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Microwave-assisted rapid electrophilic fluorination of 1,3-dicarbonyl derivatives with Selectfluor®

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Dedicated to Professor Richard D. Chambers on the occasion of his 70th birthday.

Abstract

A microwave-assisted fluorination method for 1,3-dicarbonyl compounds using Selectfluor® has been developed. 2-Monofluorinated products can be obtained in high yield in neutral reaction conditions with addition of 1 eq. of Selectfluor®. Treatment of 1,3-dicarbonyls with 3 eq. of Selectfluor® in the presence of tetrabutylammonium hydroxide (TBAH) as the base results in the formation of 2,2-difluorinated derivatives only.

Keywords: Microwave; Electrophilic fluorination; Selectfluor; 1,3-Dicarbonyl compounds

1. Introduction

Electrophilic fluorination is one of the most direct and useful methods to introduce fluorine selectively into organic compounds [1]. There continues to be considerable interest in the electrophilic fluorination of 1,3-dicarbonyl compounds since the α-fluoro carbonyl compounds are valuable building blocks in constructing potentially useful biological compounds [2–14]. While 1,3-dicarbonyl derivatives can be fluorinated directly by a variety of electrophilic fluorinating agents, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]-octane bis(tetrafluoroborate) (Selectfluor®, F-TED-A-BF_4, 1), first reported by Banks et al. [15,16], is an efficient site-selective, commercially available electrophilic fluorinating agent. Banks et al. demonstrated the fluorination of β-dicarbonyl compounds with **1** [17]. However, for some substrates, long reaction times are required to bring about those transformations.

Microwave irradiation is a powerful and easily controllable heating source [18–20]. Since significant rate acceleration for reactions carried out in a conventional microwave oven were first observed in 1986, microwave irradiation has found increasing application in organic synthesis [18–20]. Recently, microwave-assisted fluorination of aromatic rings using **1** was reported [21]. Considering the slow fluorination rates of some 1,3-dicarbonyls with **1**, we were interested in examining the impact of microwave irradiation on yields and reaction times when mono and/or difluorinated compounds were the desired products. As described below, microwave methodology can play a major role.

2. Results and discussion

Under microwave irradiation conditions, 1,3-dicarbonyls **2a–d** reacted readily with 1 eq. of **1** in acetonitrile to give α-fluoro products **3a–d** in 10 min (Scheme 1, Table 1).

One of the important features of these reactions is the rapid rate. Generally, 1,3-ketoesters are less reactive than 1,3-diketones. The monofluorination of 1,3-ketoesters, **2b** and **c**, required 54 and 120 h, respectively, under conventional reaction conditions [17]. However, while utilizing

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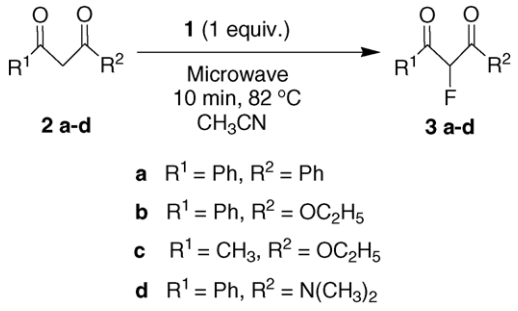
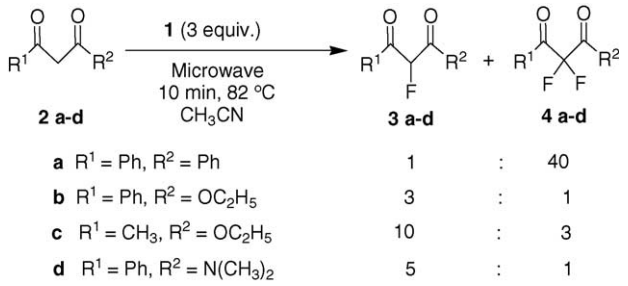
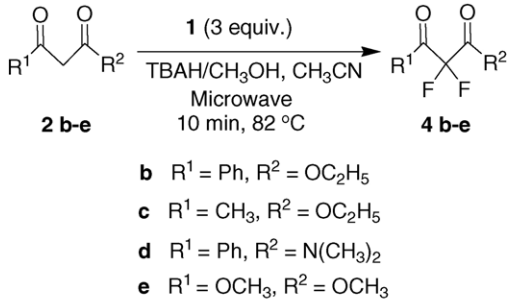


Scheme 1.



Scheme 2.



Scheme 3.

microwave irradiation, we found that these reactions could be accelerated dramatically and with comparable yields. The microwave-assisted fluorination reactions proceeded smoothly with essentially no tar formation despite being carried out at approximately reflux conditions.

At the end of the reaction process, NMR spectral analyses showed that traces of α,α-difluorinated products often formed in these reactions. The pure products can be obtained either via column chromatography or distillation. All of the monofluorinated products existed predominantly in their keto tautomers and no change was observed upon workup.

The facile monofluorination of these 1,3-dicarbonyls prompted us to investigate the efficacy of difluorination. Utilizing the same microwave reaction conditions, when the highly reactive β-diketone, **2a**, was treated with 3 eq. of **1**, 81% yield of the corresponding α,α-difluorodiketone, **4a**, was obtained in 10 min (Scheme 2, Table 1). Under classical reaction conditions, difluorination of **2a** requires 8 days to reach completion [17]. For the less reactive ketoesters, **2b** and **c**, and the ketoamide, **2d**, difluorination is not complete even when the reaction time is increased to 30 min and the amount of **1** raised to 5 eq.. In these cases, mixtures of mono- and difluoro-compounds were obtained (Scheme 2). Monofluorinated **3b–d** resists further fluorination under these conditions.

Our earlier work showed that tetrabutylammonium hydroxide (TBAH) facilitated the fluorination of 1,3-dicarbonyl compounds when electrophilic fluorination is carried out with trifluoroamine oxide [22]. Therefore, the difluorination reactions of **2b–d** with the addition of 2 eq. of TBAH in one pot was attempted. The desired products, **4b–d**, were obtained in high yield after microwave irradiation for 10 min (Scheme 3, Table 1). No monofluorinated products were observed in these reactions. To investigate the effects of TBAH, the reaction of **2c** with 3 eq. of **1** in CH_3OH (2 mL) and CH_3CN (1 mL) was carried out without TBAH. After irradiation under microwave for 10 min, the main product was the monofluorinated compound, **3c**, with a trace of difluorinated compound, **4c**. TBAH does play a key role in the difluorination of 1,3-dicarbonyl compounds.

Fluorination of β-diesters with **1** under conventional conditions does not occur in the absence of base [17]. This lack of fluorination is also observed in similar reactions with other electrophilic fluorinating reagents [10]. In our case, microwave irradiation reactions appear to suffer from the same limitation. However, in the presence of TBAH, dimethyl malonate, **2e**, reacted with **1** easily to give only the difluorinated product **4e**.

The results of the mono- and difluoro-products are summarized in Table 1.

Table 1
Microwave-assisted fluorination of 1,3-dicarbonyl compounds with **1**

Substrate	Product	Yield (%)
2a	**3a**	84[a]
2b	**3b**	81[a]
2c	**3c**	70[a]
2d	**3d**	86[a]
2a	**4a**	81[a]
2b	**4b**	88[b]
2c	**4c**	78[b]
2d	**4d**	83[b]
2e	**4e**	77[b]

[a] Isolated yields: neutral conditions.
[b] Isolated yields: basic conditions.

3. Conclusions

The rate of electrophilic fluorination of 1,3-dicarbonyl derivatives with Selectfluor® can be dramatically accelerated under microwave irradiation while still retaining high product yields. Using neutral reaction conditions, monofluorination can be obtained by carefully controlling the

stoichiometry of the reagents. With the addition of TBAH as the base, difluorination can be achieved successfully in single step reactions.

4. Experimental

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor®, F-TEDA-BF_4, **1**) and all other reagents employed were purchased from commercial sources and used without further purification. *N*,*N*-dimethyl benzoylacetamide, **2d**, was synthesized from ethyl benzoylacetate, **2e**, according to the literature [23]. CH_3CN was freshly distilled under N_2 from phosphorus pentoxide prior to use. Microwave-assisted reactions were carried out in a self-tuning single mode CEM Discover$^{\beta}$ Focused Synthesizer operated at 100 W. TLC analysis was performed with Al backed plates pre-coated with silica gel and examined under UV fluorescence (254 nm). Flash column chromatography was executed on silica gel (Acros, 60–200 μm, 60 A). ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ on a 300 MHz spectrometer. Chemical shifts are reported in ppm relative to the appropriate standards: TMS as an internal standard for ^{1}H NMR and $CFCl_3$ as external standard for ^{19}F NMR.

4.1. General procedure for the electrophilic fluorination of β-dicarbonyl derivatives with Selectfluor®(1) under microwave irradiation

4.1.1. Neutral conditions

Into a septum-sealed microwave tube, the substrate (1 mmol), acetonitrile (2 mL) and **1** (equivalent as required) were charged. The resulting mixture was irradiated in a microwave cavity at 82 °C (by modulation of power) for 10 min. The solution was cooled rapidly to room temperature by passing compressed air through the microwave cavity. Any insoluble material was filtered off. The solvent was removed from the filtrate in vacuo, and the crude products were purified directly by flash chromatography over SiO_2 or by distillation. The pure products were identified by comparing their NMR spectral data with those of literature.

4.1.2. Basic conditions

In a typical reaction, a 1,3-dicarbonyl compound (1 mmol), **1** (3 mmol), acetonitrile (1 mL), and TBAH (1 M solution in CH_3OH, 2 mL) were placed in a septum-sealed microwave tube. The reaction mixture was irradiated in a monomode microwave cavity at 82 °C for 10 min. The workup procedures were the same as in neutral conditions.

2-Fluoro-1,3-diphenylpropane-1,3-dione (**3a**) [24]: ^{1}H NMR ($CDCl_3$): $\delta = 8.08$ (d, $J = 8.1$ Hz, 4H), 7.44–7.62 (m, 6H), and 6.51 (d, $J = 49.2$ Hz, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -186.7$ (d, $J = 49.2$ Hz, 1F).

Ethyl 2-fluoro-3-oxo-3-phenyl-propanoate (**3b**) [10]: ^{1}H NMR ($CDCl_3$): $\delta = 8.02$ (d, $J = 8.1$ Hz, 2H), 7.46–7.65 (m, 3H), 5.84 (d, $J = 48.9$ Hz, 1H), 4.29 (q, $J = 7.1$ Hz, 2H), and 1.24 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR ($CDCl_3$): $\delta = -190.2$ (d, $J = 48.9$ Hz, 1F).

Ethyl 2-fluoro-3-oxo-butanoate (**3c**) [10]: ^{1}H NMR ($CDCl_3$): $\delta = 5.16$ (d, $J = 49.4$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.32 (d, $J = 4.1$ Hz, 3H), and 1.31 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR ($CDCl_3$): $\delta = -193.0$ (dq, $J = 49.4$, 4.1 Hz, 1F).

N,*N*-dimethyl 2-fluoro-3-oxo-3-phenyl-propanoate (**3d**) [17]: ^{1}H NMR ($CDCl_3$): $\delta = 8.12$ (d, $J = 7.6$ Hz, 2H), 7.43–7.61 (m, 3H), 6.14 (d, $J = 48.9$ Hz, 1H), 3.10 (d, $J = 1.8$ Hz, 3H), and 2.96 (s, 3H); ^{19}F NMR ($CDCl_3$): $\delta = -186.6$ (d, $J = 48.9$ Hz, 1F).

2,2-Difluoro-1,3-diphenylpropane-1,3-dione (**4a**) [24]: ^{1}H NMR ($CDCl_3$): $\delta = 8.07$ (d, $J = 7.5$ Hz, 4H), 7.45–7.66 (m, 6H); ^{19}F NMR ($CDCl_3$): $\delta = -106.6$ (s, 2F).

Ethyl 2,2-difluoro-3-oxo-3-phenyl-propanoate (**4b**) [10]: ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (d, $J = 7.6$ Hz, 2H), 7.48–7.68 (m, 3H), 4.37 (q, $J = 7.1$ Hz, 2H), and 1.30 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR ($CDCl_3$): $\delta = -107.6$ (s, 2F).

Ethyl 2,2-difluoro-3-oxo-butanoate (**4c**) [10]: ^{1}H NMR ($CDCl_3$): $\delta = 4.35$ (q, $J = 7.1$ Hz, 2H), 2.39 (t, $J = 1.5$ Hz, 3H), and 1.33 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR ($CDCl_3$): $\delta = -113.7$ (s, 2F).

N,*N*-dimethyl 2,2-difluoro-3-oxo-3-phenyl-propanoate (**4d**) [17]: ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (d, $J = 7.5$ Hz, 2H), 7.45–7.64 (m, 3H), 3.13 (t, $J = 3.0$ Hz, 3H), and 3.02 (s, 3H); ^{19}F NMR ($CDCl_3$): $\delta = -102.7$ (s, 2F).

Dimethyl 2,2-difluoro-malonate (**4e**) [25]: ^{1}H NMR ($CDCl_3$): $\delta = 3.92$ (s, 6H); ^{19}F NMR ($CDCl_3$): $\delta = -111.7$ (s, 2F).

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