Synthesis of 5-Fluoro-1,3-dioxin-4-ones: Versatile Building Blocks of Fluorinated Compounds

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Fluorination of 5,6-unsubstituted 1,3-dioxin-4-ones by fluorine followed by treatment with triethylamine affords the title compounds, which can be converted into fluorinated derivatives of either formylacetic acid or of heterocyclic systems.

Owing to their expected greater biological activity, fluorinated organic molecules have attracted much attention in the field of medicinal chemistry.[1] Because of the scarcity and/or high cost of the reagents as well as the exceptional experimental conditions needed, fluorination reactions are not always a suitable means for their preparation (especially on a large scale). An attractive alternative preparation for this kind of compounds is *via* versatile intermediates carrying a fluorine atom, which can be used as building blocks.[2] Because of the two characteristics shown in Scheme 1 [ring opening of (**A**) to give the acylketene (**B**) and participation of the C–C double bond in (**A**) in pericyclic reactions], 1,3-dioxin-4-ones (**A**) have proved to be versatile building blocks.[3] We now report the synthesis of 5-fluoro-1,3-dioxin-4-ones and some of their reactions.

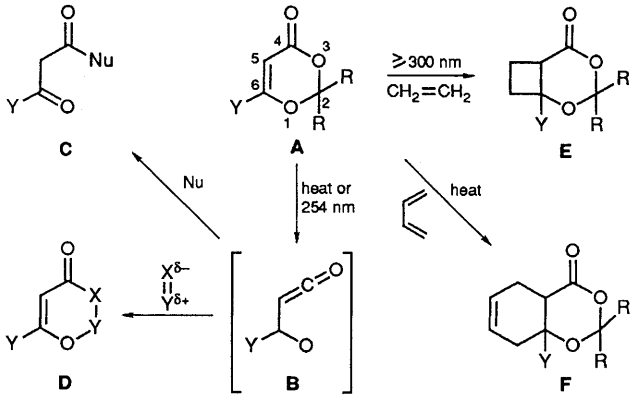
5-Iodo- and 5-bromo-1,3-dioxin-4-ones **3a,b** have been synthesized previously from 5,6-unsubstituted dioxinones[4] by the two-step reaction shown in Scheme 2.[5]

The spiro compound **3c** was first synthesized.† Thus, by the procedure used in the synthesis of **3a,b**, compound **1** was treated with *N*-chlorosuccinimide (NCS) in acetic acid to give the 5-chlorodioxinone (**3c**, oil).‡ The intermediate **2c** corresponding to **2a,b** was not detected. Use of fluorinating reagents such as *N*-fluoropyridinium trifluoromethanesulphonate and its 3,5-dichloro derivative in the above reaction failed to give the 5-fluorinated product, but resulted only in the formation of a tarry material.

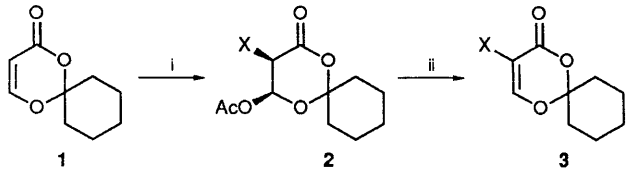
After thorough investigation, we have succeeded in synthesizing 5-fluorodioxinone **3d**. Thus, bubbling of fluorine into an acetonitrile solution of **1** at −20 °C afforded the adduct **4**,§ which on treatment with triethylamine in CH_2Cl_2 at room temperature gave **3d** (m.p. 61–62 °C).§ The overall yield of **3d** from **1** was 84%, for reactions without isolation of the adduct **4** (Scheme 3).

We tentatively assigned the *cis*-configuration to the fluoro substituents in the adduct **4**, because the coupling constant of the vicinal protons in its NMR spectrum was rather small (*J* 4.4 Hz).

In order to confirm that the 5-halogenated dioxinone **3** still can serve as the equivalent of halogenated formylketene, the following transformations were carried out using **3d** (Scheme 4). Reaction of dimethylcyanamide with **3d** proceeded smoothly in refluxing mesitylene to give the expected oxazinone **5d** (m.p. 215–217 °C).§ The fact that the same reaction using the corresponding 5-chloro derivative **3c** proceeded under milder conditions (reflux in xylene) implies that ease of ring opening to give halogenated formylketene depends upon the halogen. Trapping of the formylketene by urea would be expected to afford 5-fluorouracil **7d**.[6] In order to overcome the problem of insolubility of urea in xylene, we have developed an alternative method. Thus, **3d** was first heated in refluxing xylene containing benzylisothiourea. The pyrimidine **6d** (m.p. 223–224 °C)§ thus obtained was hydrolysed with conc. hydrochloric acid to give **7d**. Finally, conversion of **3** to the formylester **9d** was realized without using the ketene

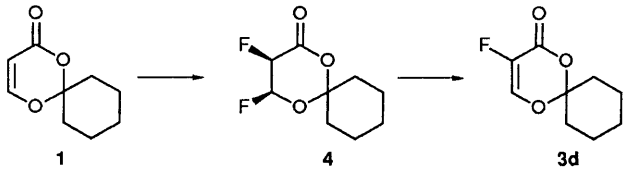


Scheme 1



a; X = I
b; X = Br
c; X = Cl

Scheme 2 *Reagent and conditions*: i, NXS, AcOH; ii, Et_3N, CH_2Cl_2



Scheme 3

† This paper reports reactions using dioxinones having a spiro-linked pentamethylene chain at the 2-position; reactions of the corresponding 2,2-dimethyl derivatives proceeded similarly.

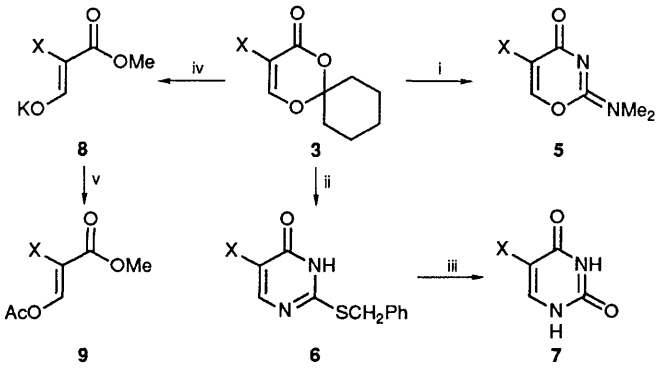
‡ All new compounds exhibited satisfactory spectroscopic (NMR, IR, UV) and combustion or high resolution mass spectral analytical data.

§ **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: *inter alia* 5.00 (1H, d,d,d, *J* 48.0, 24.3, 4.4 Hz, 5-H) and 6.06 (1H, d,d, *J* 56.4, 4.4 Hz, 6-H); ^{19}F NMR (282 MHz, $CDCl_3$) δ: 137.9 (d,d,d, 6-F) and 209.4 (d,d, 5-F) with $J_{F,F}$ 17.7 Hz.

3d: ^{1}H NMR (300 MHz, CD_3CN) δ: 1.40–1.80 (10H, m) and 7.46 (1H, d, *J* 2.7 Hz, 6-H); ^{19}F NMR (282 MHz, CD_3CN) δ: 178.0 (d).

5d: ^{1}H NMR ($CDCl_3$) δ: 3.17 (6H, s, 2 × CH_3) and 7.60 (1H, d, *J* 2 Hz, 6-H).

6d: ^{1}H NMR ($CDCl_3$) δ: 4.44 (2H, s, CH_2), 7.30 (5H, s, Ph) and 7.80 (1H, d, *J* 2 Hz, 6-H).



Scheme 4 *Reagent and conditions*: i, Me_2NCN, mesitylene (30 min for **3d**) and xylene (20 min for **3c**), reflux; ii, $H_2NC(=NH)SCH_2Ph$, xylene, reflux 2 h; iii, conc. HCl, heat; iv, K_2CO_3, MeOH, room temp.; v, Ac_2O

trapping reaction.[7] Thus, treatment of **3d** with methanol containing potassium carbonate gave the formyl ester **8d** which on acetylation with acetic anhydride gave the enol acetate **9d**.¶ The solvolytic ring opening of the dioxinone ring in methanol proceeded at room temperature irrespective of the substituents in the ring and, hence, seems to have wide applicability.[8]

We are now studying the use of **3d** in pericyclic reactions (*cf.* Scheme 1).

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¶ The configuration of **9d** was determined as *Z* by the large coupling constant ($J_{F,H}$ 19.0 Hz).

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