the obtained acyl fluorides were not purified and in situ reacted with benzyl alcohol. To acquire the pure acyl fluorides, a varied procedure was filtrated the reaction mixture, concentrated the filtrate, and finally distilled the concentrated solution. To our knowledge, the fluorination of carboxylic acids has not been reported under these conditions until now (Scheme 1).

2. Results and discussion

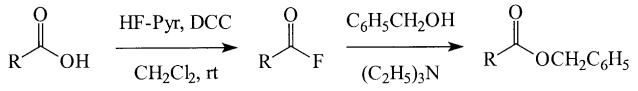
Table 1 summarizes the yield of the fluorination of carboxylic acids in situ converted to the corresponding benzyl carboxylic esters, and the yield of acyl fluorides in 50 mmol scale purified by distilling. The fluorination of *trans*-cinnamic acid (Entry 6) indicates that hydrogen fluoride-pyridine and DCC is a feasible means of preparing acyl fluorides containing unsaturated double bonds.

Experimental results indicated not only that pyridine increases the solubility of carboxylic acid in dichloromethane, but also promotes the fluorination of carboxylic acid with hydrogen fluoride-pyridine and DCC. The amount of hydrogen fluoride-pyridine in excess of 2 eq., a side reaction was occurred, and a cyclohexylisocyanate and the corresponding *N*-cyclohexylalkanoylamides were produced (Scheme 2). When the amount of hydrogen fluoride-pyridine is in large excess (12 eq.), the carboxylic acids with an α-hydrogen leads to an unexpected dehydration reaction, subsequently producing the corresponding ketones (Scheme 3).

In the syntheses of natural and non-natural products, the mild reaction conditions are always preferred in key bond-

* Corresponding author. Tel.: +886-38-663875; fax: +886-38-661487.
E-mail address: chinpiao@mail.ndhu.edu.tw (C. Chen).

0022-1139/02/$ – see front matter
PII: S0022-1139(02)00004-0

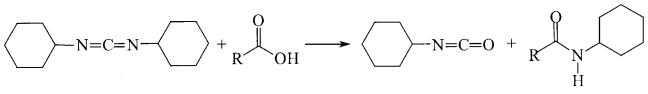


Scheme 1.

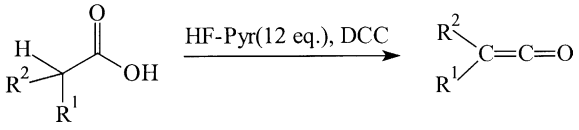
Table 1
Fluorination of carboxylic acids with HF-pyridine and DCC in situ converted to the corresponding benzyl carboxylic esters

Entry	R–C(=O)–OH	R–C(=O)–F[a] yield (%)	R–C(=O)–OCH2C6H5 yield (%)
1	Benzoic acid	98	85
2	*p*-Anisic acid	100	88
3	*p*-Nitrobenzoic acid	84	84
4	Phenylacetic acid	82	88
5	Diphenylacetic acid	60	88
6	*trans*-Cinnamic acid	75	99
7	Cyclohexanecarboxylic acid	97	84
8	Stearic acid	89	93

[a] The acyl fluorides were prepared in 50 mmol scale and purified by distillation.



Scheme 2.



Scheme 3.

forming steps. The fluorination of carboxylic acids by using hydrogen fluoride-pyridine and DCC satisfies the economical, mild and efficient reaction conditions. Moreover, under these conditions, we are currently investigating the fluorination of amino acids to amino acid fluorides for peptide synthesis.

3. Experimental

The general procedure is illustrated as follows to synthesize benzoyl fluoride. To a solution of 1,3-dicyclohexylcarbodiimide (10.3 g, 50.0 mmol) and hydrogen fluoride-pyridine (~70% HF, 1.43 ml, 55.0 mmol) in dichloromethane (30 ml) was added using cannula at room temperature for a solution of benzoic acid (6.1 g, 50.0 mmol) and pyridine (10 ml) in dichloromethane (135 ml). After 3 h the reaction was completed (as monitored by GC-MS, HP 5973), the reaction mixture was filtrated through Buchner funnel. The filtrate was concentrated to obtain a yellow solution and purified by distilling lead to benzoyl fluoride (6.1 g, 98% yield).

The general procedure is illustrated as follows to synthesize benzyl benzoate. To a solution of 1,3-dicyclohexylcarbodiimide (1.13 g, 5.5 mmol) and hydrogen fluoride-pyridine (~70% HF, 143 μl, 5.5 mmol) in dichloromethane (10 ml) was added using cannula at room temperature for a solution of benzoic acid (0.66 g, 5 mmol) and pyridine (1 ml) in dichloromethane (40 ml). The reaction mixture was then stirred for 2 h. After the reaction was completed (as monitored by GC-MS, HP 5973) and when the benzoic acid was consumed entirely, benzyl alcohol (1.04 ml, 10 mmol) and triethylamine (0.79 ml, 20 mmol) were added to the reaction mixture, and at room temperature stirred for overnight. The reaction mixture was filtered through celite, and the filtrate was washed with 1N hydrochloric acid. The organic phase was then dried over anhydrous magnesium sulfate and concentrated. Finally, the crude product was purified by column chromatography (ethyl acetate–hexane, 1:50) lead to benzyl benzoate (0.90 g, 85% yield).

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China and Tzu Chi University for financially supporting this research under Contract No. NSC 89-2113-M-320-001.

References

[1] (a) S. Saunders, J. Chem. Soc. (1948) 1778;
(b) N. Haszeldine, J. Chem. Soc. (1959) 1084–1089;
(c) N. Ishikawa, T. Kitazume, T. Yamazaki, Y. Mochida, T. Tatsuno, Chem. Lett. (1981) 761–764;
(d) M. Tordeux, C. Wakselman, Synth. Commun. 12 (1982) 513–520;
(e) J.H. Clark, A.J. Hyde, D.K. Smith, J. Chem. Soc. Chem. Commun. 10 (1986) 791–793;
(f) H. Liu, P. Wang, P. Sun, J. Fluorine Chem. 43 (1989) 429–434;
(g) C.G. Krespan, D.A. Dixon, J. Org. Chem. 56 (1991) 3915–3923.
[2] (a) G.A. Olah, S. Kuhn, S. Beke, Chem. Ber. 89 (1956) 862–864;
(b) J. Miller, O.-L. Ying, J. Chem. Soc. Perkin Trans. 2 (1985) 323–328.
[3] (a) D. Young, J. Org. Chem. 24 (1959) 1021;
(b) G.A. Olah et al., J. Org. Chem. 44 (1979) 3872–3881;
(c) T. Abe, E. Hayashi, H. Baba, S. Nagase, J. Fluorine Chem. 25 (1984) 419–434.
[4] H. Meerwein, P. Borner, O. Fuchs, H.J. Sasse, H. Schrodt, J. Spille, Chem. Ber. 89 (1956) 2060–2075.
[5] (a) F.F. Blicke, J. Am. Chem. Soc. 46 (1924) 1515–1518;
(b) S. Swain, J. Am. Chem. Soc. 75 (1953) 246;
(c) V.G. Nenajdenko, M.V. Lebedev, E.S. Belenkova, Tetrahedron Lett. 36 (1995) 6317–6320.
[6] (a) L.N. Markovski, V.E. Pashinnik, Synthesis (1975) 801–802;
(b) L. Seel, Chem. Ber. 91 (1958) 2553–2556;
(c) B.K. Bennett, R. G Harrison, T.G. Richmond, J. Am. Chem. Soc. 116 (1994) 11165–11166;
(d) A. Haas, T. Maciej, J. Fluorine Chem. 20 (1982) 581–588;
(e) R. Wagner, B. Wiedel, W. Guenther, H. Goerls, E. Anders, Fur. J. Org. Chem. 9 (1999) 2383–2390.
[7] (a) W.R. Hasek, W.C. Smith, V.A. Engelhardt, J. Am. Chem. Soc. 82 (1960) 543–551;

(b) F.A. Bloshchitsa, A.I. Burmakov, B.V. Kunshenko, L.A. Alekseeva, L.M. Yagupol'skii, J. Org. Chem. USSR (English Translation) 21 (1985) 1286–1291;
(c) S.K. Ritter, B.K. Hill, M.A. Odian, J. Dai, R.E. Noftle, G.L. Gard, J. Fluorine Chem. 93 (1999) 73–80.

[8] G.A. Olah, M. Nojima, I. Kerekes, J. Am. Chem. Soc. 96 (1974) 925–927.

[9] (a) G.A. Olah, M. Nojima, I. Kerekes, Synthesis (1973) 487–488;
(b) L.A. Carpino, D. Sadat-Aalaee, H.G. Chao, R.H. DeSelms, J. Am. Chem. Soc. 112 (1990) 9651–9652;
(c) L.A. Carpino, E.-S.M.E. Mansour, D. Sadat-Aalaee, J. Org. Chem. 56 (1991) 2611–2614;
(d) K.M. Depew, S.P. Marsden, D. Zatorska, A. Zatorski, W.G. Bornmann, S.J. Danishefsky, J. Am. Chem. Soc. 121 (1999) 11953–11963;
(e) J.M. Schkeryantz, J.C.G. Woo, P. Siliphaivanh, K.M. Depew, S.J. Danishefsky, J. Am. Chem. Soc. 121 (1999) 11964–11975;
(f) J. Grugier, J. Xie, I. Duarte, J.-M. Valery, J. Org. Chem. 65 (2000) 979–984.

[10] (a) L.N. Markovskij, V.E. Pashinnik, A.V. Kirsanov, Synthesis (1973) 787–789;
(b) A.C. O'Sullivan, F. Struber, S.V. Ley, J. Org. Chem. 64 (1999) 6252–6256.

[11] (a) L.A. Carpino, A. El-Faham, J. Am. Chem. Soc. 117 (1995) 5041–5042;
(b) K.C. Nicolaou, H.J. Mitchell, H. Suzuki, R.M. Rodriguez, O. Baudoin, K.C. Fylaktakidou, Angew. Chem. Int. Ed. 38 (1999) 3334–3339;
(c) K.C. Nicolaou, R.M. Rodriguez, K.C. Fylaktakidou, H. Suzuki, H.J. Mitchell, Angew. Chem. Int. Ed. 38 (1999) 3340–3345.

[12] (a) H. Boehme, M. Hilp, Chem. Ber. 103 (1970) 104–111;
(b) G.A. Olah, R.J. Spear, P.W. Westerman, J.-M. Denis, J. Am. Chem. Soc. 96 (1974) 5855–5859;
(c) E.A. Noe, R.M. Young, J. Am. Chem. Soc. 194 (1982) 6218–6220.

[13] (a) G.A. Olah, S. Kuhn, S. Beke, Chem. Ber. 89 (1956) 862–864;
(b) F.S. Fawcett, C.W. Tullock, D.D. Coffman, J. Am. Chem. Soc. 84 (1962) 4275–4285;
(c) S. Yanagida, Y. Noji, M. Okahara, Tetrahedron Lett. 27 (1977) 2337–2340;
(d) C. G Wong, R.R. Rando, J. Am. Chem. Soc. 104 (1982) 7374–7375;
(e) P.E. Hansen, F.M. Nicolaisen, K. Schaumburg, J. Am. Chem. Soc. 108 (1986) 625–629;
(f) D.J. Kertesz, M. Marx, J. Org. Chem. 51 (1986) 2315–2328.