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THE REACTION OF ANIONS OF PRIMARY AMINES AND HYDRAZONES WITH *p*-TOLUENESULFONYL AZIDE

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Abstract—The conversion of anions of aliphatic and aromatic primary amines to the corresponding azides by the *diazo transfer* reaction with tosyl azide is reported. Anions of amides do not give the acyl azides while those of hydrazones are converted to the diazoalkanes presumably via the corresponding N-azidimes. The mechanisms of these transormations are discussed.

THE direct conversion of compounds containing activated methylene groups to the corresponding diazoalkanes is known as the *diazo transfer* reaction.[1] *p*-Toluenesulfonyl azide (tosyl azide) has been used in most cases as the diazo transfer agent although azidinium salts,[2] nitrous oxide[3] and even diazoalkanes[4] and aryl azides[5] have been shown to effect this conversion. Although the first examples of this reaction date back to the work of Dimroth[6] and Curtius,[7] the preparation of diazocyclopentadiene from the reaction of cyclopentadienide anion with tosyl azide[8] was the first case in which two nitrogens specifically replaced two H atoms. Over the past 5 years, Regitz and his students and other groups[9] have extended the scope and the utility of this reaction.

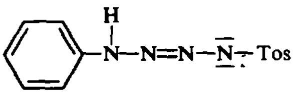
We have recently reported the transfer of two nitrogens to primary amines[10] and hydrazones,[11] and this paper describes in detail the results of our investigations.

RESULTS AND DISCUSSION

Prior to our initial report,[10] *diazo transfer* reactions to elements other than carbon were not known. Since amino hydrogens are not acidic to the usual bases, organometallic reagents such as methyllithium and methylmagnesium chloride were used to prepare the required amine anions. Our first experiments were carried out with methylmagnesium chloride as a base. The reaction of the chloromagnesium salts of aniline, *p*-toluidine and *p*-chloroaniline with *p*-toluenesulfonyl azide (tosyl azide) gave the corresponding aryl azides in about 50% conversion.[10] In all cases, 15–20% of tosyl azide was recovered and *p*-toluenesulfonamide was obtained as a by-product in varying yield. Owing to the reaction of the organometallic compounds with the nitro groups, *p*-nitrophenyl azide could not be isolated although the IR spectrum of the reaction mixture indicated its formation to a small extent. Benzylamine reacted with methylmagnesium chloride to give the anion which, with tosyl azide, gave benzyl azide in 26% conversion. The use of methyllithium instead of methylmagnesium chloride facilitated the isolation of the azides. Thus, a 43% yield of *p*-tolyl azide was obtained from the lithium *p*-toluidide and tosyl azide. Similarly, cyclohexyl azide was isolated in 35% yield from lithium cyclohexylamide. t-Butyl azide[12] was formed from t-butyl amine anion as indicated by the IR spectrum of the reaction mixture.

This reaction has been extended to anions of hydrazones.[11] When solutions of the anions of benzophenone, fluorenone and acetophenone hydrazones were treated with tosyl azide, the corresponding diazoalkanes were formed. They were isolated as the 3,5-dinitrobenzoate ester of the corresponding alcohols; with benzil monohydrazone, azibenzil was formed but no attempts were made to isolate it. In the case of the lithium salt of fluorenone hydrazone, the addition of tosyl azide gave what is presumably the adduct (II) as a yellow suspension. Addition of water and ether to this suspension generated diazofluorenone as indicated by the appearance of the characteristic red color. As in the reaction with amine anions, the starting hydrazones and tosyl azide were recovered in varying amounts. The possible intervention of N-azidimines in these reactions has been discussed.[11]

Although a complete and thorough investigation of the mechanism of the *diazo transfer* reaction has not been carried out, certain aspects of the mechanism may be defined. There seems to be little question that the *diazo transfer* reaction proceeds via the formation of an adduct (III) of the anion and tosyl azide. Both with aniline and with fluorenone hydrazone anion, the formation of this initial adduct was indicated. Evaporation of the solvent from the reaction mixture of the chloromagnesium salt of aniline with tosyl azide gave a yellowish solid which is presumably adduct I. Upon being heated at 100° under reduced pressure, I underwent decomposition and a mixture of phenyl azide and aniline was obtained.



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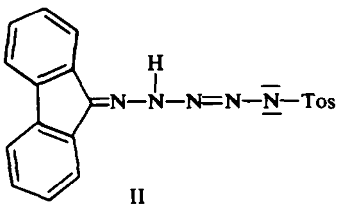


II

Phenyl azide was isolated as a yellow oil in 40% yield. The formation of the adduct (II) of fluorenone hydrazone anion and tosyl azide has been mentioned previously. Attempts to isolate the protonated adducts or derivatives thereof were unsuccessful.

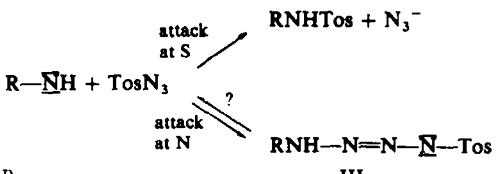
The relative stability of the $R\bar{N}H$ anion with respect to that of the tosylamide anion has been found to be of significant importance in this reaction. Earlier, we ascribed the poor conversion of *p*-nitroaniline anion to *p*-nitrophenyl azide to the reaction of the organometallic compound with the nitro group; however, the increased stability of the anion in this case may well be responsible in part for the low yield of azide. The reaction of the anion of benzamide and of t-butyl carbamate gave no detectable amount of benzoyl azide and t-butyl azidoformate.

Evidently, with such reactive intermediates, side-reactions are possible and could account for the balance of the products. In fact, with benzylamine anion, N-benzyl-*p*-toluenesulfonamide was isolated as a by-product.[13]

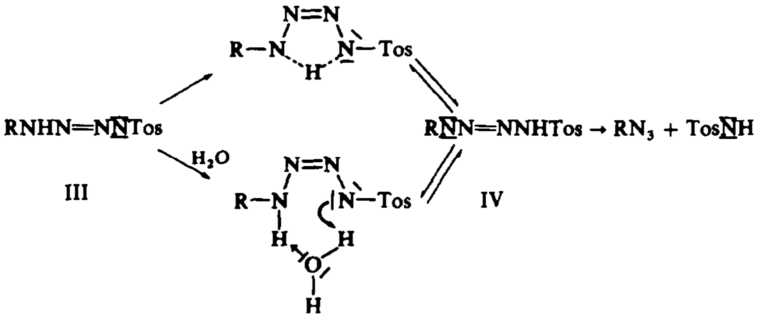
The rather remote possibility that azide formation occurred by acylation of anion followed by displacement of the tosylamide group by azide ion[14] was eliminated as follows. Treatment of N-phenyl-*p*-toluenesulfonamide with sodium azide gave no detectable amount of phenyl azide. The reaction of phenyl azide with *p*-tosylamide anion gave no tosyl azide, thus eliminating the reverse reaction as a possible cause for the recovered tosyl azide.

$$\mathrm{PhNHTos + NaN_3 \nrightarrow PhN_3 + TosNHNa}$$
$$\mathrm{PhN_3 + TosNH^- \nrightarrow PhNH^- + TosN_3}$$

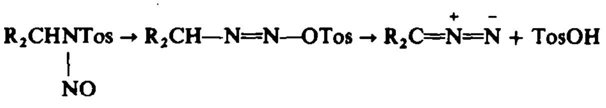
Our observations may be summarized as shown in the following equations.



(R=Alkyl, aryl, R_2^1C=N) III

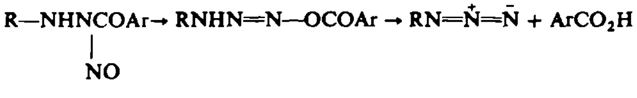


It is interesting to note the anology with the intermediates (VI) postulated for the formation of diazoalkanes from N-nitroso-N-tosylamides.[15a] Even more closely related to our reaction is the conversion of N-nitroso hydrazides to the corresponding azides.[15b] Presumably, similar intermediates (VIII) are involved also in these latter cases.



$$\mathrm{R_2CH\underset{\underset{NO}{|}}{N}Tos \rightarrow R_2CH{-}N{=}N{-}OTos \rightarrow R_2C{=}\overset{+}{N}{=}\overset{-}{N} + TosOH}$$

V VI



$$\mathrm{R{-}NH\underset{\underset{NO}{|}}{N}COAr \rightarrow RNHN{=}N{-}OCOAr \rightarrow RN{=}\overset{+}{N}{=}\overset{-}{N} + ArCO_2H}$$

VII VIII

EXPERIMENTAL

All m.p. and b.p. are uncorrected. The m.ps were determined with a Thomas–Hoover capillary apparatus. The infrared spectra were recorded on a Perkin–Elmer Infracord spectrophotometer. The organometallic reagents were used as obtained from Alpha Inorganics Inc., Beverly, Mass.

Azides from the reaction of the chloromagnesium salt[10]

General procedure. To a stirred soln of 30 mmoles of the amine in 100 ml ether, was added 10 ml of 3M soln of MeMgCl in THF. Once the evolution of gas had subsided (5 min), 6·0 g (30 mmoles) tosylazide in

10 ml ether was added dropwise. The reaction mixture was stirred at room temp for 5 hr. After the volume had been reduced to about 25%, 10 ml water was added and the reaction mixture steam-distilled. The distillate was extracted with ether. The ethereal soln was extracted with 1N HCl and washed with water. The dried soln was then stripped of solvent and the residue distilled *in vacuo* to give the corresponding azide.[10] The residue from the distillation of the azide consisted of unreacted tosyl azide, which was converted to its triphenylphosphine adduct. Acidification of the aqueous solution left in the distilling flask of the steam distillation gave *p*-toluenesulfonamide.*

Cyclohexyl azide. To a soln of 2·18 g (20 mmoles) cyclohexylamine in 150 ml THF, flushed with N_2 was added 10 ml of 2·1M MeLi in ether. After the evolution of gas had subsided. 4·0 g (20 mmoles) tosyl azide was added slowly, and the reaction mixture was stirred for an additional period of 15 min. After addition of 150 ml water, the mixture was extracted with 100 ml ether. The ethereal extract was washed successively with 2N HCl and water. The dried ethereal soln was evaporated in vacuum and the resulting oil distilled to give 0·84 g (35%), b.p. 71–73°/30 mm, lit.[16] b.p. 64–65°/21 mm. Its IR spectrum had a strong azide band at 2075 cm^{-1}.

t-Butyl azide was prepared in a similar fashion. However, owing to its volatility, no attempt was made to separate it from the reaction mixture.

p-Tolyl azide was similarly prepared from *p*-toluidine anion (from MeLi) in a 43% yield. Its IR spectrum was superimposable upon that of an authentic sample.

Phenyl azide from the pyrolysis of initial adduct (1). To a soln of 2·8 g (30 mmoles) aniline in 100 ml THF was added 10 ml 3·0M MeMgCl in the same solvent. After the evolution of gas was complete, 6·0 g (30 mmoles) tosyl azide was added and the mixture stirred for 0·5 hr. The solvent was removed *in vacuo* and the yellowish residue was heated to 100° under reduced pressure (3 mmHg). The distillate, collected at −70°, consisted of a mixture of phenyl azide and aniline. It was dissolved in ether, washed with 5% HCl and water. The dried ethereal soln was evaporated to give 1·43 g (40%) yellow phenyl azide. Its IR spectrum was identical to that of an authentic sample.

Reaction of phenyl azide with the sodium salt of p-*toluenesulfonamide.* To a soln of *p*-toluenesulfonamide, dissolved in the minimum amount of pyridine, was added an equimolar amount of MeLi. After the evolution of gas had ceased, an equimolar amount of phenyl azide was added. Work up of the reaction mixture gave an oil whose IR spectrum indicated the presence of phenyl azide (2110 and 2080 cm^{-1}). No detectable amount of tosyl azide (1178 and 1360 cm^{-1}) was present.

Diphenyldiazomethane and 1-phenyldiazomethane.† To a soln of 5·9 g (30 mmoles) benzophenone hydrazone in 150 ml THF, was added 10 ml 3·0M MeMgCl in THF. After the evolution of gas had subsided, a soln of 5·9 g (30 mmoles) tosyl azide in 20 ml THF was added. The change in color from yellow to red was accompanied by copious evolution of gas. After addition of 100 ml ether and 50 ml 10% NaOH aq, the aqueous layer was separated and acidified. *p*-Toluenesulfonamide was isolated in 48% yield. The organic layer was dried and 6·3 g (30 mmoles) 3,5-dinitrobenzoic acid was added. The color slowly changed from red to yellow. The soln was washed with a 10% Na_2CO_3 aq and then water. The dried soln was evaporated to dryness and the yellow residue dissolved in hot EtOH. Upon cooling, 5·65 g (50%) benzhydryl 3,5-dinitrobenzoate, m.p. 141–142°, was isolated as yellow crystals. A mixture m.p. with an authentic sample was not depressed. Evaporation of the filtrate, left 1·3 g (22%) unreacted benzophenone hydrazone and small amounts of tosyl azide.

Similarly, from 2·7 g (20 mmole) acetophenone hydrazone (Li salt), a 35% yield of the 3,5-dinitrobenzoate of 1-phenylethyl alcohol, m.p. 95–96°, was obtained. Its IR spectrum was superimposable upon that of an authentic sample.

From benzil monohydrazone anion, azibenzil was formed as indicated by the red orange color and the IR spectrum of the reaction mixture.

Diazofluorene. To a soln of 4·08 g (21 mmoles) fluorenone hydrazone in 150 ml THF, was added 10 ml 2·1M MeLi in the same solvent. The evolution of gas was accompanied by the appearance of a green color. After the gas evolution was complete, a soln of 4·15 g (21 mmoles) tosyl azide in 20 ml THF was added. The color gradually changed to orange and a yellow suspension was formed. The reaction mixture was poured into water and extracted with 100 ml ether. The red ethereal soln was separated from the aqueous layer which upon acidification gave 2·60 g (72%) tosylamide, m.p. 135–137°. The red ethereal layer was dried and evaporated. The red mass obtained was dissolved in hot benzene, and hexane added

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* In the case of benzylamine, N-benzyl tosylamide, m.p. 117–118°, was also isolated.

† All operations were carried out under a N_2 blanket in order to exclude the possibility of air oxidation.[17]

until the soln became cloudy. The ppt was filtered and was identified as fluorenone hydrazone (0·28 g, 20% yield). Concentration of the red filtrate gave 2·82 g (70%) diazofluorene, m.p. 93–94°.

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