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THE ALKYLATION AND HALOGENATION OF SULFONES CATALYZED BY HYDROXIDE ION IN APROTIC SOLVENTS

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ABSTRACT: Alkylations and halogenations of sulfones normally requiring the use of strong bases such as butyl lithium are shown to proceed smoothly and in good to excellent yield using sodium hydroxide in N,N-dimethylformamide.

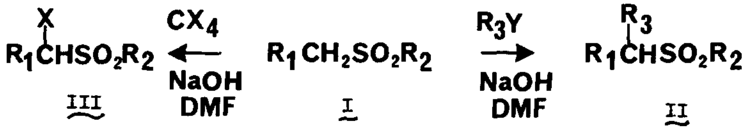
INTRODUCTION

In the course of our investigations concerning the chemistry of a recently patented class of herbicides and plant growth regulants comprising variously substituted 2-phenylmethylsulfonylpyridine-1-oxides,[1,2] we have discovered the general utility of the sodium hydroxide-N,N-dimethylformamide system in the alkylation and halogenation of active methylene sulfonyl compounds. Previously reported alkylations of this type have generally required the use of strong bases such as alkali metal amides or butyl lithium.[3-5] Halogenations using tetrahalomethanes and strong bases have led to undesired polyhalogenated and rearranged products.[6] More recently, a phase transfer system has been reported which utilizes tetrabutylammonium bromide in hexamethylphosphoric triamide/excess 50% NaOH.[7]

RESULTS

We have found the NaOH/DMF system of general utility in both alkylations and halogenations as shown in Scheme 1.[8] N,N-Dimethylformamide was used without drying.[9] The starting compounds (**I**) were obtained by methods previously published.[1,2,10] The general methods for alkylation and halogenation are illustrated in the following examples, and are further illustrated by the examples in Tables 1 and 2. Analytical data were consistent with structures proposed.[11]

Scheme 1.



The synthesis of 2-[α-(2,5-dimethylphenyl)-α-propargylmethanesulfonyl]pyridine-1-oxide (**IIf**) is described: To a well-stirred solution of sodium hydroxide (1.80g, 45.0 mmol) and

Table 1. Alkylations Using NaOH/DMF - Synthesis of **IIa**-**IIf**

R_1	R_2	R_3Y	Product	mp	%Yield
4-nitrophenyl	4-methylphenyl	$(CH_3)_2SO_4$	**IIa**	115°d	72[a]
4-*t*-butylphenyl	pyrid-2-yl	"	**IIb**	b	100
3-fluorophenyl	1-oxo-pyrid-2-yl	"	**IIc**	147-49°	59
2,5-dimethylphenyl	"	CH_3Cl[c]	**IId**	157-59°	92
"	"	Allyl Chloride	**IIe**	147-50°	74
"	"	Propargyl Chloride	**IIf**	169-70°	64

[a] Product contained 28% dimethylated adduct. [b] Syrup [c] 4 h reaction time. Methyl iodide and dimethylsulfate were also used with comparable yields and reaction times of 30-60 min.

Table 2. Halogenations Using NaOH/DMF - Synthesis of **IIIa**-**IIIf**

R_1	R_2	X	Product	mp	%Yield
phenyl	1-oxo-pyrid-2-yl	Cl[a]	**IIIa**	149-50°d	86
3-fluorophenyl	"	"	**IIIb**	160-61°d	68
4-methylphenyl	"	"	**IIIc**	166°d	78
4-*t*-butylphenyl	"	"	**IIId**	153°d	94
2,2-dichloro-1-methyl cyclopropyl	"	"	**IIIe**	188-89°d	88
naphth-2-yl	"	"	**IIIf**	160-63°	96

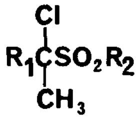
[a] alpha-bromination could also be carried out using CBr_4, for example, 2-[α-(2,5-dimethylphenyl)-α-bromomethylsulfonyl]pyridine-1-oxide was obtained from 2-(2,5-dimethylphenylmethylsulfonyl)pyridine-1-oxide in 85% yield.

propargyl bromide (5.4g, 45.4 mmol) in 25 mL of N,N-dimethylformamide was added in one portion 2-(2,5-dimethylphenylmethanesulfonyl)pyridine-1-oxide (11.0g, 39.7 mmol). The temperature reached 50° within a few minutes whereupon the reaction mixture was cooled and maintained at 30° for 1 h. The mixture was then poured into 300 mL of ice-cold water to afford a flocculent precipitate which was filtered off, washed with water and air-dried to give 10g of crude product. Crystallization from ethanol afforded 8.0g of pure **IIf**, mp 169-170° (64% yield).

The synthesis of 2-[α-(2,2-dichloro-1-methylcyclopropyl)-α-chloromethylsulfonyl]pyridine-

1-oxide (IIIe) is described: Carbon tetrachloride (1.28g, 8.3 mmol) and sodium hydroxide (0.31g, 7.6 mmol) were dissolved in 15 mL of N,N-dimethylformamide stirring at 0°. To this was added in one portion 2-(2,2-dichloro-1-methylcyclopropylmethanesulfonyl)pyridine-1-oxide (2.03g, 6.9 mmol). The reaction temperature was maintained at 0° for 35 min. The mixture was poured into 200 mL of ice-cold water, yielding a precipitate which was filtered off, washed with water and air-dried to afford 2.00g of pure IIIe, mp 188-189°dec (88% yield).

The data of Tables 1 and 2 demonstrate the ability of solvated hydroxide ion to remove the proton of a sulfonyl methylene group activated by adjacent unsaturation or electron withdrawal. The hydroxide ion/aprotic solvent system has several advantages over the prior art: The use of strong bases and anhydrous conditions is avoided;[12] the reaction is complete within a short time (alkylation: 15-60 min, halogenation: 5-15 min); with the exception of IIa, where a strongly electron-withdrawing *para*-nitro group is present, only mono-alkylated or mono-halogenated products have been observed.



$R_1C(Cl)(CH_3)SO_2R_2$

	R_1	R_2
IVa	2,5-dimethylphenyl	1-oxo-pyrid-2-yl
IVb	phenyl	"

Type IV α-disubstituted adducts were obtained using the methods described. The synthesis of IVa, using methyl iodide and 2-[α-(2,5-dimethylphenyl)-α-chloromethylsulfonyl]pyridine-1-oxide was carried out in 44% yield. Furthermore, it was possible to carry out both halogenation and alkylation in the same flask: low temperature chlorination of 2-phenylmethylsulfonylpyridine-1-oxide followed by methylation at ambient temperature (using carbon tetrachloride and methyl iodide) afforded 2-(1-chloro-1-phenylethylsulfonyl)pyridine-1-oxide (IVb) in an overall yield of 77%.

ACKNOWLEDGMENT

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8. Sodium hydroxide (97-98%) was freshly ground to a powder prior to use. Potassium hydroxide (85%) was found to be inferior to sodium hydroxide in the methylation of 2-(2,5-dimethylphenylmethanesulfonyl)pyridine-1-oxide, affording **IId** in 59% yield.

9. Other polar, aprotic solvents such as N,N-dimethylacetamide and dimethylsulfoxide were found suitable for use in these reactions.

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11. Analytical Data:

    Elemental analysis for all compounds (**II**a-f,**III**a-f,**IV**a,b) was within 0.3% of theoretical.

    IR Data: [**II**a-f,**III**a-f,**IV**a,b] ν (SO_2) 1140-1160 cm^{-1}, 1300-1340 cm^{-1}
    [**II**c-f,**III**a-f,**IV**a,b] ν (N-O) 830-850 cm^{-1}, 1260-1300 cm^{-1}

    H-NMR Data: (Chemical shifts given in ppm)

IIa	1.85(3H,d,J=7Hz),2.45(3H,s),4.4(1H,q,J=7Hz),7.2-8.3(8H,m)
IIb	1.35(9H,s),1.75(3H,d,J=7Hz),4.65(1H,m),7.2-8.5(8H,m)
IIc	1.85(3H,d,J=7Hz),5.55(1H,q,J=7Hz),6.8-8.4(8H,m)
IId	1.65(3H,d,J=7Hz),2.3(3H,s),2.5(3H,s),6.0(1H,q,J=7Hz),7.05-8.4(7H,m)
IIe	2.3(3H,s),2.45(3H,s),2.85(2H,t,J=7Hz),4.7-6.05(4H,m),7.1-8.3(7H,m)
IIf	1.85(1H,s),2.45(3H,s),2.7(3H,s),3.2(2H,m),6.2(1H,t,J=7Hz),7.0-8.5(7H,m)
IIIa	7.15(1H,s),7.2-8.5(9H,m)
IIIb	7.05-8.45(9H,m)
IIIc	2.35(3H,s),7.0(1H,s),7.1-8.4(8H,m)
IIId	1.3(9H,s),7.0(1H,s),7.2-8.3(8H,m)
IIIe	1.7(3H,s),2.1(2H,q,J=7Hz),6.2(1H,s),7.4-8.3(4H,m)
IIIf	7.1-8.3(11H,m)
IVa	2.20(3H,s),2.65(3H,s),2.80(3H,s),6.95-8.3(7H,m)
IVb	2.70(3H,s),7.1-8.2(9H,m)

12. The reaction system can tolerate the presence of water to a limited degree. If more than several percent water is present in the solvent, hydrolysis of the sulfone becomes a significant problem (reactions carried out in 50/50 mixtures of DMF and 50% NaOH afforded low yields of methylated products [25-40%]).

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