Convenient Synthesis of N-Sulfinylamines Catalytic Effects of Tertiary Amines

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Catalytic effects of tertiary amines on N-sulfinylation of *p*-toluenesulfonamide, *p*-toluidine, and *p*-toluamide have been investigated by proton NMR studies. Though the catalytic effects were dependent on the substrates, 4-dimethylaminopyridine, pyridine and triethylamine exerted stronger catalytic effects than imidazole and N,N-dimethylaniline. Among the substrates employed, *p*-toluenesulfonamide turned out to be catalyzed greater than *p*-toluidine and *p*-toluamide.

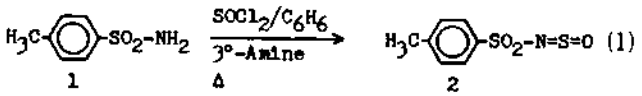
Introduction

Numerous methods have been developed to prepare N-sulfinylamies[1] which are widely used in organic synthesis.[2,3] The known methods are quite successful in yields but still there have been remaining problems to be solved in the preparative methods of N-sulfinylamines. For examples the standard preparative method of compound 2 in which compound 1 and excess of thionyl chloride are refluxed, takes from several days[4] to 8 hours[1b] for the reaction to be finished, while Hori[5] reports that addition of catalytic amount of N,N-dichlorobenzenes ulfonamide (1%) to the mixture of *p*-toluenesulfonamide and thionyl chloride requires 16 hours of reflux to complete the reaction. Kim's methods make the reaction finished in less than 30 minutes but require either excess of imidazole[6] or equivalent amount of di-2-pyridylsulfite[7] as a *trans*-sulfinylation agent.

In this investigations, our aim was to find good catalysts and compare their efficiencies towards N-sulfinylation of derivatives of aromatic amines, such as *p*-toluenesulfonamide, *p*-toluidine, and *p*-toluamide, by carrying out proton nmr studies. In order to follow the progress of the N-sulfinylation by nmr spectra, aromatic amines which have a methyl group on benzene ring were chosen.

Results and Disscussion

Our previous recognitions[8] that triethylamine exerts catalytic effect on sulfinylation gave an impetus to undertake the present work. As a matter of fact, it is well known that tertiary amines catalyze nucleophilic substitutions.[9,10] With this in mind, 4-dimethylaminopyridine (DMAP), pyridine, triethylamine (TEA), imidazole, and N,N-dimethylaniline (DMA) were chosen as catalysts. The results from the reaction of 1 with thionyl chloride in the presence of various tertiary amines (equation 1) are listed in Table 1.



1 2 (1)

It can be seen in Table 1 that N-sulfinylation of 1 is enhanced to a great extent dependending on tertiary amines. For examples, N-Sulfinylation is completed in less than an hour by either DMAP or pyridine, while it takes more than 35 hours to complete 70% of reaction in a control experiment

Table 1. Catalystic Effects of Tertiary Amines on N-Sulfinylation of 1

Catalyst	Reaction time (hour)	Conversion %*
DMAP	< 1	100
Pyridine	< 1	100
TEA	1.5	90
Imidazole	1.5	90
DMA	1.5	60
-**	35	70

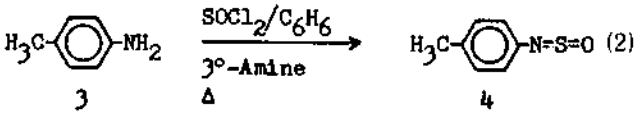
*NMR yield. **Excess of $SOCl_2$ was used without solvent.

in which no tertiary amine is present (Table 1). The results of control experiment obtained in this work well corroborates with the earlier reports[4] that several days of reflux are needed. The sequence of catalytic activities of tertiary amines are as follows.

Pyridine = DMAP > TEA > Imidazole > DMA

Reaction time and the corresponding conversion(%) in Table 1 were determined from the ^{1}H-nmr spectra. For an example the progress of reaction when pyridine was employed as a catalyst is shown in Figure 1 where a peak at 1.85 ppm is grown up at the expense of a peak at 1.95 ppm as the reaction proceeds finally the latter being coalesced to the former. It needs to be pointed out that the spectra in Figure 1 were taken directly from an aliquot of the reaction mixture containing benzene as a solvent. When dichloromethane is employed as a solvent instead of benzene, a growing and a disappearing peak are observed at 2.5 and 2.4 ppm respectively. The solvent effects on the chemical shift of compound 1 and 2 are quite large by about 0.6 ppm.

Similarly N-sulfinylation of *p*-toluidine(3) were carried out (equation 2). The effects of tertiary amines on the formation of 4 are summarized in Table 2. It can be seen that N-sulfinylation of 3 is completed in 10-40 minutes depending on tertiary amines used.



3 4 (2)

The faster reaction of 3 than 1 is well explained by the dif-

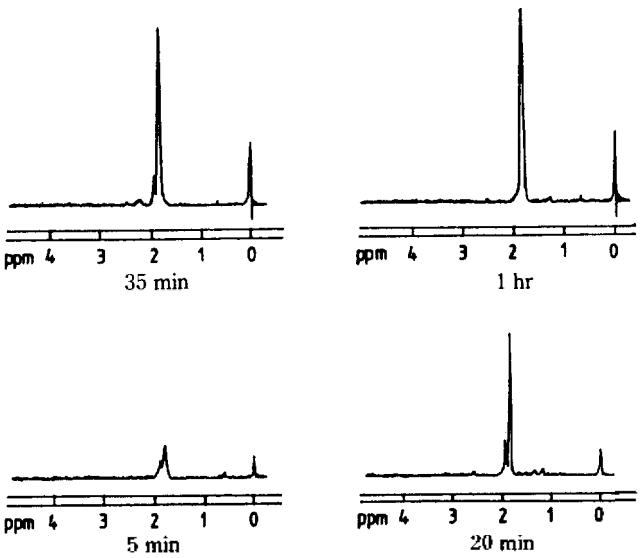


Figure 1. Time dependence of N-Sulfinylation of *p*-toluenesulfonamide in the presence of pyridine

Table 2. Catalytic Effects of Tertiary Amines on N-Sulfinylation of 3

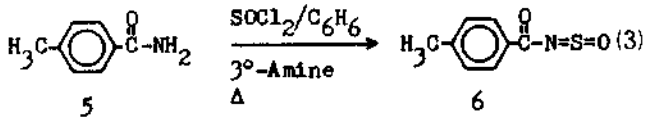
Catalyst	Reaction Time (min)	% Conversion*
DMAP	10	100
Pyridine	15	100
TEA	20	100
Imidazole	30	100
DMA	40	100
—**	60	100

*Determined by ^{1}H-NMR spectra. **Excess of $SOCl_2$ was used without solvent.

ferences in the nucleophilicities between the two compounds. The sequence of catalytic activities of tertiary amines in N-sulfinylation of 3 are as follows.

DMAP > Pyridine > TEA > Imidazole > DMA

This method has been extended to 5 (equation 3), where there are again catalytic effects of tertiary amines (Table 3), though smaller than those obtained in equation 1.



5 6

The sequence of catalytic activities of tertiary amines in N-sulfinylation of 5 are as follows.

TEA = DMAP > Pyridine > Imidazole > DMA

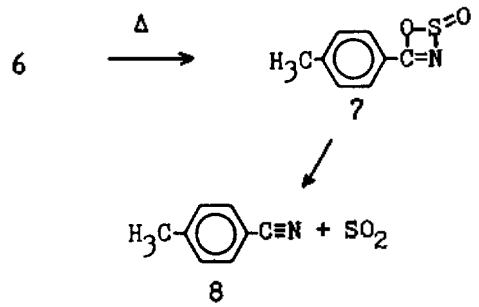
Noteworthy is the thermal unstability of 6, which can be understood by the lower activation energy resulting from the driving force that is gained by the decomposition of compound 6 to stable compound 8 (Scheme 1).

We have observed increasing amount of *p*-tolunitrile (8) upon both reflux time and temperature. Therefore in many

Table 3. Catalytic Effect of Tertiary Amines on N-Sulfinylation of 5

Catalyst	Reaction time	% Conversion*
TEA	1 hr 20 min	100
DMAP	1 hr 20 min	100
Pyridine	1 hr 30 min	95
Imidazole	1 hr 30 min	90
DMA	1 hr 30 min	80
—**	2 hr	50

*Determined by ^{1}H-NMR spectra. **Excess of $SOCl_2$ was used without solvent.



Scheme 1.

instances our trials to purify 6 by Kugelrohr distillation above 100 °C under reduced pressure ended up to get 8. However, it needs to be pointed out that a reaction shown in equation 3 is free from thermal decomposition due to short reaction period and insufficient reaction temperature.

As is discussed in reactions (equations 1-3), the larger catalytic activities of DMAP, pyridine, and TEA than imidazole and DMA (Table 1-3) are generally in accord with relative nucleophilicities between them.[11] Also it is seen in Table 1-3 that the relative sensitivities of substrates upon catalysts (tertiary amines) are as follows.

p-Toluenesulfonamide > *p*-Toluamide > *p*-Toluidine

The relative order shown above can also be understood by the relative nucleophilicities among the substrates. Catalysis of a tertiary amine on N-sulfinyation reaction is obviously believed to be similar to that of imidazole in ester hydrolysis.[12] The procedure developed in this work will give wide applications in synthetic organic reactions.

Experimental

^{1}H-NMR spectra were taken on either a Varian EM 360-A or a Bruker AC 80 FT spectrometer. IR and UV spectra were recorded on JASCO A-1 and Beckmann UV-5260 spectrophotometer, respectively. All experiments were carried out under nitrogen to avoid ambient water as much as possible and before use each solvent and thionyl chloride were purified by distillation with appropriate drying agents. *p*-Toluenesulfonamide was prepared from *p*-toluenesulfonyl chloride by the known procedure.[13] Commercially available *p*-toluidine *p*-toluamide, and tertiary amines were used without further purification.

Reaction Procedure.

Three main procedures (Procedure A-C) have been carried out to study N-Sulfinylation reaction of

p-toluenesulfonamide, *p*-toluidine, and *p*-toluamide in the presence of tertiary amines as catalysts. Procedure A in which nmr studies are employed, is a standard one and its results are mainly discussed in this paper. Prodedure B has been used to check 100% conversion of *p*-toluenesulfonamide and *p*-toluamide. Procedure C in which excess of triethylamine is used as HCl acceptor turned out to be unsuccessful since triethylamine itself participated as a catalyst.

(Procedure A). Each of *p*-toluenesulfonamide, *p*-toluidine, and *p*-toluamide is reacted with thionyl chloride in the presence of one of the tertiary amines such as 4-dimethylaminopyridine, pyridine, triethylamine, imidazole, and N,N-dimethylaniline. Therefore 15 experiments and 3 control reactions (without any tertiary amine) are required in order ot get a complete data. Each experiment is repeated at least twice to get reproducible data.

Following is a typical procedure for the N-sulfinylation of compound 1 in the presence of pyridine as a catalyst.

To a flask containing dry benzene (10 mL) is added 1 (500 mg, 2.9 mmol). Thionyl chloride (0.25 m*l*, 3.4 mmol) and pyridine (23 mg, 0.29 mmol) are introduced rapidly at the beginning of reflux. At time intervals of 5-, 20-, 35-, and 60 minutes, an aliquot (1 m*l*) of reaction mixture is taken out for the ^{1}H-NMR spectra.

(Procedure B). Each of *p*-toluenesulfonamide and *p*-toluamide is made to react with thionyl chloride in the presence of a tertiary amine as described in Procedure A. In this procedure, the reaction is continued until no precipitate is obtained, where the reaction is completed as checked by ^{1}H-NMR spectrum. The results obtained in this procedure are utilized to compare the catalytic efficiencies of tertiary amines.

(Procedure C). To the reaction mixture (solvent: dichloromethane 10 m*l*) containing equimolar amount (2.9 mmol) of *p*-toluenesulfonamide and HCl acceptor (triethylamine) is added one of tertiary amines (10 mol%) as a catalyst followed by thionyl chloride (2.9 mmol). The progress of N-sulfinylation as is checked by ^{1}H-NMR spectra was not so much different compared to that obtained from control experiment in which all the conditions are the same except the absence of a catalyst (tertiary amine). Therefore the results of this procedure were discarded.

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