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Oxygen transfer from sulfoxide: formation of aromatic aldehydes from dihalomethylarenes ☆

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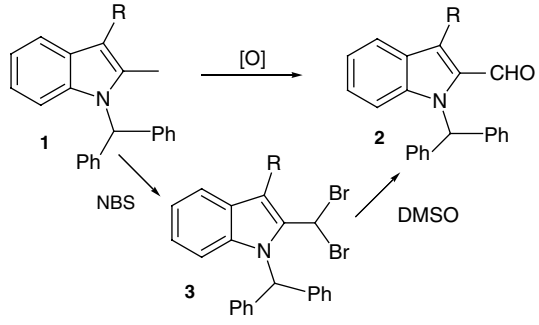
Abstract—The conversion of dihalomethylarenes to the corresponding aldehydes is accomplished conveniently by using sulfoxides as the oxygen donor under neutral conditions.

In an ongoing project we desired the conversion of **1** into **2**. This transformation requiring oxidation of a CH_3 group to an aldehyde has been previously reported for simpler systems using oxidizing agents such as IBX[1] [1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide], potassium permanganate/triethylamine,[2] oxygenation by photoinduced electron transfer methods,[3] SeO_2 or even enzymatic reactions with laccase/diammonium salt of 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid).[4]

The direct conversion of **1** into **2** (Scheme 1) in our hands failed to give good yields of products presumably due to the highly substituted nature of the indole ring, the electronic effects of the substituents, and over oxidation to acids. Our attention then turned to an alternative mild and selective transformation via the intermediacy of the 2-dibromomethyl indole derivative **3**, which should afford **2** upon hydrolysis. Therefore, synthesis of compound **3** was undertaken. To our satisfaction, when **3** was dissolved in DMSO for purification purposes, an exothermic reaction occurred leading to the desired aldehyde isolated as the sole product.



Scheme 1.

Conversion of *gem*-dihalo compounds to aldehydes is a widely used method for the preparation of aldehydes. Hydrolysis of the *gem*-dihalo compounds to the corresponding aldehydes often employs harsh reaction conditions such as use of strong acid (e.g., 95% H_2SO_4) or strong base (aq NaOH) at high temperatures.[5] Although mild reaction conditions have been reported,[6] development of good procedures for such transformations is of continued interest. In this communication, we wish to report our discovery that under neutral conditions DMSO converts the *gem*-dihalides into the corresponding aldehydes conveniently without the use of metal salts such as silver carbonate.

Representative examples and reaction conditions are given in Table 1. All the starting dihalides are commercially available and were used as received. All the products were characterized by ^1H or ^{13}C NMR or MS. All reported yields are isolated yields. Unlike the indole derivative **3**, which was converted into the corresponding aldehyde at room temperature, all the benzal halides listed required elevated temperature for the transformation. Although the reactions in Table 1 were carried

Keywords: Benzal bromides; Benzal chlorides; Aldehydes; DMSO; Dihaloarene.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.11.072

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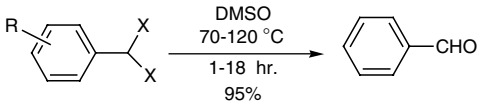
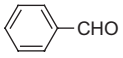
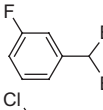
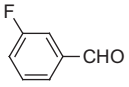
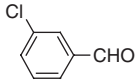
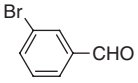
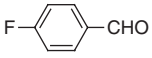
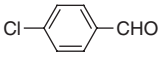
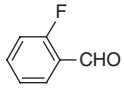
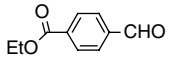
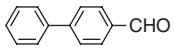
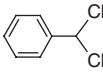
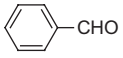
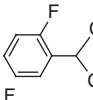
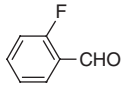
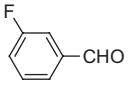
Table 1. Conversion of benzal halides into the corresponding aldehydes with DMSO



Entry	Reactant	Product	Temperature/time	Yield (%)
1			100 °C/2 h	95
2			120 °C/12 h	92
3			100 °C/2 h	95
4			120 °C/1 h	95
5			120 °C/12 h	93
6			100 °C/10 h	96
7			120 °C/18 h	100
8			120 °C/2 h	92
9			100 °C/2 h	97
10			100 °C/2 h	95
11			120 °C/18 h	98
12			100 °C/10 h	93

out in neat DMSO, using solvents such as THF or ethyl acetate gave similar results.

The ease of formation of aldehydes is demonstrated with *gem*-dibromo and dichloro compounds (entries 1 and 10). In all cases the isolated yields were high and synthetically relevant. It should be noted that *ortho*-, *meta*-, and *para*-fluoro benzal bromides and chlorides (entries 2, 5, 7, 11, and 12) reacted slower than either the chloro- or bromo-substituted compounds (3 and 4).

Aliphatic *gem*-dihalo compounds are inert toward DMSO for this transformation. For example, 1-dibromomethyladamantane did not provide the desired aldehyde under similar reaction conditions (100 °C, 2 h), only starting material was recovered. It seems necessary that the dihalomethyl group should be activated by its α-substituents such as the phenyl ring in order for the reaction to occur.

We also expand our investigation to other compounds bearing electron-withdrawing groups α- to the *gem*-dihalo methine (Fig. 1). Conversion of these compounds into aldehydes was carried out in DMSO-d_6 using microwave irradiation. All these compounds were less reactive than the aromatic *gem*-dihalo compounds. Only 30% of 1,1-dibromopinacolone was converted into the glyoxal derivative at 100 °C within 3 h, whereas the 2,2-dichloroacetophenone was much less active with only 10% conversion under the same conditions as indicated by the ^{1}H NMR. The ethyl α,α-dichloroacetate showed even less activity than the acetophenone. The lower

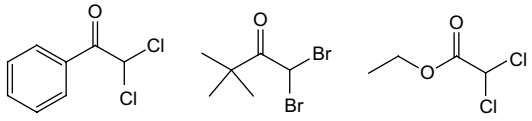
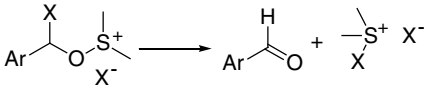


Figure 1.



Scheme 2.

reactivity of these α,α-dihalo ketones may be the result of keto–enol tautomerization, with the less active enol form being favored at elevated temperature.

As a comparison, it is worth noting the oxidation of monohalides such as benzyl bromides and α-bromo ketones to the corresponding aldehydes. Among all the oxidizing agents,[7] DMSO is one of the earliest discovered for such transformations.[8] For most of the benzyl bromides, activation of the halide is necessary (silver salts), as well as the presence of base like tertiary amine or alkaline carbonate.[8b–d] As to the α-bromo ketones, mild conditions were reported to convert them into the corresponding glyoxals.[8a] Although DMSO was used in these reactions, it is obvious that conversions of the monobromide and the *gem*-dibromide into aldehydes are fundamentally different processes. The former transfer is an oxidative process, while what we have described here is a nonoxidative reaction. The oxidation states of the methine bearing the dibromo atoms remain unchanged from the starting material to the product. Displacement of the dibromo atoms by oxygen from DMSO accomplished this nonoxidative conversion of the *gem*-dibromo compound into the aldehyde. Therefore, oxygen transfer from sulfoxide could occur in both oxidative and nonoxidative reactions depending on the substrates.

It has also been reported that N-oxide in DMSO afforded advantages of rapid oxidation of variety of alkyl halides to aldehydes in very good yield at mild reaction conditions.[9] In our case, N-oxides alone such as trimethylamine N-oxide and pyridine N-oxide did not work well compared to DMSO. Combination of N-oxides with DMSO did not offer advantages. The DMSO alone seems to work better.

Other sulfoxides, both alkyl and aryl, such as tetramethylene sulfoxide, diphenyl sulfoxide, and methyl phenyl sulfoxide were also investigated. These all worked as well as DMSO to afford the corresponding aldehydes.

Sulfoxides are often used as oxygen-donating agents in organic synthesis. One widely used reaction is the conversion of structurally diverse alcohols into their corresponding carbonyl compounds by dimethyl sulfoxide (DMSO) in the presence of activating reagents. (The original oxygen atom in DMSO is not directly donated to the alcohol substrate during this oxidative process. It is donated to the activating agents. However, such donation is necessary for the completion of the transformation.)[10] In the recent development of transition metal catalyzed oxidation of alcohols to aldehydes or ketones, the sulfoxide serves as a catalytically activated oxygen donor.[11] What we have described here is a unique example in which the sulfoxide serves as an oxygen donor in the absence of activating reagents.

Mechanistically, it would seem plausible to propose the intermediacy of an alkoxysulfonium species[12] (Scheme 2) upon displacement of a halo moiety. This species under the thermal reaction conditions undergoes a 1,2-elimination to give the desired aldehyde and a byproduct bromodimethylsulfonium bromide, which could also be isolated from the reaction mixture as a crystalline solid.[10b] Structure of the crystalline was further confirmed by a thorough analysis.[13] To monitor the progress, a reaction (Table 1, entry 1) was carried out in an NMR tube using DMSO-d_6. Only the product and starting material were seen from the ^{1}H NMR spectrum during the progress of the reaction (the reaction was checked every hour). No alkoxysulfonium intermediate was detected. This observation suggests that the displacement of the first bromo atom is slow, and the 1,2-elimination occurred immediately following the first displacement. Details of the mechanism for this novel transformation are under investigation and will be reported shortly.

In conclusion, a simple method for the transformation of dihalo compounds into the corresponding aldehydes is described herein. The reaction can be carried out conveniently and proceeds with excellent yield and purity. The reaction has been run up to one mole scale with similar yield and purity and used for a multi-step organic synthesis of complex molecules. Conversion of the dihalo compounds into the corresponding aldehydes constitutes an alternative route for the transformation of an aromatic methyl group to aromatic aldehyde via a two step, but relatively mild process.

To the best of our knowledge, this is the first example using sulfoxide as the sole reagent to convert a *gem*-dihalo precursor into the corresponding aldehyde.[14] The scope and limitations of this reaction for the preparation of other important functional groups as well as building blocks are currently under investigation.

A typical procedure for the reaction is illustrated by the preparation of 4-biphenylcarboxaldehyde: a solution of 4-phenylbenzal bromide (3.26 g, 0.01 M) in 30 mL of DMSO was heated at 100 °C for 2 h. The reaction mixture was poured into water (30 mL), and the resulting mixture was extracted with ethyl acetate (60 mL × 2). The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 1.71 g (yield 94%) of the 4-biphenylcarboxaldehyde as a white solid. ^{1}H NMR δ (400 MHz, DMSO-d_6) 10.09 (s, 1H), 8.01 (d, $J = 8.3$ Hz,

2H), 7.90 (d, $J = 8.3$ Hz, 2H), 7.77 (d, $J = 7.8$ Hz, 2H), 7.53 (d, $J = 7.8$ Hz, 2H), 7.46 (t, $J = 7.4$ Hz, 1H); ^{13}C NMR δ 192.97, 146.21, 139.15, 135.46, 130.48 (2C), 129.45 (2C), 128.91, 127.68 (2C), 127.46 (2C); LC-ESMS observed $[M+H]^+$ 183.16 (calcd 183.08).

Supplementary data

Typical experimental procedures for the preparation of aldehydes with supporting analytical data. The supplementary data is available online with the paper in ScienceDirect.

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References and notes

1. Nicolaou, K. C.; Baran, S.; Zhong, Y. *J. Am. Chem. Soc.* **2001**, *123*, 3183.
2. Li, W. S.; Liu, L. K. *Synthesis* **1989**, *293*, 7881.
3. Ohkubo, K.; Fukuzumi, S. *Org. Lett.* **2000**, *2*, 3647.
4. Potthast, A.; Roseenau, T.; Chen, C. L.; Gratzl, S. *J. Org. Chem.* **1995**, *60*, 4320.
5. Selected literature: (a) Langer, O.; Dolle, F.; Valette, H.; Halldin, C.; Vaufrey, F.; Fuseau, C.; Coulon, C.; Ottaviani, M.; Någren, K.; Bottlaender, M.; Maziére, B.; Crouzel, C. *Bioorg. Med. Chem.* **2001**, *9*, 677; (b) Chung, S. J.; Kim, D. H. *Tetrahedron* **1995**, *51*, 12549; (c) Goodman, M. S.; Hamilton, A. D.; Weiss, J. *J. Am. Chem. Soc.* **1995**, *117*, 8447; (d) Adediran, S. A.; Cabaret, D.; Drouillat, B.; Pratt, R. F.; Wakselman, M. *Bioorg. Med. Chem.* **2001**, *9*, 1175.
6. Selected literature: (a) Semmelhack, M. F.; Ho, S.; Cohen, D.; Steigerwad, M.; Lee, M. C.; Lee, G.; Gilbert, A. M.; Wufll, W. D.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7108; (b) Shamblee, D. A.; Gillespie, S. G., Jr. *J. Med. Chem.* **1979**, *22*, 86; (c) Blicke, F. F.; Patelski, R. A. *J. Am. Chem. Soc.* **1936**, *58*, 559; (d) Khatuya, H. *Tetrahedron Lett.* **2001**, *42*, 2643; (e) Angelini, G.; Giancaspro, C.; Illuminati, G.; Sleiter, G. *J. Org. Chem.* **1980**, *45*, 1786.
7. For N-oxides as oxidants, see: (a) Feely, W.; Lehn, W. M.; Boekelheide, V. *J. Org. Chem.* **1957**, *22*, 1135; (b) Franzen, V. *Org. Synth.* **1973**, *5*, 872; (c) Mukaiyama, S.; Inanga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2221; (d) Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3287; (e) Barbry, D.; Champagne, P. *Tetrahedron Lett.* **1996**, *43*, 7725; (f) Chandrasekhar, S.; Sridhar, M. *Tetrahedron Lett.* **2000**, *41*, 5423; (g) For other oxidizing reagents, see: Hass, H. B.; Bender, M. L. *J. Am. Chem. Soc.* **1949**, *71*, 1767; (h) Das, S.; Panigrahi, A. K.; Maikap, G. C. *Tetrahedron Lett.* **2003**, *44*, 1375, and references cited therein.
8. (a) Kornblun, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562; (b) Kornblun, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113; (c) Ganem, B.; Boekman, R. K. *Tetrahedron Lett.* **1974**, *15*, 917; (d) Ghera, E.; Plementitas, A.; Ben-David, Y. *Synthesis* **1984**, 504; (e) Maslak, P.; Narvaez, J. N.; Kula, J.; Malinski, D. S. *J. Org. Chem.* **1990**, *55*, 4550.
9. Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *34*, 4825.
10. For a review, see Tidwell, Y. T. *Org. React.* **1990**, *39*, 297; See also: (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661, 5670; (b) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1762; (c) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247; (d) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416; (e) Parikh, J. R.; von Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505; (f) Corey, E. J.; Kim, C. U. *Tetrahedron Lett.* **1973**, *14*, 919; (g) Albright, J. D. *J. Org. Chem.* **1974**, *39*, 1977; (h) Omura, K.; Sharma, A.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957; (i) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
11. (a) Peterson, K. P.; Larock, B. C. *J. Org. Chem.* **1998**, *63*, 3185; (b) Arterburn, J. B.; Perry, M. C. *Org. Lett.* **1999**, *5*, 769; (c) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766; (d) Coleman, K. S.; Bedel, L. J. L.; Osborn, J. A. *C.R. Acad. Sci., Ser. IIC—Chem.* **2000**, *3*, 765, and references cited therein.
12. (a) Johnson, C. R.; Jones, M. P. *J. Org. Chem.* **1967**, *32*, 2014; (b) Johnson, C. R.; Rigau, J. J. *J. Am. Chem. Soc.* **1969**, *91*, 5398; (c) Khuddus, M. A.; Swern, D. *J. Am. Chem. Soc.* **1973**, *95*, 8393; (d) Zhang, J.; Saito, S.; Koizumi, T. *J. Org. Chem.* **1998**, *63*, 5265; (e) Smith, G.; Winstein, S. *Tetrahedron* **1958**, *3*, 317.
13. Analytical data for bromodimethylsulfonium bromide: ^{1}H NMR δ (400 MHz, CD_2Cl_2) 2.66 (s, –CH_3), ^{13}C NMR δ 27.12. MS: only the cation fragment was observed (calcd for $C_2H_6SBr^+$: 140.94, observed: 140.82). Also see Megyeri, G.; Keve, T. *Synth. Commun.* **1989**, *19*, 3415.
14. A footnote in a report mentioned the conversion of benzal bromides into aldehydes by hydrolysis. Such study was carried out in the presence of K_2CO_3 (d_6-DMSO) at 60 °C for 1 day. The authors attributed the conversion of the benzal bromides as the result of hydrolysis by water generated from the K_2CO_3. Apparently, DMSO here was intentionally used as NMR solvent. Xu, H.; Gibb, C. L. D.; Gibb, B. C. *J. Org. Chem.* **1999**, *64*, 9286.