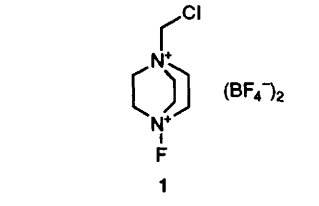
# Efficient Electrophilic Fluorination of β-Dicarbonyl Compounds with the Selectfluor Reagent F-TEDA-$BF_4$ {1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)}

**R. Eric Banks,* Nicholas J. Lawrence* and Allan L. Popplewell**

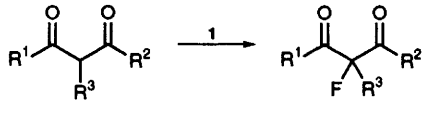
*Chemistry Department, University of Manchester Institute of Science and Technology, Manchester, UK M60 1QD*

1,3-Dicarbonyl compounds (acyclic and cyclic 1,3-diketones, β-ketoesters, β-ketoamides) are converted efficiently to 2-monofluoro derivatives, and thence to 2,2-difluoro derivatives, with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

Although the site-selective introduction of fluorine into biologically active molecules is now well-established as an invaluable stratagem in medicinal chemistry,[1] progress is still hampered by the lack of more generally acceptable fluorinating agents of both the $F^-$ and $F^+$ delivery classes.[2] The situation in the latter case has improved markedly recently with the discovery of easily-handled 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts,[3–5] especially since the cost-effective bis(tetrafluoroborate) **1** [F-TEDA-$BF_4$ (TEDA = triethylenediamine)] has rapidly become a commercial chemical[6] with established applications in the pharmaceutical industry.[7] The great research potential of **1** and its congeners[3] has been revealed in but a few publications so far (fluorination of resonance stabilized carbanions;[8] of styrene and related olefins;[8] of substituted benzenes;[3,8] of steroidal enol acetates and silyl enol ethers;[7] of enamines;[3,4,8] and of compounds containing carbon–metal[8,9,10] or carbon–sulfur[8] bonds).



**1**



**2a–g** **3a–g**

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **a** | $-(CH_2)_3-$ | | Me |
| **b** | Ph | Ph | H |
| **c** | Ph | OEt | H |
| **d** | Me | OEt | H |
| **e** | OEt | OEt | Ph |
| **f** | Ph | $NMe_2$ | H |
| **g** | Ph | NMeCH(Ph)Me | H |

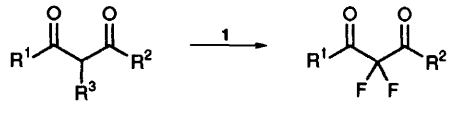
**Scheme 1**

The present report aims to establish the important case of selective monofluorination of 1,3-diketones and related substrates (including β-ketoamides) under neutral conditions—a synthetic manipulation which best precedes *gem*-difluorination *via* sodium salts; also revealed is the first example of fluorination α to a cyano group with F-TEDA-$BF_4$ **1**. The results reveal that Selectfluor reagent **1** is just as effective a fluorinating agent as the DesMarteau reagent $(CF_3SO_2)_2NF$,[11] which is not available commercially and is both costly and hazardous to prepare.[12]

The reaction of 1,3-diketones **2a** and **2b** with one equivalent of F-TEDA-$BF_4$ **1** under neutral† conditions in acetonitrile at room temp. proceeds smoothly to give α-fluoro derivatives in very good yields (Scheme 1 and Table 1). Under the same conditions fluorination of the ketoesters **2c** and **2d** is a little slower, but after two days the monofluoro derivatives **3c** and **3d** can be obtained (these resist further fluorination under neutral conditions); the diethyl ester **2e** is not attacked by **1** under neutral conditions, but its sodium derivative‡ gives the fluorodiester **3e** in excellent yield.

Monofluorination of the *N*,*N*-dimethylketoamide **2f**§ occurs rapidly under neutral conditions to give the monofluoro derivative. Its *N*-methyl-*N*-(α-methylbenzyl)amide analogue **2g**¶ suffers fluorination under neutral conditions to give, perhaps not surprisingly, an equal mixture of diastereoisomeric monofluoroamides **3g**. Even if the initial fluorination is stereoselective, the monofluoro derivative might epimerize under the reaction conditions. These are the first examples of the α-fluorination of secondary amides with F-TEDA-$BF_4$ **1**.

Nitriles seem compatible with F-TEDA-$BF_4$ **1**, as indicated by conversion of the cyanoester $PhCH(CN)CO_2Et$ to the corresponding α-fluoro product $PhCF(CN)CO_2Et$ under neutral conditions (1.5 equiv. **1**, at 40 °C) in excellent yield (92%). Significant applications in synthesis stem from this result, and examples will be reported in due course.



**2b, 2f** **4**
**3c, 3f**

**Scheme 2**

**Table 1** Conversion of 1,3-dicarbonyl substrates **2** to monofluorides **3** with **1**, at room temp.

| **2** | $R^1$ | $R^2$ | $R^3$ | Method[a] | Time/h | Yield (%) (crude product)[b] | Purif. method[c] | Yield (%) (pure **3**) |
|---|---|---|---|---|---|---|---|---|
| **a** | $-(CH_2)_3-$ | | Me | n | 19 | — | Tritur. | 84 |
| **b** | Ph | Ph | H | n | 5 | 100 | Recryst. | 84 |
| **c** | Ph | OEt | H | n | 54 | 88 | Chrom. | 22 |
| **d** | Me | OEt | H | n | 120 | 57 | — | — |
| **e** | OEt | OEt | Ph | b | 20 | 96 | Chrom. | 93 |
| **f** | Ph | $NMe_2$ | H | n | 3 | 96 | Recryst. | 87 |
| **g** | Ph | (±)-N(Me)CH(Ph)Me | H | n | 67 | 87 | Chrom. | 80 |

[a] n = neutral conditons, b = basic conditions. [b] Crude yields were estimated from percentage conversions judged by $^1H$ NMR analysis. [c] Recryst. = recrystallisation; Chrom. = flash or dry flash chromatography; Tritur. = trituration.

**Table 2** Synthesis of *gem*-difluorocarbonyl compounds **4** from **2** or **3**

| | $R^1$ | $R^2$ | $R^3$ | Method[a] | Reactant ratio [molar, **1**:**2** (or **3**)] | Temp/°C | Time/h | Yield (%) (crude)[c] | Purif. method[d] | Yield (pure) |
|---|---|---|---|---|---|---|---|---|---|---|
| **2b** | Ph | Ph | H | n | 2.1 | RT[b] | 192 | 96 | Recryst. | 78 |
| **3c** | Ph | OEt | F | b | 1.1 | RT | 24 | 95 | — | 95 |
| **2f** | Ph | $NMe_2$ | H | n | 3.2 | 40 | 647 | 93 | Chrom. | 91 |
| **3f** | Ph | $NMe_2$ | F | b | 1.2 | RT | 27 | 84 | Chrom. | 73 |

[a] n = neutral conditions, b = basic conditions. [b] RT = room temp. [c] Crude yields were estimated from percentage conversions judged by $^1H$ NMR analysis. [d] Recryst. = recrystallisation; Chrom. = flash or dry flash chromatography.

Prompted by the increasing utility of biologically-active compounds containing difluoromethylene groups,[13–16] difluorination of dicarbonyl compounds with F-TEDA-$BF_4$ was studied (Table 2). Difluorination of **2b** under neutral conditions proved extremely slow; when treated with two equivalents of **1**, a near-quantitative yield of the corresponding α,α-difluorodiketone was obtained, but only after an eight day reaction period at room temp. Difluorination of **2c** occurred even more slowly. However, the sodium enolate of **3c** reacted rapidly to give the difluoro derivative **4c** in excellent yield. Difluorination of the amide **2f** proceeded only slowly, but nevertheless gave the difluoroamide **4f** when treated with an excess of **1** for 27 days at 40 °C in acetonitrile. Alternatively, and more conveniently, the sodium derivative of the monofluoride **3f** can be converted cleanly to **4f** after only one day.

In summary, electrophilic fluorination of all the dicarbonyl compounds studied, except for diester **2e**, proceeds efficiently at 20 °C under neutral conditions with F-TEDA-$BF_4$. The monofluoro derivatives **3** resist attack under these conditions, as indicated by their extremely slow difluorination when the reagent is present in excess. Fluorination occurs more rapidly with those compounds which exist (at least in part) in enolic form (as measured by $^1H$ NMR in $CDCl_3$). For example, **2f** and **2g** have keto:enol contents of 2:1 and 2.4:1, respectively. The monofluoro derivatives exist solely as their keto forms and consequently are not easily fluorinated further by **1**. This appears to indicate that the reaction is occurring *via* the enol or enolate and is ionic in nature.

We thank Dr Ray Fisher (Peakdale Fine Chemicals, Glossop) for helpful discussions and financial support.

*Received, 14th September 1993; Com. 3/05529I*

## Footnotes

† *Neutral conditions*: The substrate (1 mmol) was stirred with F-TEDA-$BF_4$ **1** (1 mmol) in acetonitrile (10 $cm^3$) at room temp. When fluorination was complete (as judged by TLC), the reaction solution was concentrated *in vacuo*, and the residue was partitioned between water and dichloromethane. The organic layer was washed twice with water, dried ($MgSO_4$) and evaporated *in vacuo*. Residues were purified further as indicated in Tables 1 and 2.

‡ *Basic conditions*: A solution of the substrate (1 mmol) in dry tetrahydrofuran (THF) (15 $cm^3$) was added to an oil-free suspension of NaH (1.22 mmol) in THF (2 $cm^3$). The resulting suspension (or solution) was stirred at room temp. until no more hydrogen was evolved (*ca.* 15 min). F-TEDA-$BF_4$ **1** reagent (equiv. as stated) was then added and the resulting suspension stirred at room temp. until the reaction was complete (as judged by TLC). The solvent was removed *in vacuo* and the residues purified as stated in Tables 1 and 2.

§ Made by Claisen condensation of *N*,*N*-dimethylacetamide with methyl benzoate.

¶ Made by Claisen condensation of *N*-methyl-*N*-(α-methylbenzyl)-acetamide with methyl benzoate.

## References

1 J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, John Wiley, New York, 1991.
2 J. A. Wilkinson, *Chem. Rev.*, 1992, **92**, 505.
3 R. E. Banks, US Pat. 5086178, 1992 (to Air Products and Chemicals, Inc.).
4 R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, I. Sharif and R. G. Syvret, *J. Chem. Soc., Chem. Commun.* 1992, 595.
5 R. E. Banks, I. Sharif and R. G. Pritchard, *Acta Crystallogr. Sect. C*, 1993, **49**, 492.
6 An MSDS (Material Safety Data Sheet) is available from Dr Helen M. Marsden, Air Products PLC, European Technology Group, Chineham, Basingstoke, Hampshire RG24 0FE, UK or Dr G. P. Pez, Air Products and Chemicals Inc., 7201 Hamilton Boulevard, Allentown, PA 18195-1501, USA.
7 G. P. Pez, personal communication.
8 G. S. Lal, *J. Org. Chem.*, 1993, **58**, 2791.
9 M. A. McClinton and V. Sik, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1891.
10 D. P. Matthews, S. C. Miller, E. T. Jarvi, J. S. Sabol and J. R. McCarthy, *Tetrahedron Lett.*, 1993, **34**, 3057.
11 Z.-Q. Xu, D. D. DesMarteau and Y. Gotoh, *J. Fluorine Chem.*, 1992, **58**, 71; G. Resnati and D. D. DesMarteau, *J. Org. Chem.*, 1991, **56**, 4925; 1992, **57**, 4281.
12 S. Singh, D. D. DesMarteau, S. S. Zuberi, M. Witz and H.-N. Huang, *J. Am. Chem. Soc.*, 1987, **109**, 7194; D. D. DesMarteau and M. Witz, *J. Fluorine Chem.*, 1991, **52**, 7.
13 Difluorostatone, a potent inhibitor of human renin; S. Thaisrivongs, H. J. Schostarez, D. T. Pals and S. R. Turner, *J. Med. Chem.*, 1987, **30**, 1837.
14 Difluorostatone type inhibitors of HIV-1 protease; D. Schirlin, S. Baltzer, V. VanDorsselaer, F. Weber, C. Weill, J. M. Altenburger, B. Neises, G. Flynn, J. M. Rémy and C. Tarnus, *Biorg. Med. Chem. Lett.*, 1993, **3**, 253.
15 2,2-Difluoro-5-hexyne-1,4-diamine; a potent inhibitor of ornithine decarboxylase, D. A. Kendrick, C. Danzin and M. Kolb, *J. Med. Chem.*, 1989, **32**, 170.
16 3,3′-Difluoro-3′-deoxythymidine, a nucleoside analogue with poor anti-HIV activity; D. E. Bergstrom, A. W. Mott, E. De Clercq, J. Balzarini and D. J. Swartling, *J. Med. Chem.*, 1992, **35**, 3369.