ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 4, pp. 541–544. © Pleiades Publishing, Inc., 2006.
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Dehydrogenation of 4-Phenyl-Substituted Spinaceamine and Spinacine

N. N. Smolyar, M. G. Abramyants, and Yu. M. Yutilov

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R. Lyuksemburg 70, Donetsk, 83114 Ukraine
e-mail: yutilov@skif.net

Received April 6, 2005

Abstract—The dehydrogenation of 4-phenyl-substituted spinaceamine and spinacine with elemental sulfur in dimethylformamide at 120–150°C leads to the corresponding imidazo[4,5-*c*]pyridines. Sulfur may be regarded as a specific reagent for oxidative decarboxylation which accompanies dehydrogenation of 4-phenyl-substituted spinacine derivatives.

DOI: 10.1134/S1070428006040099

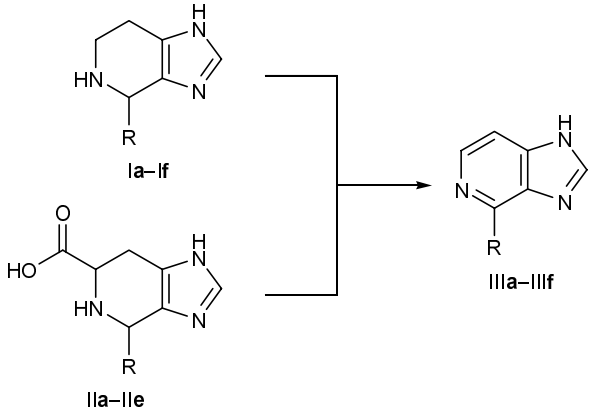
We previously showed that catalytic hydrogenation (over Pd/C) of 4-phenyl-substituted spinaceamine and spinacine in acetic acid under atmospheric pressure leads to formation of 5-benzyl derivatives of histamine and histidine [1]. In continuation of our studies on the chemical properties of 4-phenylspinaceamine derivatives, we thought it interesting to effect their dehydrogenation with a view to obtain difficultly accessible 4-phenylimidazo[4,5-*c*]pyridines as promising synthons for the preparation of biologically active substances.

Only a few published data are available on dehydrogenation of spinaceamine derivatives. Cain *et al.* [2] reported on dehydrogenation of spinacine and 4-phenylspinacine methyl esters by heating in glacial acetic acid in the presence of selenium dioxide as oxidant. Dehydrogenation of 4-trifluoromethylspinacine and 4,6-bis(trifluoromethyl)spinaceamine under analogous conditions gave the corresponding imidazo-[4,5-*c*]pyridines in 49 and 12% yield, respectively [3]. Analysis of published data on dehydrogenation of heterocyclic systems containing a tetrahydropyridine fragment indicates that there is no oxidant (among those used for this purpose) which can be regarded as universal dehydrogenating agent.

By reaction of histamine and histidine with various benzaldehydes we synthesized 4-aryl-substituted spinaceamines **Ia**–**If** and spinacines **IIa**–**IIe**. As oxidant we selected elemental sulfur due to its low toxicity, high accessibility, and simplicity of monitoring of the reaction progress and isolation of the products. In addition, we took into account the lack of published data on the application of sulfur in dehydrogenation of spinaceamine and spinacine derivatives. Dehydrogenation of related systems, e.g., tetrahydro-β-carboline, was effected with the aid of sulfur [4], selenium dioxide [5], chloranil [6], lead tetraacetate [7], potassium dichromate [8], manganese dioxide [9], and Pd/C [10].

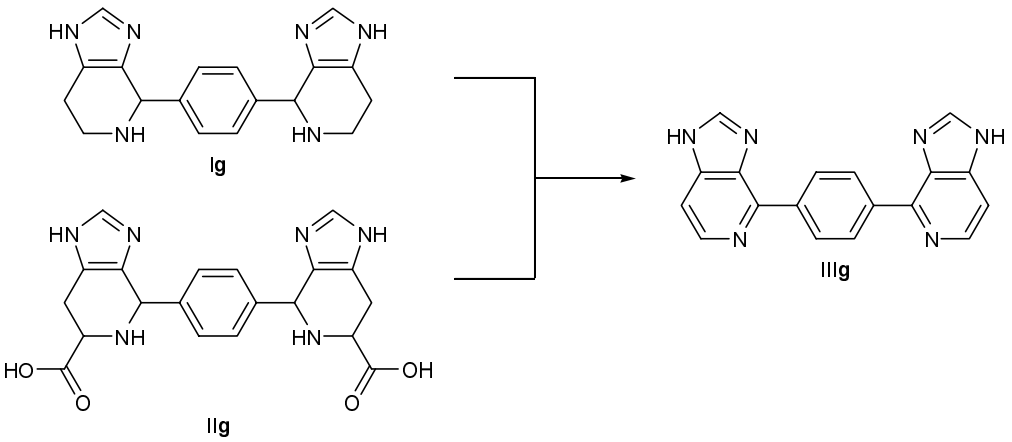
Heating of spinaceamines **Ia**–**If** with elemental sulfur in DMF at 140–150°C until hydrogen sulfide no longer evolved (reaction time 2–7 h) resulted in formation of the corresponding 4-substituted imidazo[4,5-*c*]-pyridines **IIIa**–**IIIf** in 47–71% yield (Scheme 1). The ^{1}H NMR spectra of compounds **IIIa**–**IIIf** contained

Scheme 1.



R = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-BrC$_6$H$_4$ (**c**), 2,4-Cl$_2$C$_6$H$_3$ (**d**), 4-PhCH$_2$OC$_6$H$_4$ (**e**), 3,4,5-(MeO)$_3$C$_6$H$_2$ (**f**).

Scheme 2.



signals from the 2-H proton of the imidazole ring, aromatic protons, and 6-H and 7-H in the pyridine fragment with a coupling constant of 4.8–6.6 Hz. We also found that dehydrogenation of spinacines **IIa**–**IIe** is accompanied by decarboxylation to give products identical to those obtained from spinaceamines **Ia**–**Ie** in melting points and ^{1}H NMR spectra.

Dehydrogenation of bis-spinaceamine **Ig** and bis-spinacine **IIg** (prepared by reaction of histamine and histidine, respectively, with benzene-1,4-dicarbaldehyde [11]) afforded the same product **IIIg** (Scheme 2) whose structure was confirmed by the ^{1}H NMR data.

We can conclude that elemental sulfur is a convenient reagent for dehydrogenation of 4-phenylspinaceamines and that it is a specific reagent effecting oxidative decarboxylation of spinacines. Analogous properties are intrinsic to potassium dichromate. The latter promoted oxidative decarboxylation in the dehydrogenation of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid derivatives [8].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Gemini-200 spectrometer at 200 MHz using $CDCl_3$ or CD_3OD as solvent; the chemical shifts were measured relative to HMDS as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates using ethanol or chloroform as eluent; development with UV light or iodine vapor. Initial compounds **Ia**–**Ic** and **Ig** were synthesized as described in [12], compounds **Id** and **If** were prepared according to [13], compounds **Ie**, **IIb**, **IIc**, **IIe**, and **IIg** were obtained by the procedures reported in [11], and compound **IIa** was synthesized as described in [2].

4-(2,4-Dichlorophenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid (IId). L-Histidine, 1.55 g (10 mmol), was dispersed in 15 ml of water, and a solution of 0.8 g (20 mmol) of sodium hydroxide in 5 ml of water and a solution of 1.75 g (10 mmol) of 2,4-dichlorobenzaldehyde in 40 ml of propan-2-ol were added. The mixture was heated for 4 h on a boiling water bath, propan-2-ol was distilled off, and the residue was neutralized with 6 N hydrochloric acid to pH 7 and evaporated to dryness. The residue was extracted with anhydrous methanol, and the extract was evaporated to dryness. Yield 2.96 g (95%). mp 240–243°C (from propan-2-ol). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 3.35 m (2H, 7-H), 3.87 m (1H, 6-H), 6.14 s (1H, 4-H), 7.07 d (1H, 5'-H, J = 8.4 Hz), 7.93 s (1H, 3'-H), 7.65 d (1H, 6'-H, J = 6.8 Hz), 7.79 s (1H, 2-H). Found, %: C 49.79; H 3.60; N 13.28. $C_{13}H_{11}Cl_2N_3O_2$. Calculated, %: C 50.02; H 3.55; N 13.46.

4-Phenyl-1*H*-imidazo[4,5-*c*]pyridine (IIIa). *a*. Compound **Ia**, 2.0 g (10 mmol), was dissolved in 50 ml of DMF, 0.7 g (22 mmol) of elemental sulfur was added to the solution, and the mixture was heated at 140°C until hydrogen sulfide no longer evolved (2 h). The solvent was distilled off under reduced pressure on heating on a water bath, and the residue was dissolved in 10 ml of 10% hydrochloric acid. The unreacted sulfur was filtered off, and the filtrate was adjusted to pH 9 by adding 10% aqueous sodium hydroxide. The precipitate was filtered off, dried, and recrystallized from water. Yield 1.2 g (61%), mp 81–83°C. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 7.55–7.64 m (3H, C_6H_5), 7.70 d (1H, 7-H, J = 5.7 Hz), 8.14–8.19 m (2H, C_6H_5), 8.44 d (1H, 6-H, J = 5.7 Hz), 8.45 s (1H, 2-H). Found, %: C 73.58; H 4.72; N 21.38. $C_{12}H_9N_3$. Calculated, %: C 73.83; H 4.65; N 21.52.

b. A mixture of 2.4 g (10 mmol) of compound **IIa** and 0.7 g (22 mmol) of elemental sulfur in 50 ml of DMF was heated at 150°C until hydrogen sulfide no longer evolved (6 h). The mixture was evaporated under reduced pressure on a water bath, and the product was isolated as described above in *a*. Yield 1.2 g (61%), mp 82–83°C (from water).

4-(*p*-Methoxyphenyl)-1*H*-imidazo[4,5-*c*]pyridine (IIIb). *a*. Compound **Ib**, 2.3 g (10 mmol), was dissolved in 50 ml of DMF, 0.7 g (22 mmol) of elemental sulfur was added to the solution, and the mixture was heated at 150°C until hydrogen sulfide no longer evolved (3 h). The product was isolated as described above for compound **IIIa** (pH 8). Yield 1.5 g (66%), mp 185–187°C (from water). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.84 s (3H, OCH_3), 7.01 d (2H, 3'-H, 5'-H, J = 6.2 Hz), 7.35 d (1H, 7-H, J = 6.0 Hz), 8.09 s (1H, 2-H), 8.31 d (2H, 2'-H, 6'-H, J = 6.2 Hz), 8.42 d (1H, 6-H, J = 6.0 Hz). Found, %: C 69.21; H 4.98; N 18.52. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.66.

b. A mixture of 2.7 g (10 mmol) of compound **IIb** and 0.7 g (22 mmol) of elemental sulfur in 50 ml of DMF was heated at 120°C until hydrogen sulfide no longer evolved (4 h). The mixture was then treated as described above for compound **IIIa** (the product was isolated at pH 8). Yield 1.6 g (71%), mp 185–187°C (from water).

4-(*p*-Bromophenyl)-1*H*-imidazo[4,5-*c*]pyridine (IIIc). *a*. Compound **Ic**, 2.8 g (10 mmol), was dissolved in 50 ml of DMF, 0.7 g (22 mmol) of elemental sulfur was added to the solution, and the mixture was heated at 145°C until hydrogen sulfide no longer evolved (3 h). The product was isolated as described above for compound **IIIa**. Yield 2.0 g (71%), mp 216–218°C (from aqueous propan-2-ol, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.53 d (1H, 7-H, J = 4.8 Hz), 7.70 d (2H, 3'-H, 5'-H, J = 8.4 Hz), 8.24 s (1H, 2-H), 8.44 d (2H, 2'-H, 6'-H, J = 8.4 Hz), 8.54 d (1H, 6-H, J = 4.8 Hz). Found, %: C 52.41; H 3.09; N 15.23. $C_{12}H_8BrN_3$. Calculated, %: C 52.58; H 2.94; N 15.33.

b. A mixture of 3.2 g (10 mmol) of compound **IIc** and 0.7 g (22 mmol) of elemental sulfur in 50 ml of DMF was heated at 140°C until hydrogen sulfide no longer evolved (5 h). The mixture was then treated as described above for compound **IIIa**. Yield 1.6 g (59%), mp 216–218°C (from aqueous propan-2-ol, 1:1).

4-(2,4-Dichlorophenyl)-1*H*-imidazo[4,5-*c*]pyridine (IIId). *a*. Compound **Id**, 2.7 g (10 mmol), was dissolved in 50 ml of DMF, 0.7 g (22 mmol) of elemental sulfur was added to the solution, and the mixture was heated at 150°C until hydrogen sulfide no longer evolved (4 h). The product was isolated as described above for compound **IIIa** (pH 8). Yield 1.25 g (47%), mp 195–198°C (from aqueous propan-2-ol, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.53–7.60 m (2H, 5'-H, 6'-H), 7.69 s (1H, 3'-H), 7.77 d (1H, 7-H, J = 5.5 Hz), 8.41 s (1H, 2-H), 8.46 d (1H, 6-H, J = 5.5 Hz). Found, %: C 54.32; H 2.80; N 15.79. $C_{12}H_7Cl_2N_3$. Calculated, %: C 54.57; H 2.67; N 15.91.

b. A mixture of 3.1 g (10 mmol) of compound **IId** and 0.7 g (22 mmol) of elemental sulfur in 50 ml of DMF was heated at 120°C until hydrogen sulfide no longer evolved (5 h). The mixture was then treated as described above for compound **IIIa** (the product was isolated at pH 8). Yield 1.4 g (53%), mp 197–198°C (from aqueous propan-2-ol, 1:1).

4-(*p*-Benzyloxyphenyl)-1*H*-imidazo[4,5-*c*]pyridine (IIIe). *a*. Compound **Ie**, 3.0 g (10 mmol), was dissolved in 50 ml of DMF, 0.7 g (22 mmol) of elemental sulfur was added to the solution, and the mixture was heated at 140°C until hydrogen sulfide no longer evolved (5 h). The product was isolated as described above for compound **IIIa** (pH 8). Yield 1.7 g (58%), mp 231–232°C (from water). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.24 m (2H, CH_2), 7.29 d (2H, 3'-H, 5'-H, benzyl, J = 8.5 Hz), 7.35–7.47 m (5H, C_6H_5), 8.02 d (1H, 7-H, J = 6.6 Hz), 8.37 d (2H, 2'-H, 6'-H, benzyl, J = 8.5 Hz), 8.49 d (1H, 6-H J = 6.6 Hz), 8.73 s (1H, 2-H). Found, %: C 75.57; H 5.13; N 13.88. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94.

b. A mixture of 2.5 g (10 mmol) of compound **IIe** and 0.7 g (22 mmol) of elemental sulfur in 50 ml of DMF was heated at 145°C until hydrogen sulfide no longer evolved (2 h). The mixture was then treated as described above for compound **IIIa** (the product was isolated at pH 8). Yield 2.1 g (70%), mp 230–232°C (from water).

4-(3,4,5-Trimethoxyphenyl)-1*H*-imidazo[4,5-*c*]-pyridine (IIIf). Compound **If**, 2.9 g (10 mmol), was dissolved in 50 ml of DMF, 0.7 g (22 mmol) of elemental sulfur was added to the solution, and the mixture was heated at 150°C until hydrogen sulfide no longer evolved (7 h). The product was isolated as described above for compound **IIIa**. Yield 1.9 g (68%), mp 148–150°C (from benzene). ^{1}H NMR spectrum (CD_3Cl), δ, ppm: 3.91 s (9H, OCH_3), 7.38 d (1H, 7-H, J = 6.0 Hz), 7.76 s (2H, 2'-H, 6'-H), 8.18 s (1H, 2-H), 8.40 d (1H, 6-H, J = 6.0 Hz). Found, %: C 63.12; H 5.35; N 14.60. $C_{15}H_{15}N_3O_3$. Calculated, %: C 63.15; H 5.30; N 14.73.

1,4-Bis(1*H*-imidazo[4,5-*c*]pyridin-4-yl)benzene (IIIg). *a*. Compound **Ig**, 3.2 g (10 mmol), was dissolved in 100 ml of DMF, 1.4 g (44 mmol) of sulfur was added, and the mixture was heated at 140°C until hydrogen sulfide no longer evolved (7 h). The solvent was distilled off under reduced pressure on a water bath, the residue was dissolved in 20 ml of 20% hydrochloric acid, the unreacted sulfur was filtered off, the filtrate was adjusted to pH 9 by adding 20% aqueous sodium hydroxide, and the precipitate was filtered off, dried, and recrystallized from water. Yield 2.2 (72 %), mp > 300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.55 d (2H, 6-H, J = 5.6 Hz), 8.51 s (2H, 2-H), 8.38–8.51 m (4H, C_6H_4), 7.75 d (2H, 7-H, J = 5.6 Hz). Found, %: C 69.12; H 3.90; N 26.79. $C_{18}H_{12}N_6$. Calculated, %: C 69.22; H 3.87; N 26.91.

b. A mixture of 4.1 g (10 mmol) of compound **IIg** and 1.4 g (44 mmol) of sulfur in 100 ml of DMF was heated for 7 h at 150°C until hydrogen sulfide no longer evolved. The product was isolated as described above in *a*. Yield 2.27 g (72.5%), mp >300°C (from water).

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