radiochromatogram showed a clean peak for [$^3H_1$]thioanisole: yield 28 μL (96%); specific activity 20 Ci/mmol; ^3H NMR ($CDCl_3$) δ 2.6 (s, T).

(b) Chloromethyl phenyl sulfide (1, 30 μL, 0.26 mmol) and triethylamine (30 μL, 0.22 mmol) were dissolved in ethyl acetate (2 mL), Pd/C (30%, 22 mg) was added, and the substrate was tritiated under 1 atm of T_2 for 1 h. Rapid uptake of tritium gas was complete after 40 min. The reaction was discontinued at this stage, the catalyst was filtered off, and a portion of the filtrate was analyzed by radio-HPLC. The radiochromatogram showed the corresponding peak for [$^3H_1$]thioanisole: yield 28 μL (96%); specific activity 28.5 Ci/mmol; ^3H NMR ($CDCl_3$) δ 2.6 (s, T).

Synthesis of Monotritiomethyl Iodide (3) from [$^3H_1$]-Thioanisole (2). (a) [$^3H_1$]Thioanisole (2, 28 μL, 0.25 mmol) in ethyl acetate (2 mL) was mixed with benzyl iodide (300 μL, 2.3 mmol) and placed in the generation flask of the apparatus described above. The system was kept at a pressure of $^1/_2$ atm. In the reaction flask were placed *N*-methylaniline (30 μL, 0.27 mmol), DMF (0.5 mL), and anhydrous potassium carbonate (150 mg). The generation flask was then heated at 140 °C for 48 h and the liberated tritiated methyl iodide passed over into the reaction flask where it reacted with the substrate. After this 48 h, the solvent containing the remaining methyl iodide was vacuum transferred into the reaction flask and the entire mixture was stirred overnight. Analysis by radio-HPLC and GC showed that the generation flask contained unreacted [$^3H_1$]thioanisole (2, 8%) and benzyl phenyl sulfide (4, 90%): mp 39 °C (lit.[7] mp 41-43 °C); ^1H NMR ($CDCl_3$) δ 4.1 (s, 2 H), 7.2-7.3 (m, 10 H). Similarly, the reaction flask was shown to contain [$^3H_1$]-*N*,*N*-dimethylaniline (5, 25%), specific activity 28.5 Ci/mmole.

(b) [$^2H_1$]Thioanisole (28 μL, 0.25 mmol) was synthesized by the same procedure and used as the precursor. [$^2H_1$]Methyl iodide was generated and reacted with *N*-methylbenzylamine (40 μL, 0.31 mmol) in DMF (0.5 mL) and anhydrous potassium bicarbonate (150 mg). Gas chromatographic analysis of the reaction flask showed a single peak corresponding to [$^2H_1$]-*N*,*N*-dimethylbenzylamine (6, 69%): ^1H NMR ($CDCl_3$) δ 2.3 (s, 5 H), 3.5 (s, 2 H), 7.4 (m, 5 H); ^2H NMR ($CHCl_3$) δ 2.3 (s, 1 D).

Acknowledgment. This research was supported by the Biomedical Research Technology Program, Division of Research Resources, National Institutes of Health, under grant P41 RR0247-06 and by the Department of Energy under Contract DE-AC03-76SF00098.

(7) Tuleen, D. L.; Marcum, V. C. *J. Org. Chem.* **1967**, *32*, 204.

Novel Synthesis of 4-[Alkyl(aryl)sulfonyl]benzaldehydes: Alkyl(aryl)sulfinate Anion as a Nucleophile in Aromatic Substitutions

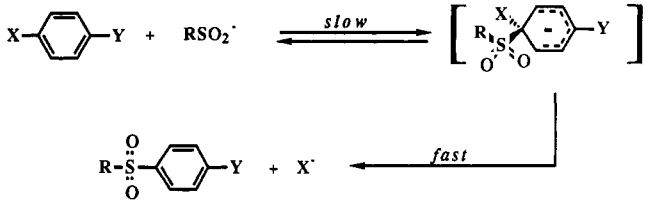
Abraham Ulman* and Edward Urankar

Corporate Research Laboratories, Eastman Kodak Co., Rochester, New York 14650-2109

Received April 17, 1989

4-[Alkyl(aryl)sulfonyl]benzaldehydes are intermediates in the preparation of fluorescent brighteners,[1] liquid crystals,[2] antiobesity and hypoglycemic drugs,[3] β-lactam antibiotics,[4] antiinflammatory and antiarthritic materials,[5] and other bioactive materials.[6-8] The preparation of 4-(methylsulfonyl)benzaldehyde was accomplished previously by either of two routes: (a) dibromination of 4-tolyl methyl sulfone and hydrolysis with dilute sulfuric acid[9] and (b) oxidation of 4-(methylthio)benzaldehyde dimethyl acetal with *m*-chloroperbenzoic acid in CH_2Cl_2.[10] 4-(Phenylsulfonyl)benzaldehyde was prepared by the reduction of 4-(phenylsulfonyl)benzoyl chloride,[11] while 4-(phenylsulfonyl)acetophenone was prepared by the oxidation of the corresponding sulfide.[12] 4-(Phenylsulfonyl)benzophenone was prepared by the reaction of 4-(chlorosulfonyl)benzoyl chloride with benzene.[13] The displacement of a nitro group of substituted nitrobenzenes by different nucleophiles was described by Korenblum et al.[14] In that paper they described the reaction of sodium benzenesulfinate with 4-nitrobenzonitrile and with *p*-dinitrobenzene in hexamethylphosphoramide (HMPA) to give 4-(phenylsulfonyl)benzonitrile and 4-(phenylsulfonyl)nitrobenzene, respectively. However, we did not find any evidence in the literature for a reaction of sulfinate anions with benzaldehyde derivatives.

We explored the possibility of preparing this type of molecule in one step by sulfinate anion replacement of an activated halide in an aromatic nucleophilic substitution (S_NAr mechanism)[15] with DMSO as the solvent. (A wide variety of sulfinic acids can be prepared by the reduction of the corresponding sulfonyl chlorides.[16])



Therefore, we have examined the reaction of 4-fluorobenzaldehyde (X = F, Y = CHO) with sodium methanesulfinate (R = CH_3) in dry DMSO. It was found that at 100 °C the reaction is clean, and we isolated 4-(methylsulfonyl)benzaldehyde in 85% yield. The reaction of 4-fluorobenzaldehyde with sodium benzenesulfinate (R = Ph) was carried out at 100 °C, and 4-(phenylsulfonyl)-benzaldehyde was isolated in 72% yield.

Since fluoroorganic materials are more expensive than the corresponding chloro derivatives, we reacted 4-chlorobenzaldehyde (X = Cl, Y = CHO) with sodium benzenesulfinate (R = Ph) at 130 °C and isolated 4-(phenylsulfonyl)benzaldehyde in 70% yield.[17] Repeating

(1) Mayer, H. R.; Guglielmetti, L. Eur. Pat. Appl. EP 252009, 7 Jan 1988.
(2) Pohl, L.; Scheunble, B.; Krause, J. Ger. Offen. DE 3333168 A1, 28 March 1985.
(3) Duckworth, D. M.; Hindley, R. M. Eur. Pat. Appl. EP 89154 A2, 21 Sept 1983.
(4) Feyen, P.; Preiss, M.; Metzger, K. G. Ger. Offen. DE 2727586, 4 Jan 1979.
(5) Nuss, G. W., Jr.; Santora, N. J.; Douglas, G. H. Can CA 1120946 A1, 30 March 1982.
(6) Klaus, K.; Bollag, W.; Huber, P.; Kueng, W. *Eur. J. Med. Chem.—Chim. Ther.* **1983**, *18*, 425.
(7) Klaus, M.; Weiser, H.; Loeliger, P. Eur. Pat. Appl. EP 98591 A1, 18 Jan 1984.
(8) Bossert, F.; Meyer, H.; Vater, W. Ger. Offen. DE 2218644, 25 Oct 1973.
(9) Yamad, H.; Tohiki, H. Japan JP 49/40706 [74/40706], 5 Nov 1974.
(10) Creary, X.; Mehrsheikh-Mohammadi, M. F. *J. Org. Chem.* **1986**, *51*, 1110.
(11) Arnold, H.; Vogeslag, D. Ger. 939,325, 23 Feb 1956.
(12) Barabas, D.; Spyroudis, S.; Varvogkis, A. *J. Chem. Res., Synop.* **1985**, 186.
(13) Dart, E. C.; Holt, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1403.
(14) Korenblum, N.; Cheng, L.; Kerber, R. C.; Kestner, M. M.; Newton, B. N.; Pinnick, H. W.; Smith, R. G.; Wade, P. A. *J. Org. Chem.* **1976**, *41*, 1560.
(15) For a review on aromatic nucleophilic substitution, see: Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
(16) Smiles, S.; Stewart, J. *Org. Synth.* **1941**, *1*, 8.

0022-3263/89/1954-4691$01.50/0

Table I. Analytical Data for Compounds I-VI

compd	yield, %	mp (solvent)	elemental anal.	^{1}H NMR	^{13}C NMR
I	85[a]	158-9 (ethyl acetate) (lit.[18] 158-9)		DMSO-d_6: 3.28 (s, 3 H), 8.12 (s, 4 H), 10.1 (s, 1 H)	DMSO-d_6: 43.13, 127.76, 130.22, 139.27, 145.27, 192.60
II	88[a]	132-3 (ethyl alcohol) (lit.[11] 124-5)		$CDCl_3$: 7.43 (m, 3 H), 7.95 (m, 2 H), 8.03 (AB, J_{AB} = 8.3, $\Delta\nu$ = 32.6, 4 H), 10.05 (s, 1 H)	$CDCl_3$: 127.44, 127.86, 129.14, 129.91, 133.42, 138.66, 140.02, 146.07, 190.50
III	50[b]	137-8 (ethyl alcohol)	calcd for $C_{14}H_{12}O_3S$: C, 64.60; H, 4.65; S, 12.32 (found: C, 64.56; H, 4.62; S, 12.20)	$CDCl_3$: 2.61 (s, 3 H), 7.55 (m, 3 H), 7.96 (m, 2 H), 8.05 (AB, J_{AB} = 6.1, $\Delta\nu$ = 6.9, 4 H)	$CDCl_3$: 26.48, 127.35, 127.49, 128.66, 129.07, 133.28, 139.86, 140.24, 144.85, 196.32
IV	84[b]	139-40 (ethyl alcohol) (lit.[14] 139-40)		$CDCl_3$: 7.56 (m, 2 H), 7.65 (m, 1 H), 7.98 (d, J = 8.7, 2 H), 8.24 (AB, J_{AB} = 8.8, $\Delta\nu$ = 71.11, 4 H)	$CDCl_3$: 124.41, 127.87, 128.85, 129.58, 134.02, 139.80, 147.14, 150.16
V	95[b]	126-7 (ethyl alcohol) (lit.[14] 125-6)		$CDCl_3$: 7.53 (m, 2 H), 7.59 (m, 1 H), 7.78 (d, J = 9, 2 H), 7.93 (d, J = 9, 2 H), 8.03 (d, J = 9, 2 H)	$CDCl_3$: 116.66, 117.15, 127.80, 128.14, 133.06, 133.95, 139.88, 145.58
VI	61[b]	151-2 (ethyl alcohol) (lit.[19] 144)		$CDCl_3$: 7.52 (m, 4 H), 7.61 (m, 2 H), 7.75 (m, 2 H), 7.95 (AB, J_{AB} = 8.14, $\Delta\nu$ = 55.35, 4 H), 7.97 (m, 2 H)	$CDCl_3$: 127.22, 127.43, 128.17, 129.11, 130.09, 132.89, 133.29, 135.85, 140.35, 141.21, 144.22, 194.63

[a] Reaction temperature = 100 °C. [b] Reaction temperature = 130 °C.

the reaction of 4-fluorobenzaldehyde with sodium benzenesulfinate at 130 °C gave 4-(phenylsulfonyl)benzaldehyde in 88% yield.

The reaction of sodium benzenesulfinate with different activated aromatic halides (Y = CN, NO_2, CH_3CO, and PhCO) was then examined, and the corresponding 4-phenylsulfonyl derivatives were isolated in 50% yield (for X = F, Y = CH_3CO) to 95% yield (for X = F, Y = CN).

We believe that the route described in this paper represents a significant improvement in the preparation of sulfone derivatives of benzaldehyde.

Experimental Section

Sodium methanesulfinate (Fairfield), sodium benzenesulfinate (Kodak), 4-fluorobenzaldehyde (Aldrich), 4-chlorobenzaldehyde (Kodak), 4-fluorobenzophenone (Aldrich), 4-fluoronitrobenzene (Kodak), 4-chloronitrobenzene (Kodak), 4-fluorobenzonitrile (Aldrich), 4-chlorobenzonitrile (Kodak), 4-fluoroacetophenone (Aldrich), 4-fluoropropiophenone (Aldrich), and 4-chlorophenyl phenyl sulfone (Aldrich) were used as received. DMSO (Kodak) was dried over 4-Å molecular sieves (Aldrich) for 24 h.

NMR spectra were obtained on a GE QE-300 instrument at 300 MHz for proton and 75 MHz for ^{13}C spectra in $CDCl_3$ solution, and shifts are referenced to TMS internal standard. All chemical shifts (δ) are in parts per million, and coupling constants are in hertz units. Melting points are not corrected. Elemental analyses were performed by Analytical Technologies Division, Eastman Kodak Company.

General Procedure. The substrate (0.1 mol) and sodium methane(benzene)sulfinate (0.11 mol) were dissolved in dry DMSO (75 mL), under nitrogen. The mixture was stirred at 100 or 130 °C (see Table I) for 16 h and then poured over ca. 200 g of ice. The solid thus formed was collected and crystallized. All the yields reported in this paper are of crystallized materials.

The following materials have been prepared: 4-(methylsulfonyl)benzaldehyde (I) from 4-fluorobenzaldehyde, 4-(phenylsulfonyl)benzaldehyde (II) from 4-fluorobenzaldehyde, 4-(phenylsulfonyl)acetophenone (III) from 4-fluoroacetophenone, 4-(phenylsulfonyl)nitrobenzene (IV) from 4-fluoronitrobenzene, 4-(phenylsulfonyl)benzonitrile (V) from 4-fluorobenzonitrile, and 4-(phenylsulfonyl)benzophenone (VI) from 4-fluorobenzophenone.

Table I summarizes the yields and analytical data for compounds I-VI. No attempt was made to improve reaction conditions and optimize yields.

Registry No. I, 5398-77-6; II, 66-39-7; III, 65085-83-8; IV, 1146-39-0; V, 28525-13-5; VI, 54687-39-7; 4-fluorobenzaldehyde, 459-57-4; 4-fluoroacetophenone, 403-42-9; 4-fluoronitrobenzene, 350-46-9; 4-fluorobenzonitrile, 1194-02-1; 4-fluorobenzophenone, 345-83-5; sodium methanesulfinate, 20277-69-4; sodium benzenesulfinate, 873-55-2; 4-chlorobenzaldehyde, 104-88-1; 4-chloronitrobenzene, 100-00-5; 4-chlorobenzonitrile, 623-03-0; 4-chlorophenyl phenyl sulfone, 80-00-2.

(17) For papers on the effect of the leaving group in the S_NAr mechanism, see: (a) London, J. D.; Shulman, N. *J. Chem. Soc.* **1941**, 722. (b) Suhr, H. *Chem. Ber.* **1964**, *97*, 3268. (c) Reinheimer, J. D.; Taylor, R. C.; Rohnbaugh, P. E. *J. Am. Chem. Soc.* **1961**, *83*, 835. (d) Ross, S. D. *J. Am. Chem. Soc.* **1959**, *81*, 2113. (e) Bunnet, J. F.; Garbisch, E. W.; Pruitt, K. M., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 385.

(18) Eistert, B.; Schade, H. *Chem. Ber.* **1964**, *97*, 1470.

(19) Burton, H.; Hu, P. F. *J. Chem. Soc.* **1948**, 601.

A New Method for the Enzymatic Synthesis of Nucleosides Using Purine Nucleoside Phosphorylase

William J. Hennen and Chi-Huey Wong*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received March 27, 1989

Nucleoside analogues have been used extensively as antibiotic substances and as biological probes.[1-3] Recent interest in this class of compounds has been stimulated by the efficacy of certain nucleosides as antiparasitic[4] and antiviral[5-6] agents. Zidovudine (3′-azido-3′-deoxythymidine, AZT) and the various 2′,3′-dideoxynucleosides have received especial attention due to their virucidal activity in the treatment of AIDS patients.[7] The broad-spectrum antiviral activity of virazole (ribavirin, 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide) has recently been shown to extend to the treatment of plant as well as animal viruses.[8]

Traditionally nucleosides have been prepared by various chemical methods.[3] Recently, however, a number of papers and patents have appeared reporting the enzymatic preparations of both natural and unnatural nucleosides.[9] These works employed two basic strategies (see Scheme I). The first strategy used a pyrimidine nucleoside as the glycosyl donor and a purine or purine analogue as the glycosyl acceptor. This was conducted as a one-pot reac-

* Current address: Department of Chemistry, The Research Institute of Scripps Clinic, La Jolla, CA 92037.

0022-3263/89/1954-4692$01.50/0