Synthesis of Dimethyl Aryl Acylsulfonium Bromides from Aryl Methyl Ketones in a DMSO-HBr System

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Abstract: A new, simplified method for the synthesis of dimethyl aryl acylsulfonium salts has been developed. A series of dimethyl aryl acylsulfonium bromides were prepared by the reaction of aryl methyl ketones with hydrobromic acid and dimethylsulfoxide (DMSO). This sulfonium salt confirms that bromine production and the bromination reaction take place in the DMSO-HBr oxidation system. What’s more, it is also a key intermediate for the synthesis of arylglyoxals.

Keywords: dimethyl aryl acylsulfonium; aryl methyl ketones; DMSO-HBr; synthesis; arylglyoxals

1. Introduction

In 1957, Kornblum first reported oxidation of α-bromoketones into α-ketoaldehydes by dimethylsulfoxide (DMSO) [1]. Schipper also found that 1,3-diketones could be directly oxidized to 1,2,3-trione derivatives in a DMSO-HBr system [2]. This method has been modified by Folyd and applied to the preparation of aryl diketone (aryl glyoxal) derivatives from arylmethyl ketones in high yield [3]. Aryldiketones and arylglyoxals are important building blocks in organic synthesis, particular in the synthesis of biologically active phenylimidazoles, oxazoles, and quinolines [4–7].
The DMSO-HBr system has been proved to be extremely efficient for the oxidation of the α-methyl group of arylketones [8]. Compared with the traditional selenium dioxide oxidation [9], DMSO-HBr oxidation is milder, less toxic and easy to perform. Furthermore, arylalkynes and alkenes were found to be suitable as substrates for this oxidation system [10,11].

However, when we tried to prepare arylglyoxals 2 from aryl methyl ketones 1 with the DMSO-HBr oxidation system in a sealed flask, we observed that aryl acylsulfonium bromides 3 were unexpectedly produced (Scheme 1). Sulfonium salts, characterized by low sulfur valence and relatively unstable carbon-sulfur bonds, are very useful in practical applications [12]. For example, dimethyl phenacylsulfonium salts can form stable sulfur ylides, which have aroused great interest among researchers [13–15]. David recently reported the synthesis of trisubstituted cyclopropanes by condensation of sulfonium ylides with α,β-unsaturated aldehydes [16]. Aryl acylsulfonium bromides can also be used to synthesize 1,4-dicarbonyl compounds by condensation with arylglyoxals [17]. Acylsulfonium bromide salts are normally prepared from dimethyl sulfide and an α-bromoketone. In this study, we report a new and efficient route to aryl acylsulfonium salts and α-bromoacylsulfonium salts from aryl methyl ketones using the DMSO-HBr oxidation system.

Scheme 1. Reaction of aryl methyl ketones in the DMSO-HBr system.

Sulfonium salts 3 have never been reported as key intermediate products in DMSO-HBr oxidations of arylmethyl ketones. The formation of salt 3 confirms that the production of bromine and the bromination reaction take place in the DMSO-HBr system. Catalytic oxidation of methyl ketones by vinyl bromide in DMSO is another piece of evidence to support this approach [18]. The mechanism of DMSO-HBr mediated oxidation is still under intense and controversial discussion. Sulfonium salt 3 provides a new basis and reference mechanism for the oxidation of methyl ketones in DMSO-HBr system.

2. Results and Discussion

The transformation of aryl acetones 1a–h into sulfonium salts 3a–h in moderate yields (48%–75%, Table 1) was achieved in a mixture of 48% hydrobromic acid (HBr) and DMSO in a sealed flask over 10 h. White solid precipitates could be collected after addition of ether and ethyl acetate to the reaction mixtures. These crystalline solids were readily soluble in water, but insoluble in organic solvents. The 1H- and 13C-NMR spectra of the products clearly indicated the formation of the sulfonium salt derivatives. Various substituents at the aromatic ring have been shown to affect the yields of the
final products. What’s more, in the case of aryl acetones 3e–h, α-bromoacysulfonium salt products were obtained.

Table 1. Synthesis of dimethyl aryl acysulfonium bromides 3a–h.

| Entry | Aryl Acetone | Product | Yield (%) |
|-------|--------------|---------|-----------|
| a     | O           | O       | 69        |
| b     | O           | O       | 57        |
| c     | O           | O       | 71        |
| d     | O           | O       | 62        |
| e     | O           | O       | 75        |
| f     | O           | O       | 55        |
| g     | O           | O       | 57        |
| h     | O           | O       | 48        |

Table 2 collects data on the reaction of acetophenone (1a) with DMSO–HBr under different experimental conditions. It is revealed that the reaction time and temperature were very crucial for the synthesis of 3. An increased molar ratio of HBr not only increases the yield, but also shortens the reaction time. We thus obtained the best results using 3 equiv. of HBr (aq 48%) at 40 °C in the presence of DMSO (Table 2, entry 2).

The proposed mechanism for the synthesis of acysulfonium bromides 3 is shown in Scheme 2. First, oxidation of HBr with DMSO results in the formation of molecular bromine, which reacts with the arylacetone 1 to form the α-bromoketone 4a and α-dibromoketone 4b. In addition, dimethyl sulfide is also produced in this oxidation step. The whole reaction is performed in a sealed flask to minimize the escape of dimethyl sulfide which on condensation with bromoketones 4a and 4b affords the sulfonium salt 3.
Table 2. Optimization of reaction conditions for synthesis of sulfonium salt 3a.

| Entry | Molar Ratio Methyl Ketone/HBr | Time (h) | Temp. (°C) | Yield (%) |
|-------|-------------------------------|----------|------------|-----------|
| 1     | 1:3                           | 6        | 40         | 41        |
| 2     | 1:3                           | 10       | 40         | 69        |
| 3     | 1:3                           | 12       | 40         | 56        |
| 4     | 1:3                           | 10       | 55         | 45        |
| 5     | 1:1                           | 12       | 40         | 12        |
| 6     | 1:5                           | 6        | 40         | 61        |

*All reactions were heated in a sealed flask containing the same volume of DMSO; † Isolated yields.

Scheme 2. Mechanism for the formation and decomposation of acylsulfonium bromide 3.

The oxidation of aryl methyl ketones with DMSO is complicated and two mechanisms were proposed recently in the literature. According to the Kornblum reaction, α-bromoketone 4a is rapidly converted into arylglyoxal 2 through an alkoxydimethyl sulfonium intermediate 5 [8]. Floyd et al. have suggested that the hydrolysis and bromination of α-bromoketone 4a gives an α-hydroxy-α-bromo intermediate, which is hydrolyzed to glyoxal 2 [3]. In the present paper, sulfonium salt 3 exists in the DMSO-HBr oxidation system. The above observations suggest that sulfonium salt 3 is also a key intermediate for synthesis of glyoxal 2, and it would be decomposed to α-bromoketone 4a and α-dibromoketone 4b by heating in an open system. As shown in Scheme 2, both the reaction of 4a with DMSO and the hydrolysis of 4b yield the same product 2. Sulfonium salt 3 is soluble in water and DMSO, and its conversion is very rapid in an open system. In this study, a series of acylsulfonium bromide salts were successfully synthesized by controlling the reaction conditions and precipitation using ether and ethyl acetate.

3. Experimental

3.1. General

All reagents for synthesis were purchased from TCI Shanghai Co. (Shanghai, China) unless otherwise specified. Melting points were measured on an XT-4 melting point apparatus (Beijing Tech Instrument, Beijing, China) and are uncorrected. NMR spectra were measured using a Bruker AQS AVANCE 300 MHz spectrometer ((Bruker Instruments, Karlsruhe, Germany) with tetramethylsilane
as the internal standard. Mass spectra were recorded with an Agilent Technologies MSD SL Trap mass spectrometer (Agilent Technologies, Palo Alto, CA, USA) with an ESI source coupled with an 1100 Series HPLC system. Silica gel GF254 plates (Yantai Chemical Industries, Yantai, China) was used for thin-layer chromatography (TLC). UV light (λ 254 nm) detection was used.

3.2. General Procedure for the Synthesis of Sulfonium Salts 3a–h

Aryl methyl ketones 1a–h (39.5 mmol) were dissolved in a mixture of 48% hydrobromic acid (20 mL) and dimethylsulfoxide (20 mL) in a sealed flask. This mixture was heated at 40 °C for 10 h and then cooled. After the addition of ethyl acetate (15 mL) and ethyl ether (15 mL), the solution was stirred for another 0.5 h and allowed to stand overnight in the ice box. The precipitate was filtered and washed with ethyl ether to afford the desired sulfonium salt as white crystals.

**Dimethylphenacylsulfonium bromide** (3a). Yield: 69%, mp 145–147 °C (lit. [3] 148–152 °C).

1H-NMR (DMSO-d6) δ 8.03 (d, 2H, J = 7.5 Hz, Ar-H), 7.8 (t, J = 7.4 Hz, 1H, Ar-H), 7.64 (t, J = 7.7 Hz, 2H, Ar-H), 5.53 (s, 2H, CH2), 2.99 (s, 6H, 2CH3); 13C-NMR (DMSO-d6) δ 191.37, 133.96, 135.09, 129.22, 128.70, 52.88, 24.63; MS (ESI) m/z: 180.9 [C10H13OS]+.

**Dimethyl-(4-hydroxyphenacyl)sulfonium bromide** (3b). Yield: 57%, mp 151–152 °C.

1H-NMR (DMSO-d6) δ 10.83 (s, 1H, OH), 7.90 (d, J = 8.7 Hz, 2H, Ar-H), 6.94 (d, J = 8.7 Hz, 2H, Ar-H), 5.41 (s, 2H, CH2), 2.95 (s, 6H, 2CH3); 13C-NMR (DMSO-d6) δ 189.21, 163.84, 131.58, 125.40, 115.84, 52.68, 24.57. MS (ESI) m/z: 197.2 [C10H13O2S]+; Anal. calcd. for C10H13BrO2S: C, 43.33; H, 4.73. Found: C, 43.19; H, 4.62.

**Dimethyl-(3-bromophenacyl)sulfonium bromide** (3c). Yield: 71%, mp 142–143 °C.

1H-NMR (DMSO-d6) δ 8.20 (s, 1H, Ar-H), 8.01 (t, J = 7.8 Hz, 2H, Ar-H), 7.61 (t, J = 7.9 Hz, 1H, Ar-H), 5.52 (s, 2H, CH2), 2.98 (s, 6H, 2CH3); 13C-NMR (DMSO-d6) δ 190.54, 137.53, 136.02, 131.46, 131.31, 127.59, 122.44, 52.73, 24.74. MS (ESI) m/z: 259.1 [C10H12BrOS]+; Anal. calcd. for C10H12Br2OS: C, 35.32; H, 3.56. Found: C, 35.25; H, 4.37.

**Dimethyl-(furan-2-acyl)sulfonium bromide** (3d). Yield: 62%, mp 132–135 °C.

1H-NMR (DMSO-d6) δ 8.21 (d, J = 1.1 Hz, 1H, Ar-H), 7.74 (d, J = 3.7 Hz, 1H, Ar-H), 6.87 (dd, J = 3.7, 1.6 Hz, 1H, Ar-H), 5.28 (s, 2H, CH2), 3.00 (s, 6H, 2CH3); 13C-NMR (DMSO-d6) δ 178.64, 149.99, 149.58, 121.96, 113.51, 50.70, 24.70. MS (ESI) m/z: 171.2 [C8H11O2S]+; Anal. calcd. for C8H11BrO2S: C, 38.26; H, 4.41. Found: C, 38.34; H, 4.58.

**Dimethyl-(a-bromo-4-methylphenacyl)sulfonium bromide** (3e). Yield: 75%, mp 144–145 °C.

1H-NMR (DMSO-d6) δ 7.99 (d, J = 7.8 Hz, 2H, ArH), 7.86 (s, 1H, CH), 7.47 (d, J = 7.8 Hz, 2H, Ar-H), 3.07 (s, 3H, SCH3), 3.01 (s, 3H, SCH3), 2.44 (s, 3H, Ar-CH3); 13C-NMR (DMSO-d6) δ 188.74, 146.83, 129.96, 129.33, 128.76, 56.20, 24.71, 24.63, 21.51. MS (ESI) m/z: 273.2 [C11H14BrOS]+; Anal. calcd. for C11H14Br2OS: C, 38.26; H, 4.13. Found: C, 38.07; H, 3.99.

**Dimethyl-(a-bromo-4-nitrophenacyl)sulfonium bromide** (3f). Yield: 55%, mp 138–139 °C.

1H-NMR (DMSO-d6) δ 8.49 (d, J = 8.9 Hz, 2H, Ar-H), 8.30 (d, J = 8.8 Hz, 2H, Ar-H), 7.94 (s, 1H, CH), 3.07
Dimethyl-(α-bromo-4-chlorophenacyl)sulfonium bromide (3g). Yield: 57%, mp 152–153 °C. 1H-NMR (DMSO-d6) δ 8.09 (d, J = 8.5 Hz, 2H, Ar-H), 7.83 (s, 1H, CH), 7.78 (d, J = 8.5 Hz, 2H, Ar-H), 3.06 (s, 3H, SCH3), 3.00 (s, 3H, SCH3); 13C-NMR (DMSO-d6) δ 188.23, 140.63, 131.61, 130.14, 129.60, 56.25, 24.65; MS (ESI) m/z: 293.2 [C10H11BrClOS]+; Anal. calcd. for C10H11Br2ClOS: C, 32.07; H, 2.96. Found: C, 32.15; H, 2.85.

Dimethyl-(α-bromo-4-fluorophenacyl)sulfonium bromide (3h). Yield: 48%, mp 141–143 °C. 1H-NMR (DMSO-d6) δ 8.17 (dd, J = 8.8, 5.4 Hz, 2H, Ar-H), 7.77 (s, 1H, CH), 7.54 (t, J = 8.8 Hz, 2H, Ar-H), 3.05 (s, 3H), 2.98 (s, 3H); 13C-NMR (DMSO-d6) δ 190.12, 166.05 (d, J = 254.5 Hz), 131.96 (d, J = 10.0 Hz), 130.83 (d, J = 2.8 Hz), 116.46 (d, J = 22.3 Hz), 52.82, 24.71; MS (ESI) m/z: 277.1 [C10H11BrFOS]+; Anal. calcd. for C10H11Br2FOS: C, 33.54; H, 3.10. Found: C, 33.46; H, 3.21.

4. Conclusions

In conclusion, the combination DMSO and aqueous HBr has been utilized here for the efficient synthesis of dimethyl aryl acylsulfonium bromides from aryl methyl ketones under mild reaction conditions. In some cases, α-bromoacylsulfonium salt products were obtained.

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Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds 3e–h are available from the authors.