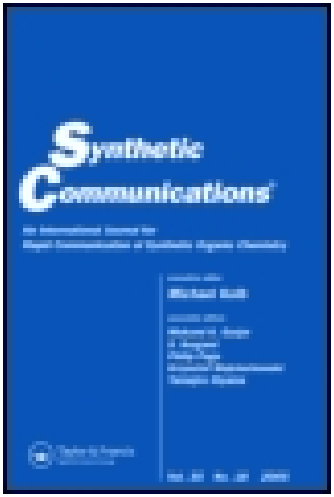


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

N-Nitrosodiphenylamine as an Alternative Nitrosating Agent for Indoles

Liberato Cardellini [a] , Lucedio Greci [a] & Pierluigi Stipa [a]
[a] Dipartimento di Scienze dei Materiali e della Terra , Università, via Brecce Bianche , I-60131, Ancona, Italy
Published online: 23 Sep 2006.

To cite this article: Liberato Cardellini , Lucedio Greci & Pierluigi Stipa (1994) N-Nitrosodiphenylamine as an Alternative Nitrosating Agent for Indoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:5, 677-682, DOI: 10.1080/00397919408012645

To link to this article: http://dx.doi.org/10.1080/00397919408012645

SYNTHETIC COMMUNICATIONS, 24(5), 677-682 (1994)

N-NITROSODIPHENYLAMINE AS AN ALTERNATIVE NITROSATING AGENT FOR INDOLES

Liberato Cardellini, Lucedio Greci* and Pierluigi Stipa

Dipartimento di Scienze dei Materiali e della Terra, Università,

via Brecce Bianche , I-60131 Ancona, Italy.

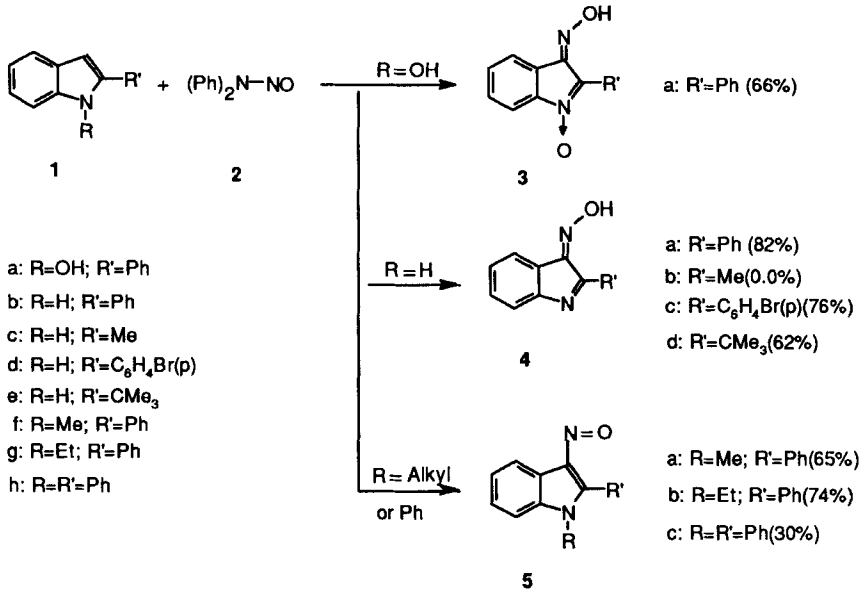
Abstract: *N*-nitrosodiphenylamine reacts in the presence of catalytic amounts of trichloroacetic acid with indoles forming the corresponding nitroso and isonitroso derivatives in good yields.

Amyl nitrite has been reacted with Grignard reagents to synthetize nitroxides,[1] and years ago has been reacted with indoles in ethanol/sodium ethylate to prepare isonitrosoindoles.[2,3] Since we have found that *N*-nitrosodiphenylamine reacts with Grignard reagent affording symmetric nitroxides in very high yields,[4] we investigated the nitrosation of indoles using *N*-nitrosodiphenylamine.

The nitrosation of indoles has been achieved previously in different manners: 1-hydroxy-2-phenylindole (**1a**),[2] 2-phenylindole (**1b**)[3] and 2-methylindole (**1c**)[5] have been nitrosated by amyl nitrite in alkaline medium, whereas 1-methyl- 2-phenylindole (**1f**),[6] 1-ethyl-2-phenylindole

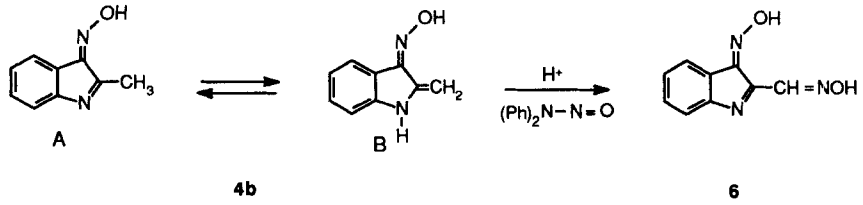
* To whom correspondence should be addressed

(**1g**),[7] 1,2-diphenylindole (**1h**)[7] and 2-*tert*-butylindole[8] were nitrosated with sodium nitrite in acetic acid. The reactions of indoles **1a-h** with *N*-nitrosodiphenylamine reported in Scheme 1 were carried out in chloroform at room temperature in the presence of trichloracetic acid. The yields varied from 62 - 82%, when the reaction of 2-methylindole (**1c**) and 2,3-diphenylindole (**1h**) are excluded.

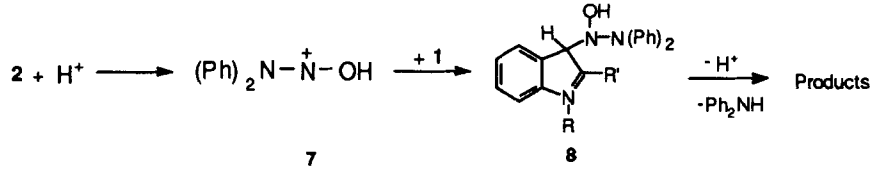


Scheme 1

The failure of the reaction of **1c** could be due to the fact that 2-methyl-3*H*-indole-3-oxime **4b** is an equilibrium of the two tautomeric forms **4bA** and **4bB**.[9] The **B** form contains an en-amino group and could react further with



another molecule of activated *N*-nitrosodiphenylamine forming compounds such as **6**. However, only an untreatable polymeric material was isolated, as has been found in the reaction of 2-methylindole with nitrous acid .[10] The same result was obtained when pure **4b**, obtained from 2-methylindole and amyl nitrite in alkaline medium,[5] was subjected to our experimental conditions. The reason why in alkaline medium this reaction stops at the formation of the isonitroso **4b** can be ascribed to the fact that the equilibrium **4bA** $\rightleftharpoons$ **4bB** is shifted to left. In the reaction of **1h**, the presence of the phenyl substituent at the indolic nitrogen decreases the nucleophilicity of the indole nucleus and, as a consequence, the efficiency of the electrophilic attack of the activated *N*-nitrosodipenylamine is also decreased, as in the yield of **5c** (30%). The behaviour of **1h** and the fact that, in the absence of acids, *N*-nitrosodiphenylamine reacts with indole **1a** in benzene under reflux affording products derived from the oxidation of **1a**,[11] represent an indirect evidence that the reaction probably occurs through nitrenium ion **7**, formed by protonation of the nitroso group, and the σ-complex **8**, as reported in Scheme 2.



Scheme 2

Diphenylamine formed in the rearrangement of σ-complex **8** was isolated in good yield (80-90%) in all cases.

Experimental

M.p.s were measured on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded in Nujol mulls on a Perkin-

Elmer 298 spectrophotometer. ^1H NMR were recorded on Varian Gemini 200 in $CDCl_3$ using $SiMe_4$ as internal standard. Mass spectra were recorded in EI+ mode on a Carlo Erba QMD 1000 spectrometer equipped with a direct probe apparatus. Compounds 1a,[12] 1d,[13] 1f,[6] 1g[7] and 1h[8] were prepared according to the literature reports. Compounds 1b and 1c were Aldrich reagent and used as purchased. Compound 2 was purchased from Fluka and manipulated with care being toxic cancer suspect agent.

Synthesis of 2-*tert*-butylindole (1e)

Phenylhydrazine (11,15 g 97%, 0.1 mmoles) and pinacolone (10,22 g 98%, 0.1 mmoles) were mixed with zinc chloride (54.5 g, 0.4 mmoles) and heated at 190°C with an oil bath under efficient mechanical stirring. The reaction mixture was kept at this temperature for 20 min and poured into boiling 5% hydrochloric acid (200 ml) under stirring. After cooling, the mixture was extracted with benzene (3x50 ml). The organic layer, dried over Na_2SO_4, was chromatographed on a SiO_2 column eluted with cyclohexane/ethyl acetate 9:1: 7,2 g (41.6% yield) of compound **1e** was isolated; m. p. 71-2°C (lit.,[14] 73°C); ^1HNMR, δ: 1.40(9H, s, Bu^t), 6.25(1H, broad, arom), 7.0-7.6(4H, m, arom), 7.88(1H, broad, NH).

Reactions of Indoles (1a-h) and N-Nitrosodiphenylamine (2). *General Procedure.* To a solution of 2-phenylindole (386 mg, 2 mmoles) and *N*-nitrosodiphenylamine (396 mg, 2 mmoles) in 10 ml of CH_2Cl_2 trichloroacetic acid (16 mg, 0.1 mmoles) in 5 ml of CH_2Cl_2 was added dropwise at room temperature under magnetic stirring . After 1 h the reaction mixture was treated with 20 ml of 10% aqueous $NaHCO_3$ and the aqueous layer extracted with CH_2Cl_2 (2x20 ml). The combined organic

extracts, dried on Na_2SO_4, was then evaporated to dryness at reduced pressure. Taking up the residue with benzene 367 mg, 82,5% yield of isonitroso **4a** separated. The diphenylamine was recovered in 87% yield from the benzene solution by chromatography on column of silica gel eluting with cyclohexane/ethyl acetate 9:1. In the case of indoles **1f**, **1g** and **1h**, the corresponding products were directly isolated by chromatography of the reaction mixture. Compounds **3a**, **4a**, **5a**, **5b** and **5c** were identified by comparison with authentic samples wereas compounds **4c**, and **4d** by their analytical and spectroscopic data.

Compound **4c**: m. p. 273-4°C from benzene; IR, ν_{max} (cm^{-1}): 2650 (broad, =NOH), 1590, 1520. ^1H NMR, δ: 7.35(1H, broad, OH), 7.58(3H, m, arom), 7.65(2H, d, J=8.6Hz, arom), 8.05(1H, d, J=8.6Hz, arom), 8.27(2H, d, J=8.6Hz, arom). MS, m/e, (relative intensity); 302(M^++1, 26%); 300(M^+-1, 26); 285(51); 283(51); 205(14); 157(9); 102(39); 76(31). Analysis: calcd for $C_{14}H_9N_2OBr$, C, 55.84; H, 3.013; N, 9.305. Found C, 55.6; H, 2.90; N, 9.19.

Compound **4d**: m. p. 240°C from benzene; IR, ν_{max} (cm^{-1}): 2700(broad, =NOH), 1530. ^1H NMR, δ: 1.05(3H, s, Me), 1.30(6H, s, 2Me), 7.34(1H, s, OH), 7.46(2H, m, arom), 8.15(2H, m, arom). MS, m/e (relative intensity); 203(M^++1, 39%), 201(M^+-1, 52), 186(81), 183(45), 160(61), 145(66), 130(59), 103(80), 76(66). Analysis: calcd for $C_{12}H_{14}N_2O$, C, 71.28; H, 6.979; N, 13.86. Found C, 71.4; H, 6.86; N, 13.8.

Acknowledgements

We thank the M. U. R. S. T. (Rome) for financial support.

References

1. Berti C., *Synthesis*, 1983, 793.
2. Angeli, A. and Angelico, F., *Rend. Accad. Lincei*, 1906, **15** II, 98.

3. (a) Spica, M. and Angelico, F., *Gazz. Chim. Ital.*, 1899, 29 II, 49;(b) Chiorboli, E. and Greci, L.,*Synthesis*, 1986, 219.
4. Cardellini, L., Greci, L. and Tosi, G., *Synthetic Comm.* 1992, 22(2), 201.
5. Noland, W. E., Smith, L. R. and Rush, K. R. , *J.Org.Chem.* 1965, *30*, 3457.
6. Campbell, N. and Cooper, R. C. , *J. Chem. Soc.*, 1935, 1208.
7. Crowther, A. F. and Mann, G., *J. Chem. Soc.*, 1943, 58.
8. (a) Piozzi, F. and Dubini, M., *Gazz. Chim. Ital.*, 1959, 89, 638; (b) Verkade, P. E., Lieste, J. and Warner, E. G. G., *Rec. Trav. Chim. Pays-Bas*, 1945, *64*, 289.
9. Greci, L., Stipa, P. and Tosi, G., *J. Chem. Res.*, (S) 1987, 217; (M) 1987, 1967, and references reported therein.
10. Rush, K., "*Indoles*", Ed. by Houlihan, W. J., Part two, Chapter VII, John Wiley, New York, 1972, p. 542, and references reported therein.
11. Colonna, M. and Bruni, P., *Gazz. Chim. Ital.*, 1964, *94*, 1448.
12. Fisher, E., *Chem. Ber.*, 1896, *29*, 2062.
13. Cardillo, B., Giorgini, E., Greci, L., Tosi, G., Rizzoli, C., Sgarabotto, P. and Ugozzoli, F., *J. Chem. Res.*, (S) 1992, 222; (M) 1992, 1801.
14. Planker, G. and Ciamician, G., *Rend. Accad. Lincei*, 1902, **1** II, 23.

(Received in The Netherlands 10 August 1993)