Tetrahedron Letters,Vol.30,No.32,pp 4241-4244,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

A NEW AMINO PROTECTING GROUP READILY REMOVABLE WITH NEAR ULTRAVIOLET LIGHT AS AN APPLICATION OF ELECTRON-TRANSFER PHOTOCHEMISTRY

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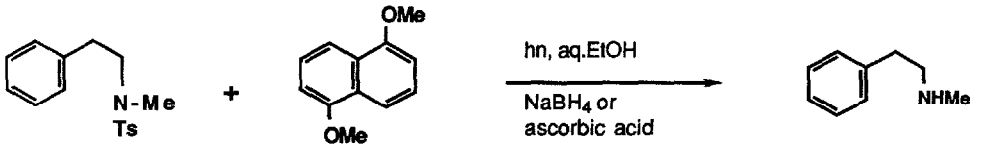
Summary As an extension of organic photochemistry via intermolecular electron-transfer in donor-acceptor pair systems between electron-rich aromatic compounds and electron-deficient tosyl groups, we report here a new protecting group for the amino function, 4-(4,8-dimethoxynaphthylmethyl)benzenesulfonyl (DNMBS) group, which is readily removed, via an intramolecular electron-transfer followed by hydrolysis, with a high quantum efficiency on irradiation with light longer than 300 nm.

Many protecting groups for the amino function, mainly removable under acidic, basic, or reductive conditions, are now available.[1] However, new protecting groups selectively removable by a method other than the usual are still required in many cases of organic synthesis, especially in the synthesis of complex natural products which have many functional groups to be protected and distinguished from each other. The MPM (4-methoxybenzyl) protecting group, recently developed in this laboratory and applied to the synthetic work of macrolide and polyether antibiotics, is selectively removable by the DDQ oxidation.[2] This method has provided a new type of protection for the hydroxy function.

As part of our study of electron-transfer photochemistry, we report here a protecting group for the amino function, 4-(4,8-dimethoxynaphthylmethyl)benzenesulfonyl (DNMBS), which is removable by irradiation with UV light of wavelength longer than 300 nm, though stable to usual acids, bases, and catalytic reduction as well as to visible light. There are two important requirements in the design of photoremovable protecting groups.[3] (1) The protecting groups should be as stable as possible under various experimental conditions other than light irradiation. (2) They should be removed by irradiation with near or low energy UV light of wavelength longer than 300 nm[4] in order to avoid side reactions that arise from light absorption by other parts of the protected molecules, because most of the usual functional groups and mono-nuclear aromatics absorb UV light of shorter wavelength than 300 nm. Colored protecting groups are also undesirable, otherwise the protected compounds must be handled in dark rooms.

Recently, electron-transfer reactions in excited donor-acceptor pairs have been widely studied and proven to be most fertile in organic photochemistry, although they are not necessarily useful in synthetic organic chemistry. We recently reported that, on irradiation with light of wavelength longer than 300 nm in the presence of dimethoxynaphthalene (2) and a reductant such as sodium borohydride, ascorbic acid, etc., the tosylamide (1) was hydrolyzed to give the corresponding amine (3) in high yield via the initial electron transfer from the

singlet excited state of the electron-donating aromatic compound (2) to the electron-accepting tosylamide (1).[6,7]

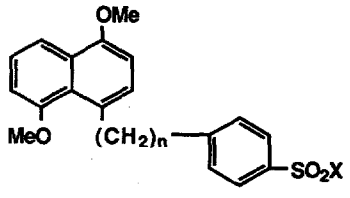


1 2 3

The tosyl group is one of the most stable protecting groups for the amino function, and reduction with an alkali metal in liquid ammonia is the only practical method for its cleavage,[1] although it is responsible for many side-reactions because of low selectivity.[10] Since the electron-transfer photolysis described above occurs only at a site able to form an ion pair with the excited electron-donor (2), the tosyl group can be distinguished even from a mesyl group because no aliphatic sulfonamide has such a reactivity.

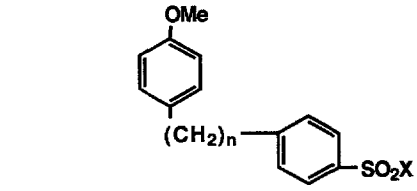
Because of the intermolecular nature of this reaction, the quantum efficiency of this photolysis is dependent upon the concentration of **1** and is not very high under the usual conditions [1(10 mM), ϕ = 0.069]. A much higher quantum yield would be expected if this photoreaction is changed to an intramolecular process, because the quantum yield of disappearance of **1** extrapolated to infinite concentration was calculated to be 0.83.[6b]

Therefore, a series of new sulfonylation reagents, **4**, **5**, and **6**, were synthesized[11] and readily reacted with amines in the usual way to give the corresponding sulfonamides, e.g., **7**, **8**, and **9**, in almost quantitative yields. The fluorescence of the dimethoxynaphthalene moiety of **7**, **8**, and **9** was quenched intramolecularly by the benzenesulfonamide moiety, and the observed fluorescence intensities were respectively 9, 15, and 43% of that of **2**. Disappearance quantum yields of **7**, **8**, and **9** by irradiation with monochromatic light at 333 nm in the presence of ammonia borane as a reductant[6b] were measured to be 0.65, 0.43, and 0.21, respectively.[12] It is obvious that the shorter the length of methylene chains connecting the donor and the acceptor, the more efficient is the photo-deprotection.

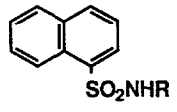


4 : n=1, X=Cl
5 : n=2, X=Cl
6 : n=3, X=Cl
7 : n=1, X=NH(CH$_2$)$_2$Ph
8 : n=2, X=NH(CH$_2$)$_2$Ph
9 : n=3, X=NH(CH$_2$)$_2$Ph
20 : n=1, X=Na

Similarly, three reagents (**10**, **11**, **12**) having methoxybenzene as the electron-donor were synthesized and photolysis of the corresponding sulfonamides (**13**, **14**, **15**) were also examined, though a shorter wavelength light (<300 nm) was required. Fluorescence intensities of **13**, **14**, and **15** were 19, 33, and 71 % of that of methoxybenzene, respectively. Disappearance quantum yields of **13**, **14**, and **15** using 283 nm light were 0.13, 0.069, and 0.044, respectively. Conjugated naphthalenesulfonamides (**16**, **17**, **18**, **19**), though synthesized more easily, gave only very poor results. Disappearance quantum yields of **16**, **17**, **18**, and **19** at 310 nm were <0.001, 0.074, 0.089, and <0.001,[14] respectively.



10 : n=1, X=Cl
11 : n=2, X=Cl
12 : n=3, X=Cl
13 : n=1, X=NH(CH$_2$)$_2$Ph
14 : n=2, X=NH(CH$_2$)$_2$Ph
15 : n=3, X=NH(CH$_2$)$_2$Ph



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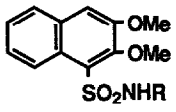

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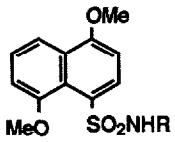


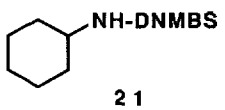
18

19

R=NH(CH$_2$)$_2$Ph

The results presented here clearly show that the DNMBS protecting group is most promising because the quantum efficiency for disappearance with near UV light is remarkably high as exemplified by the photolysis of **7** (ϕ = 0.65). Finally, in a typical preparative experiment, a 95% ethanol solution of **7** (2.5 mM) and ammonia borane (10 mM) was irradiated with light of wavelength longer than 300 nm (high pressure mercury lamp with pyrex filter); the photolysis proceeded quite smoothly and the resulting phenethylamine was isolated in 92% yield as its hydrochloride. From the residue, the original reagent (**4**) was easily regenerated in 62% yield via the sulfuryl chloride treatment of the isolated sodium sulfinate (**20**).

On irradiation as described above, the removal of DNMBS groups of **21** ~ **28** proceeded selectively to give the corresponding amines in high yields (Table). The electron accepting Ts group as well as typical protecting groups for the amino function, Bn, Boc, Cbz, Ms and Bz,[1] remained unchanged, and the electron donating indole group was also intact.



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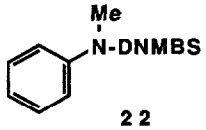

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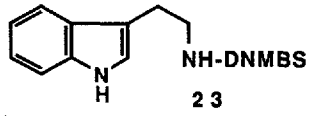

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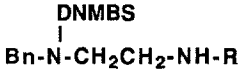
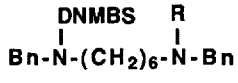


24 : R=Boc
25 : R=Cbz



26 : R=Ts
27 : R=Ms
28 : R=Bz

Table. Photolysis of DNMBS Protected Amines (21~28)

DNMBS-Amine	**21**[a]	**22**[b]	**23**[a]	**24**[a]	**25**[a]	**26**[b]	**27**[b]	**28**[b]
Yield (%)	90[c]	91[c]	78	77[c]	85[c]	82	91	90

[a] In 95% aq. EtOH. [b] In 90% aq. MeCN.
[c] *Isolated as its hydrochloride.*

In conclusion, the DNMBS protecting group may provide the first application of the concept of electron-transfer photochemistry to the area of photoremovable protection. Various applications, especially in peptide chemistry, are now under study.

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(Received in Japan 22 March 1989)