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# Reductive Desulfonylation of 2-Aryl-2-benzylsulfonylacetates and -propionates with Sodium Amalgam. A New Synthesis of 2-Arylacetic and 2-Arylpropionic Acids[1)]

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Benzyl 2-aryl-2-benzylsulfonylacetates (**4**) and -propionates (**9**), of which the latter compounds were easily prepared by methylation of **4**, have been conveniently converted to 2-arylacetic and -propionic acids (**8** and **10**) with sodium amalgam in methanol followed by aqueous treatment.

**Keywords**——2-sulfonylacetate; 2-sulfonylpropionate; methylation; reductive desulfonylation; sodium amalgam reduction; 2-arylacetic acid; 2-arylpropionic acid

Our previous communications have reported that 2-benzylsufonyl-2-substituted acetic acids (**2**) can be prepared[2)] from acyl chlorides and benzylsulfonyldiazomethane (**1**), a stable and safe substitute for hazardous diazomethane, and also that reductive desulfonylation of **2** giving 2-substituted acetic acids **3** can be achieved[3)] with sodium-ethanol in tetrahydrofuran,[4)] as shown in Chart 1.

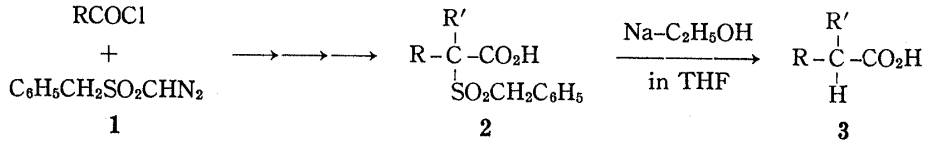


Chart 1

Although this reduction procedure seemed to have generality and was effective for the conversion of 2-benzylsulfonyl-2-phenylpropionic acid (**2**, $R=C_6H_5$, $R'=CH_3$) to 2-phenylpropionic acid (**3**, $R=C_6H_5$, $R'=CH_3$), 2-benzylsulfonyl-2-phenylacetic acid (**2**, $R=C_6H_5$, $R'=H$) and its methyl ester did not undergo the reductive desulfonylation. Since 2-aryl acetic and -propionic acids constitute an important group of nonsteroidal antiinflammatory agents,[5)] we focused our attention on the reductive desulfonylation of various 2-aryl-2-benzylsulfonylacetic and -propionic acid derivatives.

As described in our previous paper,[3)] treatment of benzyl 2-benzylsulfonyl-2-phenylacetate (**4a**) with sodium amalgam in methanol containing disodium hydrogen phosphate, according to a procedure developed by Trost and co-workers,[6)] resulted in removal of the benzyl ester function to give dibenzylsulfone (**5**) preferentially. The corresponding methyl ester **6**, prepared from **4a** by ester exchange with methanol, was unaffected by Trost's procedure. However, treatment of **4a** with sodium amalgam in methanol without disodium hydrogen phosphate afforded a mixture of the methyl ester **6** and methyl phenylacetate (**7**), as revealed by the nuclear magnetic resonance (NMR) spectrum of the reaction mixture. Prolonging the reaction time increased the formation of the latter (**7**) while decreasing that of the former (**6**). The corresponding desulfonylated benzyl ester could not be detected. These results suggested that the initial formation of methyl esters from benzyl esters might be essential to effect the desulfonylation, as shown in Chart 2.

In fact, successive treatment of **4a** with sodium methoxide at 0°C (transesterification),

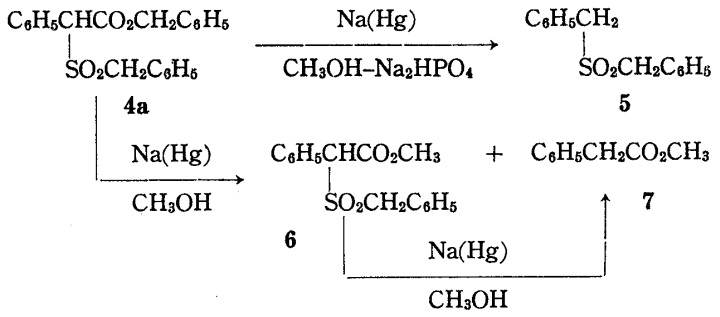

Chart 2

sodium amalgam in methanol at 0°C (reductive desulfonylation), and alkaline water at reflux (hydrolysis) afforded phenylacetic acid (**8a**) in 47% yield. Since the transesterification was observed with sodium amalgam only,[3] **4a** was treated with an excess of sodium amalgam in methanol at room temperature followed by alkaline hydrolysis, giving phenylacetic acid (**8a**) in 93% yield. Similar treatment of benzyl 2-benzylsulfonyl-2-phenylpropionate (**9a**) afforded 2-phenylpropionic acid (**10a**) in 83% yield. We extended this reductive desulfonylation procedure to various benzyl 2-aryl-2-benzylsulfonylacetates (**4**) and -propionates (**9**), of which the latter compounds were efficiently prepared by methylation of the former with methyl iodide in acetone in the presence of potassium carbonate, as shown in Chart 3. Most of **4** and **9** except **4f** and **9e** conveniently furnished 2-arylacetic and -propionic acids (**8** and **10**) in good yields. The results are summarized in Tables I and II.

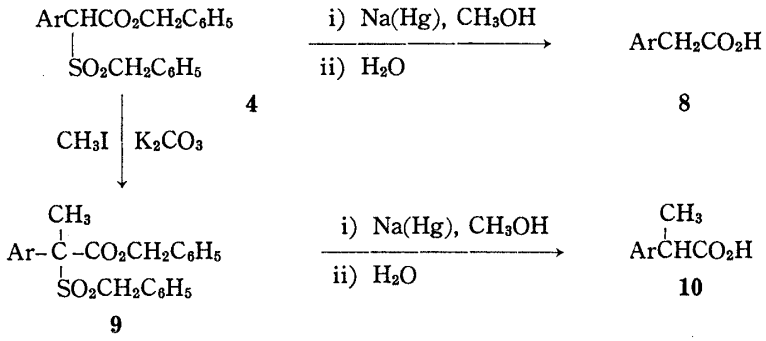

Chart 3

Table I. Synthesis of 2-Arylacetic Acids (**8**) by Reductive Desulfonylation of Benzyl 2-Aryl-2-benzylsulfonylacetates (**4**)[a]

| Compd. No. | Ar | Yield (%) |
|---|---|---|
| **8a** | Phenyl | 47[b] |
| **8a** | Phenyl | 88[c] |
| **8a** | Phenyl | 93 |
| **8b** | 4-Chlorophenyl | 87 |
| **8c** | 3-Chlorophenyl | 86 |
| **8d** | 4-Anisyl | 83 |
| **8e** | 1-Naphthyl | 51 |
| **8f** | 2-Furyl | 9[d] |

*a*) Unless otherwise stated, desulfonylation was carried out at room temperature as described in "Experimental."
*b*) The ester **4a** (1 mmol) was first treated with sodium methoxide in methanol [prepared from 50% sodium hydride (1.2 mmol) and methanol (20 ml)] at 0°C for 5 h under argon, then subjected to desulfonylation at 0°C.
*c*) The ester **4a** was first treated as in b), then subjected to desulfonylation at room temperature.
*d*) Reflux was required; see "Experimental."

Table II. Synthesis of 2-Arylpropionic Acids (**10**) by Reductive Desulfonylation of Benzyl 2-Aryl-2-benzylsulfonylpropionates (**9**)[a]

| Compd. No. | Ar | Yield (%) |
|---|---|---|
| **10a** | Phenyl | 88[b] |
| **10a** | Phenyl | 83 |
| **10b** | 4-Chlorophenyl | 87 |
| **10c** | 3-Chlorophenyl | 86 |
| **10d** | 4-Anisyl | 93 |
| **10e** | 1-Naphthyl | 31[c] |
| **10f** | 2-Furyl | 71 |

*a*) Unless otherwise stated, desulfonylation was carried out at room temperature as described in "Experimental."
*b*) The ester **10a** (1 mmol) was first treated with sodium methoxide in methanol [preparede from 50% sodium hydride (1.2 mmol) and methanol (20 ml)] at room temperatur for 4h under argon, then subjected to desulfonylation at room temperature.
*c*) Reflux was required; see "Experimental."

Desulfonylation with sodium amalgam in methanol complements that with sodium–ethanol in tetrahydrofuran, and the overall process from the acylation of benzylsulfonyldiazomethane (**1**) not only provides a new alternative method for the preparation of medicinally important 2-arylacetic and -propionic acids, but also extends the synthetic utility of benzylsulfonyldiazomethane.[1]

## Experimental

General experimental procedures employed were essentially the same as described in our pr vious paper.[3] Commercial 5% sodium amalgam (Kishida Chemicals, Co.) was used without pulverization.

**Methylation of Benzyl 2-Aryl-2-benzylsulfonylacetates (4)**[3]——General Procedure: A mixture of **4** (0.5 mmol), potassium carbonate (138 mg, 1 mmol), and methyl iodide (142 mg, 1 mmol) in acetone (25 ml) was refluxed for 24 h, then concentrated *in vacuo*. The residue was extracted with chloroform. The extracts were concentrated *in vacuo* and the resid··e was purified by silica gel column chromatography (Merck Kieselgel 60, 70—230 mesh, Art. 7734) with hexane–ethyl acetate to give benzyl 2-aryl-2-benzylsulfonylpropionate (**9**). Analytical and spectral data (except for **9a**) are listed in Table III. Preparation and physical data of the ester **9a** were described in our previous paper.[3]

**Reductive Desulfonylation of Benzyl 2-Aryl-2-benzylsulfonylacetates (4) and -propionates (9)**——General Procedure: Sodium amalgam (1.8 g) was added to **4** or **9** (1 mmol) in methanol (20 ml). The mixture was stirred at room temperature under argon. After 4 h, sodium amalgam (1 g) was further added and the mixture was stirred at room temperature for 5 h. Water was added, then the reaction mixture was refluxed for 3 h. The mixture was poured into water and washed with chloroform. The aqueous layer was acidified with 1 N hydrochloric acid and extracted with chloroform. The extracts were dried over sodium sulfate and concentrated *in vacuo*, and the residue was purified by preparative layer chromatography (Merck Silica Gel $60F_{254}$) using benzene–methanol–acetic acid (10: 2: 0.5) to give **8** or **10**.

In the case of desulfonylation of **4f** or **9e**, the starting ester (3 mmol) in methanol (20 ml) was first treated with sodium amalgam (1.8 g) for 4 h at room temperature under argon, then with further sodium amalgam (1.8 g) for 5 h at room temperature. After another addition of sodium amalgam (1.8 g), the mixture was refluxed for 5 h, then more sodium amalgam (1.8 g) was added. The mixture was refluxed for 10 h, and worked up as above.

2-Arylacetic acids (**8a—e**) and 2-arylpropionic acids (**10a—b**) were identified by comparisons of their IR and NMR spectra with those of authentic samples.[7,8]

2-Furylacetic Acid (**8f**): mp 63—64.5°C (lit.[9] mp 67—67.5°C). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400—3000, 1700. NMR ($CDCl_3$) $\delta$: 3.73 (2H, s), 6.13—7.53 (3H, m), 8.73 (1H, s).

2-(3-Chlorophenyl)propionic Acid (**10c**): mp 69.5—72°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400—3000, 1705. NMR ($CDCl_3$) $\delta$: 1.48 (3H, d, $J$=7 Hz), 3.68 (1H, q, $J$=7 Hz), 7.1—7.4 (4H, m), 11.6 (1H, s). *Anal.* Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.91. Found: C, 58.58; H, 4.94.

2-(4-Anisyl)propionic Acid (**10d**): mp 47—49.5°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400—3000, 1700. NMR ($CDCl_3$) $\delta$: 1.48 (3H, d, $J$=7 Hz), 3.70 (1H, q, $J$=7 Hz), 3.75 (3H, s), 6.75—7.5 (4H, m), 11.43 (1H, s). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.26; H, 6.56.

2-(1-Naphthyl)propionic Acid (**10e**): mp 144.5—146°C (lit.[10] mp 148—149°C). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400—

TABLE III. Analytical and Spectral Data for Benzyl 2-Aryl-2-benzylsulfonylpropionates (**9**)[a]

| Compd. No. | Ar | Yield (%) | mp (°C) | Formula |
|---|---|---|---|---|
| **9b** | 4-Chlorophenyl | 90 | 83.5—85 | $C_{23}H_{21}ClO_4S$ |
| **9c** | 3-Chlorophenyl | 92 | 97—98.5 | $C_{23}H_{21}ClO_4S$ |
| **9d** | 4-Anisyl | 89 | 103—104.5 | $C_{24}H_{24}O_5S$ |
| **9e** | 1-Naphthyl | 82 | 142.5—144 | $C_{27}H_{24}O_4S$ |
| **9f** | 2-Furyl | 95 | 71—73 | $C_{21}H_{20}O_5S$ |

| Compd. No. | Analysis (%) Calcd (Found) C | H | IR $\nu_{max}^{Nujol}$ cm$^{-1}$ | NMR $\delta$ ppm ($CDCl_3$) $CH_3$ (s) | $CH_2SO_2$ (AB q) ($J$=13—14 Hz) | $CO_2CH_2$ (s) |
|---|---|---|---|---|---|---|
| **9b** | 64.40 (64.41 | 4.93 4.87) | 1740, 1305, 1140, 1130 | 2.10 | 4.05, 4.70 | 5.47 |
| **9c** | 64.40 (64.82 | 4.93 5.01) | 1720, 1305, 1135, 1130, 1100 | 2.10 | 4.10, 4.70 | 5.47 |
| **9d** | 67.91 (67.76 | 5.70 5.40) | 1740, 1305, 1135, 1130, 1100 | 2.03 | 3.88, 4.65 | 5.37 |
| **9e** | 72.95 (72.97 | 5.44 5.31) | 1712, 1345, 1317, 1155, 1135, 1125, 1105 | 2.10 | 4.50, 4.73 | 5.13 |
| **9f** | 65.61 (65.77 | 5.24 5.50) | 1745, 1310, 1160, 1140, 1100 | 2.13 | 4.12, 4.79 | 5.42 |

a) Recrystallized from either diethyl ether or diethyl ether–hexane.

3000, 1700. NMR ($CDCl_3$) $\delta$: 1.67 (3H, d, $J$=7 Hz), 4.57 (1H, q, $J$=7 Hz), 7.37—8.23 (7H, m).

2-(2-Furyl)propionic Acid (**10f**): A colorless oil. IR $\nu_{max}^{cap.}$ cm$^{-1}$: 3400—3000, 1712. NMR ($CDCl_3$) $\delta$: 1.70 (3H, d, $J$=7 Hz), 3.90 (1H, d, $J$=7 Hz), 3.90 (1H, q, $J$=7 Hz), 6.3—7.6 (3H, m), 10.20 (1H, s). MS: Calcd for $C_7H_8O_3$: 140.0473. Found: M$^+$ $m/e$ 140.0470.

## References and Notes


1) New Methods and Reagents in Organic Synthesis. 33. For Part 32, see T. Aoyama, K. Sudo, and T. Shioiri, *Chem. Pharm. Bull.*, **30**, 3849 (1982).
2) Y.-C. Kuo, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, **30**, 526 (1982).
3) Y.-C. Kuo, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, **30**, 2787 (1982).
4) This procedure was originally developed by Tsuchihashi and co-workers. See K. Ogura, T. Noguchi, S. Mitamura, and G. Tsuchihashi, Abstracts of Papers, 7th Symposium on Organosulfur and Organophosphorus Compounds, Kyoto, February 1979, p. 76; G. Tsuchihashi, K. Ogura, S. Mitamura, and T. Noguchi, Japan Kokai, 55-108824 (1980).
5) D. Lednicer and L.A. Mitscher, "The Organic Chemistry of Drug Synthesis," Vol. 1, John Wiley and Sons, New York, 1977, Chapter 6 and Vol. 2, 1980, Chapter 4.
6) B.M. Trost, H.C. Arndt, P.E. Strege, and T.R. Verhoeven, *Tetrahedron Lett.*, **1976**, 3477.
7) C.J. Pouchert, "The Aldrich Library of Infrared Spectra," 3rd ed., Aldrich Chemical Co., Inc., Milwaukee, 1981; *a*) 930A for **8a**; *b*) 940G for **8b**; *c*) 939B for **8c**; *d*) 942G for **8d**; *e*) 949E for **8e**; *f*) 930B for **10a**; *g*) 940H for **10b**.
8) C.J. Pouchert and J.R. Campbell, "The Aldrich Library of NMR Spectra," Vol. VI, Aldrich Chemical Co., Inc., Milwaukee, 1974; *a*) 105A for **8a**; *b*) 119B for **8b**; *c*) 115D for **8c**; *d*) 123C for **8d**; *e*) 131B for **8e**; *f*) 105D for **10a**; *g*) 119C for **10b**.
9) J. Plucker, III, and E.D. Amstutz, *J. Am. Chem. Soc.*, **62**, 1512 (1940).
10) F.F. Blicke and R.F. Feldkamp, *J. Am. Chem. Soc.*, **66**, 1087 (1944).