Synthesis of 14π-electron *peri*-annelated tricyclic heteroaromatic systems based on 2,4,6-trinitrotoluene

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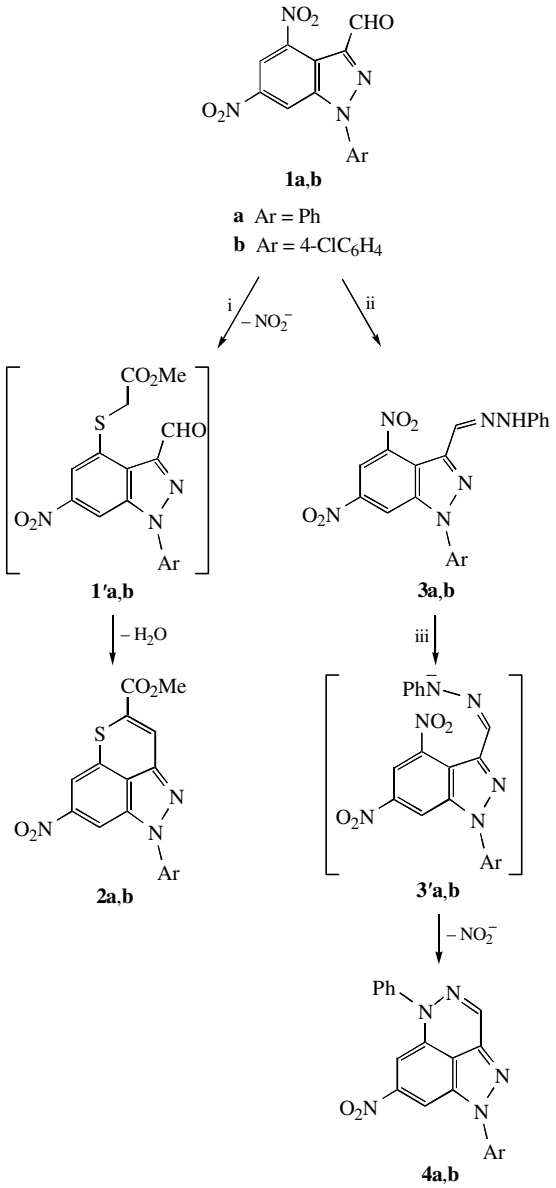
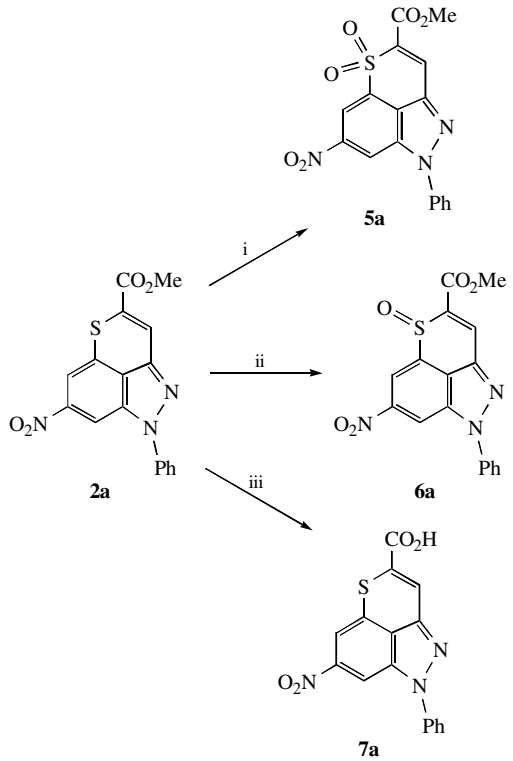
Methyl 1-aryl-7-nitro-1*H*-thiopyrano[4,3,2-*cd*]indazol-4-carboxylates **2** and 1,5-diaryl-7-nitro-1,5-dihydropyrazolo[3,4,5-*de*]-cinnolines **4** were prepared based on 1-aryl-3-formyl-4,6-dinitro-1*H*-indazoles **1**, which were synthesised previously starting from 2,4,6-trinitrotoluene.

Previously,[1] we prepared 1-aryl-3-formyl-4,6-dinitroindazoles **1** starting from 2,4,6-trinitrotoluene (TNT). We found that the action of anionic N-, O- and S-nucleophiles on compounds **1** under mild conditions resulted in selective substitution for the nitro group at the 4-position. In this work, we used this property of compounds **1** for the synthesis of 14π-electron *peri*-annelated tricyclic heteroaromatic systems.



Scheme 1 *Reagents and conditions*: i, 1 equiv. $HSCH_2CO_2Me$, 2 equiv. K_2CO_3, N-MP, 60 °C, 10 h; ii, 1 equiv. $PhNHNH_2$·HCl, EtOH, 78 °C, 3 h; iii, 1 equiv. K_2CO_3, N-MP, 80 °C, 10 h.



Scheme 2 *Reagents and conditions:* i, 35% H_2O_2 (8 equiv.), CF_3COOH, 20 °C, 0.5 h; ii, 35% H_2O_2 (120 equiv.), AcOH, 60 °C, 12 h; iii, 10 equiv. NaOH, H_2O, 100 °C, 20 h.

Thus, the interaction of formyldinitroindazoles **1a**,**b** with the methyl ester of thioglycolic acid in *N*-methylpyrrolidone or DMF in the presence of solid K_2CO_3 resulted in *peri*-annelated heterocyclic compounds, methyl 1-aryl-7-nitro-1*H*-thiopyrano-[4,3,2-*cd*]indazol-4-carboxylates **2a**,**b** (Scheme 1). It is believed that 4-NO_2 is initially replaced under the action of the thioglycolate–K_2CO_3 system with the formation of product **1′**. This product undergoes the base-catalysed intramolecular condensation of the formyl group with the active methylene unit of the SCH_2CO_2Me substituent (Scheme 1). Another reaction path, precondensation at the methylene unit with the subsequent intramolecular substitution for 4-NO_2 under the action of the condensation product, seems improbable because substitution for 4-NO_2 in formyldinitroindazoles **1** under the action of aliphatic thiols occurs in milder conditions (~20 °C) than the formation of tricyclic compounds **2** (at 60 °C).

Under standard conditions, formyldinitroindazoles **1a**,**b** form phenylhydrazones **3a**,**b**, which undergo intramolecular cyclization with substitution for 4-NO_2 in *N*-methylpyrrolidone or DMF in the presence of K_2CO_3 to give *peri*-annelated aromatic heterocycles, 1,5-diaryl-7-nitro-1,5-dihydropyrazolo[3,4,5-*de*]-cinnolines **4a**,**b**. It is believed that the reaction occurs *via* the deprotonation of phenylhydrazones with the formation of N-anions **3′** (Scheme 1).

Reactions of thiopyranoindazoles **2** were studied using tricyclic compound **2a** as an example. Compound **2a** was readily and selectively oxidised with aqueous H_2O_2 in CF_3COOH or AcOH to sulfone **5a** or sulfoxide **6a**, respectively (Scheme 2). The alkaline hydrolysis of compound **2a** resulted in tricyclic carboxylic acid **7a** (Scheme 2).

Thus, starting from 1-aryl-3-formyl-4,6-dinitro-1*H*-indazoles **1**, which in turn were prepared from TNT, we synthesised two types of 14π-electron *peri*-annelated tricyclic heteroaromatic systems: 1*H*-thiopyrano[4,3,2-*cd*]indazoles and 1,5-dihydropyrazolo[3,4,5-*de*]cinnolines.

Note that 14π-electron *peri*-annelated heteroaromatic systems containing two six-membered rings and one five-membered ring are a rare type of heterocycles (*e.g.*, see refs. 2, 3). As for tricyclic systems prepared in this work, we failed to find published procedures for the synthesis of such systems; only the pharmacological properties of 1*H*-thiopyrano[4,3,2-*cd*]indazoles with other substituents were reported previously.[4]

The structure and composition of the prepared compounds were supported by ^{1}H NMR spectroscopy, electron-ionization mass spectrometry (the formation of molecular ions was detected in all cases), IR spectroscopy and elemental analysis.†

† ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer with TMS as a standard compound.

2a: 60% yield, mp 230–231 °C ($CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 4.0 (s, 3H, Me), 7.45 (t, 1H, Ph, $^3J_{H–H}$ 7.2 Hz), 7.6 (t, 2H, Ph, $^3J_{H–H}$ 7.2 Hz), 7.7 (s, 1H, H_{arom}), 7.75 (d, 2H, Ph, $^3J_{H–H}$ 7.2 Hz), 7.95 (s, 1H, H_{arom}), 8.15 (s, 1H, H_{arom}).

2b: 77% yield, mp > 300 °C ($CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.95 (s, 3H, Me), 7.55 (d, 2H, H_{arom}, $^3J_{H–H}$ 8.8 Hz), 7.6 (d, 3H, H_{arom}, $^3J_{H–H}$ 8.8 Hz), 7.95 (s, 1H, H_{arom}), 8.1 (s, 1H, H_{arom}).

3a: 74% yield, mp 260–261 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.8 (t, 1H, Ph), 7.0 (d, 2H, Ph), 7.2 (t, 2H, Ph), 7.6 (t, 1H, Ph), 7.7 (t, 2H, Ph), 7.85 (d, 2H, Ph), 8.2 (s, 1H, CH=N), 8.55 (s, 1H, H_{arom}), 8.75 (s, 1H, H_{arom}), 10.6 (s, 1H, NH).

3b: 61% yield, mp 267–269 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.9 (m, 1H, Ph), 7.1–7.3 (m, 4H, Ph), 7.7 (s, 1H, CH=N), 7.8 (d, 2H, H_{arom}, $^3J_{H–H}$ 8.0 Hz), 8.05 (d, 2H, H_{arom}, $^3J_{H–H}$ 8.0 Hz), 8.8 (s, 1H, H_{arom}), 8.9 (s, 1H, H_{arom}), 11.75 (s, 1H, NH).

4a: 47% yield, mp 257–259 °C. ^{1}H NMR ($CDCl_3$) δ: 7.1 (s, 1H, H_{arom}), 7.4–7.55 (m, 2H, Ph), 7.6–7.7 (m, 6H, Ph), 7.8 (d, 2H, Ph, $^3J_{H–H}$ 7.2 Hz), 7.9 (s, 1H, H_{arom}), 8.1 (s, 1H, CH=N).

4b: 52% yield, mp 264–265 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.95 (s, 1H, H_{arom}), 7.5 (m, 1H, Ph), 7.6 (m, 6H, Ph), 8.9 (m, 3H, Ph, H_{arom}), 8.2 (s, 1H, CH=N).

5a: 81% yield, mp 218–220 °C ($CHCl_3$). ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.0 (s, 3H, Me), 7.5–7.8 (m, 3H, Ph), 7.9 (d, 2H, Ph, $^3J_{H–H}$ 7.9 Hz), 8.55 (s, 1H, CH), 8.75 (s, 1H, H_{arom}), 8.9 (s, 1H, H_{arom}).

6a: 38% yield, mp 224–225 °C ($CHCl_3$). ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.0 (s, 3H, Me), 7.6–7.8 (m, 3H, Ph), 7.9 (d, 2H, Ph, $^3J_{H–H}$ 7.3 Hz), 8.05 (s, 1H, CH), 8.6 (s, 1H, H_{arom}), 8.9 (s, 1H, H_{arom}).

7a: 81% yield, mp 303–304 °C ($CHCl_3$). ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.45 (t, 1H, $^3J_{H–H}$ 6.7 Hz, Ph), 7.6 (t, 2H, Ph, $^3J_{H–H}$ 7.3 Hz, Ph), 7.8 (m, 3H, Ph, CH), 8.1 (s, 1H, H_{arom}), 8.25 (s, 1H, H_{arom}).

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References

1 V. M. Vinogradov, A. M. Starosotnikov and S. A. Shevelev, *Mendeleev Commun*., 2002, 198.
2 V. V. Mezheritskii and V. V. Tkachenko, in *Adv. Heterocycl. Chem*., 1990, vol. 51, p. 1.
3 S. Tumkevicius, *Liebigs Ann. Chem*., 1995, 1703.
4 L. M. Werbel, E. F. Elslager and D. F. Worth, *Adv. Pharmacol. Ther., Proc. 7th Int. Congr. Pharmacol*., 1979, vol. 10, pp. 3–8 (*Chem. Abstr*., 1980, **92**, 215).

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