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REACTION OF ALDEHYDES AND KETONES WITH t-BUTYL BROMIDE-DIMETHYL SULPHOXIDE

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Abstract - Reacting aldehydes and ketones with the "Bu^tBr-Me_2SO" system produces the corresponding α-bromoderivatives 2. In the case of ketones, where more than one regioisomer is possible, bromination is obtained exclusively at the more highly substituted α-position. With slight modifications of the reaction conditions (addition of Me_2S, Me_2SO) it is possible to obtain "in situ" formation of either dimethyl(2-oxo-2-phenylalkyl)sulphonium salts 3 or of α-methylthioderivatives 4. Dimethyl(1-methyl-2-oxo-2-phenylethyl)sulphonium bromide (3h) during crystallization undergoes spontaneous resolution of the two enantiomers, as demonstrated by single crystal X-ray analysis and absolute configuration assignment.

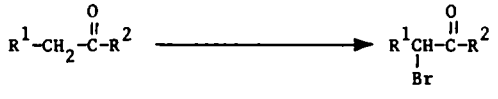
We have recently reported that the "Bu^tBr-Me_2SO" system can give rise either to "Pummerer-like" reactions or to bromination.[1] The substrates studied were carboxylic acids,[2,3] N-protected aminoacids,[2,3,4] phenols,[1] indoles,[5] alkenes and alkynes.[6] In particular, during the aforementioned studies, it became evident that in the presence of a base the t-butyl bromide activated dimethyl sulphoxide could react with the nucleophiles produced in situ from acid substrates giving alkylation reactions, whereas in the absence of a base the reagent was slowly releasing a brominating species, capable of electrophilic attack on π-systems.[1,5,6]

In order to explore furtherly the efficiency of the new brominating species generated in situ, we have investigated the reactions of "Bu^tBr-Me_2SO" with aldehydes and ketones with the aim of introducing a bromo or a sulphur containing substituent α to the carbonyl group, which is often a key step in organic synthesis.[7] Although recent advances have removed some of the difficulties associated with the methods of bromination and sulphenylation of aldehydes and ketones,[8] the convenience and mildness of this method may provide further improvement.

Herein we report the details of this method as well as a tentative rationalization of the mechanisms involved in these reactions.

RESULTS AND DISCUSSION

Aliphatic aldehydes and ketones (1a-d) were reacted with the "Bu^tBr-Me_2SO" reagent (in the molar ratio substrate : Me_2SO : Bu^tBr = 1:2:4) at 65°C for 6 h. With both substrates bromination was obtained with a very high yield, without further oxidation of the aldehydes. In the case of ketones, bromination occurred exclusively at the more highly substituted α-position. No reaction was observed with carboxylic acids and esters under the same conditions. Results are reported in Scheme 1 and Table 1.



1 → 2

a R^1 = n-C_5H_{11}, R^2 = H
b R^1 = n-C_6H_{13}, R^2 = H
c R^1 = n-C_4H_9, R^2 = CH_3
d R^1 = n-C_5H_{11}, R^2 = CH_3

Scheme 1

Table 1.
Raction of aldehydes and ketones with the "Bu^tBr-Me_2SO" reagent[a]

Substrate (1)	Reaction time(h)	Product[b]	Yield[c]	B.p. or m.p. °C/mm Hg
a $n\text{-}C_6H_{13}CHO$	6	$n\text{-}C_5H_{11}CHBrCHO$	93	75-77/12
b $n\text{-}C_7H_{15}CHO$	6	$n\text{-}C_6H_{13}CHBrCHO$	90	100-102/20
c $n\text{-}C_5H_{11}COCH_3$	6	$n\text{-}C_4H_9CHBrCOCH_3$	88	81-83/16
d $n\text{-}C_6H_{13}COCH_3$	6	$n\text{-}C_5H_{11}CHBrCOCH_3$	90	92-94/12
e CH_3COOH	-	-	0	
f $C_6H_5CH_2COOCH_3$	-	-	0	
g $C_6H_5COCH_3$	24	$C_6H_5COCH_2\overset{+}{S}(CH_3)_2Br^-$	90	132
h $C_6H_5COCH_2CH_3$	7	$C_6H_5COCHBrCH_3$	90	134-136/20
i $C_6H_5COCH(CH_3)_2$	24	$C_6H_5COCBr(CH_3)_2$	70	117-120/20
j $C_6H_5CH_2COCH_3$	5	$C_6H_5CHBrCOCH_3$ and $C_6H_5COCOCH_3$	d	126-128/15 108-110/15

[a] Substrate: Me_2SO:Bu^tBr = 1:2:4 at 65°C

[b] Known products with b.p. or m.p. and spectroscopic properties in agreement with the literature.

[c] Yields reported are referred to isolated products, obtained by distillation. GLC yields were in the range 95-98%.

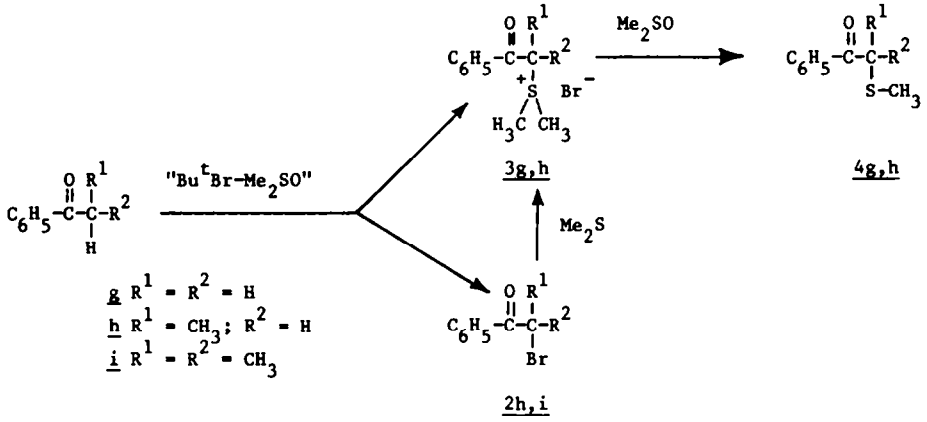
[d] Difficult to estimate owing to the fast oxidation rate of the bromo-derivative.

With alkyl aryl ketones the reaction can proceed further. With 1-phenylpropanone (1h) and 1-phenyl-2-methylpropanone (1i) α-bromination was observed under the same conditions, whereas with acetophenone (1g) the reaction proceeded quantitatively to dimethylphenacylsulphonium bromide (3g) (see Table 1 and Scheme 2).

On treatment with Me_2S the 2-bromo-1-phenylpropanone (2h) was converted in situ to the corresponding dimethyl(1-methyl-2-oxo-2-phenylethyl)sulphonium bromide (3h), whereas the 2-bromo-2-methyl-1-phenylpropanone (2i) did not react further.

The two sulphonium salts 3g,h were isolated as white crystals and examined by X-ray analysis.[9] R,S-(±)-dimethyl(1-methyl-2-oxo-2-phenylethyl)sulphonium bromide (3h) during the course of crystallization underwent spontaneous resolution of the two enantiomers, as demonstrated by single crystal X-ray analysis and absolute configuration assignment.[10]

Finally, with 1-phenylpropan-2-one, the 1-bromoderivative, present as the main product until 3-4 h, was oxidized to the diketo deriva



Scheme 2

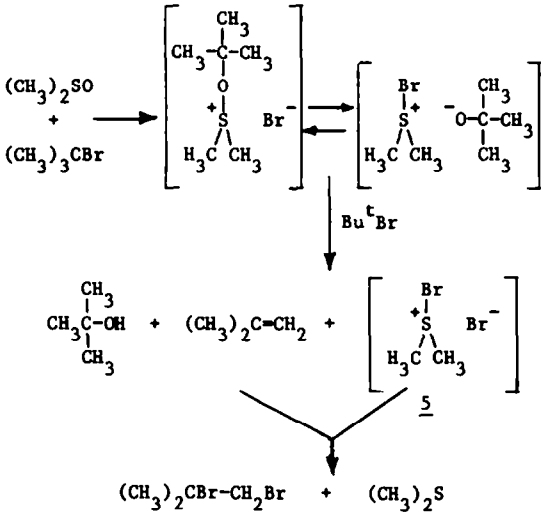
tive,[11] as the reaction proceeded.

When Me_2SO was added in excess, the two sulphonium salts 3h,g reacted giving the corresponding α-methylthioderivatives 4h,g.

Aliphatic α-bromo ketones and aldehydes did not react unless when an excess of Me_2S and Me_2SO was added and gave a mixture where α-methylthioketones and α,β-unsaturated-α-methylthioaldehydes were the main products (4a-d) (Table 2).

α-Bromination

The "Bu^tBr–Me_2SO" system releases a brominating species, able to react with the easily enolizable aldehydes and ketones, but not with carboxylic acids and esters. We have previously proposed[1] that the brominating species is bromo dimethylsulphonium bromide (5) arising from Me_2SO and Bu^tBr according to the mechanism reported in Scheme 3:



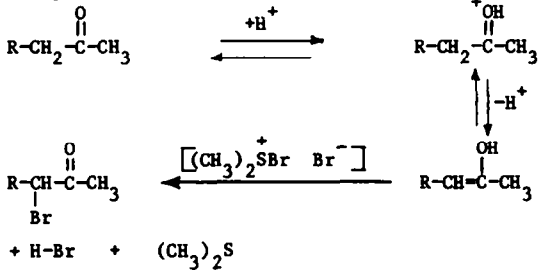
Scheme 3

We have followed the progress of the reaction of Me_2SO and Bu^tBr by ^1H NMR spectroscopy and GM. Dimethyl sulphide, t-butyl alcohol and 1,2-dibromo-2-methylpropane were actually detected, whereas no evidence of formation of other intermediates was obtained[3].

That bromodimethylsulphonium bromide is indeed able to brominate carbonyl derivatives was demonstrated with the following experiment. When bromodimethylsulphonium bromide, preformed from Me_2S and bromine, reacted with 1-phenylpropanone in CH_2Cl_2, the reaction was very fast and effective: it gave rise to the α-bromoderivative quantitatively within 1 h. The longer time required for the reaction of the same substrate with Me_2SO and Bu^tBr suggests that the brominating species bromodimethylsulphonium bromide is released slowly in the system.

The first step for the reaction is postulated to be a fast conversion of the keto into the enol form, following the initial protonation of the carbonyl oxygen (Scheme 4).

When two α-positions are present in the ketone, bromination always occurs exclusively on the more highly substituted α-position, which is the kinetically and thermodynamically favoured position according to the mechanism normally accepted for acid catalysis[12] (Scheme 4).



Scheme 4

Synthesis of dimethyl(2-oxo-phenylalkyl)sulphonium salts and α-thiomethylation

When acetophenone was reacted with "Bu^tBr–Me_2SO", phenacyl bromide could not be detected since the reaction proceeded further to dimethyl phenacylsulphonium bromide (3g), which precipitated from the reaction mixture. The reaction occurring is probably a SN_2 performed by the nucleophile dimethyl sulphide, formed during the reaction of Scheme 4 on the activated phenacyl halide (2g).

If the reaction is performed with diphenyl sulphoxide and Bu^tBr, the less nucleophilic and more bulky $(C_6H_5)_2S$ formed does not give the nucleophilic substitution and phenacyl bromide may be actually isolated.

Indeed, the reaction is very sensitive to steric effects. With 1-phenylpropanone the reaction with "Bu^tBr–Me_2SO" ends at the bromination step. Only by addition of an excess of Me_2S it was possible to obtain the sulphonium salt 3h in quantitative yield.

The more substituted 2-bromo-2-methyl-1-phenylpropanone (2i), obtained from 2-methyl-1-phenylpropanone (1i) did not react even in the presence of excess Me_2S.

The polarity of the system and the reactant ratio are crucial to determine the final composition of the reaction products. If Me_2SO is added in excess, dimethylphenacyl and dimethyl-(1-methyl-2-oxo-2-phenylethyl)sulphonium bromide (3g and 3h) are maintained in solution and can

react further as methylating agents towards Me_2S, giving the corresponding α-methylthio-derivatives 4g,h (70% yield) and trimethylsulphonium bromide (which has been actually isolated) (Scheme 2 and Table 2).

The less electrophilic aliphatic α-bromoketones and aldehydes do not react with excess Me_2S unless in the presence of excess Me_2SO, giving a product mixture, where α-methylthioketones and α-methylthio-α,β-unsaturated aldehydes were the main components. The mechanism of formation of the latter compounds is still under study.

Table 2. α-Thiomethylation

Reagent (1)	Product (4)	Yield (%)
a $n\text{-}C_6H_{13}CHO$	$n\text{-}C_4H_9CH{=}C(SCH_3)\text{-}CHO$	36
b $n\text{-}C_7H_{15}CHO$	$n\text{-}C_5H_{11}CH{=}C(SCH_3)\text{-}CHO$	38
c $n\text{-}C_5H_{11}COCH_3$	$n\text{-}C_4H_9CH(SCH_3)COCH_3$	43
d $n\text{-}C_6H_{13}COCH_3$	$n\text{-}C_5H_{11}CH(SCH_3)COCH_3$	41
g $C_6H_5COCH_3$	$C_6H_5COCH_2SCH_3$	70
h $C_6H_5COCH_2CH_3$	$C_6H_5COCH(SCH_3)CH_3$	80

In conclusion, although many brominating systems are available in the literature, bromination by "Bu^tBr-Me_2SO" represents a new and convenient procedure for the synthesis of α-bromoketones, where more than one regioisomer are possible, and of α-bromoaldehydes, which are normally difficult to prepare. Such a procedure, which avoids the need for enolate formation, provides additional versatility and should have special promise with base sensitive molecules. With slight modifications, the reagent can provide an easy and efficient method of "in situ" conversion of ketones (specially alkyl aryl ketones) into either sulphonium salts or α-methyl thioderivatives.

EXPERIMENTAL

M.ps were determined on a Büchi apparatus and are uncorrected. UV spectra were measured with a Jasco IVIDEC 505 spectrophotometer. IR spectra of solids (KBr) and liquids (film) were recorded on a Perkin Elmer model 437 spectrophotometer. ^1H NMR spectra were obtained on a Varian EM 360 spectrometer with Me_4Si as internal standard. Mass spectra were recorded on a Finnigan 1020 spectrometer, at 60 eV sometimes associated to gaschromatography. Analytical TLC was carried out on Merck Kieselgel PF_{254} coated plates. GLC was performed on Varian Aerograph 1200, 1400, and 2700 instruments, using flame ionization detectors and a SE 30 - 5% column with programmed temperature from 80° to 250°C.

Commercial grade reagents were used without any purification or drying procedure.

α-Bromination of ketones and aldehydes

20 mmol of ketone or aldehyde were dissolved in 40 mmol of Me_2SO and 80 mmol of Bu^tBr and heated at 60-65°C under reflux and stirring. The reaction mixture was extracted three times with a H_2O-Et_2O mixture. The organic phase was washed twice with water, dried on $MgSO_4$, evaporated to small volume, analyzed by GLC and distilled under vacuum. Products were identified by the usual spectroscopic methods or by comparison with commercial samples, when available. M.ps or b.ps were in agreement with the literature. Yields were calculated first by GLC, then on the isolated products obtained by distillation.

Preparation of dimethyl(2-oxo-2-phenylethyl)-sulphonium bromide (3g)

20 mmol of acetophenone were dissolved in 40 mmol of Me_2SO and 80 mmol of Bu^tBr. The solution was refluxed at 65°C and continuously stirred for 24 h. The white precipitate formed was filtered, recrystallized from a Et_2O/CH_3OH mixture and spectroscopically characterized.

M.p 132°C. UV (EtOH): 249 (ε 12200) and 283 (4800) nm. IR (KBr): 3060, 2960 and 1680 cm^{-1}. ^1H NMR (DMSO-d_6): 8.15-7.30 (5H, m, C_6H_5), 5.75 (2H, s, CH_2) and 3.10 (6H, s, CH_3). (MS m/z, intensity in %): 198-200 (1), 166 (71), 120 (2), 105 (100) and 77 (75).

Preparation of dimethyl(1-methyl-2-oxo-2-phenyl ethyl)sulphonium bromide (3h)

The crude of the reaction between 1-phenyl propanone and "Bu^tBr-Me_2SO" was extracted with a H_2O/Et_2O mixture (3 times). The organic phase; washed twice with water and dried on $MgSO_4$, added of an excess of Me_2S, was heated at 65°C and continuously stirred for 24 h. The sulphonium salt precipitated in the reaction course. It was filtered, recrystallized from a Et_2O/CH_3OH mixture and spectroscopically characterized (yield 70%).

M.p. 129°C. UV (EtOH) 253 (12700) and 276 (2820) nm. IR (KBr): 3060, 2990 and 1680 cm^{-1}. ^1H NMR (DMSO-d_6): 8.20-7.45 (5H, m, C_6H_5), 6.40 (1H, q, SCH), 3.13 (3H, s, SCH_3), 3.10 (3H, s, SCH_3) and 1.75 (3H, d, CH_3). (MS m/z, intensity in %): 212-214 (4), 180 (6), 134 (16), 105 (100) and 77 (95).

Preparation of α-methylthioaldehydes and ketones: general procedure

The α-bromoderivative, separated by distillation, was added of an excess of Me_2S and Me_2SO (1:3:3 molar ratio) and heated at 65°C at reflux for 24 h (ketones) or 10 h (aldehydes). The reaction mixture was cooled, extracted with a H_2O/Et_2O mixture (3 times). The combined ethereal extracts were reduced to small volume and analyzed by GLC. The main products were the α-methyl thioketones or the α-methyl-α,β-unsaturated aldehydes, which were purified by distillation and characterized by spectroscopic methods.

3-Methylthio-3-hepten-2-al (4a). B.p. 140-150/760°C/mm Hg (decomposes). UV (EtOH): 221

(10877) nm. IR (film) 2960, 1690 and 1600 cm^{-1}. ^1H NMR (CCl_4): 9.30 (1H, s, HCO), 6.85 (1H, t, =CH, J=7 Hz), 2.60 (2H, q, $CHCH_2$, J=7 Hz), 2.30 (3H, s, SCH_3), 1.20-1.60 (6H, m, $(CH_2)_2$) and 0.90 (3H, t, CH_3). MS (m/z, intensity in %): 158 (M^+, 75), 143 (18), 129 (15), 113 (25), 102 (42), 87 (85), 81 (95) and 45 (100).

3-Methylthio-3-octen-2-al (4b). B.p. 155-160/760°C/mm Hg. UV (EtOH): 221 (10730) nm. IR (film): 2960, 1690 and 1600 cm^{-1}. ^1H NMR (CCl_4): 9.30 (1H, s, HCO), 6.85 (1H, t, =CH, J=7 Hz), 2.60 (2H, q, $CHCH_2$, J=7 Hz), 2.30 (3H, s, SCH_3), 1.20-1.60 (6H, m, $(CH_2)_3$) and 0.90 (3H, t, CH_3). MS (m/z, intensity in %): 172 (M^+, 85), 157 (32), 143 (10), 127 (30), 116 (30), 87 (85), 81 (75), 47 (30) and 45 (100).

3-Methylthio-2-heptanone (4c). B.p. 190-196/760°C/mm Hg. IR (film) 2950 and 1710 cm^{-1}. ^1H NMR (CCl_4): 3.00 (1H, t, CHS), 2.20 (3H, s, CH_3CO), 1.85 (3H, s, SCH_3), 1.36-1.25 (6H, m, $(CH_2)_3$) and 0.90 (3H, t, CH_3). MS (m/z, intensity in %): 160 (M^+, 10), 117 (45), 103 (12) and 61 (100).

3-Methylthio-2-octanone (4d). B.p. 205-210/760°C/mm Hg. IR (film) 2950 and 1710 cm^{-1}. ^1H NMR (CCl_4): 3.00 (1H, t, CHS), 2.20 (3H, s, CH_3CO), 1.85 (3H, s, SCH_3), 1.35-1.25 (8H, m, $(CH_2)_3$) and 0.90 (3H, t, CH_3). MS (m/z, intensity in %): 174 (M^+, 12), 131 (72), 83 (43) and 61 (100).

2-Methylthio-1-phenylpropan-1-one (4h). B.p. 268-272/760°C/mm Hg. UV (EtOH): 243 (11700) and 266 (3750) nm. IR (film): 3080, 2920 and 1685 cm^{-1}. ^1H NMR (CCl_4): 8.10-7.15 (5H, m, C_6H_5), 4.15 (1H, q, CHS), 1.85 (3H, s, SCH_3) and 1.40 (3H, d, CH_3). MS (m/z, intensity in %): 180 (M^+, 6), 134 (27), 105 (99), 77 (100) and 51 (76).

Preparation of 2-methylthio-1-phenylethan-1-one (4g).

Dimethylphenacylsulphonium bromide was dissolved in Me_2SO (or CH_3OH), and heated under reflux at 65°C for 30 h. Then the reaction mixture was cooled, extracted with a H_2O/Et_2O mixture. The product was purified on TLC plates using hexane/EtOAc (95:5) as eluent and spectroscopically characterized.

B.p. 255-260/760°C/mm Hg. UV (EtOH): 243 (12100) and 266 (3950) nm. IR (film) 3080, 2920 and 1680 cm^{-1}. ^1H NMR (CCl_4): 8.05-7.10 (5H, m, C_6H_5), 3.60 (2H, s, CH_2) and 2.10 (3H, s, SCH_3). MS (m/z, intensity in %): 166 (M^+, 18), 120 (8), 105 (100) and 77 (58).

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