ELSEVIER

Journal of Fluorine Chemistry 78 (1996) 165–166

JOURNAL OF FLUORINE CHEMISTRY

Elemental fluorine. Part 3 [1]. The preparation of dialkyl fluoromalonates by direct fluorination

R.D. Chambers [a,*], J. Hutchinson [a,b], J. Thomson [a,c]

[a] *Department of Chemistry, University of Durham Science Laboratories, South Road, Durham DH1 3LE, UK*

[b] *BNFL Fluorochemicals Ltd.*

[c] *BNFL Fluorochemicals Ltd., Springfields, Salwick, Preston, Lancs. PR4 0XJ, UK*

Received 6 November 1995; accepted 2 February 1996

Abstract

Dialkyl fluoromalonates have been prepared by treating the sodium derivatives of the parent dialkyl malonates with elemental fluorine.

Keywords: Elemental fluorine; Preparation; Dialkyl fluoromalonates; Direct fluorination; NMR spectroscopy; Mass spectrometry

1. Introduction

Due to the increasing demand for biologically active molecules containing fluorine, considerable effort has been devoted to developing the methodology for introducing single fluorine atoms into small molecules which can then be used as building blocks for making more complex structures. In this context, the preparation of dialkyl fluoromalonates has attracted much attention since they are particularly useful in the preparation of fluorinated heterocyclic systems [2–8]. Their preparation has been accomplished by multi-step syntheses [4–6,9,10], by the more direct procedures of halogen exchange [11] and by the treatment of alkali metal derivatives of the parent esters with perchloryl fluoride [7,12–14] or one of the 'electrophilic fluorinating agents' that have been introduced over recent years [15–22]. We have already shown that elemental fluorine can be used to fluorinate 1,3-diketones and 1,3-ketoesters in high yield [1], but when we attempted to carry out the fluorination of 1,3-diesters (dialkyl malonates) under similar conditions (i.e. passing fluorine through formic acid solutions of substrates at ambient temperatures), no reaction with the substrate occurred. To our knowledge, the only successful use of elemental fluorine for the preparation of dialkyl fluoromalonates is from the fluorination of the carbanion derived from diethyl nitromalonate [23]. In this experiment, the dialkyl malonate was dissolved in aqueous sodium bicarbonate and fluorine was passed through the resulting solution. However, this technique does not have general applicability since most other dialkyl malonates are insufficiently acidic to form solutions in this way. We now wish to report a general procedure for the conversion of salts of dialkyl malonates into the corresponding 2-fluoro compounds using elemental fluorine.

2. Results and discussion

A series of sodium salts of dialkyl malonates was prepared by treating the parent esters with sodium hydride or sodium alkoxide in acetonitrile, and then fluorine (10% v/v in nitrogen) was passed through the resulting suspensions at ca. −15 °C (Scheme 1).

$$RCH(COOR')_2 \xrightarrow{\text{NaH or NaOAlk}} R\bar{C}(COOR')_2 \; Na^+ \xrightarrow[-15\ ^\circ C]{10\%\ F_2\ \text{in}\ N_2} RCF(COOR')_2$$

Scheme 1.

The results of these experiments are summarised in Table 1.

Where the overall conversion was less than complete, it is believed to be due to incomplete salt formation, rather than incomplete reaction between the salt and fluorine. Improving the conditions required for complete salt formation should enable total conversion to be achieved.

Simply passing fluorine through acetonitrile solutions of the above diesters failed to give any fluorinated product,

* Corresponding author.

*PII*S0022-1139(96)03422-7

Table 1
Fluorination of sodium derivatives of esters of malonic and substituted malonic acids

R	R′	NaH	NaOEt	F_2	Conversion (%)	Yield (%)	Reference
H	Et	1	–	2	71	37 [a] + 23 [b]	[2,4–7,9–14]
H	Et	2.25	–	3	94	14 [a] + 37 [b]	
Me	Et	1	–	2	74	59	[16,19]
Me	Et	–	1	2	42	59	
^{n}Bu	Et	1.25	–	2.3	66	69	[6]
OMe	Me	1.25	–	2.9	75	51	
NO_2	Et	1.25	–	2	100	73	[22,23]
NO_2	Et	–	1	2	77	89	
Cl	Et	1.25	–	2	97	40	[18]
Ph	Et	1.25	–	1.2	72	41	[7,12,15,16,18,21]

[a] Diethyl fluoromalonate.
[b] Diethyl difluoromalonate.

except in the case of diethyl nitromalonate. Due to the electron-withdrawing effect of the nitro group in this compound, the acidity of the 2-hydrogen was sufficient for limited fluorination to occur when an acetonitrile solution of the compound was exposed to fluorine. But more importantly, when the experiment was repeated in the presence of a base (potassium fluoride), the conversion was 70% and the yield of diethyl fluoronitromalonate was 85%.

This work represents yet another example of how elemental fluorine can be used in a controlled way for site-specific fluorination.

3. Experimental details

In a typical experiment, the dialkyl malonate (12.5 mmol) in dry acetonitrile (10 ml) was added over 30 min to a suspension of degreased sodium hydride (12.5 mmol) in dry acetonitrile (50 ml) at room temperature under an atmosphere of dry nitrogen. After some 45–60 min, the mixture was cooled and maintained at ca. −15 °C while fluorine (diluted to 10% v/v in nitrogen) was passed through the stirred suspension over ca. 1 h. After purging the system with nitrogen, the reaction mixture was filtered, the filter cake washed with acetonitrile and the combined filtrate and washings fractionated under reduced pressure. The identity of the products was determined by NMR spectroscopy and mass spectrometry [dimethyl fluoromethoxymalonate (nc) isolated by preparative GC; m/z (CI, NH_3): 198 ($M^+ + NH_4^+$). ^{19}F NMR ($CDCl_3$ δ: −124.4 (s) ppm. ^{1}H NMR δ: 3.90 (s, $COOCH_3$); 3.57 (s, OCH_3) ppm] and the yields and conversions calculated from the composition (determined by NMR spectroscopy) of the weighed fractions.

Diethyl fluoronitromalonate [23] was also prepared by (i) passing fluorine (ca. 55 mmol) diluted to 10% v/v with nitrogen through a cooled (ca. −15 °C) suspension of dry potassium fluoride (100 mmol) in a solution of diethyl nitromalonate (25 mmol) in dry acetonitrile (50 ml) over 2 h or (ii) first adding a solution of diethyl nitromalonate (25 mmol) to a suspension of sodium ethoxide (25 mmol) in dry acetonitrile (50 ml) at room temperature, and then passing fluorine (ca. 55 mmol) diluted to 10% with nitrogen through the cooled (ca. −15 °C) suspension. Both of these reactions were worked-up in a similar manner to the general method outlined above.

References

[1] For Part 2, see R.D. Chambers, M.P. Greenhall and J. Hutchinson, *Tetrahedron, 52* (1996) 1.
[2] E.D. Bergmann, S. Cohen and I. Shahak, *J. Chem. Soc.*, (1959) 3286.
[3] E. Kimura, M. Shionoya, M. Okamoto and H. Nada, *J. Am. Chem. Soc., 110* (1988) 3679.
[4] N. Ishikawa and A. Takaoka, *Chem. Lett.*, (1981) 107.
[5] N. Ishikawa and A. Takaoka, Eur. Pat. Appl. 133 322, 1985; [*Chem. Abs., 102* (1985) 185 113e].
[6] N. Ishikawa, A. Takaoka and M.K. Ibrahim, *J. Fluorine Chem., 25* (1984) 203.
[7] Pennsalt, UK Pat. 865 321, 1962; [*Chem. Abs., 56* (1962) 331g].
[8] A. Takaoka, I. Kamal, S.R.F. Kagaruki and N. Ishikawa, *Nippon Kagaku Kaishi, 11* (1985) 2169; [*Chem. Abs., 105* (1986) 226 472d].
[9] A.L. Henne and E.G. De Witt, *J. Am. Chem. Soc., 70* (1948) 1548.
[10] R.N. Haszeldine, *J. Chem. Soc.*, (1955) 4302.
[11] S. Boehm and A. Marhold, Ger. Offen. DE 4237882, 1994; [*Chem. Abs., 121* (1994) 108 005m].
[12] C.E. Inman, R.E. Oesterling and E.A. Tyczkowski, *J. Am. Chem. Soc., 80* (1958) 6533.
[13] H. Gershon, J.A.A. Renwick, W.K. Wynn and R. D'Ascoli, *J. Org. Chem., 31* (1966) 916.
[14] C.M. Sharts and W.A. Sheppard, *Org. React., 21* (1974) 225.
[15] R.E. Banks, N.J. Lawrence and A.L. Popplewell, *J. Chem. Soc., Chem. Commun.*, (1994) 343.
[16] G.S. Lal, *J. Org. Chem., 58* (1993) 2791.
[17] O. Lerman and S. Rozen, *J. Org. Chem., 48* (1983) 724.
[18] T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada and K. Tomita, *J. Am. Chem. Soc., 112* (1990) 8563.
[19] E. Differding and M. Wehrli, *Tetrahedron Lett., 31* (1991) 3819.
[20] E. Differding and H. Ofner, *Synlett*, (1991) 187.
[21] Z.Q. Xu, D.D. Desmarteau and Y. Gotoh, *J. Fluorine Chem., 58* (1992) 71.
[22] G. Resnati and D.D. Desmarteau, *J. Org. Chem., 56* (1991) 4925.
[23] H.G. Adolph, R.E. Oesterling and M.E. Sitzmann, *J. Org. Chem., 33* (1968) 4296.