Synthesis of Mono-Fluorinated Quinones by an Unusual $S_{RN}1$ Reaction : Difluoromethyl Quinones as Substrates

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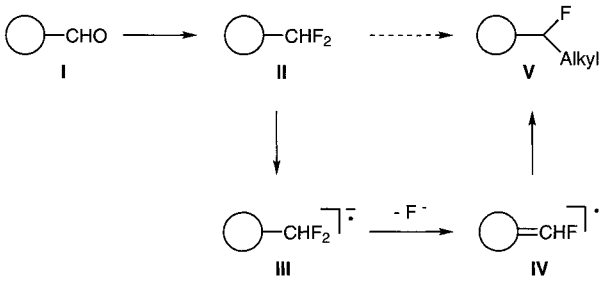
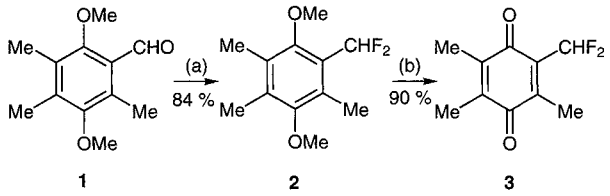
Abstract: Aldehydes are transformed into stable *gem*-difluoro compounds. Upon standard $S_{RN}1$ reaction conditions, they generate anion radicals that undergo a very fast fluoride elimination to produce methylene quinones which are alkylated by a nucleophile. This process gives rise to facile access to new fluorinated species having any side chain. It is the first reported example of *gem*-difluoro compounds reacting by the $S_{RN}1$ mechanism.

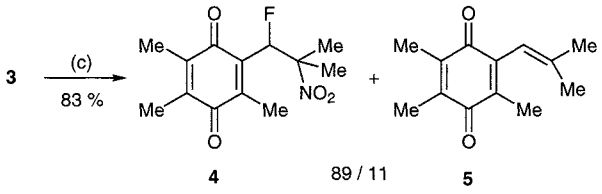
Quinones are versatile organic compounds endowed with rich and fascinating chemistry. Many of them are important therapeutic agents,[1,2] quite often they serve as intermediates in organic synthesis and in the dye industry.[3,4] Quinones (as well as anthracyclines, adriamycin and daunorubicin) are important antitumor agents presenting a clinical effectiveness against many types of human cancers. However, their utilization for cancer chemotherapy is seriously restricted by their side effects, the most notable of which is dose-related cardiotoxicity. Recent studies in the field of anthracyclines have shown that derivatives fluorinated at the sugar moiety or at the D-ring enhanced the anticancer activity. The observed IC_{50} decrease is accompanied by a diminution of the side effects.[5] As bioreductible agents, quinones are potential substrates for the radical nucleophilic substitution or $S_{RN}1$ reaction.[6] This has been studied extensively in benzylic[7] and heterocyclic[8] systems. Norris[9-11] has investigated it in the *p*-nitrobenzylidene dichloride and diacetate systems and there is only one reported example of such a reaction in the isoquinoline series with a heterocyclic *gem*-dichloride.[12] Finally, our group has recently reported the displacement of a fluoride[13] or a chloride[14] by $S_{RN}1$ reaction at sp^3 carbon in quinonic series.

In connection with our program directed toward the development of novel synthetic quinone congeners as anticancer agents, we report here a new preparative method based on the fluoride elimination of *gem*-difluoride of type **II**. The intermediate anion radical **III** is expected to lose fluoride easily to the more stable *ortho*-quinone methide radical **IV**. The latter can be intermolecularly alkylated to form a new C,C-bond.



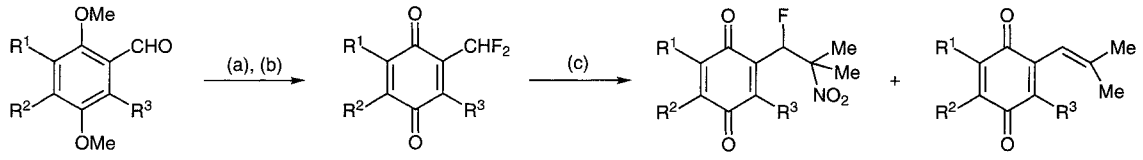
A preliminary study was run starting from 2,5-dimethoxy-3,4,6-trimethylbenzaldehyde (**1**).[14] The *gem*-difluoro compound **3** was prepared by adding diethylaminosulfur trifluoride (DAST) to **1** in CH_2Cl_2, according to the Middleton method.[15] The stable *gem*-difluoride **2** obtained was then oxidized with cerium ammonium nitrate (CAN) in CH_3CN giving the quinone **3** in 76 % yield (procedure A).[16] Radical reduction of **3** with lithium 2-nitro-2-propanide (1 equiv) in degassed DMSO under irradiation (procedure B) gave good yields of both the monosubstituted fluoro compound **4**[17] and the ethylenic compound **5**.[18] It is possible to favour the formation of **5** by using an excess of anion.





Scheme 1. *Reagents* : (a) DAST, CH_2Cl_2 reflux, 16 h; (b) CAN, CH_3CN/H_2O; (c) $LiC(CH_3)_2NO_2$, DMSO degassed, hv, 24 h

The study of the nature of the reaction in the presence of classical radical inhibitors and the fact that compound **2** is recovered unchanged after 24 h when submitted to the same experimental conditions provide clear evidence that the C-alkylation product **4** is formed via a $S_{RN}1$ process. This is, to our knowledge, the first example of C,C-bond formation by an $S_{RN}1$ process occurring with a *gem*-difluoro compound. The conversion of compound **3** into the ethylenic compound **5**[18] takes place by the heterolytic cleavage of the radical anion of **4** by loss of fluoride anion. The intermediate "benzylic" radical accepts an electron to give the corresponding "benzylic" anion. The latter loses a nitrite ion to give the compound **5**. For this process the appropriate label is $E_{RC}1$, standing for unimolecular radical chain elimination.[11] The scope and limitations of the method were investigated by preparing *gem*-difluoroquinones starting from the different protected aldehydes **6-9** according to procedure A (DAST, CAN), with satisfactory yields. Finally we have investigated the nucleophilic addition of the 2-nitropropane salt starting from the *gem*-difluorides **10-13** (procedure B). The addition products **14-17** were isolated in good to excellent yields (> 72 %).



6 : $R^1 = R^2 = Me$, $R^3 = H$ — **10** : 70 % — **14** : 72 % — **18** : 9 %
7 : $R^1 = R^2 = R^3 = OMe$ — **11** : 85 % — **15** : 87 % — **19** : 4 %
8 : $R^1 = R^2 = OMe$, $R^3 = H$ — **12** : 82 % — **16** : 78 % — **20** : 6 %
9 : $R^1 = R^2 = Me$, $R^3 = Br$ — **13** : 91 % — **17** : 88 % — **21** : 3 %

Scheme 2. *Reagents* : (a) DAST, CH_2Cl_2, reflux, 16 h; (b) CAN, CH_3CN / H_2O, r.t., 1 h; (c) $LiC(CH_3)_2NO_2$ (2 equiv.), DMSO degassed, hv, 24 h

In conclusion, we have demonstrated here that reductive alkylation of *gem*-difluoroquinones derived from aldehydes via their *ortho*-methylene quinones is a valuable and general method for the synthesis of potentially active fluoroquinones. Moreover, the transient *ortho*-methylene quinone radicals can be used for intermolecular C,C-bond forming reactions.

References and Notes

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(16) Procedure A : General procedure for the formation of **3**, **10-13** from aldehydes **1**, **6-9**. Under an atmosphere of N_2, a mixture of 5.0 g (24 mmol) aldehyde **1**, 3.2 ml (24.2 mmol) of DAST in CH_2Cl_2 (30 ml) was refluxed for 16 h. After extraction with CH_2Cl_2, the crude product was purified by flash chromatography to give **2**. To a mixture of 2.5 g (1.1 mmol) of *gem*-difluoro **2** in CH_3CN (5 ml) was added a solution of 1.5 g (2.7 mmol) of CAN in H_2O (3 ml). The mixture was stirred for 1 h at r.t., extracted with CH_2Cl_2 and purified by flash chromatography to afford **3.** **2**, orange solid, mp 52°C (cyclohexane), ^1H NMR ($CDCl_3$) δ : 7.04 (t, J_{HF} = 55, 1H, CHF_2); 3.68 (s, 3H, OCH_3); 3.65 (s, 3H, OCH_3); 2.40 (t, J_{HF} = 1.9, 3H, CH_3); 2.21 (s, 3H, CH_3); 2.16 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ : 153.8 (d, J_{CF} = 2.3, C-O); 153.4 (d, J_{CF} = 7.0, C-O); 134.5 (d, J_{CF} = 2.1); 126.8 (s); 126.5 (s); 123.5 (d, J_{CF} = 21.6, C-CHF_2); 113.6 (d, J_{CF} = 233, CHF_2); 62.5 (s, OCH_3); 60.1 (s, OCH_3); 13.1 (s, CH_3); 12.4 (s, CH_3); 11.7 (d, J_{CF} = 3.7, CH_3). ^{19}F NMR ($CDCl_3$) δ : -48.84 (dt, J_{FH} = 55, 1.6). **3**, yellow solid, mp 39°C (cyclohexane), ^1H NMR ($CDCl_3$) δ : 6.96 (t, J_{HF} = 54, 1H, CHF_2); 2.26 (t, J_{HF} = 3, 3H, CH_3); 2.05 (d, J_{HF} = 1.3, 3H, CH_3); 2.04 (d, J_{HF} = 1.4, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ : 187.0 (s, CO); 184.9 (s, CO); 145.9 (s); 141.7 (s); 140.5 (s); 133.2 (t, J_{CF} = 21, C-CHF_2); 110.7 (t, J_{CF} = 238, CHF_2); 12.6 (s, CH_3); 12.2 (s, CH_3); 12.0 (s, CH_3). ^{19}F NMR ($CDCl_3$) δ : -56.14 (d, J = 55).

(17) Procedure B : Typical procedure for the formation of **4**, **14-17**. A degassed solution of *gem*-difluoro quinones **3**, **10-13** (2.5 mmol), lithium 2-nitro-2-propanide (0.12 g, 2.5 mmol) in DMSO (20 ml) was irradiated with a 300 W sun lamp for 24 h at r.t. under an inert atmosphere. After extraction with Et_2O, the crude product was purified by flash chromatography. **4**, yellow liquid, ^1H NMR ($CDCl_3$) δ : 6.46 (dd, J_{HF} = 48, 2, 1H, CHF); 2.07 (s, 3H, CH_3); 2.00 (s, 3H, CH_3); 1.88 (d, J_{HF} = 2, 3H, CH_3); 1.26 (s, 3H, CH_3); 1.20 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ : 188.2 (s, CO); 185.2 (s, CO); 145.9 (s); 141.7 (s); 140.5 (s); 133.2 (d, J_{CF} = 15, C-CHF); 115.6 (d, J_{CF} = 180, CHF); 88.1 (s, C-NO_2); 22.9 (s, CH_3); 16.9 (s, CH_3); 13.5 (s, CH_3); 13.2 (s, CH_3).

$C_{13}H_{16}FNO_4$	calc.	C 57.99	H 5.99	N 5.20
(269.27)	found	C 58.12	H 6.04	N 5.12

Structures for **14-17** were confirmed by spectroscopic datas (NMR and MS) as well as by elemental analysis.

(18) The compound **5** (2,3,5-trimethyl-6-(2-methyl-1-propenyl)benzo-1,4-quinone) has already been described, see ref. 13.