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A Convenient Synthesis of α-Bromophenylacetic Acid from Benzaldehyde Using Methyl (Methylthio) methyl Sulfoxide

Katsuyuki OGURA, Shigeko FURUKAWA, and Gen-ichi TSUCHIHASHI

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229

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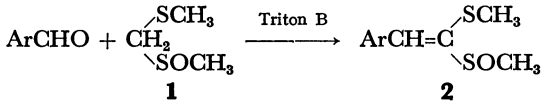
Synopsis. 1-Methylsulfinyl-1-(methylthio)-2-phenylethylene (**2a**) and 1-methylsulfinyl-1-(methylthio)-2-(*p*-chlorophenyl)ethylene (**2b**) reacted with bromine in various solvents to give α-bromophenylacetic acid derivatives. It should be noted that α-bromophenylacetic acid and α-bromo(*p*-chlorophenyl)acetic acid were mainly obtained by the reaction of bromine with **2a** and **2b**, respectively, in acetic acid.

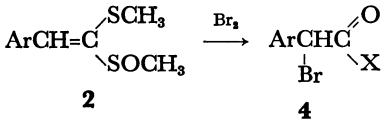
As previously reported,[1] methyl (methylthio) methyl sulfoxide (**1**)[2,3] can condense with aromatic aldehydes in the presence of trimethylbenzylammonium hydroxide (Triton B) to afford the corresponding 1-methylsulfinyl-1-(methylthio)-2-arylethylenes (**2**), which are easily converted into ethyl arylacetates (**3**) on treatment with hydrogen chloride in ethanol, providing a new method for the synthesis of ethyl arylacetates (Scheme 1). Further, the reaction of the condensation product (**2**) with bromine has been examined, and we now wish to describe on a novel synthetic route from benzaldehyde to α-bromophenylacetic acid.



(a, Ar=C_6H_5; b, Ar=*p*-ClC_6H_4)

Scheme 1.

The reaction of 1-methylsulfinyl-1-(methylthio)-2-phenylethylene (**2a**) with bromine was carried out in carbon tetrachloride, methanol, and acetic acid. When **2a** was treated with bromine in carbon tetrachloride, methanethiol ester (**4a**) of α-bromophenylacetic acid was isolated in 25% yield. The structure of **4a** was assigned by its IR and NMR spectra and elemental analysis (see Experimental Section).

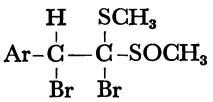


a	Ar=C_6H_5	X=SCH_3
b	=C_6H_5	=OCH_3
c	=C_6H_5	=OH
d	=*p*-ClC_6H_4	=OH
e	=*p*-ClC_6H_4	=OCH_3

Scheme 2.

In methanol, bromine reacted with **2a** to give methyl α-bromophenylacetate (**4b**) in 64% yield. It should be noted that a better result was obtained when acetic acid was used as a solvent. Thus, the reaction with bromine in acetic acid afforded α-bromophenylacetic acid in 73% yield.

By a similar reaction in acetic acid, α-bromo(*p*-chlorophenyl)acetic acid (**4d**) was also obtained in 60% yield, starting from 1-methylsulfinyl-1-(methylthio)-2-(*p*-chlorophenyl)ethylene (**2b**).[4,5] Since **2a** and **2b** were easily derived from the corresponding aldehydes by the reaction with methyl (methylthio) methyl sulfoxide (**1**),[1] the present reactions completed a simple two-step synthesis of α-bromophenylacetic acid and α-bromo(*p*-chlorophenyl)acetic acid from benzaldehyde (over-all yield: 66%) and *p*-chlorobenzaldehyde (over-all yield: 44%), respectively.



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The transformation of **2** into **4** may be accounted for by a mechanism which involves an intermediacy of **5**, which is finally converted into **4** by the subsequent hydrolysis.

Experimental

*Reaction of 1-Methylsulfinyl-1-(methylthio)-2-phenylethylene (**2a**) with Bromine.* *a) In Carbon Tetrachloride*: Bromine (0.21 ml, 4.0 mmol) was added to a solution containing **2a** (798 mg, 3.8 mmol) in carbon tetrachloride (10 ml) under cooling with ice, and the resulting solution was stirred at room temperature for 2 hr. After the addition of water (5 ml) and extraction with methylene chloride, the organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed (silica-gel column, eluted with *n*-hexane and benzene) to give 263 mg (0.95 mmol, 25%) of a pale yellow oil, which was identified as methanethiol ester (**4a**) of α-bromophenylacetic acid by its physical properties and elemental analysis. IR (neat): 1685 cm^{-1} ($\nu_{C=O}$); NMR ($CDCl_3$): δ 2.33 (s, 3H, $COSCH_3$), 5.36 (s, 1H, –CHBr–), 7.34 (m, 5H, C_6H_5); Found: C, 44.16; H, 3.50; S, 13.00%. Calcd for C_9H_9BrOS: C, 44.09; H, 3.70; S, 13.08%.

b) In Methanol: A solution containing **2a** (526 mg, 2.5 mmol) in methanol (5 ml) was stirred at room temperature for 41.5 hr after the addition of bromine (0.33 ml, 5.7 mmol) under cooling with ice. The solution was evaporated under reduced pressure, and the residue was chromatographed [silica-gel column, eluted with benzene–*n*-hexane (1:4)] to afford 363 mg (1.58 mmol, 64%) of a pale yellow oil, which was identified as methyl α-bromophenylacetate (**4b**) by the comparison of its IR and NMR spectra with those of an authentic specimen prepared by esterification (conc. sulfuric acid–methanol) of α-bromophenylacetic acid.

c) In Acetic Acid: Bromine (0.13 ml, 2.6 mmol) was added,

together with acetic acid (1 ml), to a solution containing **2a** (533 mg, 2.5 mmol) in acetic acid (1 ml). The resulting solution was stirred at room temperature for 17.5 hr and, after the evaporation under reduced pressure, the residue was chromatographed (silica-gel column, eluted with methylene chloride) to give 394 mg (1.83 mmol, 73%) of pale yellow crystals, which were once recrystallized from cyclohexane to afford colorless crystals, mp 51.5—52 °C; IR (KBr): 3100—2300 and 1700 cm^{-1}; NMR (CCl_4): δ 5.24 (s, 1H), 7.33 (m, 5H), 11.35 (s, 1H); Found: C, 44.82; H, 3.28%. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28%.

The structure of this product was assigned as α-bromophenyacetic acid (**4c**) by its physical properties and elemental analysis. Furthermore, its NMR and IR spectra were completely accordant with those of an authentic sample (mp 71.5—72 °C; lit,[6] mp 68—69 °C) obtained by the reaction of mandelic acid with hydrobromic acid and sulfuric acid.[6] The melting point of the crystals obtained by the reaction of **2a** with bromine was raised to 81—82 °C, after several recrystallizations from cyclohexane. This melting point is in accord with those reported in the other literatures (ranging from 78.5 to 84 °C).[7]

*Reaction of 1-Methylsulfinyl-1-(methylthio)-2-(*p*-chlorophenyl)-ethylene (2b) with Bromine.* *a) In Methanol*: Bromine (0.09 ml, 1.8 mmol) was added to a solution containing **2b** (408 mg, 1.7 mmol) in methanol (5 ml) and the resulting solution was stirred at room temperature for 22 hr. After the evaporation under reduced pressure, the residue was chromatographed [silica-gel column, eluted with benzene–*n*-hexane (1:4)] to give 189 mg (0.72 mmol, 43%) of methyl α-bromo(*p*-chlorophenyl)acetate (**4e**) and 198 mg (1.06 mmol, 52%) of methyl (*p*-chlorophenyl)acetate. The structures of these products were assigned by the comparison of their IR and NMR spectra with those of the corresponding authentic samples.

b) In Acetic Acid: Bromine (0.11 ml, 2.1 mmol) was added, together with acetic acid (1 ml), to a solution containing **2b** (502 mg, 2.0 mmol) in acetic acid (1 ml) and the resulting solution was stirred at room temperature for 19 hr. After the evaporation under reduced pressure, the residue was chromatographed [silica-gel column, eluted with benzene–*n*-hexane (1:4)] to give 342 mg of colorless crystals, which were shown by the NMR analysis to consist of (*p*-chlorophenyl)acetic acid (35 mg, 0.21 mmol, 10%) and α-bromo-(*p*-chlorophenyl)acetic acid (307 mg, 1.23 mmol, 60%). The latter was isolated by recrystallization from cyclohexane as colorless crystals, mp 83—86 °C (lit,[8] mp 95—96 °C), which were identified with α-bromo(*p*-chlorophenyl)acetic acid (**4d**) by the comparison of their NMR ($CDCl_3$) and IR ($CHCl_3$) spectra with those of an authentic specimen.[8]

References

1) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1972**, 1383.

2) K. Ogura and G. Tsuchihashi, This Bulletin, **45**, 2203 (1972).

3) We have also reported new synthetic methods for making aldehydes, α-hydroxyaldehydes, α-amino acids and cyclobutanone derivatives: K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1971**, 3151; **1972**, 2681; K. Ogura, S. Furukawa, and G. Tsuchihashi, *Chem. Lett.*, **1974**, 659; K. Ogura and G. Tsuchihashi, *J. Amer. Chem. Soc.*, **96**, 1960 (1974); K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **1974**, 3653.

4) The reaction of 2-(3′,4′-dimethoxyphenyl)-1-methylsulfinyl-1-(methylthio) ethylene resulted in the formation of α-bromo(3,4-dimethoxyphenyl)acetic acid (21%) and (3,4-dimethoxyphenyl)acetic acid (18%). The structures of these compounds were assigned by their NMR spectra.

5) When bromine was reacted with **2b** in methanol, methyl α-bromo(*p*-chlorophenyl)acetate and methyl (*p*-chloropheny)acetate were formed in 43% and 52% yields, respectively (see Experimental Section).

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7) K. C. Kemp and D. Metsger, *J. Org. Chem.*, **33**, 4165 (1968); Distillers Co. Ltd., Belg. Pat. 622439 (1963), *Cf. Chem. Abstr.*, **59**, 11352c (1963); The literatures cited in Ref. 6.

8) J. Krapcho, U.S. Pat. 3166544 (1965), *Cf. Chem. Abstr.*, **62**, 13157e (1965).