Tetrahedron Letters, Vol. 33, No. 8, pp. 1063-1064, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Fluoride as Leaving Group in $S_{RN}1$ Reactions of a Tetrasubstituted-1,4-Benzoquinone

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Key Words: Quinone; Fluoride as Leaving group; Electron-Transfer; Nitronate; $S_{RN}1$

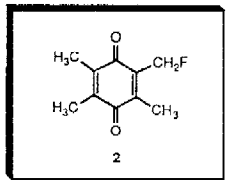
Abstract: 2-Fluoromethyl-3,5,6-trimethyl-1,4-benzoquinone was synthesized and its reactivity in $S_{RN}1$ reactions compared to the reactivity of the chloro derivative previously described. This study reports the first examples of the displacement of fluoride in $S_{RN}1$ reactions involving a substitution at an sp^3 carbon atom.

In the mechanistic studies of $S_{RN}1$ reactions of quinones, we have recently reported the C-alkylation of 2-chloromethyl-3,5,6-trimethyl-1,4-benzoquinone ($TMBQCH_2Cl$) **1** by 2-nitropropane anion followed the $S_{RN}1$ mechanism[1]. If the displacement of fluoride is well documented for aromatic radical-nucleophilic substitution reactions[2], there is no study showing fluoride as leaving group in $S_{RN}1$ reaction at an sp^3 carbon[3]. In order to prepare new bioreductive alkylating agents exhibiting only electron transfer reactivity and to extend the $S_{RN}1$ reaction to a fluoro compound, we have synthesized 2-fluoromethyl-3,5,6-trimethyl-1,4-benzoquinone ($TMBQCH_2F$) **2** and studied its reactivity in a classical electron-transfer C-alkylation reaction.

The fluoro compound **2**[4] was prepared from trimethylhydroquinone as described for the chloro derivative **1** following Middleton method[5] with diethylaminosulfur trifluoride (DAST) for the fluorination step.

The quinone **2** reacts with **3** under various experimental conditions to give the products reported in the table.

$TMBQCH_2F$ (**2**) + $Li^+ {}^-C(CH_3)_2NO_2$ (**3**) ⟶ $TMBQCH_2C(CH_3)_2NO_2$ (**4**) + $TMBQCH{=}C(CH_3)_2$ (**5**) + $TMBQCH_2NO_2$ (**6**) + $TMBQCH_2ONO$ (**7**) + $TMBQCH_2OCH_3$ (**8**)



2

Table

Influence of experimental conditions in the reaction of **2** with **3**.

Entry[a]	Solvent	Scavenger (mol. equiv.)	% Yield C-alkylation	% Proportions[b] **4**	**5**	**6**	**7**	**8**	**2** (rec.)
1	CH_3OH	-	50	52	14	14	7	13	-
2	DMF	-	50	40	25	8	27	-	3
3	DMSO[c]	-	66	43	35	4	18	-	-
4	DMSO	-	70	53	29	3	15	-	-
5	DMSO	$CuCl_2$ (0.01)	54	42	31	3	19	-	5
6	DMSO	$CuCl_2$ (0.1)	32	28	29	3	20	-	20
7	DMSO	$CuCl_2$ (1)	10	8	12	3	6	-	71
8	DMSO	(*tert*-Bu)$_2$NO$^\cdot$ (0.1)	40	16	39	6	16	-	23
9	DMSO	(*tert*-Bu)$_2$NO$^\cdot$ (1)	38	26	28	3	18	-	25

[a]All reactions were irradiated at room temperature during 24h by using one equivalent of **2** and **3** under argon in a degassed solvent with two 60 W fluorescent lamps. [b]Proportions calculated from ^{1}H NMR spectra. [c]Solvent not degassed.

The best yield (70%) of C-alkylation products is obtained in degassed DMSO (entry 4) but this yield is lower than from **1** and the proportion of ethylenic product **5** is noteworthy more higher. In this case, the nitrous acid elimination leading to **5** is favoured by the presence of the basic fluoride anion. As from **1**, we also have observed the formation of nitro and nitrite derivatives **6** and **7** but in higher proportions, which can be explained as a result of the nitrite ion formed in elimination reaction. An ionic substitution of fluoride being unlikely[6], **6**, **7** and **8** also are formed by $S_{RN}1$ reaction resulting of entrainment[7] by the nitronate.The addition of classical scavengers[3] ($CuCl_2$, di-*tert*-butylnitroxide) gives effective inhibition of C-alkylation (entries 5 to 9) which increases when using higher concentrations.

In conclusion, these results show that 2-fluoromethyl-3,5,6-trimethyl-1,4-benzoquinone **2** reacts with the anion of 2-nitropropane **3** in good yields to give C-alkylation by $S_{RN}1$ mechanism and thence other fluoro electrophiles should be designed for electron transfer reactions at sp^3carbon atoms.

ACKNOWLEDGMENT

The support of this work by Rhône-Poulenc Rorer S. A. is gratefully acknowledged.

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(Received in France 21 November 1991)