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PHOTODETOSYLATION OF SULFONAMIDES INITIATED BY ELECTRON TRANSFER FROM AN ANIONIC SENSITIZER.

J.F. ART, J.P. KESTEMONT and J.Ph. SOUMILLION*

Catholic University of Louvain, Laboratory of Physical Organic Chemistry,
Place Louis Pasteur,1, B-1348 Louvain-la-Neuve, Belgium.

Summary : *A new and efficient photosensitized process for the detosylation of a wide variety of sulfonamides is presented. The excited β-naphthoxide anion is used as sensitizer, in methanol as solvent. Electron transfer from the excited naphthoxide anion to the electron-accepting sulfonamide leads, in the presence of sodium borohydride, to the recovering of amines after cleavage of the radical anion.*

The utility of the N-tosyl group as a removable protecting group for the amino function has been shown in peptide synthesis[1]. This group is stable under various experimental conditions like catalytic hydrogenation, treatment with acids, bases or reductants commonly used for the removal of other protective groups. This stability contributes to its usefulness[2], but makes it difficult to remove. Most often, metallic sodium in liquid ammonia solution is necessary[3]. Electron transfer from an arene radical anion[4] and/or electrochemical reduction[5] are other ways to cleave the sulfonamides. Nevertheless, serious side reactions have been reported and the yields in regenerated free amine are poorer[6].

Direct photolysis of sulfonamide has been reported[7] but the use of 254 nm light limits the applicability of this reaction to substrates bearing no chromophore other than the tosyl group. On irradiation in the presence of $NaBH_4$, 1-substitued 6,7-dimethoxytetraisoquinoline N-tosylate was cleaved to the corresponding tetrahydroisoquinoline readily and in high yield[8]. The photolysis proceeded via intramolecular formation of an excited donor-acceptor pair. This photolysis was extended to intermolecular reactions between a series of dimethoxyaromatics and various sulfonamides[9].

In this paper and within the frame of the study of excited naphthoxide anions as electron donors[10,11], the efficiency of an anionic photoreductive detosylation of N-tosylamides is demonstrated, according to the following equation:

$$\mathrm{ArSO_2NRR'} \xrightarrow[\mathrm{CH_3OH,\ NaBH_4}]{\mathrm{Ar'O^-}\ \ h\nu} \mathrm{ArSO_2^-} + \mathrm{HNRR'}$$

A similar reactivity was already shown in the case of the anionic photodechlorination of chloroaromatic derivatives[10].

In a first series of experiments, solutions of ß-naphtol (NOH), sodium hydroxide and N-tosyl ß-phenethylamine were irradiated in methanol with "black light phosphor" lamps (around 3500 Å). Under these conditions, the amine is recovered in very low yield but, when a coreductant ($NaBH_4$) is added to the solution before irradiation, the reaction becomes quantitative, giving beside the amine a high yield of p-toluenesulphinic acid. This last photo-product was identified by UV spectroscopy after isolation from preparative HPLC and by GC-MS analysis, after transformation by diazomethane into its methyl ester. Results of a typical run on ß-phenethylamine (entries 1 to 5) and on other tosylamides are presented in the table.

All the blank experiments necessary to show that the reaction is really photoinitiated by the excited naphtoxide anion were performed and it was demonstrated that the reaction starts from the naphthoxide singlet state. The naphthoxide fluorescence is quenched by the tosylamides and K_{sv} values between 27 and 42 M^{-1} were obtained. The quantum yields for the appearance of ß-phenethylamine (Φ_p) have been measured by using the photoreductive anionic dechlorination of 4-chlorobiphenyl as an actinometer[10]. When plotting Φ_p^{-1} versus the inverse of the tosylamide concentration a linear relationship is obtained with a slope to intercept ratio of 22. This corresponds rather well to the slope of the Stern-Volmer plot for the fluorescence quenching of the same tosylamide (27 M^{-1}).

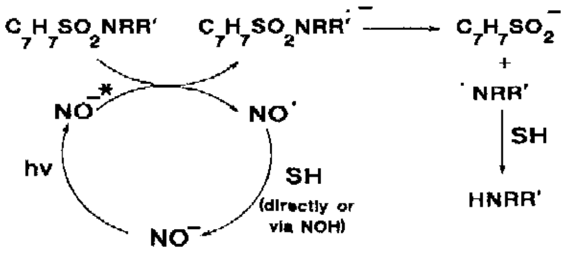
The results of the table suggest the following observations: 1) Whatever the way of measuring it (tosylamide + sulfinic acid or amine + tosylamide) the material balance is always in the vicinity of 100% and always better than 93%. 2) The amine recovery is quantitative on the basis of the chromatographic reported yields: the duration of the photo-lysis only needs to be adapted for each molecule. 3) The process of photo-cleavage is really photosensitized: the anion is efficiently regenerated as shown by the residual naphthoxide concentration measurements. Some naphthoxide anion is rapidly consumed at the very early stages of the reaction and it is then almost stable. We do not know the reason for the initial loss of about 3-10% of the anion (consumption by residual oxygen?). If this initial loss is ignored and according to the slow variations of the naphthoxide concentrations during the growth of the recovered amine, the turnover may be estimated to 75 as a minimum, in the case of ß-phenethyltosylamide.

TABLE: Photodeprotection of tosylamides in the presence of ß-naphtholate and sodium borohydride, in methanol.

Entry	Tosylamide of(a)	hrs(b)	Yields(%)(c)			
			Amine	Tosylamide	$C_7H_7SO_2H$	Naphtholate(d)
1	ß-Phenethylamine	1	46.9	53.6	40.5	93.6
2	" (5)	2	78.1	25.5	68.4	92.9
3	"	3	84.5	17.1	83.1	93.2
4	"	4	92.2	7.7	89.2	93.0
5	"	5	100	1.7	95.2	93.1
6	Benzylamine	1	25.9	69.9	26.4	98.2
7	" (6)	2	54.2	47.0	54.3	97.5
8	"	3	80.1	19.8	77.6	96.5
9	N-Methylbenzylamine	1	33.3	67.2	35.4	96.5
10	" (3)	2	80.4	16.3	79.1	95.0
11	"	3	98.3	4.1	100	93.9
12	n-Hexylamine	1	26.0	68.8	24.4	91.1
13	" (3.5)	2	50.9	47.0	52.2	80.0
14	"	3	83.1	18.7	80.1	82.1

(a) Numbers between parentheses are times, in hours, for complete tosylamide disappearance. (b) Irradiation time in hours, with 6 RUL 3500 Å "black light phosphor" lamps, in Pyrex tubes. Solutions were deaerated by a 20 min argon bubbling. $[NOH]_0=2.10^{-2}$ M, $[Tosylamide]_0=1.5-2.10^{-2}$ M, $[NaOH]_0= 4.8-5.10^{-2}$ M, $[NaBH_4]_0=5.10^{-1}$ M. (c) With respect to the engaged tosylamide. The yields are measured by GC or HPLC. (d) Residual naphtholate.

The reaction almost certainly starts by an electron transfer from the excited naphthoxide singlet to the electron-accepting tosylamides. However, uncertainties remain about the mechanism of the naphthoxide regeneration cycle and concerning the direction of the cleavage of the radical anion. One possibility of presenting the reaction mechanism is shown in the scheme: the role of $NaBH_4$ (electron or hydrogen atom transfer, salt effect) has not been fixed. Further experiments are in progress in order to delimitate the scope of the reaction and to enlight the reaction mechanism.



SH = $NaBH_4$ and MeOH

This process presents several advantages over other cleavage systems of tosylamide : 1) Being performed at room temperature, our process is milder than most of the non photochemical other ones. 2) The photochemistry relies to a common sensitizer bathochromic relative to the tosylamides, allowing selective excitation. 3) With an electron transfer starting from an anion, a radical-radical anion pair is formed: this doesn't inhibit the diffusion from the solvent cage and avoids back electron transfer and side reactions. 4) We have still to measure the relative quantum efficiency of our process compared to the one of Yonemitsu[9,12], but with a limiting value of more than 0.6, our process seems at least interesting. Furthermore, the absorption spectrum of the naphthoxide anion fits very well with the emission of black light phosphor lamps, giving efficient light collection. 5) The electron-donor sensitizer is catalytically regenerated.

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