protocol by using a common microwave oven in solid-phase peptide synthesis. The procedure not only reduced the needed reaction time of 2–3 h reacting at room temperature, or of 30 min by reacting at 60 °C, to less than 6 min via the microwave irradiation method but also accomplished the complete coupling of difficult sequence peptides. The reaction apparatus is simple and can potentially be designed for an autosynthesizer. Under microwave irradiation conditions, the peptide fragments have higher reactivity than do the amino acid derivatives, which is very useful for the synthesis of big peptides. That using a dipeptide or a tripeptide instead of amino acid derivatives in the same synthesis steps will make a peptide which has longer amino acid residue. Also, in the synthesis of same peptide, the fragment coupling will only need half or one-third of the coupling steps especially for sterectically hindered amino acid. The development of a convenient method for preparation of peptide fragment will be very useful for the synthesis of big peptides.[19]

Acknowledgment. Support for this research provided by the National Science Council, Taiwan (NSC 81-0208-N-001-70), is gratefully acknowledged.

(19) (a) Nakagawa, S. H.; Lau, H. S. H.; Kezdy, F. J.; Kaiser, E. T. *J. Am. Chem. Soc.* **1985**, *107*, 7087–7092. (b) Nakagawa, S. H.; Kaiser, E. T. *J. Org. Chem.* **1983**, *48*, 678–685. (c) Chen, S. T.; Hsiao, S. C.; Chang, C. H.; Wang, K. T. *Synth. Commun.* **1992**, *22*(3), 391–398. (d) Chen, S. T.; Wang, K. T. *J. Chem. Soc., Chem. Commun.* **1990**, 1045–1047.

Amination of Nitroarenes with Sulfenamides via Vicarious Nucleophilic Substitution of Hydrogen[1]

Mieczysław Mąkosza* and Maciej Białecki

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Received May 4, 1992

Summary: Nitroarenes react with sulfenamides $RSNH_2$ in the presence of strong bases to give *p*- and *o*-nitroanilines.

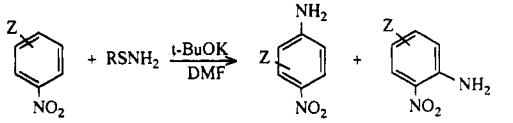
The vicarious nucleophilic substitution of hydrogen (VNS) is presently a well-established methodology for introduction of carbon substituents into electrophilic aromatic rings.[2] Recently, a similar reaction was discovered between nitroarenes and the anions of alkyl hydroperoxides to produce nitrophenols.[3]

Although direct nucleophilic amination of electrophilic arenes, particularly heterocycles, has been thoroughly investigated,[4] and important methods such as the Chichibabin reaction or oxidative amination[5] are known, no simple and general method for direct amination of mononitroarenes is available. An old method of amination with hydroxylamine is applicable only to nitro derivatives of bicyclic arenes or dinitroarenes.[6] A much more general method of amination with 4-amino-1,2,4-triazoles, described recently by Katrizky, is of somewhat limited use because of moderate availability of the triazoles and some limitations of its scope.[7]

Our experience in the VNS reaction with carbanions suggested that X in an aminating agent of general structure $X-NH_2$ should be able to stabilize the negative charge on the neighboring atom and to be eliminated from the intermediate σ-adduct in the form of HX. These requirements should be best fulfilled by groups X = RS which are known to stabilize carbanions[8] and are widely used in the VNS reactions.[9] We expected therefore that sulfenamides of general structure $RSNH_2$ should be able to aminate nitroarenes in the presence of strong bases, similarly as $RSCH_2CN$[10] or $RSCH_2SR$[11] effect corresponding alkylation.

The possibility of using sulfenamides for nucleophilic amination of nitroarenes was, however, not obvious to us, because very little is known about anions of sulfenamides and existing data indicate that they are of low stability.[12] Only sulfenamides which contain additional electron-withdrawing substituents at the nitrogen atom form stable anions,[13] but the latter are insufficiently nucleophilic for

Table I



Z	$RSNH_2$	position of NH_2	yield (%)
H	1	2	14
		4	71
	2	2	34
		4	35
2-MeO	1	4	39
2-CF_3	1	4	71
3-Cl	1	4	86
3-CF_3	1	4	91[a]
4-tBu	2	2	63
4-Cl	2	2	60

[a] The reaction was carried out using KOH in liquid NH_3.

(1) Reactions of Organic Anions. 194. Part 193: Ostrowicz, A.; Baloniak, S.; Mąkosza, M.; Rykowski, A. *Tetrahedron Lett.*, in press.

(2) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. Mąkosza, M. *Uspekhi Khim.* **1989**, *58*, 1298.

(3) Mąkosza, M.; Sienkiewicz, K. Polish Patent Appl. Nr PL 273927, 1988, *J. Org. Chem.* **1990**, *55*, 4979. Mattersteig, G.; Pritzkow, W.; Voerckel, V. *J. Prakt. Chem.* **1990**, *332*, 569.

(4) Vorbruggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117.

(5) Mc Gill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 1. Pozarskij, A. F.; Simonow, A. M.; Doronkin, V. N. *Usp. Khim.* **1978**, *47*, 1933. Van der Plas, H. C. *Janssen Chim. Acta* **1985**, *3*, 23. Van der Plas, H. C.; *Croat. Chim. Acta* **1986**, *59*, 33. Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Tetrahedron* **1988**, *44*, 1.

(6) Nasielski-Hinkenes, R.; Kotel, J.; Ledeux, T.; Nasielski, J. *Synth. Commun.* **1984**, *19*, 511. Neidlein, R.; Lautenschlager, G. *Chem. Zeitung* **1988**, *112*, 143. Möller, F. In *Houben-Weil Metoden der Organische Chemie*; Müller, E., Ed.; G. Thieme: Stuttgart, 1957; Vol. 11/1; p 17.

(7) Katrizky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039; **1988**, *53*, 3978.

(8) Bielmann, J. F. Ducep, J. B. *Org. React.* **1982**, *27*, 1.

(9) Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Phosphorus, Sulfur, Silicon* **1990**, *53*, 457.

(10) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494.

(11) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 5272.

(12) De Maria, P. In *Chemistry of Sulfenic Acids and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1990; p 293.

(13) Koval, I. V. *Uspekhi Khim.* **1990**, *35*, 681. Sandler, S. R.; Karo, W. *Organic Functional Groups Preparations*; Academic Press: New York, 1989; Vol. 3, p 162.

0022-3263/92/1957-4784$03.00/0

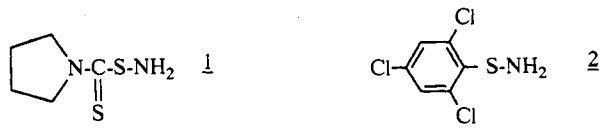


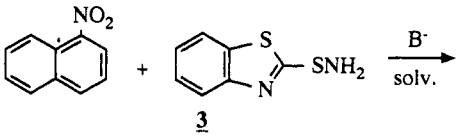
Figure 1.

the VNS reaction. For the preliminary amination experiments *N,N*-tetramethylenethiocarbamoyl sulfenamide (**1**) and 2,4,6-trichlorobenzenesulfenamide (**2**) (Figure 1) were chosen because they are sufficiently stable and the RS substituents assure proper NH acidity and facile elimination of RSH. These sulfenamides are easily available via the reaction of sodium salts of the corresponding thiols with ammonia and a chlorinating agent.[14]

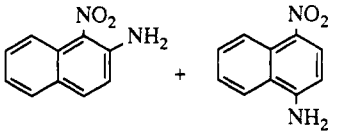
$$RSNa + NH_3 + NaOCl \xrightarrow{H_2O} RSNH_2 + NaCl \quad (1)$$

Both of these sulfenamides **1** and **2** reacted satisfactorily with nitrobenzene in the presence of *t*-BuOK in DMF, affording mixtures of *o*- and *p*-nitroanilines in good overall yield, with an ortho/para ratio of 1:5 and 1:1 correspondingly. Similarly positive results were obtained in the amination of other mononitroarenes with **1** and **2**. Some results are given in Table I.[15,16]

Differences in the orientation of the amination process with **1** and **2** allow the achievement of practically selective para amination of 2- and 3-substituted nitrobenzene derivatives with **1** and synthesis of *o*-nitroaniline derivatives via the amination of 4-substituted nitrobenzene derivatives with **2**. Orientation of the amination of 1-nitronaphthalene is of particular interest because it can be controlled by the conditions. This control is the most efficient when 2-benzothiazolesulfenamide (**3**) was used as the aminating agent.



3

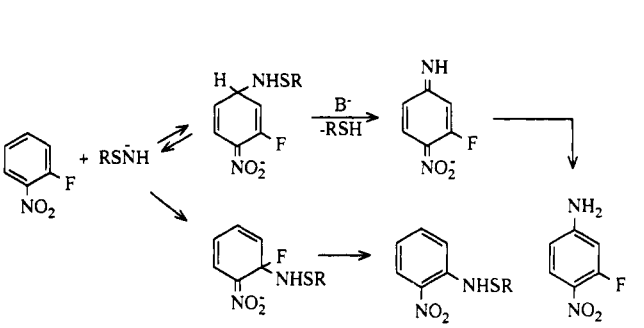


(2)

t-BuOK/DMF	71%	6%
KOH/DMSO	11%	75%

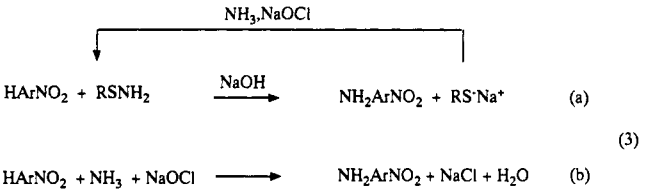
The mechanism of the amination of nitroarenes with sulfenamides appears to be the same as the vicarious nucleophilic substitution of hydrogen with α-halo carbanions[17] and alkyl hydroperoxide anions.[3] This conclusion is based on the results of the competition between the amination and the conventional nucleophilic substitution of halogen (S_NAr) in 2- and 4-fluoronitrobenzenes (Scheme I).[17] Similarly, in the reaction of **2** with 4-fluoronitrobenzene, the ratio of the VNS of hydrogen to S_NAr of the fluorine changes from 1.13 (excess of *t*-BuOK in DMF) to 0.11 (low concn of *t*-BuOK which was slowly added to a solution of the substrates).

Scheme I



Reagents added to solution of t-BuOK in DMF	30%	48%
t-BuOK in DMF added to solution of reagents	56%	19%
Reagents mixed at once with KOH in DMSO	78%	-

The aminating agents for the VNS amination process can be easily regenerated after the reaction (eq 3a); hence,



(3)

overall stoichiometry of the VNS amination process is as in eq 3b.

It should be also stressed that because of low stability of N-anions of sulfenamides their reactions with typical electrophilic partners such as aldehydes, alkyl halides, and Michael acceptors have not been reported. To the contrary, as it was shown in this paper, such anions react efficiently with nitroarenes.

Taking into account the simplicity of the VNS amination of nitroarenes with sulfenamides and its large scope of application, this method can be of significant value for laboratory synthesis of nitroanilines as well as in large-scale operations.

Supplementary Material Available: Mp and NMR spectral data of nitroanilines (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Drabowicz, J.; Kiełbasiński, P.; Mikołajczyk, M. ref 12, p 255. Petrov, K. A.; Rudner, G. V.; Sorokin, V. D. *Uspekhi Khim.* **1990**, *59*, 1431. Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.

(15) Mąkosza, M.; Białecki, M. Polish Patent Appl. Nr. PL 284896, 1990; Eur. Pat. Appl. 105749-5, 1991.

(16) Typical procedure: A solution of **1** or **2** (2 mmol) and a nitroarene (2 mmol) in DMF (2 mL) was added dropwise to a stirred solution of *t*-BuOK (5 mmol) in DMF (8 mL) at ca. 20 °C. After 20 min the mixture was poured into water, and the products were extracted with methylene chloride and purified via column chromatography. In some cases the solid product could be simply filtered and recrystallized.

(17) This approach was used earlier by us in order to establish the mechanism of the VNS reaction with α-halo carbanions (Mąkosza, M.; Glinka, T. *J. Org. Chem.* **1983**, *48*, 3860) and alkyl hydroperoxide anions (ref 3).