Tetrahedron Letters,Vol.29,No.36,pp 4501-4504,1988
Printed in Great Britain

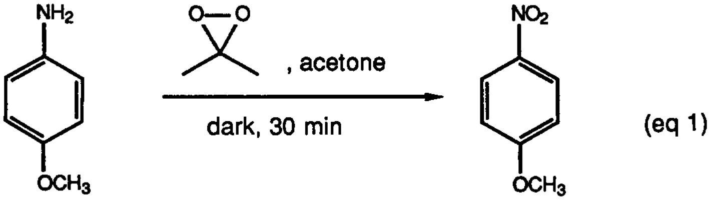
0040-4039/88 $3.00 + .00
Pergamon Press plc

THE OXIDATION OF AROMATIC AMINES IN THE PRESENCE OF "ELECTRON-RICH" AROMATIC SYSTEMS

Daniel L. Zabrowski*, Alan E. Moormann, and Kenneth R. Beck, Jr.
Gastrointestinal Diseases Research Department,
G.D. Searle & Co., Skokie, IL 60077

Summary: The oxidation of aromatic amines to the corresponding nitro substituents is performed under mild, nonacidic conditions in the presence of highly nucleophilic aromatic systems such as indoles and furans.

During the course of synthesizing compounds for a structure/activity relationship study, we needed to convert an aromatic amine into the corresponding nitro functionality. In 1986 Murray and co-workers[1] reported the transformation of p-anisidine to p-nitroanisole in excellent yield using dimethyldioxirane in acetone and conducting the reaction in the dark (eq 1).



Until this disclosure, the few examples[2] cited in the literature where an aromatic amine is oxidized to a nitro substituent in the presence of electron-donating groups required acidic conditions and ambient temperatures.

In our hands, Murray's procedure[3] for synthesizing and isolating dimethyldioxirane was not practical for large-scale synthesis. Although OXONE®, the oxidant used by Murray[3] to generate dimethyldioxirane, is inexpensive, the amount required to produce mole quantities of dioxirane would be enormous. Edwards and Curci[4], as well as Murray,[3] reported a method for forming an excess of dimethyldioxirane *in situ* under phase-transfer conditions. We wish to report that this phase-transfer reaction can be conducted at 0°C using only a slight excess[5] of OXONE® to effect the oxidative transformation. Also, by employing our modification of the reaction conditions, the oxidation of amines to nitro compounds can be performed in the presence of various "electron-rich" aromatic systems. Our results are summarized in Table 1.

®A trademark of the DuPont Corp.

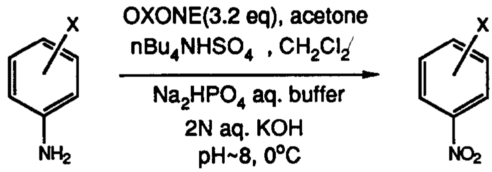


TABLE 1: OXIDATION OF SUBSTITUTED ANILINES WITH DIMETHYLDIOXIRANE

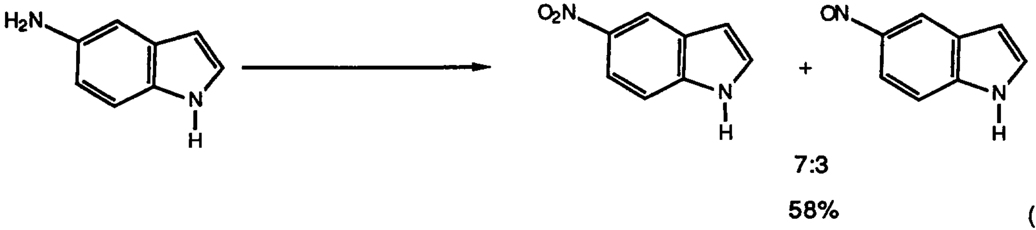
ENTRY	SUBSTRATE	YIELD[a,b]
1	2-methoxy	100
2	3-methoxy	73
3	3-methoxy-4-carbomethoxy	78
4	3,4-methylenedioxy	57
5	2,4-dimethoxy	85
6	2,5-dimethoxy	52[c]
7	3,5-dimethoxy	20[d]
8	3,4,5-trimethoxy	52

a) All percent yields were determined after liquid chromatography purification and were not optimized.
b) All compounds produced satisfactory spectral and analytical data.
c) Produced a 1:1 ratio of nitro and nitroso adducts.
d) Gave a 1:2 mixture of 3,5-dimethoxynitrobenzene and its corresponding nitroso analogue respectively.

Yields are fair to good for the majority of examples. Some nucleophilic anilines, unsubstituted at the para-position, produced a mixture of nitro and nitroso compounds. Murray proposes[1] that the nitroso group is an intermediate in the mechanism of this oxidation. Since we are using only a small excess of OXONE®, any competition for the oxygen electrophile would leave an insufficient amount of oxidant to complete the final transformation of the nitroso functionality to the nitro substituent. Consequently when 2,5-dimethoxyaniline was submitted to an excess of OXONE® (8 eq), only the corresponding nitro compound was isolated in 51% yield.

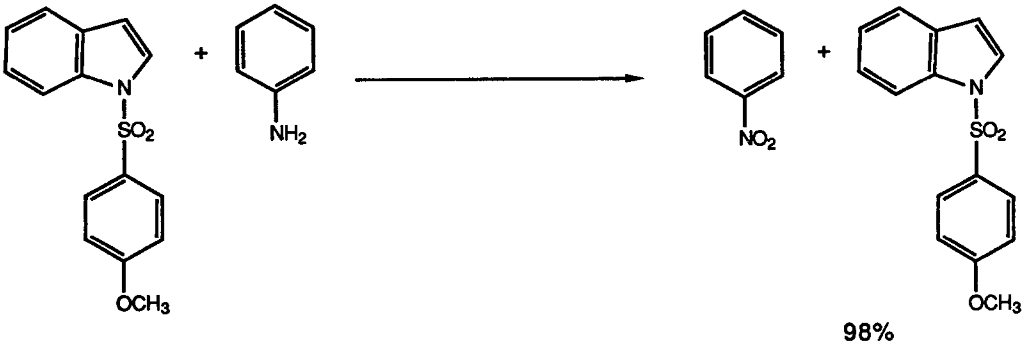
There are some minor limitations that we observed during the course of our investigation. Anilines containing a carboxylic acid or phenol produced the corresponding nitro compounds in poor yields. However, the analogous esters and methyl ethers provided nitro compounds in good yields (entries 2 and 3).

Particularly noteworthy is the oxidation of 5-aminoindole (eq 2). In view



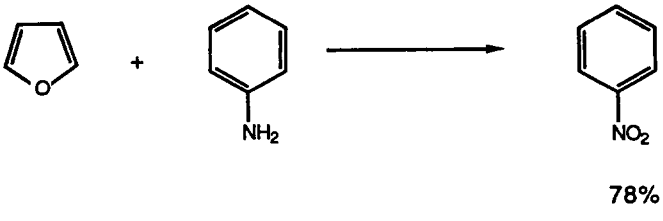
(eq 2)

of the mixture of products and the lack of recovered starting material, we theorized that the nucleophilic 2,3-double bond of the indole system was competing for the dioxirane reagent and preventing complete conversion to the nitro compound. To test this concept, *N*-*p*-methoxybenzenesulfonyl indole was prepared by *N*-alkylation of indole with *p*-methoxybenzenesulfonyl chloride under phase-transfer conditions[6]. When a mixture of this less reactive indole system and aniline was exposed to our reaction conditions, a 98% yield of nitrobenzene and quantitative recovery of starting indole were observed (eq 3). On the other hand, when aniline was oxidized in the presence of indole, a 1:1 mixture of nitro- and nitrosobenzene was isolated in 35% yield while none of the indole was recovered. This constitutes the first example in which oxidation to a nitro substituent occurs in the presence of an indole.



(eq 3)

Since furan is more reactive[7] than pyrrole, we decided to study furans in light of our success with indoles. When furfuryl amine was subjected to this procedure, no furfuryl nitromethane or starting amine was isolated. With the likelihood in mind that the desired product is unstable to the reaction conditions, as opposed to the possibility that the aromatic system is competing for the oxidant, we set up a competitive oxidation experiment with aniline and furan. Thus a mixture of furan and aniline was subjected to our mild oxidative conditions for 15 min at 0°C to afford only nitrobenzene in 78% yield (eq 4). This result illustrates the high selectivity of dimethyldioxirane for an amine even in the presence of highly "electron-rich" systems such as furan.



(eq 4)

A representative reaction occurs as follows: In a three-neck round bottom flask fitted with two addition funnels and a pH electrode was placed 100 mL of dichloromethane, 100 mL of acetone, 50 mL of a 0.8M aqueous solution of sodium phosphate, 170 mg (0.5 mmol) of tetrabutylammonium hydrogen sulfate, and 1.1 mL (10 mmol) of o-anisidine. In one addition funnel was added a solution of 20 g (32 mmol) of OXONE® in 150 mL of water. In the other addition funnel was placed 100 mL of a 2N aqueous solution of potassium hydroxide. After cooling the mixture to 0°C, the aqueous solution of OXONE® was added dropwise over 30 min while maintaining a pH of 7.5–8.5 with the addition of the aqueous solution of potassium hydroxide. Once addition was complete the mixture was stirred at 0°C for 15 min and treated with 1 mL of methyl sulfide. The resulting suspension was filtered and the filtrate partitioned. The organic layer was washed with 50 mL of water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Filtration through a 50 g plug of silica gel (CH_2Cl_2) afforded 1.5 g (100%) of o-nitroanisole. Anal. calcd for $C_7H_7NO_3$: C, 54.89; H, 4.62; N, 9.15. Found: C, 55.30; H, 4.94; N, 9.03.[8]

In summary, this method for oxidizing amines to nitro compounds should find use where acidic conditions to effect oxidation cannot be employed. More importantly our procedure provides nitro groups in the presence of reactive aromatic systems. Considering the ease in which nitro moieties are reduced to amines, this reaction allows a nitro substituent to be used as a protecting group for the corresponding aromatic primary amines.

Acknowledgements:

We are grateful to Drs. P.W. Collins and P.H. Jones for their encouragement and to Professor A.G.M. Barrett for several stimulating discussions.

References:

1. Murray, R.W., Jeyaraman, R., Mohan, L., Tetrahedron Lett. 27, 2335 (1986).

2. a)Emmons, W.E., J. Am. Chem. Soc. 76, 3470 (1954). b) Emmons, W.D., J. Am. Chem. Soc. 79, 5528 (1957). c) McKillop, A., Tarbin, J.A., Tetrahedron Lett. 24, 1505 (1983).

3. Murray, R.W., Jeyaraman, R., J. Org. Chem. 50, 2847 (1985).

4. a)Edwards, J.O., Pater, R.H., Curci, R., DiFuria, F., Photochem. Photobiol. 30, 63 (1979). b) Curci, R., Fiorentino, M., Troisi, L., Edwards, J.O., Pater, R.H., J. Org. Chem., 47, 2670 (1982).

5. Edwards and Curci[4a] observed that peroxybisulfate anion decomposed dimethyldioxirane to oxygen and acetone. By using our modification of the reaction conditions, we found that this competitive side reaction was minimized.

6. Illi, V.O., Synthesis, 136 (1979).

7. Paquette, L.A., Principles of Modern Heterocyclic Chemistry; W.A. Benjamin, Inc., New York; 1968; pp. 115-118 and references cited therein.

8. As suggested by a referee, we conducted a control experiment on entry 3 using our reaction conditions in the absence of acetone. An unstable oxidized intermediate was recovered in modest yield along with some (<10%) starting material. However, none of the nitro adduct was isolated.

(Received in USA 16 May 1988)