Alkylation of Sulfoximines and Related Compounds at the Imino Nitrogen under Phase-Transfer Conditions

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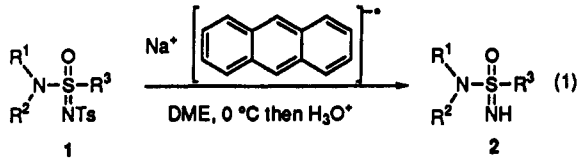
We have previously described a convenient method for the preparation of *N*-hydridosulfoximine compounds by treatment of the corresponding *N*-tosyl compounds **1** with sodium anthracenide (eq 1).[1] This procedure gives access

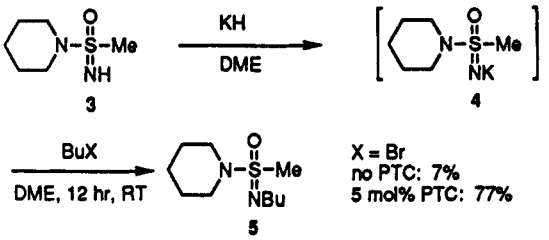


R^1R^2N = pyrrolidinyl, 1-piperidinyl, dibutylamino, R^3 = methyl

the *N*-hydrido-*N'*,*N'*-dialkyl sufonimidamides (**2**), a new class of sulfoximine analogs. Since sulfoximines have been found to be useful reagents for a variety of applications including the preparation of chiral molecules with a high enantiomeric purities,[2] we wanted to explore the possibilities offered by these new sulfonimidamides. This led us to face the task of alkylating the sulfonimidamides at the imino nitrogen since the most successful developments employed *N*,*S*-dimethyl-*S*-phenylsulfoximine. This paper reveals a new method for the preparation of sulfoximine compounds alkylated at the imino nitrogen which displays more versatility than the previously described procedures.

Direct alkylation of sulfoximine compounds at the imino nitrogen is not a trivial task because the steric and electronic effects of the adjacent tetracoordinate sulfur dramatically decrease the nucleophilicity of the nitrogen. *N*-Methyl or *N*-ethyl compounds are available by use of strongly electrophilic alkylating reagents such as trialkyloxonium salts[3] or methyl trifluoromethanesulfonate.[4] The Eschweiler–Clarke reaction provides an efficient method of N-methylation in the sulfoximine series.[5] Unfortunately, in our hands, treatment of the related sulfonimidamides under Eschweiler–Clarke conditions resulted in degradation of the starting materials. Potentially a more general procedure would consist of treatment of *N*-alkali metal salts with alkyl halides. Unfortunately, anions such as *N*-sodio sulfoximines usually display poor reactivity in such alkylations and completion of the reaction usually

Scheme I



requires the use of dipolar aprotic solvents at elevated temperatures.[6] We considered that the utility of such reactions might be enhanced by the addition of a phase-transfer catalyst (PTC).[7]

A simple preliminary experiment established the validity of this rationale (Scheme I). Addition of sulfonimidamide **3** dissolved in 1,2-dimethoxyethane (DME) to potassium hydride gave the corresponding potassium salt **4** as a suspension. Treatment of this suspension with 1-bromobutane for 12 h at room temperature gave only a 7% isolated yield of N-butylated product **5**. Similar treatment in the presence of 5 mol % tetrabutylammonium bromide as a PTC increased the yield of **5** to 77%.

Table I summarizes the results obtained when this phase-transfer alkylation procedure was applied to sulfonimidamides **6** (G = 1-piperidinyl and 1-pyrrolidinyl) and sulfoximine **6** (G = Ph). Tetrabutylammonium bromide, benzyltriethylammonium chloride, and tributylhexadecylphosphonium bromide all performed equally well as catalysts at 5 mol %. Benzylic, allylic, and primary alkyl bromides reacted smoothly in this process. In contrast, typical secondary bromides did not give alkylated products, although moderate yields were observed when an activated secondary bromide was used.

The data in Table II show that leaving groups such as chloride and sulfonates may be used as alternatives to bromide. However, iodide was found to be slightly less efficient. This phenomenon, already observed by others in liquid–liquid[8] as well as solid–liquid[9] phase-transfer catalysis, is assumed to arise from the preferential association of the iodide ion with the onium cation. As a consequence, the ion exchange capability of the PTC is markedly diminished.

Table III summarizes the metal and solvent effects observed in this process. The sodium and potassium salts derived from *N*,*N*-dibutylmethanesulfonimidamide (**8**) were treated with benzyl bromide and 5 mol % of tetrabutylammonium bromide. These reactions were repeated in three different ethereal solvents: DME, tetrahydrofuran (THF), and diethyl ether. The yields of *N*-benzyl sulfonimidamide **9** were determined by ^{1}H NMR. The potassium salt gave better results in this process than the sodium salt. With a larger atomic radius than sodium (0.96 Å vs 1.33 Å),[10] potassium salts have a stronger ionic character than the corresponding sodium salts and undergo ion exchange more readily. The ion metathesis should

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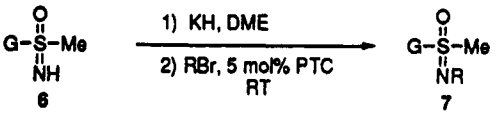
Table I. N-Alkylation of Sulfonimidamides and Sulfoximines under Phase-Transfer Catalysis



N-H sulfoximine compound 6, G =	alkylating agent, R =	PTC[a] (5 mol %)	reaction time (h)	alkylated product	yield (%)
1-piperidinyl	n-C_4H_9Br	NBr	15	**7a**	87
	n-$C_7H_{15}Br$	NBr	15	**7b**	97
	$C_6H_5CH_2Br$	PBr	6	**7c**	78
	EtO_2CCH_2Br	PBr	10	**7d**	58
	$EtO_2CCH(CH_3)Br$	PBr	10	**7e**, **7f**[b]	30, 15
	c-$C_6H_{11}Br$	NBr	8	**7g**	0
	s-C_4H_9Br	NBr	9	**7h**	0
1-pyrrolidinyl	n-C_4H_9Br	NBr	10	**7i**	94
	$C_6H_5CH_2Br$	NCl	10	**7j**	94
	p-$CH_3OC_6H_4CH_2Br$	NBr	10	**7k**	97
	(2-naphthyl)CH_2Br	NBr	10	**7l**	98
phenyl	n-C_4H_9Br	NBr	10	**7m**	91
	n-$C_7H_{15}Br$	NBr	9	**7n**	97
	CH_2=$CHCH_2Br$	NBr	10	**7o**	93
	$C_6H_5CH_2Br$	NBr	8	**7p**	90

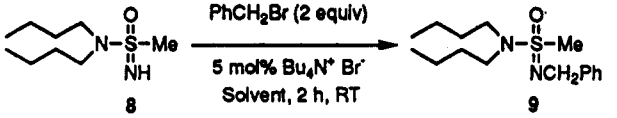
[a] NBr, tetrabutylammonium bromide; NCl, benzyltriethylammonium chloride; PBr, tributylhexadecylphosphonium bromide. [b] Major and minor diastereomers.

Table II. Leaving Group Effect in the Butylation of 3 in the Presence of 5 mol % n-Bu_4NBr (Scheme I)[a]

butylating agent	yield of 5 (%)	butylating agent	yield of 5 (%)
n-BuBr	77	n-BuOTs	81
n-BuCl	79	n-BuOMs	77
n-BuI	57		

[a] Reactions were conducted at rt in DME for 12 h.

Table III. Solvent and Metal Effects in the N-Benzylation of 8



metal hydride	solvent	yield of 9 (%)	metal hydride	solvent	yield of 9 (%)
KH	DME	97	NaH	DME	30
	THF	66		THF	13
	Et_2O	47		Et_2O	12

also be facilitated if the metal is better solvated by a more coordinating solvent. This is in accordance with the solvent effect observed since DME turned out to be the solvent of choice among three conventional ether solvents.

Another feature of this reaction is its excellent chemoselectivity. Although an excess of potassium hydride and alkyl halide were employed in all cases, no significant amounts of C-alkylated material were ever observed. This renders the process efficient and explains the high yields generally obtained.

Experimental Section

General Procedure for Sulfoximine and Sulfonimidamide N-Alkylation. A solution of sulfoximine or sulfonimidamide[1] in DME (2 mL/mmol) was added rapidly to a suspension of potassium hydride (35% wt/wt suspension in mineral oil, 1.05 to 1.2 equiv) in DME (2 mL/mmol). The resulting suspension was stirred 15 min at rt. Then the appropriate phase-transfer catalyst (5 mol %) and alkylating reagent (1.1 to 2 equiv) were added. The reaction mixture was stirred at rt and monitored by TLC (1/9 MeOH/EtOAc). Upon completion the reaction mixture was quenched with saturated aqueous NH_4Cl, transferred to a separatory funnel, diluted with diethyl ether, and extracted with 3 N HCl. Combined acidic extracts were neutralized by careful addition of solid potassium carbonate and extracted with dichloromethane. The combined organic fractions were dried ($MgSO_4$) and filtered. Solvent removal gave the crude N-substituted product which was further purified by chromatography on silica gel. All purified *N*-alkylmethanesulfonimidamides were oily compounds. Specific conditions (PTC, alkylating agent, reaction time) and isolated yields are given in Table I.

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Supplementary Material Available: General experimental details for Tables II and III and spectroscopic and analytical data for compounds **7a–f,i–p** and **9** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.