Pergamon

Tetrahedron Letters, Vol. 35, No. 51, pp. 9569-9572, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02112-0

Medium Effects in Unsymmetrical Disulfides Compounds Synthesis from Bunte Salts

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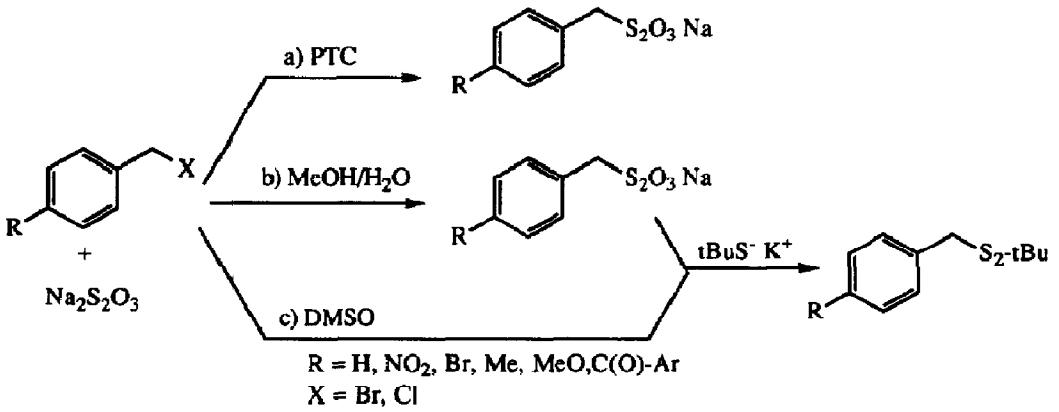
Abstract *: The present study allows us to show the influence of the polarity of the reaction medium as well as the electron-donating and withdrawing character of para substituents of α-halogeno toluenes in the preparation of unsymmetrical disulfides using the Bunte salt method. The use of DMSO as a reaction solvent permits not only to dissociate the sodium salt, but also to synthesise unsymmetrical disulfides from compounds which are inadequate using conventional methods*

The increasing interest for sulfur-containing compounds in various fields varying from biology[1,2], biomedical chemistry[3-5] to lubrication[6-8] is at the origin of the development of new active molecules. Although preparation methods are well documented[9-13], the synthesis of alkyl benzyl disulfides from sodium thiosulfate is more complex because of the low solubility of this salt in organic solvents[14].

In the present work, we studied the influence of the reaction medium and the nature of the para substituent in the preparation of benzylic unsymmetrical disulfides using Footner's method[14]. Our study led us to use DMSO as reaction solvent, a solvent that turns out to be original in its ability to dissociate sodium thiosulfate. This synthesis, not yet described in the literature, seems to be particularly efficient for the preparation of unsymmetrical disulfides, especially in the case of alkyl benzyl compounds substituted by electron-donating groups in the *para* position.

Therefore, among the different methods proposed in the literature, we used and adapted Footner's method[14] which consists in adding, in a homogeneous medium, a thiolate and an alkyl thiosulfate also known as Bunte salt[15]. Although the aliphatic halides lead always to Bunte salts in good yields[16], our results show that for some benzylic *para*-substituted halides, these salts are not formed. In a homogeneous medium (methanol/water), the strong solvation of the nucleophile would slow down and even prevent the reaction process. In order to ascertain this assumption, we have chosen to synthesise the Bunte salts from *para* substituted benzylic compounds in a heterogeneous medium by PTC[17] and the disulfides in homogeneous medium.



The results are reported in Table 1.

starting materials		N° (d)	Bunte salts	Unsymmetrical disulfides	
			PTC	Methanol/water	DMSO
R	X		Yield (%) (a)	Yield (%)	Yield (%) (c)
H	Br	1	100	70 (b)	-
NO2	Br	2	100	-	62
Br	Br	3	100	37 (b)	62
Me	Br	4	45	68	75
MeO	Cl	5	46	0	66
O-C(O)-Ar	Br	6	0	0	51

Table 1 : Synthesis of Bunte salts of *para*-substitued-α-halogeno toluenes in heterogeneous medium (PTC) and of unsymmetrical disulfides in homogeneous medium (methanol/water and DMSO).
(a) : [17], (b) : [14], (c) : experimental results, [d] : [18].

Heterogeneous medium :

Phase Transfer Catalysis (toluene/water) :

In order to carry out the reaction in a non protic solvent (the sodium thiosulfate salt being completely insoluble in this case), we have proceeded by PTC. Under these conditions, our results show that the reaction is sensitive to the nature of the para-substituent (donating or withdrawing character) : for the electron-withdrawing groups (**2**) and even for the unsubstituted derivative (**1**), we obtain the corresponding disulfide in quantitative yields while the yield slow down in case of **4** and **5**, and no reaction occurs for **6**.

Homogeneous medium :

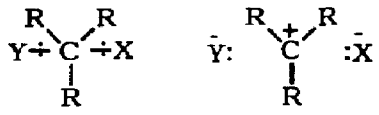
Dipolar protic solvent (methanol/water) :

In mixed dipolar protic solvent (methanol/water), Nambury[19] has shown that the presence of an electron-withdrawing group leads to an important decrease of the yield compared to the unsubstituted benzylic derivative. With methyl electron-donating groups, our results produce a satisfactory yield. Some limitations have been encountered with methoxy and carboxylic ester groups giving rise to solvolysis of the halides.

Dipolar aprotic solvent (DMSO) :

With DMSO, we observed a notable yields improvement, especially for the electron-donating groups. Moreover, we obtain the expected disulfides with no by-products.

The essential step for the synthesis of unsymmetrical disulfides is the formation of Bunte salts probably from an SN_2 reaction[20]. Parker[21] clearly shows that the structure of the transition state is dependent on the electron-withdrawing or donating character of the substituent. With electron-withdrawing groups, the transition state leads to an undissociated conformation (type I), whereas for electron-donating groups, the transition state adopts a dissociated structure (type II), which confers to the reaction a behaviour close to SN_1.



Type I Type II

These inquiries lead to a better understanding of the yield variations of the reaction.

• A heterogeneous medium which favors the SN_2[22] explains the quantitative yields obtained with the electron-withdrawing groups.

• A homogeneous polar medium leads to a improvement of the yield of the reactions which go through a type II intermediate. In a protic polar medium however, the strong nucleophile solvation leads to a decrease of its reactivity and proves the absence of results. On the other hand, our aprotic conditions which stabilise the intermediate and do not solvate the nucleophile, explains the better yields obtained even in presence of methoxy or ester substituents.

The importance of the solvent polarity and the nature of the *para* groups in the synthesis of Bunte salts or unsymmetrical disulfides from *para*-substituted-α-halogeno toluenes have been clearly shown. The use of DMSO as a reaction solvent leads to the total dissociation of the sodium thiosulfate and to the formation of unsymmetrical benzylic disulfides whatever the nature of the substituent in the *para* position. Moreover, the reaction proceeds by a *one pot* synthesis.

Typical procedure

The starting materials are commercially available except for the compound with the carboxylic ester substituent we have prepared according to usual procedures (protection of the hydroxylic group by carboxylic ester group and bromation).

Bunte salt synthesis :

In a 500 ml round bottomed flask equipped with stirrer and reflux condenser, 5 g (20 mmol) of sodium thiosulfate is dissolved in the presence of 200 ml of DMSO. The mixture is heated to 80°C until the sodium thiosulfate dissolved. After cooling, 20 mmol of the halide is added dropwise. The mixture is stirred at 80°C during 4 hours.

Thiolate synthesis :

A mixture of 1.2 g (20 mmol) of potassium hydroxide in 20 ml of water and 1.8 g (20 mmol) of 2-methyl-2-propanethiol is refluxed for 30 minutes. The resulting thiolate is maintained at 0°C.

Disulfide synthesis :

The aqueous mixture of the thiolate is added to the aqueous solution of alkyl thiosulfate and the mixture is stirred during one hour. 200 ml of chloroform is added to the residue and the organic layer is washed several times with water. The organic layer is dried on sodium sulfate and the solvent was removed under vacuum.

Acknowledgements

The financial support provided by SOLLAC (Florange), CED (Montataire) and IRSID (Unieux) is gratefully acknowledged.

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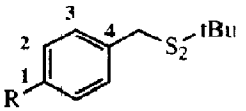
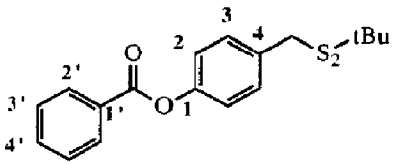
18. Spectroscopic data.

The ^1H NMR and ^{13}C NMR analyses of the disulfides 1-6 have been obtained on a Bruker AC 250. The solvent used is $CDCl_3$ and the chemical shifts are measured in ppm in relation to the internal standard (TMS).The following nomenclature has been used for the ^{13}C NMR :





R = NO_2, Br, H, Me, MeO

[1] : ^{13}C NMR : 136.0 (C1) ; 129.0 (C2) ; 128.0 (C3) ; 127.0 (C4) ; 45.2 (CH_2-S_2) ; 47.9 (C) ; 29.7 (CH_3). ^1H NMR : 7.2 (m, 4H) ; 3.9 (s, 2H) ; 1.3 (s, 9H). [2] : ^{13}C NMR : 146.7 (C1); 123.3 (C2) ; 129.7 (C3) ; 145.0 (C4) ; 43.8 (CH_2-S_2) ; 48.0 (C) ; 29.6 (CH_3). ^1H NMR : 7.6 (m, 4H) ; 4 (s, 2H) ; 1.5 (s, 9H). [3] : ^{13}C NMR : 121.0 (C1) ; 131.3 (C2) ; 130.7 (C3) ; 136.2 (C4) ; 44.5 (CH_2-S_2) ; 47.8 (C) ; 29.8 (CH_3). ^1H NMR : 7.3 (m, 4H) ; 3.8 (s, 2H) ; 1.2 (s, 9H). [4] : ^{13}C NMR : 137.0 (C1) ; 129.3 (C2) ; 129.2 (C3) ; 134.0 (C4) ; 45.6 (CH_2-S_2) ; 21.3 (CH_3) ; 48.0 (C) ; 30.2 (CH_3). ^1H NMR : 7.1 (m, 4H) ; 3.9 (s, 2H) ; 1.3 (s, 9H) ; 2.3 (s, 3H). [5] : ^{13}C NMR : 158.3 (C1) ; 113.3 (C2) ; 129.8 (C3) ; 128.7 (C4) ; 44.6 (CH_2-S_2) ; 54.5 (CH_3) ; 47.3 (C) ; 30.0 (CH_3). ^1H NMR : 7 (m, 4H) ; 4 (s, 2H) ; 1.2 (s, 9H) ; 3.8 (s, 3H). [6] : ^{13}C NMR : 150.0 (C1) ; 121.6 (C2) ; 130.0 (C3) ; 134.9 (C4) ; 164.9 (CO) ; 44.8 (CH_2-S_2) ; 47.9 (C) ; 29.9 (CH_3) ; 130.2 (C1') ; 130.1 (C2') ; 128.4 (C3') ; 133.5 (C4'). ^1H NMR : 7-8 (m, 4H) ; 4 (s, 2H) ; 1.5 (s, 9H).

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(*Received in France* 4 *October* 1994; *accepted* 24 *October* 1994)