Pergamon

Tetrahedron Letters 43 (2002) 3585–3587

TETRAHEDRON
LETTERS

Mild conversion of electron deficient aryl fluorides to phenols using 2-(methylsulfonyl)ethanol

John F. Rogers and Daniel M. Green*

Chemical Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA

Received 10 January 2002; revised 11 March 2002; accepted 19 March 2002

Abstract—Useful yields are achieved in the synthesis of phenols from aryl fluorides via a mild one-pot procedure using commercially available 2-(methylsulfonyl)ethanol. Examples and representative yields are shown. © 2002 Elsevier Science Ltd. All rights reserved.

Phenols are widespread as intermediates and targets in synthetic organic chemistry. Unfortunately direct synthesis of the phenol moiety is limited. Most synthetic routes utilize ether based protecting groups, which are later unmasked to the phenol.[1] Alternatively, anilines can be diazotized and then hydrolyzed to yield phenols, however, this chemistry requires drastic oxidative and thermal conditions.[2] Other rearrangements and oxygen insertions have been reported in the literature but are too narrow in scope to have much synthetic utility.[3]

Due to their wide commercial availability and/or their easy preparation, aryl halides are ideal starting materials for phenol synthesis using nucleophilic aromatic substitution. Traditionally, this involved the reaction of aryl halides with alkoxides under strongly basic conditions and with prolonged heating. Recently, Hartwig and Buchwald have reported the intermolecular conversion of aryl bromides and chlorides to phenols via a silyl or *tert*-butyl ether which is easily cleaved.[4,5] This involves the use of nickel or palladium catalysts and expensive phosphine reagents. Additionally the reactions were run at elevated temperatures for several hours.

We now wish to report a mild, one-pot procedure for converting electron deficient aryl fluorides to phenols at room temperature by way of a nucleophilic aromatic substitution reaction. This reaction requires only commercially available 2-(methylsulfonyl)ethanol and sodium hydride. We have found that aryl fluorides containing a variety of common *ortho* and *para* electron withdrawing functional groups can produce high yields of products after purification by simple silica gel chromatography.[6] The yields correspond well to the degree of electron withdrawing character of the ring, and the amount of steric hindrance seen by the approaching nucleophile.

In an extension of our work to generate functionalized 4-ether derivatives of methyl 3-(morpholino-4-sulfonyl) benzoate from aromatic fluoride **1** via a nucleophilic aromatic displacement mechanism, we reacted 2-(methylsulfonyl)ethanol with **1** and sodium hydride in DMF. This reaction failed to provide the desired product but instead gave phenol **3** in good yield (see Fig. 1).

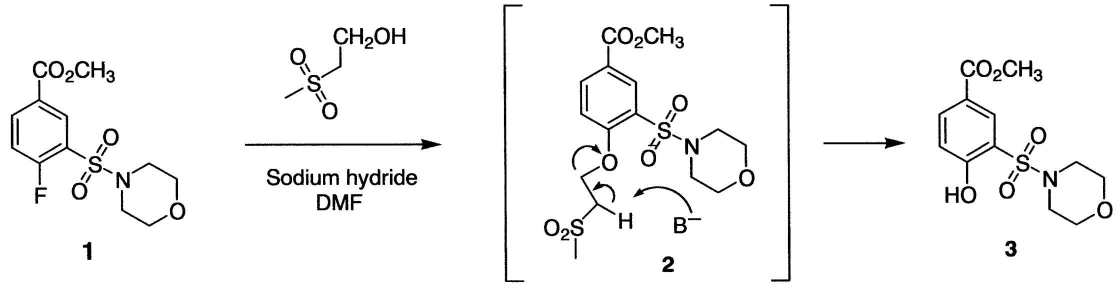


Figure 1.

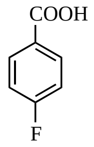
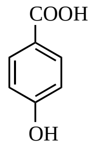
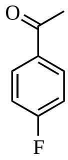
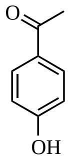
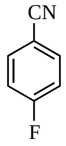
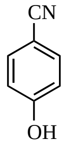
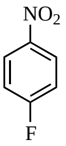
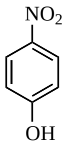
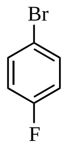
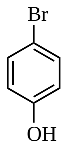
---

* Corresponding author. Tel.: 484-865-2147; fax: 484-865-9399; e-mail: greend@war.wyeth.com

PII: S0040-4039(02)00561-0

Examination of the reaction conditions suggested a possible explanation. Since excess sodium hydride was used in the reaction, we postulated that the first equivalent deprotonated the alcohol to yield the alkoxide. In turn the alkoxide displaced the fluoro of **1** to form ether derivative **2**. This ether derivative was quite unstable and was never isolated even using 1 equiv. of sodium hydride. The abstraction of a proton alpha to the sulfonyl group by another hydride apparently caused an elimination of the phenol and generation of a vinyl sulfoxide. The vinyl sulfoxide apparently decomposed rapidly under the reaction conditions and was never observed.

Table 1. Reactions of 2-(methylsulfonyl)ethanol with fluorides using sodium hydride and DMF[a]

Substrate	Product	Yield[b]
		0 %
		61%
		95%
		99%
		10 %

[a] Ratio of substrate to sodium hydride to 2-(Methylsulfonyl)ethanol= 1:3:1.5. was used in 0.66 M DMF.

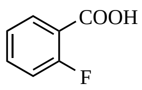
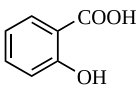
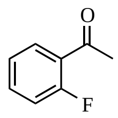
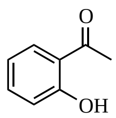
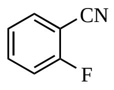
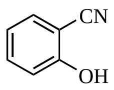
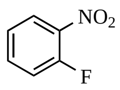
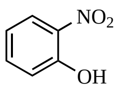
[b] Yields of isolated compound after chromatography. All products were identical to commercially available material.

The results of the reaction of 2-(methylsulfonyl)ethanol and sodium hydride with various *p*-substituted fluorobenzenes is shown in Table 1. The reaction was quenched in 2 h with dilute HCl to produce a relatively clean crude product, which was further purified by silica gel chromatography. The yields were good to excellent for fluorobenzene substrates containing electron withdrawing substituents. As expected the carboxylic acid derivative was unreactive presumably due to an inability to stabilize an additional negative charge.

Additionally, the *p*-bromo analog was not very reactive although minor amounts of desired product were observed. We did not observe any sign of product resulting from the substitution of the bromide in this case. We observed similar results for *ortho* substituted aryl fluorides (see Table 2). The *o*-acetophenone derivative showed lower yields than its *para* counterpart presumably because of steric effects.

In conclusion, we have developed a mild, one-pot, well tolerated synthesis of phenols from aryl fluorides. We

Table 2. Reactions of 2-(methylsulfonyl)ethanol with fluorides using sodium hydride and DMF[a]

Substrate	Product	Yield[b]
		0 %
		33 %
		100%
		94%

[a] Ratio of substrate:sodium hydride:2-(Methylsulfonyl)-ethanol= 1:3:1.5 was used in 0.66 M DMF.

[b] Yields of isolated compound after chromatography. All products were identical to commercially available material.

expect that this method will be a very useful addition in the repertoire of reagents to prepare phenols.

Acknowledgements

The authors would like to thank Dr. Jay Wrobel and Dr. Jeff Pelletier for their advice and encouragement in exploring this chemistry.

References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; pp. 143–162.
2. *Organic Synthesis*; Gilman, H., Ed.; Collective Vol. 1, 2nd ed.; John Wiley and Sons: New York, 1941.
3. *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; Interscience: New York, 1971.
4. Mann, G.; Incarvito, C.; Rheingold, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.
5. Parrish, C.; Buchwald, S. *J. Org. Chem.* **2001**, *66*, 2498–2500.
6. General procedure: To a stirring solution of aryl fluoride (1.0 equiv.) in DMF (0.66 M) was added 2-(methylsulfonyl-ethanol) (1.5 equiv.) and the solution cooled to 0°C. Sodium hydride (3.0 equiv.) was added and the reaction mixture allowed to warm to room temperature. The mixture was quenched with a 1N HCl solution and partitioned between ethyl acetate and brine. The organic layer was concentrated to dryness and the crude organics purified by flash column chromatography.