Tetrahedron Letters 49 (2008) 4588–4590

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselectivity of fluorine substitution by alkoxides on unsymmetrical difluoroarenes

Ronan Dirr, Cyril Anthaume, Laurent Désaubry *

UMR 7175-LC1, Université Louis Pasteur, CNRS, Faculté de Pharmacie, 67401 Illkirch, France

ARTICLE INFO

Article history:
Received 21 April 2008
Revised 19 May 2008
Accepted 20 May 2008
Available online 24 May 2008

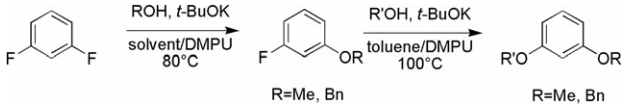
Keywords:
S_NAr
Fluorine substitution
^{19}F NMR

ABSTRACT

An efficient approach to unsymmetrical halogenated resorcinol diethers has been developed. This synthesis consists of two subsequent nucleophilic aromatic substitutions (S_NAr) of unsymmetrical difluoroarenes by alkoxides. The novelty of this approach is its control of regioselectivity during the first S_NAr, which occurs at room temperature. Interestingly, the reactivity of competing fluorines was correlated to their chemical shift in ^{19}F NMR.

The synthesis of unsymmetrical resorcinol diethers by sequential alkylation of resorcinol is tedious and low yielding. Very recently, Toczko and co-workers developed a short and efficient route to these compounds by performing two successive nucleophilic aromatic substitutions (S_NAr) of 1,3-difluorobenzene by alkoxides (Scheme 1).[1] The second fluoride displacement requires more vigorous conditions than the first one due to the deactivation by the first alkoxy substituent.

During our synthesis of benzofurans by double lithiation of 2-bromophenyl ethers according to Sanz' methodology,[2] we needed an easy and efficient access to differently substituted bromoresorcinol diethers. Towards this end, we aimed at modifying Toczko's method using a bromo (or iodo) difluorobenzene as a substrate. In the course of their studies, Toczko and co-workers examined only the reactivity of unsubstituted difluorobenzenes.[1] Thus, although much work in S_NAr of fluoroarenes has been done, as far as we know, the regioselectivity of this reaction on unsymmetrically substituted difluoroarenes remained unexplored.[3] To address this issue, we surveyed a broad spectrum of parameters such as the nature of the difluoroarene and of the alkoxide counteranion, the temperature, and solvent. The goal of this study was to establish procedures to control the selectivity of the S_NAr on variously substituted difluoroarenes.



Scheme 1. Double S_NAr on 1,3-difluorobenzene.[1]

Preliminary studies on the S_NAr were conducted with **1** and benzyl alcohol as substrates to investigate the effects of the reaction conditions on the yield and the regioselectivity (Table 1). Performing this reaction at r.t. with *t*-BuOK as a base afforded the products **2** and **3** with a 4:1 selectivity, albeit in low yield (entry 1). Replacing *t*-BuOK by *n*-BuLi did not change significantly the yield or the regioselectivity (entry 2). Gratifyingly, the use of NaH as a base improved the yield to 80% without altering the regioselectivity (entry 3). Replacing DMF by THF slightly lowered the yield but further increased the regioselectivity (9:1 ratio) (entry 4). Lowering the reaction temperature did not improve the regioselectivity further but diminished the yield to 30% (entry 5).

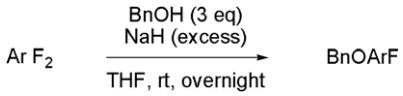
Table 1
Optimization conditions for the regioselective S_NAr on difluoroarene **1**

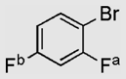
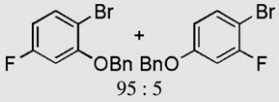
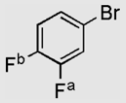
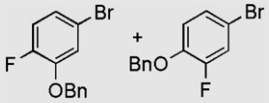
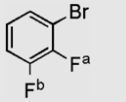
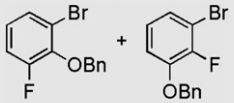
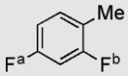
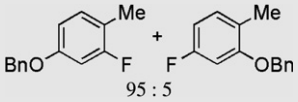
Entry	Base	Solvent	Temperature	**2**:**3**	Yield (%)
1	*t*-BuOK	DMF	rt	80:20	25
2	*n*-BuLi	DMF	rt	83:17	20
3	NaH	DMF	rt	77:23	80
4	NaH	THF	rt	90:10	70
5	NaH	THF	4 °C	90:10	30

* Corresponding author. Tel.: +33 90 244 141; fax: +33 390 244 310.
E-mail address: desaubry@chimie.u-strasbg.fr (L. Désaubry).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.091

Table 2
S_NAr of unsymmetrical difluoroarenes with benzyl alcohol, and ^{19}F NMR chemical shifts of these difluoroarenes



Entry	ArF_2	Yield (%)	Products	δF^a (ppm)*	δF^b (ppm)*	$\delta F^a - \delta F^b$
1		95	 95 : 5	−103.1	−111.1	8
2		61	 91 : 9	−134.4	−139.1	4.7
3		40	 96 : 4	−130.9	−134.8	3.9
4		0 (68)**	 95 : 5	−113.8	−114.9	1.1

* ^{19}F NMR ($CDCl_3$, 200 MHz).
** Solvent: DMSO instead of THF.

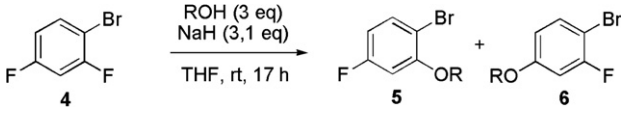
With conditions for regioselective S_NAr in hand, we undertook a study of substrate generality with a series of unsymmetrical difluoroarenes (Table 2).[4] Reactions occurred with an excellent regioselectivity ranging from 90:10 to 100:0 in a 40–95% yield. It is generally accepted that an electron-withdrawing substituent, such as bromine, orientates the S_NAr with the following regioselectivity: *ortho* > *para* > *meta*, while the electron-donating character of the methyl group favours the *para* over the *ortho* position.[3] Surprisingly, 4-bromo-1,2-difluorobenzene did not follow this general trend (entry 2), as the substitution occurred in majority at the *meta* position. The same regioselectivity had been described for the reaction of this difluoroarene with *N*-hydroxyacetimidate as a nucleophile.[5] 2,4-Difluorotoluene (entry 4) was unreactive in THF, but shifting the solvent to DMSO allowed the reaction to be performed in 68% yield with a 95:5 regioselectivity, which indicates that with a poorly reactive substrate, the use of DMSO may allow the reaction to be achieved with a good regioselectivity and in a reasonable yield.

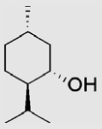
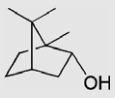
We also examined whether there is a relationship between the reactivity and the chemical shift of the fluorides, as they are both partially related to their electron density. Indeed, in each and every case, the most reactive fluorine was the most deshielded (Table 2). This observation suggests that it might be possible to predict the reactivity pattern for other polyfluoroarenes from their ^{19}F NMR data.

As shown in Table 3, the S_NAr reaction proceeded with a high regioselectivity and reasonable yields with many primary and secondary alcohols. As expected, reactions with electron deficient trifluoroethanol or sterically encumbered *tert*-butanol afforded lower yields (entries 5 and 8).

Next, with the appropriate reactants in hand, we performed a second fluorine displacement to synthesize variously substituted halogenated resorcinol diethers, which are important precursors to benzofurans according to Sanz's methodology.[2] This second S_NAr was performed in DMF at 80 °C, under milder conditions than those described by Toczko, due to the activation effect of the additional bromine or iodide[1,6] (Table 4).

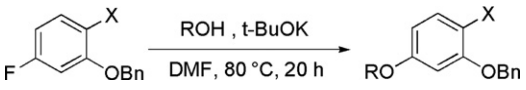
Table 3
S_NAr of various alcohols with difluoroarene **4**[4]



Entry	ROH	Yield (%)	Ratio **5**:**6**
1	MeOH	42	100:0
2	*n*-BuOH	45	100:0
3	*i*-PrOH	50	95:5
4	$Ph(CH_2)_3OH$	47	95:5
5	CF_3CH_2OH	15	95:5
6		41	95:5
7		62	91:9
8	*t*-BuOH	22	95:5

In conclusion, we have demonstrated that the S_NAr of unsymmetrical difluoroarenes by alkoxides occurs with an unprecedented high level of regioselectivity at room temperature. We have also shown that the most reactive position corresponds to the most deshielded fluorine in ^{19}F NMR. This method provides an easy access to variously substituted halogenated resorcinol diethers.

Table 4
S_NAr of various alcohols with benzyloxy-monofluoroarenes[6]



Entry	X	ROH	Yield (%)
1	Br	MeOH	80
2	I	MeOH	90
3	I	*n*-BuOH	75

References and notes

1. Kim, A.; Powers, J. D.; Toczko, J. F. *J. Org. Chem.* **2006**, *71*, 2170–2172.
2. Sanz, R.; Miguel, D.; Martinez, A.; Pérez, A. *J. Org. Chem.* **2006**, *71*, 4024–4027.
3. Vlasov, V. M. *Russ. Chem. Rev.* **2003**, *72*, 681–703.
4. Typical preparation of 1-bromo-4-fluoro-2-alkoxybenzenes: To a suspension of NaH (71 mg, 3 mmol) in THF (3 ml) was slowly added alcohol (3 mmol) under argon at 0 °C. The solution was stirred at 0 °C for 15 min. 1-Bromo-2,4-difluorobenzene (0.19 g, 1 mmol) was then added, and the solution was at room temperature for 17 h before being quenched with a satd aqueous solution of NH_4Cl (3 ml). The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated to dryness. Purification of the resulting oily residue by chromatography (pentane–Et_2O) afforded the desired product.
5. Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Org. Prep. Proc. Int.* **1997**, *29*, 594–600.
6. Typical procedure for the reaction of alkoxides with benzyloxy-monofluoroarenes: preparation of 2-benzyloxy-4-butoxy-1-iodobenzene. *n*-BuOH (0.84 ml, 9.12 mmol) was slowly added to a suspension of *t*-BuOK (743 mg, 6.08 mmol) in DMF (5 ml) under argon at 0 °C. The solution was stirred at 0 °C for 10 min and a solution of 2-benzyloxy-4-fluoro-1-iodobenzene (500 mg, 1.52 mmol) in DMF (1 ml) was then added. The solution was heated at 80 °C for 20 h, cooled to room temperature and quenched with a satd aqueous solution of NH_4Cl. The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated to dryness. Purification of the resulting oily residue by chromatography (pentane–Et_2O 7:3) afforded the desired product (435 mg, 75%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (1H, d, J = 8.6 Hz); 7.55 (2H, d, J = 7.3 Hz); 7.30–7.44 (3H, m); 6.54 (1H, d, J = 2.6 Hz); 6.36 (1H, dd, J = 2.6, 8.6 Hz); 5.14 (2H, s); 3.92 (2H, t, J = 6.2 Hz); 1.64–1.67 (2H, m); 1.47 (2H, m); 0.95 (3H, t, J = 6.9 Hz).