*Russian Journal of Organic Chemistry, Vol. 41, No. 11, 2005, pp. 1654–1656. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 11, 2005, pp. 1688–1690.*


# New Iodo- and Nitro-substituted Pyrroles

**A.F. Mironov, O.V. Kharitonova, A.G. Efimkin, and T.A. Solomentseva**

*Lomonosov Moscow State Academy of Fine Chemical Processing, Moscow, 119571Russia*
*e-mail: httos.mitht@g23.relcom.ru*

Received November 29, 2004

**Abstract**—Treating 2,5-dimethyl-4-ethoxycarbonyl- and 2,5-dimethyl-4-carboxypyrroles with iodine furnished 3-iodo-2,5-dimethyl-4-ethoxycarbonyl- and 3,4-diiodo-2,5-dimethylpyrroles. It was established that 3-iodo-2,5-dimethyl-4-ethoxycarbonylpyrrole reacted at heating with silver nitrite to afford 2,5-dimethyl-3-nitro-4-ethoxycarbonylpyrrole, and the same reagent oxidized 3,4-diiodo-2,5-dimethylpyrrole to give 3,4-diiodo-2-methyl-5-formylpyrrole.

Historically, the majority of investigations on the porphyrin chemistry have been dedicated to the study, synthesis, and evaluation of the biochemical characteristics of the natural tetrapyrrole pigments (heme, chlorophyll), but in the last two decades considerable interest is aroused by syntheses of unusual porphyrin systems and their application as new materials. Porphyrins extended by aromatic fragments function as highly modified chromophores and therewith retain the properties inherent to the porphyrin skeleton [1]. Highly conjugated porphyrins, e.g., benzoporphyrins and pyridinoporphyrins, possess specific qualities usable in the field of medicine or new materials for electronics [2, 3]. A new stage in development of the chemistry of highly conjugated porphyrins consisted in further modification of the chromophore system of the porphyrin core by introducing thereto more complicated aromatic and heteroaromatic systems. At this stage alongside the traditional procedure for expansion of the porphyrin macroring (building up of an aromatic ring basing on a functionally substituted porphyrin) a new more productive method was introduced consisting in construction of a system of pyrrole and aromatic fragment conjugated at the β-position of the pyrrole ring with subsequent bringing of the system into a porphyrin condensation [4–6]. The last approach resulted in the synthesis of phenanthroporphyrins and phenanthrolinoporphyrins, and also of thiadiazoloporphyrins which were taken up as molecular probes, photosensitizers in the photodynamic therapy of cancer, geochemical standards in the analysis of sedimentary metalloporphyrins [6].

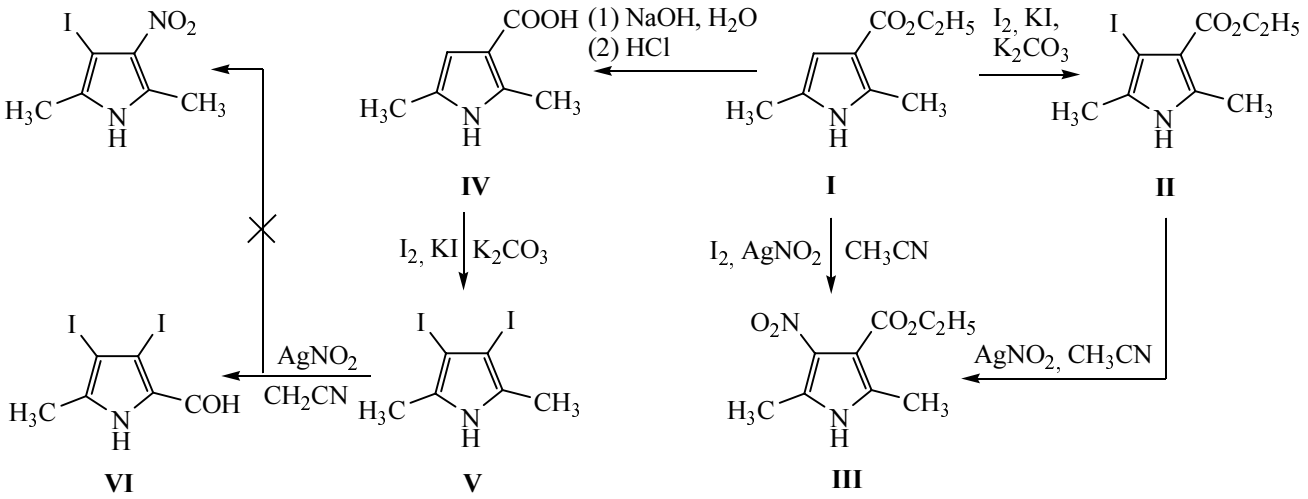
These systems were prepared by [3+1] synthesis method [7]. This approach requires a preparation of pyrrole containing various functional substituents in the β-positions.

The present study concerns preparation of β-nitro- and iodo-substituted pyrroles fit for further employment in the [3+1] pyrrole condensation. We showed formerly that direct pyrrole nitration was inefficient and frequently led to the opening of the pyrrole ring. In the newly developed synthesis we introduced the nitro group by substituting halogen in the β-position by the nitro group using silver nitrite. The reaction was performed by two procedures: in one stage by treatment with silver nitrite and iodine in acetonitrile, and in two stages involving first introduction of a halogen followed by its replacement by the nitro group.

The nitro group introduction by the first procedure consisted in treating 2,5-dimethyl-4-ethoxycarbonylpyrrole (**I**) in acetonitrile with a mixture of silver nitrite and iodine; the yield of 2,5-dimethyl-3-nitro-4-ethoxycarbonylpyrrole (**III**) was 18%. Along the second way we first prepared the β-halosubstituted pyrrole. The iodination of 2,5-dimethyl-4-ethoxycarbonylpyrrole (**I**) was carried out in aqueous methanol by the action of iodine in the presence of KI and potassium carbonate, and the yield of 3-iodo-2,5-dimethyl-4-ethoxycarbonylpyrrole (**II**) reached 80%. The replacement of iodine for nitro group was performed by boiling 3-iodo-2,5-dimethyl-4-ethoxycarbonylpyrrole (**II**) with silver nitrite in acetonitrile to get 2,5-dimethyl-3-nitro-4-ethoxycarbonylpyrrole (**III**) in a 47% yield. Thus the second procedure proved to be preferable for the overall yield along this method was 37% against 18% by the one-stage process.

We planned to use the above method for preparation of a β-halo-β-nitro-substituted pyrrole. To this end we

1070-4280/05/4111-1654©2005 Pleiades Publishing, Inc.




synthesized β,β'-diiodopyrrole. This compound was prepared in two stages. First 2,5-dimethyl-4-ethoxycarbonylpyrrole (**I**) was subjected to hydrolysis by boiling with 30% NaOH in methanol to obtain 2,5-dimethyl-4-carboxypyrrole (**IV**) in a 65% yield; the iodination was performed in aqueous methanol by the action of iodine in the presence of KI and potassium carbonate, and the yield of 3,4-diiodo-2,5-di-methylpyrrole (**V**) was 45%. The substitution of iodine by nitro group was done by the developed method of boiling 3,4-diiodo-2,5-dimethyl-pyrrole (**V**) with silver nitrite in acetonitrile for 2 h or by keeping this mixture at room temperature for 24 h. However no substitution of iodine with nitro group occurred. The main process consisted in oxidation of one of the methyls into a formyl group. Apparently the silver nitrite served as an oxidant. The oxidation product, 3,4-diiodo-2-methyl-5-formylpyrrole (**VI**), was isolated as a crystalline substance that fairly fast decomposed in air thus preventing the measuring of the melting point. The structure of compound **VI** was confirmed by spectral methods. The IR spectrum contained a strong absorption band of the C=O bond vibrations at 1670 $cm^{-1}$. In the $^1H$ NMR spectrum the singlet of the aldehyde proton was observed at 9.35 ppm. The molecular ion in the mass spectrum appeared at *m/z* 361.

## EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Shimadzu IR 435 from mulls in mineral oil. The $^1H$ and $^{13}C$ NMR spectra were registered on spectrometers Bruker 200SY at operating frequencies 200 and 50 MHz respectively and Bruker DPX-300 at operating frequencies 300 and 75 MHz. Mass spectra were taken on instruments Finnigan MAT INCOS 50 (electron impact, 70 eV) and Kratos PC-Kompact MALDI 4 (evaporation with a lazer). The melting points were measured on a Boëtius heating block. Column chromatography was carried out on Silica gel 60 (Merck), the solvents used were of "pure" and "extra pure" or Dried grade. TLC was performed on Silufol UV-254 plates, eluent hexane–ethyl acetate with different components ratio. Development was carried out in iodine vapor, or by heating to 120–140°C for 2–3 min, or under UV irradiation.

**3-Iodo-2,5-dimethyl-4-ethoxycarbonyl-pyrrole (II).** To a solution of 0.5 g (3 mmol) of 2,5-dimethyl-4-ethoxycarbonylpyrrole (**I**) in 20 ml of methanol was added dropwise at stirring a solution of 1.24 g (9 mmol) of $K_2CO_3$ in 20 ml of water, and the mixture was heated to 65°C. At this temperature to the reaction mixture was added a solution of 0.76 g (3 mmol) of $I_2$ and 1.15 g (7 mmol) of KI in 10 ml of water. The reaction mixture was stirred for 20 min and then cooled. The precipitate was filtered off and recrystallized from methanol. Yield 0.69 g (80%), $R_f$ 0.7 (hexane–ethyl acetate, 1:1), mp 116–120°C. IR spectrum, ν, $cm^{-1}$: 3256, 1675, 1217, 1099, 1029, 773. $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 1.34 t (3H, *J* 7.24 Hz), 2.22 s (3H), 2.47 s (3H), 4.26 q (2H, *J* 7.24 Hz), 8.18 br.s (1H). $^{13}C$ NMR spectrum ($CDCl_3$), δ, ppm: 13.89 (2-$CH_3$), 14.19 (3-$CH_3$), 14.30 ($OCH_2\underline{C}H_3$), 59.58 (C–I), 63.03 ($CH_2$), 129.48 ($C^5$), 129.55 ($C^4$), 135.58 ($C^2$), 164.62 (C=O). Mass spectrum, *m/z* ($I_{rel}$ %): 293 (40), 279 (20), 264 (42), 248 (28), 219 (8), 127 (12),122 (25), 93 (30), 67 (35), 51 (55), 42 (100).

**2,5-Dimethyl-3-nitro-4-ethoxycarbonyl-pyrrole (III).** To a solution of 0.4 g (1 mmol) of 3-iodo-2,5-dimethyl-4-ethoxycarbonylpyrrole (**II**) in 5 ml of acetonitrile was added 0.42 g (3 mmol) of $AgNO_2$ in 3 ml

of acetonitrile. The reaction mixture was boiled for 2 h and left standing at room temperature in the dark for 2 days. The separated precipitate was filtered off , and the product was subjected to column chromatography on silica gel, eluent ethyl ether–petroleum ether, 1:2. Yield 0.1 g (47%), $R_f$ 0.5 (hexane–ethyl acetate, 1:1), mp 110–112°C. IR spectrum, ν, $cm^{-1}$: 3300, 1720, 1680, 1600. $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 1.35 t (3H, *J* 7.1 Hz), 2.35 s (3H), 2.48 s (3H), 4.32 q (2H, *J* 7.1 Hz), 8.91 br.s (1H). Mass spectrum, *m/z* ($I_{rel}$ %): 212 (19), 166 (40), 122 (43), 92 (45), 66 (28), 54 (19), 42 (100).

**2,5-Dimethyl-4-carboxypyrrole (IV).** A mixture of 5 g (30 mmol) of 2,5-dimethyl-4-ethoxycarbonylpyrrole (**I**), 36 ml of methanol, and 18 ml of 30% solution of NaOH was boiled for 9 h, then cooled, and neutralized with concn. HCl. The separated precipitate was filtered off and dried in air. Yield 2.7 g (65%), $R_f$ 0.8 (hexane–ethyl acetate, 1:1), mp 180–184°C (decomp.). IR spectrum, ν, $cm^{-1}$: 3260, 3000–2500, 1639. $^1H$ NMR spectrum ($D_2O$), δ, ppm: 1.92 s (3H), 2.21 s (3H), 5.81 s (1H).

**3,4-Diiodo-2,5-dimethylpyrrole (V).** To a dispersion of 0.5 g (3.6 mmol) of 2,5-dimethyl-4-carboxypyrrole (**IV**) in 20 ml of methanol was added dropwise at stirring a solution of 1.24 g (9 mmol) of $K_2CO_3$ in 20 ml of water, and the mixture was heated to 65°C. At this temperature to the reaction mixture was added a solution of 0.76 g (3 mmol) of $I_2$ and 1.15 g (7 mmol) of KI in 10 ml of water. The reaction mixture was stirred for 20 min and then cooled. The precipitate was filtered off, washed with water, and recrystallized from methanol. Yield 0.56 g (45%), $R_f$ 0.8 (hexane–ethyl acetate, 3:1), mp 116–120°C (decomp.). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 2.28 s (6H), 8.01 br.s (1H). Mass spectrum, *m/z* ($I_{rel}$ %): 347 (100).

**3,4-Diiodo-2-methyl-5-formylpyrrole (VI).** A mixture of 0.6 g (1.7 mmol) of 3,4-diiodo-2,5-dimethylpyrrole (**V**), 7.5 ml of acetonitrile, and 0.63 g (4 mmol) of silver nitrite was boiled for 2 h. The acetonitrile was evaporated in a vacuum, the reaction mixture was diluted with acetone and filtered from silver salts. The reaction products were subjected to column chromatography on silica gel, eluent petroleum ether–ethyl acetate, 1:1. Yield 0.12 g (19%), $R_f$ 0.64 (hexane–ethyl acetate, 5:1). IR spectrum, ν, $cm^{-1}$: 3351, 1670. $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 2.46 s (3H), 9.35 s (1H), 10.13 br.s (1H). Mass spectrum, *m/z* ($I_{rel}$ %): 361 (100), 360 (60), 235 (21), 127 (47).

## REFERENCES

1. Lash, T.D. and Novak B.H., *Tetrahedron Lett*., 1995, vol. 36, p. 4381.
2. Lash, T.D., Chandrasekar, P., Osuma, A.T., Chaney, S.T., and Spence, J.D., *J. Org. Chem*., 1998, vol. 63, p. 8455.
3. Vicente, M., Jaquinod, L., Khoury, R., Mandrona, A., Smith, K.M., *Tetrahedron Lett*., 1999, vol. 40, p. 8763.
4. Lin, Y. and Lash, T.D., *Tetrahedron Lett*., 1995, vol. 36, p. 9441.
5. Novak, B.H. and Lash, T.D., *J. Org. Chem*., 1998, vol. 63, p. 3998.
6. Lash, T.D., Wijesinghe, C., Osuma, A.T., and Patel, J.R., *Tetrahedron Lett*., 1997, vol. 38, p. 2031.
7. Evtigneeva, R.P., Mironov, A.F., and Fleiderman, L.I., *Dokl. Akad. Nauk SSSR,* 1973, vol. 210, p. 1090.