Pergamon

Tetrahedron Letters 43 (2002) 6613–6616

TETRAHEDRON LETTERS

Vicarious C-amination of 1-methyl-4-nitroimidazole

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Received 28 May 2002; revised 4 July 2002; accepted 12 July 2002

Abstract—A one electron transfer process during the vicarious nucleophilic substitution C-amination of 1-methyl-4-nitroimidazole is detected by EPR-monitoring.

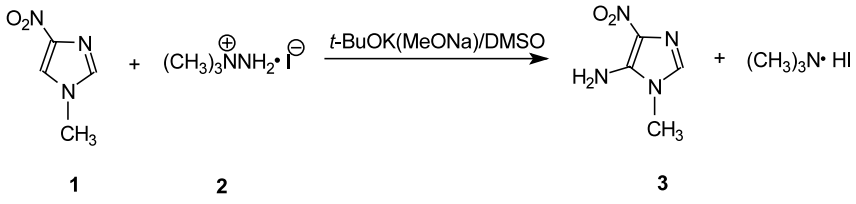
Vicarious nucleophilic substitution (VNS) of hydrogen provides a convenient method for the introduction of functional groups into aromatic[1–6] and heterocyclic rings.[7–10]

It is known that the VNS C-amination of 1,2-dimethyl-4-nitroimidazole by hydroxylamine hydrochloride in MeOH in the presence of KOH results in 5-amino-1,2-dimethyl-4-nitroimidazole (72% yield) and a minor amount (7%) of a substituted 1,2,5-oxadiazole.[11] The reaction of 1-alkyl(aryl)-2-methyl-4-nitroimidazole with 4-amino-1,2,4-triazole in MeOH in the presence of MeONa at 25°C gave substituted 1,2,4-oxadiazole-3-carboxamidines (40–87% yield) and small amounts (6–7%) of 1,2-substituted 5-amino-4-nitroimidazoles.[11]

Previously we have reported a VNS *C*-amination of 1-methyl-4-nitropyrazole with the use of 4-amino-1,2,4-triazole[12] and 1,1,1-trimethylhydrazinium halogenides[13] as amination agents.

Extending these studies we have established that 1-methyl-4-nitroimidazole **1**, under mild conditions (20°C) in the presence of dry sodium methylate or potassium *tert*-butylate in DMSO, treated with 1,1,1-trimethylhydrazinium iodide **2** gives 5-amino-1-methyl-4-nitroimidazole **3** in 56% yield. Another reaction product is trimethylamine hydroiodide (Scheme 1). When the reaction of 1-methyl-4-nitroimidazole **1** with 4-amino-1,2,4-triazole is carried out in dry DMSO in the presence of *t*-BuOK at 20°C, 5-amino-1-methyl-4-nitroimidazole **3** was obtained in 39% yield, i.e. in a higher yield than reported in the literature.[11]

When the vicarious substitution of hydrogen was conducted on 1-methyl-4-nitroimidazole under the effect of the amination agents 1,1,1-trimethylhydrazinium iodide and 4-amino-1,2,4-triazole in the MeONa/DMSO or *t*-BuOK/DMSO system, the appearance of a transitory bright-blue coloring of the reaction mixture which rapidly turned to red–brown was observed. This suggests the formation of an intermediate radical-ion species. This may be as a result of one electron transfer processes and gave a good reason to use EPR spectroscopy in order to detect possible free-radical species in the amination reactions of the nitroimidazole.



1 **2** **3**

Scheme 1.

Keywords: vicarious nucleophilic substitution of hydrogen; nitroimidazoles; radical anions; EPR.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)01457-0

In fact, in the reactions of 1-methyl-4-nitroimidazole with 1,1,1-trimethylhydrazinium iodide and 4-amino-1,2,4-triazole, the same signals with a well-resolved hyperfine structure (HFS) were recorded by EPR spectroscopy. Signal intensity is increased up to a stationary value and then is decreased, disappearing at the end.

As an example the EPR signal of the reaction mixture of 1-methyl-4-nitroimidazole with 1,1,1-trimethylhydrazinium iodide in the *t*-BuOK/DMSO system is shown in Fig. 1. The EPR signal characteristics allow the unambiguous assignment of the radical-anion of 1-methyl-4-nitroimidazole.[14]

However, an attempt to perform the VNS C-amination of 2-methyl-4-nitroimidazole and 1,2-dimethyl-4-nitroimidazole using the above amination agents was unsuccessful: only the initial nitroimidazoles were recovered quantitatively from the reaction mixture. Why these reactions do not go, still needs to be established.

Moreover, it should be noted that if the VNS C-amination does not occur (as with 2-methyl-4-nitroimidazole and 1,2-dimethyl-4-nitroimidazole), no EPR signals of primary radical-anions can be recorded, as in the cases with blank tests when at least one of the components was absent in the reaction mixture.

The results indicate the presence of a one electron transfer channel in the vicarious C-amination reaction of 1-methyl-4-nitroimidazole. Taking into account the structure of VNS reaction products, a high stationary concentration of radical-anions of 1-methyl-4-nitroimidazole and the absence of radical-anions of 2-methyl- and 1,2-dimethyl-4-nitroimidazoles in the reactions, when the amination does not occur, we think that the VNS C-amination of 1-methyl-4-nitroimidazole is likely to follow a radical-ion mechanism.[15] If this is so, radical-anions may be formed according to Scheme 2.

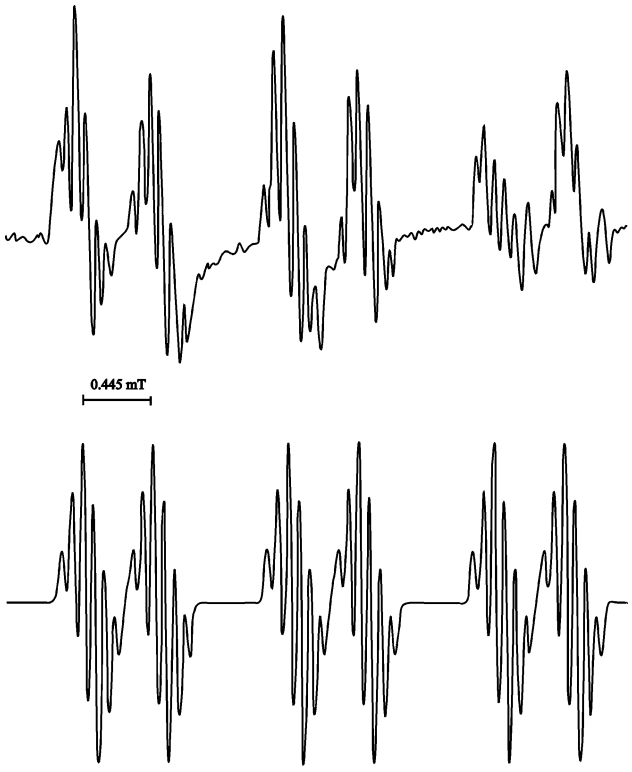
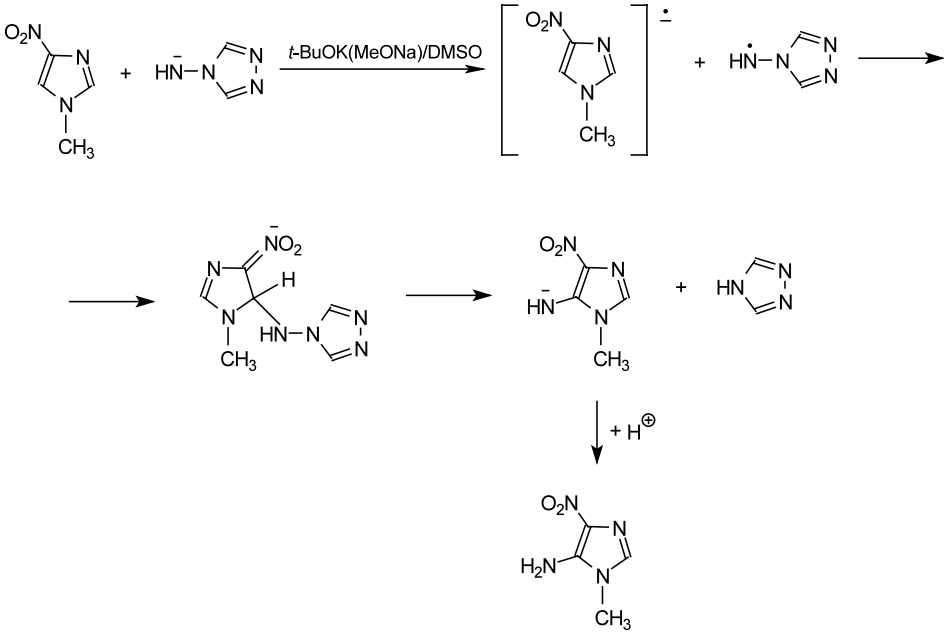


Figure 1. (Top) the EPR spectrum recorded in the reaction of 1-methyl-4-nitroimidazole with 1,1,1-trimethylhydrazinium iodide in the *t*-BuOK/DMSO system; (bottom) the simulated EPR spectrum: HFS constants, mT: 1.388 (1N, NO_2), 0.477 (1H, C-5), 0.070 (2N, N-1,3), 0.056 (1H, C-2), 0.020 (3H, N-CH_3).



Scheme 2. The suggested scheme for the reaction of 1-methyl-4-nitroimidazole with 4-amino-1,2,4-triazole.

As shown by UHF/6-31G* quantum-mechanical calculations of the 1-methyl-4-nitroimidazole radical-anion,[16] the highest spin density is concentrated in the imidazole ring position 5 (Table 1). This is a prerequisite for the amination to be conducted at position 5.

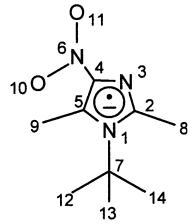
Experimental

^{1}H and ^{13}C NMR spectra were run on a Bruker DRX-400 (400 and 100.13 MHz for ^{1}H and ^{13}C, respectively, TMS as internal standard). EPR spectra were recorded on an SE/X-2547 spectrometer (Radiopan, Poland) in special ampoules at 20°C. The solvent and solutions of the initial compounds were carefully degassed by bubbling with argon before mixing. Simulated spectra were obtained using the WINEPR SimFonia 1.25 program (Bruker, Inc. 1996).

5-Amino-1-methyl-4-nitroimidazole 3. **Method A**. To a solution of 3 g (0.024 mol) of 1-methyl-4-nitroimidazole in 40 ml of dry DMSO 5.25 g (0.026 mol) of trimethylhydrazinium iodide was slowly added with stirring at 20°C until complete dissolution and then 2.81 g (0.052 mol) of dry sodium methylate was added. The first transitory blue color appeared and after 15 min the reaction mixture acquired an intensive red–brown color. The reaction mixture was stirred for 20 h at 20°C, poured onto ice and acidified to pH 3.0 with 10% HCl solution. The imidazole precipitate **3** was filtered off and the filtrate was extracted thrice with ethyl acetate. The ethyl acetate solution was dried with $MgSO_4$, the solvent was evaporated in vacuo and the residue was combined with the imidazole **3** isolated previously and recrystallized from DMF and then from hot water. Yield 1.9 g (56%), mp 295–297°C (297–299°C[17]). When the reaction is performed in the *t*-BuOK/DMSO system, the yield of imidazole **3** is 20%.

^{1}H NMR spectrum (DMSO-d_6) δ, ppm: 7.51 (s, 2H, NH_2), 7.23 (s, 1H, H-2), 3.43 (s, 3H, Me). ^{13}C NMR spectrum (DMSO-d_6) δ, ppm: 30.71 (Me), 132.46 (C-2), 143.97 (C-5), signal C-4 is not observed due to quadrupole broadening caused by ^{13}C–^{14}N (NO_2) spin–spin coupling.[18] This broadening disappears in the triplet resonance experiment ^{13}C-{^{1}H,^{14}N}.[19] Found (%): C, 33.65; H, 4.38; N, 39.16. Calcd for $C_4H_6N_4O_2$ (%): C, 33.80; H, 4.26; N, 39.43.

Table 1. UHF/6-31G*-calculated spin density distribution in the 1-methyl-4-nitroimidazole radical anion

Formula	Atom numbering	Spin density
	N(1)	−0.004541
	C(2)	−0.355882
	N(3)	0.330223
	C(4)	−0.491002
	C(5)	0.634624
	N(6)	0.542255
	C(7)	−0.005886
	H(8)	0.027645
	H(9)	−0.046539
	O(10)	0.130368
	O(11)	0.225805
	H(12)	0.006625
	H(13)	−0.000319
	H(14)	0.006625

Method B. To a solution of 5.0 g (0.04 mol) of 1-methyl-4-nitroimidazole in 60 ml of dry DMSO, 3.7 g (0.044 mol) of 4-amino-1,2,4-triazole was slowly added with stirring at 20°C until complete dissolution and then 9.86 g (0.088 mol) of dry potassium *tert*-butylate was added. The first transitory blue color appeared and after 5–7 min the reaction mixture acquired an intensive red–brown color that was accompanied by spontaneous heating to 53°C. The reaction mixture was cooled, stirred for 10 h at 20°C, poured onto ice and acidified to pH 3.0 with 10% HCl solution. The imidazole precipitate **3** was filtered off and the filtrate was extracted three times with ethyl acetate. The ethyl acetate solution was dried with $MgSO_4$, the solvent was evaporated in vacuo and the residue was combined with the imidazole **3** prepared previously and recrystallized from DMF and then from hot water. Yield 2.16 g (39%), mp 297°C.

References

1. Makosza, M.; Ludwiczak, S. *Synthesis* **1986**, 50–52.
2. Makosza, M.; Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562–4563.
3. Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711–715.
4. Katritzky, A. R.; Laurenso, K. S. *J. Org. Chem.* **1988**, *53*, 3978–3982.
5. Pagoria, P. F.; Mitchell, A. R.; Schmidt, R. D. *J. Org. Chem.* **1996**, *61*, 2934–2935.
6. Katritzky, A. R.; Xie, L. *Tetrahedron Lett.* **1996**, *37*, 347–350.
7. Bernard, M. K. *Polish J. Chem.* **1997**, *71*, 1413–1420.
8. Bernard, M. K.; Makosza, M.; Szafran, B.; Wrzeciono, U. *Liebigs Ann. Chem.* **1989**, 545–549.
9. Suwinski, I.; Swierczek, K. *Tetrahedron* **1993**, *49*, 5339–5350.
10. Ostrowski, S.; Wojciechowski, K. *Can. J. Chem.* **1990**, *68*, 2239–2241.
11. Suwinski, I.; Swierczek, K. *Khimiya Geterotsiklicheskikh Soedinenii* **1996**, 1214–1221.
12. Elokhina, V. N.; Krylova, O. V.; Larina, L. I.; Nakhmanovich, A. S.; Sorokin, M. S.; Volkova, K. A.; Lopyrev, V. A. *Khimiya Geterotsiklicheskikh Soedinenii* **2000**, 551–552 (in Russian).
13. Lopyrev, V. A.; Elokhina, V. N.; Krylova, O. V.; Nakhmanovich, A. S.; Larina, L. I.; Sorokin, M. S.; Vokin, A. I. *Khimiya Geterotsiklicheskikh Soedinenii* **1999**, 1254–1256 (in Russian).
14. Vakul'skaya, T. I.; Larina, L. I.; Nefedova, O. B.; Petukhov, L. P.; Voronkov, M. G.; Lopyrev, V. A. *Khimiya Geterotsiklicheskikh Soedinenii* **1979**, 1398–1403 (in Russian).

15. Okhlobystin, Yu. A. In *Perenos electrona v organicheskikh reaktsiyakh (Electron Transfer in Organic Reactions)*; Zhdanov, Yu. A., Ed.; Rostov University Publishers, 1974; p. 120 (in Russian); Todres, Z. V. *Ion-radikaly v organicheskom sinteze (Radical-ions in Organic Synthesis)*; Khimiya: Moscow, 1986, p. 240 (in Russian).
16. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle E. S.; Pople, J. A. *Gaussian 98*, *Revision A.6*, Gaussian, Inc.: Pittsburgh PA, 1998.
17. Sharnin, G. P.; Fassakhov, R. Kh.; Sabirzyanov, R. G. USSR Patent SU 1011643, C 07 D, 1981. *Chem. Abstr.* **1983**, *99*, 70731g.
18. Larina, L. I.; Lopyrev, V. A. In *Topics in Heterocyclic Systems—Synthesis, Reactions and Properties*; Attanasi, O. A.; Spinelli, D., Eds. Nuclear magnetic resonance of nitroazoles; Research Signpost: Trivandrum, 1996; Vol. 1, pp. 187–237.
19. Makhova, N. N.; Blinnikov, A. N.; Khmel'nitskii, L. I. *Mendeleev Commun.* **1995**, 56–58.