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Synthesis of polycyclic indole derivatives from 2,4,6-trinitrotoluene

Maxim A. Bastrakov, Aleksei M. Starosotnikov, Margarita A. Leontieva, Aleksandr Kh. Shakhnes and Svyatoslav A. Shevelev*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: shevelev@ioc.ac.ru

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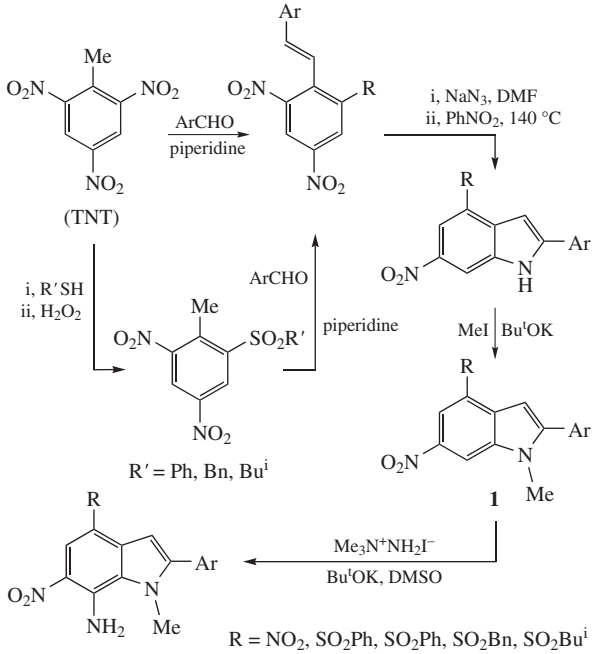
Polycyclic indole derivatives of imidazole and pyrazine series with previously unknown combination of substituents, as well as representatives of the new heterocyclic systems of triazole and furoxan series, were synthesized on the basis of 2-aryl-4-isobutylsulfonyl-6-nitroindoles – products of 2,4,6-trinitrotoluene transformations.

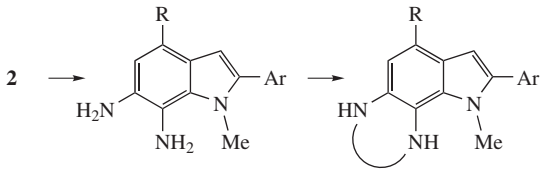
A considerable interest of scientists to the chemistry of indole, as well as to the synthesis and functionalization of its derivatives, is caused by the fact that a wide variety of indole-containing compounds was found in nature. Many of indole derivatives both of natural and synthetic origin possess various biological activity.[1(a)] Such compounds are of interest as precursors for their synthetic analogues as potential chemotherapeutic means. The significant part of data on the synthesis and reactivity of indole derivatives is summarized in the monograph.[1(b)]

Earlier,[2] a method for the synthesis of the new type of substituted indoles – 2-aryl-4-R-6-nitroindoles **1** (R = NO_2, SO_2Ph, SO_2CH_2Ph, SO_2Bu^i) from 2,4,6-trinitrotoluene (TNT) was developed. It was shown that these compounds undergo selective amination at the 7-position under vicarious nucleophilic substitution conditions and the action of 1,1,1-trimethylhydrazinium iodide (TMHI) in the presence of Bu^tOK giving rise to *ortho*-nitroamines **2**.[3,4] These chemical transformations are summarized in Scheme 1.

Reduction of the nitro group at the 6-position in amines **2** would allow one to obtain the convenient precursor for the annelation of the additional heterocyclic fragments (Scheme 2). However, in case of 7-amino-4,6-dinitroindoles (**2**, R = NO_2), this reaction does not proceed selectively and the mixture of the nitro group reduction products at the 4- and 6-positions is obtained.

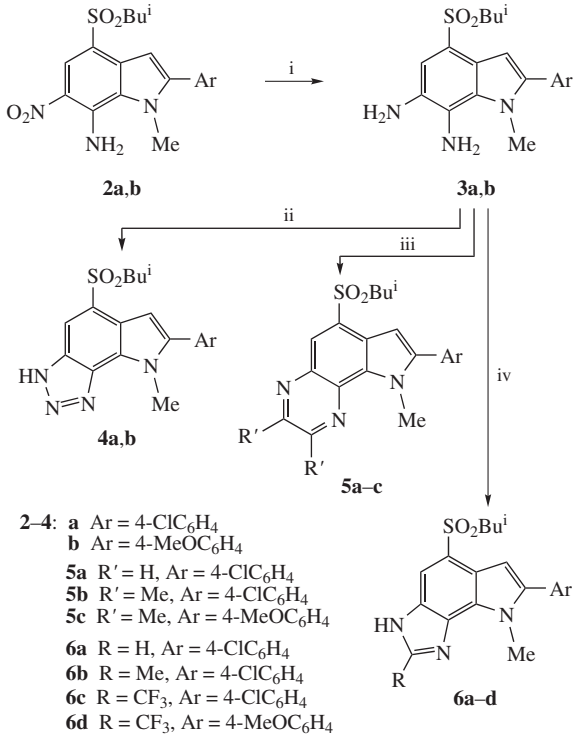


Scheme 1

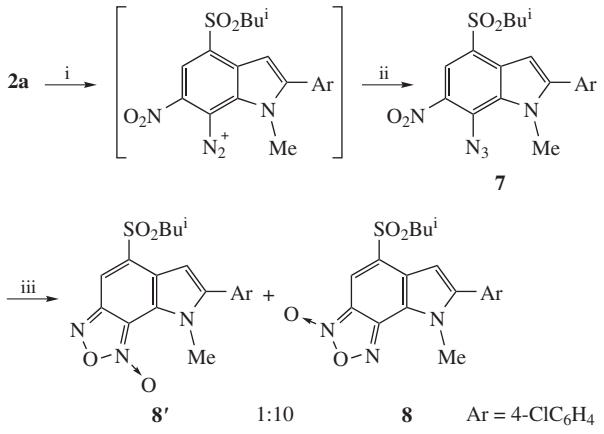


Scheme 2

In this connection, it seemed to be expedient to use in the reduction indoles **2** in which nitro group at the 4-position is



Scheme 3 *Reagents and conditions*: i, N_2H_4 (12 equiv.), $FeCl_3 \cdot 6H_2O$ (0.2 equiv.), C_{act}, MeOH, 65 °C, 48 h; ii $NaNO_2$ (1.2 equiv.), AcOH, 20 °C, 2 h; iii, R′C(O)C(O)R′ (1.2 equiv.), MeCN or EtOH, refluxing for 3 h; iv, RCOOH–HCl, refluxing for 2–8 h.



Scheme 4 *Reagents and conditions*: i, $NaNO_2$ (1 equiv.), AcOH–H_2SO_4, 10 °C, 1 h; ii, NaN_3 (4 equiv.) (aqueous solution), 20 °C, 30 min; iii, toluene, reflux, 30 h.

replaced by another electron-withdrawing substituent (SO_2Bu^i). The reduction of the 6-NO_2 group in nitroamines **2** leads to expected diamines **3**, which are convenient precursors of the wide variety of fused polycyclic systems (Scheme 3).

We found that diamines **3** on interaction with nitrous acid gave previously unknown polycyclic systems **4** of the triazole series. Heating of the initial diamines in carboxylic acids or their interaction with 1,2-dicarbonyl compounds leads to the new tricyclic systems with previously unknown combination of the substituents of imidazole (**6**) and pyrazine (**5**) series (Scheme 3).

We studied the diazotization of amine **2a**. It was found that the use of nitrosyl sulfuric acid is necessary for this reaction. On pouring of the diazonium salt solution on sodium azide aqueous solution, azide **7** is formed in good yield.

On heating of the toluene solution of azide **7** under reflux an intramolecular cyclization occurs and the representative of the new tricyclic system – [1,2,5]oxadiazolo[3,4-*g*]indole 3-oxide forms, which in DMSO solution exists as a mixture of two isomers **8** and **8′** in a ratio of 10:1. It is known that the isomers of benzofuroxans in solutions very easily pass each other and it is possible to isolate only one (the most stable) isomer.[5] Compounds **8** and **8′** isomerize in DMSO solution and achieve an equilibrium, in which the most stable isomer (**8**) predominates. It is proposed that this furoxan derivative in crystalline form exist as **8** judging by the published data[6] where the position of N-oxide moiety in 8-methyl-5-nitro-7-phenyl-8*H*-[1,2,5]oxadiazolo[3,4-*g*]indole-3-oxide was established by X-ray analysis.

The structures of the compounds synthesized were proved by ^{1}H NMR and IR spectroscopy, mass spectrometry (in all cases molecular ions were registered) and microanalysis.[†]

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† ^{1}H NMR spectra (in [$^2H_6$]DMSO) were recorded on a Bruker AM-300 spectrometer.

2a: yield 96%, mp 218–222 °C (EtOH). ^{1}H NMR, δ: 0.96 (d, 6H, 2 Me, ^3J 6.7 Hz), 2.05 (m, 1H, CH), 3.21 (d, 2H, CH_2, ^3J 5.9 Hz), 4.04 (s, 3H, NMe), 6.88 (s, 1H, H-3), 7.65 (s, 4H, Ph), 8.07 (s, 2H, NH_2), 8.29 (s, 1H, H-5).

2b: yield 94%, mp 160–165 °C (EtOH) (lit.,[4] 160–163 °C). ^{1}H NMR, δ: 0.97 (d, 6H, 2Me, ^3J 6.6 Hz), 2.06 (m, 1H, CH), 3.20 (d, 2H, CH_2, ^3J 6.4 Hz), 3.84 (s, 3H, OMe), 4.03 (s, 3H, NMe), 6.78 (s, 1H, H-3), 7.14 (d, 2H, Ph, ^3J 8.3 Hz), 7.56 (d, 2H, Ph, ^3J 8.3 Hz), 8.00 (s, 2H, NH_2), 8.29 (s, 1H, H-5).

3a: yield 60%, mp 210–215 °C. ^{1}H NMR, δ: 0.91 (d, 6H, 2Me, ^3J 6.7 Hz), 1.96 (m, 1H, CH), 3.01 (d, 2H, CH_2, ^3J 6.3 Hz), 3.88 (s, 3H, NMe), 4.68 (s, 2H, NH_2), 5.09 (s, 2H, NH_2), 6.65 (s, 1H, H-3), 7.12 (s, 1H, H-5), 7.55 (s, 4H, Ph).

3b: yield 48%, mp 137–140 °C. ^{1}H NMR, δ: 0.91 (d, 6H, 2Me, ^3J 6.7 Hz), 1.95 (m, 1H, CH), 3.00 (d, 2H, CH_2, ^3J 6.3 Hz), 3.82 (s, 3H, OMe), 3.86 (s, 3H, NMe), 4.67 (s, 2H, NH_2), 5.06 (s, 2H, NH_2), 6.52 (s, 1H, H-3), 7.07 (d, 2H, Ph, ^3J 8.7 Hz), 7.09 (s, 1H, H-5), 7.44 (d, 2H, Ph, ^3J 8.7 Hz).

4a: yield 87%, mp 270–273 °C. ^{1}H NMR, δ: 0.97 (d, 6H, 2Me, ^3J 6.7 Hz), 2.06 (m, 1H, CH), 3.33 (d, 2H, CH_2, ^3J 6.2 Hz), 4.31 (s, 3H, NMe), 7.09 (s, 1H, H-3), 7.62 (d, 2H, Ph, ^3J 8.3 Hz), 7.76 (d, 2H, Ph, ^3J 8.3 Hz), 8.08 (s, 1H, H-5), 16.41 (br. s, 1H, NH).

4b: yield 58%, mp 185–195 °C. ^{1}H NMR, δ: 0.95 (s, 6H, 2Me), 2.05 (m, 1H, CH), 3.33 (d, 2H, CH_2, ^3J 12.3 Hz), 3.83 (s, 3H, OMe), 4.26 (s, 3H, NMe), 6.97 (s, 1H, H-3), 7.11 (s, 2H, Ph), 7.63 (s, 2H, Ph), 8.05 (s, 1H, H-5), 16.77 (br. s, 1H, NH).

5a: yield 35%, mp 172–175 °C. ^{1}H NMR, δ: 0.99 (d, 6H, 2Me, ^3J 6.7 Hz), 2.11 (m, 1H, CH), 3.41 (d, 2H, CH_2, ^3J 6.4 Hz), 4.43 (s, 3H, NMe), 7.18 (s, 1H, H-3), 7.65 (d, 2H, Ph, ^3J 8.3 Hz), 7.77 (d, 2H, Ph, ^3J 8.3 Hz), 8.19 (s, 1H, H-5), 9.02 (s, 1H), 9.09 (s, 1H).

5b: yield 65%, mp 173–174 °C. ^{1}H NMR, δ: 0.96 (d, 6H, 2Me, ^3J 6.7 Hz), 2.05 (m, 1H, CH), 2.70 (s, 3H, Me), 2.75 (s, 3H, Me), 3.36 (d, 2H, CH_2, ^3J 6.6 Hz), 4.39 (s, 3H, NMe), 7.10 (s, 1H, H-3), 7.62 (d, 2H, Ph, ^3J 8.3 Hz), 7.74 (d, 2H, Ph, ^3J 8.3 Hz), 8.05 (s, 1H, H-5).

5c: yield 75%, mp 195–200 °C. ^{1}H NMR, δ: 0.96 (d, 6H, 2Me, ^3J 4.1 Hz), 2.07 (m, 1H, CH), 2.70 (s, 3H, Me), 2.75 (s, 3H, Me), 3.32 (d, 2H, CH_2, ^3J 6.6 Hz), 3.84 (s, 3H, OMe), 4.38 (s, 3H, NMe), 6.99 (s, 1H, H-3), 7.12 (d, 2H, Ph, ^3J 6.3 Hz), 7.61 (d, 2H, Ph, ^3J 6.3 Hz), 8.05 (s, 1H, H-5).

6a: yield 24%, mp 165–170 °C. ^{1}H NMR, δ: 0.93 (d, 6H, 2Me, ^3J 6.2 Hz), 2.04 (m, 1H, CH), 3.23 (d, 2H, CH_2, ^3J 5.4 Hz), 4.31 (s, 3H, NMe), 6.97 (s, 1H, H-3), 7.59 (d, 2H, Ph, ^3J 7.6 Hz), 7.73 (d, 2H, Ph, ^3J 7.6 Hz), 7.84 (s, 1H, H-5), 8.46 (s, 1H, CH), 13.05 (br. s, 1H, NH).

6b: yield 67%, mp 235–240 °C. ^{1}H NMR, δ: 0.94 (d, 6H, 2Me, ^3J 6.7 Hz), 2.02 (m, 1H, CH), 2.88 (s, 3H, Me), 3.30 (d, 2H, CH_2, ^3J 6.4 Hz), 4.20 (s, 3H, NMe), 7.08 (s, 1H, H-3), 7.63 (d, 2H, Ph, ^3J 8.3 Hz), 7.74 (d, 2H, Ph, ^3J 8.3 Hz), 7.89 (s, 1H, H-5).

6c: yield 75%, mp 280–283 °C. ^{1}H NMR, δ: 0.95 (d, 6H, 2Me, ^3J 6.6 Hz), 2.02 (m, 1H, CH), 3.28 (d, 2H, CH_2, ^3J 6.1 Hz), 4.28 (s, 3H, NMe), 7.05 (s, 1H, H-3), 7.60 (d, 2H, Ph, ^3J 8.2 Hz), 7.74 (d, 2H, Ph, ^3J 8.2 Hz), 7.87 (s, 1H, H-5), 14.63 (br. s, 1H, NH).

6d: yield 87%, mp 225–230 °C. ^{1}H NMR, δ: 0.95 (d, 6H, 2Me, ^3J 6.6 Hz), 2.08 (m, 1H, CH), 3.27 (d, 2H, CH_2, ^3J 6.3 Hz), 3.83 (s, 3H, OMe), 4.25 (s, 3H, NMe), 6.93 (s, 1H, H-3), 7.11 (d, 2H, Ph, ^3J 8.4 Hz), 7.62 (d, 2H, Ph, ^3J 8.4 Hz), 7.85 (s, 1H, H-5), 14.59 (br. s, 1H, NH).

7: yield 93%, mp 138–143 °C. ^{1}H NMR, δ: 0.98 (d, 6H, 2Me, ^3J 6.6 Hz), 2.08 (m, 1H, CH), 3.34 (d, 2H, CH_2, ^3J 6.4 Hz), 4.09 (s, 3H, NMe), 7.06 (s, 1H, H-3), 7.66–7.75 (m, 4H, Ph), 8.29 (s, 1H, H-5).

8: yield 25%, mp 237–241 °C. ^{1}H NMR, δ: (major isomer) 1.01 (d, 6H, 2Me, ^3J 6.7 Hz), 2.15 (m, 1H, CH), 3.39 (d, 2H, CH_2, ^3J 6.5 Hz), 4.17 (s, 3H, NMe), 7.09 (s, 1H, H-3), 7.55 (s, 1H, H-5), 7.63 (d, 2H, Ph, ^3J 8.4 Hz), 7.75 (d, 2H, Ph, ^3J 8.4 Hz).