Organic Process Research & Development **1997**, *1*, 328–330

Impact of Potassium Salts on Aromatic Substitution Reactions[1]

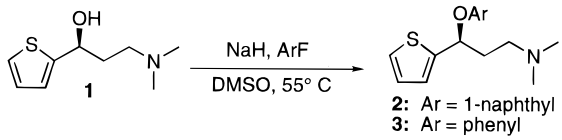
Richard A. Berglund

Tippecanoe Laboratories, Eli Lilly and Company, P.O. Box 685, Lafayette, Indiana 47902

Abstract:

Potassium salts, and potassium benzoate in particular, were shown to dramatically accelerate aromatic substitution reactions between a chiral secondary alkoxide and aryl fluoride substrates. There was no loss of chiral purity, and ether yields exceeded those obtained in trials containing no salt additive. The generality of the method was demonstrated by the observation of rate accelerations in several solvents and with several deprotonation bases.

In the course of our synthetic development, it became necessary to investigate aromatic substitution reactions between a chiral secondary alkoxide and aryl fluorides (eq 1).[2,3] From the standpoint of large-scale manufacturability,



(1)

the reaction times necessary to achieve high levels of conversion in reactions containing a slight excess of aryl fluoride were problematic. For (*S*)-naphthyl ether **2,** 40−60 h were required, and several additional days were necessary for production of (*S*)-phenyl ether **3**. Also, unreacted amino alcohol **1** proved difficult to remove by salt crystallization and resulted in the need for chromatographic purification. Although an increase in reaction temperatures to 80−90 °C did reduce reaction times, production of the undesired (*R*)-ethers increased from less than 1% to nearly 5%. As a result, an alternative strategy for shortening the reaction times and minimizing unreacted starting material without sacrificing chiral purity was needed.

Initially, alternative potassium bases such as potassium hydride and potassium *tert*-butoxide were examined in an effort to increase the nucleophilicity of the alkoxide.[4−12] While accelerated reaction rates were observed, the pyrophoric hazards associated with potassium hydride precluded its use on large scale and production of (*R*)-**2** increased to nearly 10% when potassium *tert*-butoxide was used. However, literature reports have noted that, in substitution reactions of the electronically activated aromatic substrate 1-chloro-2,4-dinitrobenzene with either lithium, sodium, or potassium methoxide, the addition of 1.0−4.0 molar equiv of either potassium iodide or potassium acetate accelerated the reaction rates.[13,14] Due to these interesting results a broader study investigating the impact of added potassium salts on the desired aromatic substitution reactions between a chiral secondary sodium alkoxide and unactivated aryl fluoride substrates was undertaken.

Table 1 displays the results of screening reactions between chiral (*S*)-alcohol **1** and 1-fluoronaphthalene in DMSO at 55 °C using sodium hydride for deprotonation and 1.0 molar equiv of various potassium salts (relative to **1**) as additives. One cesium salt also was included in the study. It was found that reaction rates increased significantly in the presence of several of the salt additives. The most favorable results were obtained with potassium benzoate ($PhCO_2K$), which afforded excellent yields and complete consumption of alcohol **1** after only 2 h.

Importantly, the production of undesired (*R*)-**2** was not enhanced, relative to the use of sodium hydride alone, in any of the trials using the salt additives. Also, while the initial screening used 1.0 molar equiv of the salt additives, it was subsequently shown under similar reaction conditions that as little as 0.1 molar equiv of the optimal additive, $PhCO_2K$, afforded comparable results. Only at an additive level of 0.05 equiv did the rate of the reaction appear to slow slightly (Table 2). Additionally, it was found that the amount of $PhCO_2K$ used had no effect on the optical purity of (*S*)-naphthyl ether **2**.

When the analogous aromatic substitution reaction using fluorobenzene was studied, a similar increase in reaction rate and yield of (*S*)-phenyl ether **3** was observed when $PhCO_2K$ was added (Figure 1). Notably, the difference in reaction rates between the naphthalene and benzene systems clearly can be observed upon comparison of the results of Table 1 and Figure 1. The second ring present in the naphthyl system provides some electronic activation for the substitution reaction allowing complete starting material consumption in 2 h, while about 10% of alcohol **1** still remains after 96 h in the reaction employing fluorobenzene.

(1) These results were initially presented at the 207th National Meeting of the American Chemical Society, San Diego, CA, March 13−18, 1994; Poster 365.

(2) Robertson, D. W.; Wong, D. T.; Krushinski, J. H., Jr. Eur. Pat. Appl. EP273658, 1988; *Chem. Abstr.* **1988**, *109*, 17024n.
(3) Deeter, J.; Frazier, J.; Staten, G.; Staszak, M.; Weigel, L. *Tetrahedron Lett.* **1990**, *31*, 7101.
(4) Zwarc, M. *Ions and Ion Pairs in Organic Reactions*; J. Wiley and Sons Inc.: New York, 1972.
(5) Gordon, J. E. *The Chemistry of Electrolyte Solutions;* J. Wiley and Sons: New York, 1975.
(6) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry;* VCH: Weinheim, 1988.
(7) Loupy, A.; Tchoubar, B. *Salt Effects in Organic and Organometallic Chemistry;* VCH: Weinheim, 1992.
(8) Berge, A.; Ugelstad, J. *Acta Chem. Scand.* **1965**, *19*, 742.
(9) Martin, D.; Weise, A.; Niclas, H.-J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 318.
(10) Bank, S. *J. Org. Chem.* **1972**, *37*, 114.
(11) Wallace, T. J.; Hofmann, J. E.; Schriesheim, A. *J. Am. Chem. Soc.* **1963**, *85*, 2739.
(12) Msayib, K. J.; Watt, C. I. F. *Chem. Soc. Rev.* **1992**, *21*, 237.
(13) Reinheimer, J. D.; Kieffer, W. F.; Frey, S. W.; Cochran, J. C.; Barr, E. W. *J. Am. Chem. Soc.* **1958**, *80*, 164.
(14) Reinheimer, J. D.; Gerig, J. T.; Cochran, J. C. *J. Am. Chem. Soc.* **1961**, *83*, 2873.

 S1083-6160(97)00103-5 CCC: $14.00

Table 1. **Results of salt screening**

additive	*in situ* yield of **2** (%)[a] 2 h	8 h
none	55.6	85.3
$PhCO_2K$	96.0	96.5
KOAc	84.4	90.8
KF	55.5	88.3
KCl	61.2	88.9
KI	70.2	93.4
$KHCO_3$	60.9	88.9
K_2CO_3	52.1	86.3
K_2SO_4	62.3	91.3
CsCl	73.1	93.3

[a] The ee of all naphthyl ethers was 99.0 ± 0.4%.

Table 2. **Screening of various amounts of $PhCO_2K$**

equiv of $PhCO_2K$	*in situ* yield of 2 (%) 2 h	4 h
0.5	96.8	96.4
0.1	96.0	94.7
0.05	91.1	94.5

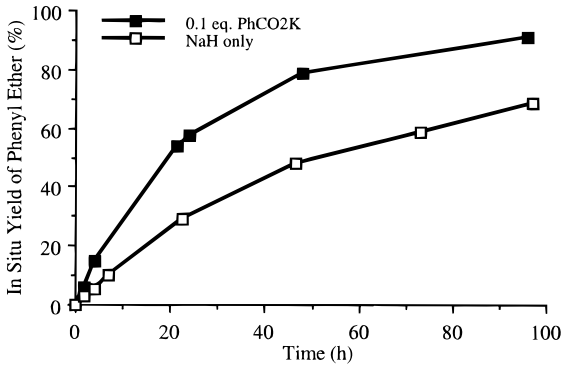


Figure 1. **Production of (*S*)-phenyl ether 3 from aromatic substitutions.**

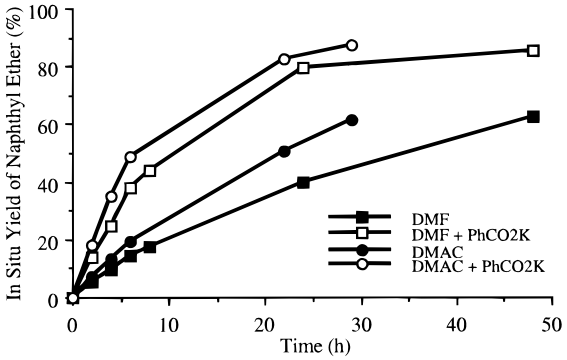


Figure 2. **Production of (*S*)-naphthyl ether 2 using $PhCO_2K$ in alternate solvents.**

At this point some additional studies were conducted to explore the generality of the salt additive process. First, the alternative solvents DMF and dimethylacetamide (DMAC) were examined. As with DMSO, in reactions containing $PhCO_2K$, increased reaction rates and higher overall yields of (*S*)-naphthyl ether **2** were observed (Figure 2).

Second, additional experimentation showed that the accelerating effect of potassium salts was not limited to systems employing sodium hydride for alkoxide formation. When sodium *tert*-butoxide or lithium hydride was used, the addition of 0.1−0.2 equiv of $PhCO_2K$ also served to accelerate the rates of the substitution reactions and afford higher yields of (*S*)-naphthyl ether **2** (Figure 3).

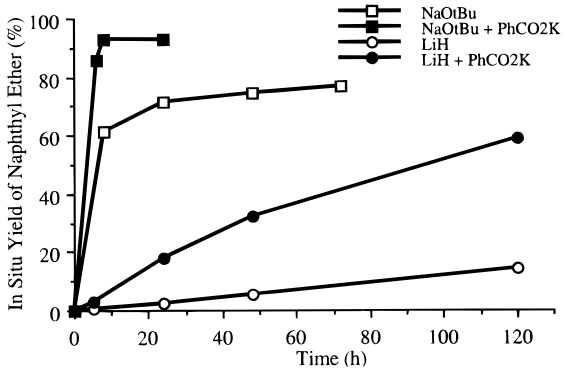


Figure 3. **Production of (*S*)-naphthyl ether 2 with alternate bases and $PhCO_2K$ additives.**

Mechanistically, we believe that the potassium ion supplied by the addition of potassium salt may be involved in exchange with the sodium alkoxide ion pair to afford a small amount of the less associated, more nucleophilic potassium alkoxide.[7,15,16] The optimal performance of $PhCO_2K$ may be linked to its increased ionic dissociation in DMSO relative to potassium salts containing harder, smaller anions.[6,9,17−19] This dissociation would enable a larger amount of potassium ions to be available for ion exchange with sodium, resulting in an overall increase in the equilibrium concentration of dissociated free alkoxide. The high yields obtained with other potassium salts containing soft anions such as KI would support this reasoning.

In conclusion, we have shown that potassium or cesium salts dramatically accelerate the rates of aromatic substitution reactions between a chiral secondary sodium alkoxide and unactivated aryl fluorides. Significantly, unlike other measures which were attempted in an effort to increase reaction rates, this approach did not result in the production of increased amounts of the undesired (*R*)-ethers. The optimal salt additive, $PhCO_2K$, is inexpensive, readily available, and nontoxic and can be used in catalytic amounts. All of these factors combined to establish the manufacturability of the substitution reaction, and in fact, the process has been successfully employed on 1000 gal scale for production of (*S*)-naphthyl ether **2**.[20]

Experimental Section

General Methods. All reagents and solvents were obtained from commercial suppliers and were used without purification. ^{1}H NMR spectra were obtained at 300 MHz in d_6-DMSO, and chemical shifts are relative to $SiMe_4$. ^{13}C NMR were recorded at 75.5 MHz in d_6-DMSO, and chemical shifts are relative to $SiMe_4$. Infrared spectra were obtained as neat films between NaCl plates.

(15) Crampton, M. R.; Grunwald, E. *J. Am. Chem. Soc.* **1971**, *93*, 2990.
(16) Simon, J. D.; Peters, K. S. *Acc. Chem. Res.* **1984**, *17*, 277.
(17) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.
(18) Choux, C.; Benoit, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 6221.
(19) Olmstead, W. O.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299.
(20) Berglund, R. A. US Patent No. 5,362,886, 1994.

General Procedure for Salt Screening Experiments. Alcohol **1**[2,3] (1.35 g, 7.30 mmol) was dissolved in 9 mL of DMSO. Sodium hydride (60% in mineral oil, 0.30 g, 7.30 mmol) was added and the slurry stirred at rt for 20 min. The potassium or cesium salt (7.30 mmol) was added and the mixture stirred for 15 min. 1-Fluoronaphthalene (1.28 g, 8.76 mmol) was added, and the mixture was heated to 55−60 °C. Reaction aliquots were removed periodically and analyzed by HPLC using a calibration curve generated from a purified sample of the oxalate salt of ether **2** for *in situ* yield determination. The chromatography system consisted of a DuPont Zorbax Rx C8 column with 70% acetonitrile, 30% phosphate buffer at pH 6.0 as eluant. Detection was at 230 nm, and the system flow rate was 1.0 mL/min. Alcohol **1** eluted at 6−8 min and naphthyl ether **2** at 13−17 min. For the $PhCO_2K$ stoichiometry study (Table 2) and the alternate solvent study (Figure 2), the same procedure was used. For the alternate base study (Figure 3), the same basic procedure was followed and 0.10 equiv of $PhCO_2K$ was used with lithium hydride and 0.20 equiv with sodium *tert*-butoxide. For the results with fluorobenzene (Figure 1), the same basic procedure was used and a purified reference sample of phenyl ether **3** was used to prepare the calibration curve for *in situ* yield determination. On the HPLC system described above, phenyl ether **3** eluted at 12−14 min.

For isolation of either naphthyl ether **2** or phenyl ether **3**, the reaction mixture was diluted with water, the pH adjusted to 5−6 by the addition of acetic acid, and the mixture extracted with hexane to remove unreacted aryl fluoride. The aqueous product solution was adjusted to pH 10−12 by the addition of sodium hydroxide solution and the mixture extracted with ethyl acetate. The organic product solution was dried over $MgSO_4$ and solvent removed to afford the aryl ethers as amber oils. Hydrochloric acid salts could be obtained by the addition of 0.9 equiv of 37% aqueous HCl to ethyl acetate solutions of the ethers (0.1 M). Alternatively, the oxalic acid salts could be prepared by the addition of a solution of 1.0 equiv of oxalic acid in a minimal amount of warm water to ethyl acetate solutions of the ethers (0.2 M).

For ee evaluation, organic reaction extracts were analyzed against reference standards of both enantiomers of naphthyl ether **2** using a Chiralcel OD HPLC column with 0.2% diethylamine, 2% 2-propanol, 97.8% hexane as eluant. Detection was at 280 nm, and the system flow rate was 1.0 mL/min. The desired (*S*)-enantiomer eluted at 5−5.5 min, and the undesired (*R*)-enantiomer at 6−6.5 min. Starting alcohol **1** had ee > 99.7%.

(*S*)-(+)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (2): IR (neat, cm^{-1}) 2960, 2810, 1590, 1475, 1270, 1220, 1100; ^1H NMR (300 MHz, d_6-DMSO) δ 2.08 (m, 1H), 2.11 (s, 6H), 2.33 (m, 3H), 5.91 (dd, J = 7.30, 5.95 Hz, 1H), 6.96 (dd, J = 5.0, 3.5 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 3.5, 1.2 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.41 (m, 2H), 7.50 (m, 2H), 7.82 (m, 1H), 8.24 (m, 1H); ^{13}C NMR (75.5 MHz, d_6-DMSO) δ 36.3, 45.2, 55.1, 73.7, 107.2, 120.2, 121.6, 125.3, 125.5, 125.5, 125.9, 126.3, 126.4, 126.6, 127.4, 134.1, 144.8, 152.7. Anal. Calcd for the HCl salt $C_{19}H_{22}NOSCl$: C, 65.69; H, 6.37; N, 4.03; O, 4.60; S, 9.22. Found: C, 65.87; H, 6.60; N, 3.93; O, 4.62; S, 8.98.

(*S*)-(+)-*N*,*N*-Dimethyl-3-(1-phenyloxy)-3-(2-thienyl)-propanamine (3): IR (neat, cm^{-1}) 2960, 2820. 2780, 1610, 1500, 1240, 690; ^1H NMR (300 MHz, d_6-DMSO) δ 1.95 (m, 1H), 2.11 (s, 6H), 2.13 (m, 1H), 2.29 (m, 2H), 5.67 (t, J = 7.30, 5.95, 1H), 6.88 (t, J = 7.20, 1H), 6.95 (m, 3H), 7.13 (dd, J = 3.5, 1.2 Hz, 1H), 7.21 (m, 2H), 7.42 (dd, J = 5.1, 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, d_6-DMSO) δ 36.3, 45.2, 55.1, 73.4, 115.9, 120.9, 125.3, 125.4, 126.6, 129.3, 145.0, 157.5. Anal. Calcd for the oxalic acid salt $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; O, 22.76; S, 9.12. Found: C, 58.33; H, 6.21; N, 3.82; O, 22.60; S, 9.40.

Acknowledgment

Analytical chemistry support provided by Dr. Mark Argentine and Dr. Bernie Olsen is gratefully acknowledged. The author also wishes to thank Dr. Jeff Levy and Ms. Amy Prill for providing production support.

Received for review March 14, 1997.[⊗]

OP970103A

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.