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Simple and efficient synthesis of substituted 1*H*-indazoles

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3-Aryl-5-aroylindazoles were prepared by a simple two-stage protocol from 3,5-diaroyl-2,6-dimethylpyridines.

Indazoles are heterocyclic compounds structurally close to indoles ('azaindoles') being their bioisosteres.[1] However, unlike indoles, derivatives of indazoles are of rare natural occurrence. For the last three decades only three alkaloids with indazole ring system, that is *Nigellicine*, *Nigellidine* and *Nigeglanine*, have been isolated from the plants of *Ranunculáceae*: *Nigella sativa* and *Nigella glandulifera* family.[2–6] Furthermore, pharmaceutically important indazoles (bendazac, benzydamine, lonidamine, bindarit, granisetron) show anti-inflammatory, anticancer, immunosuppressive, serotonergic activity.[7–16]

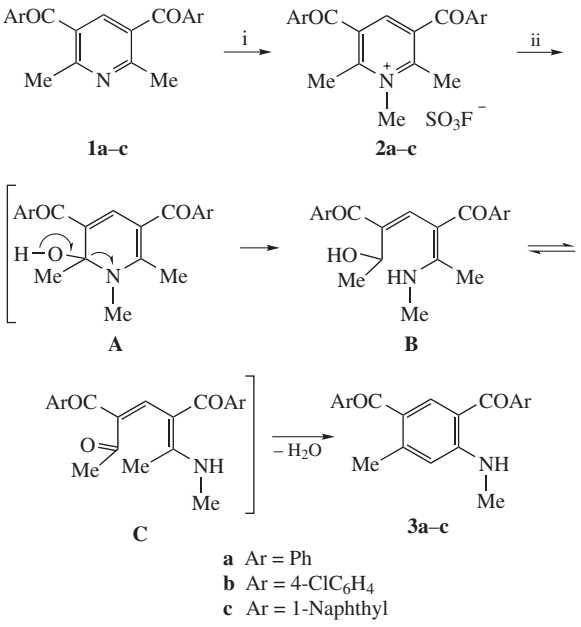
The standard synthetic methods yielding 1*H*-indazoles are based on, first, the pyrazole ring closure in *ortho*-methyl-, diazo- and *N*-nitrosoaromatic compounds by intramolecular heterocyclization; second, reaction of *ortho*-halogen- or *ortho*-hydroxyaromatic compounds with hydrazine; third, reactions of 2-azidobenzoic esters.[17–19] Intramolecular cyclization of *o*-halobenzaldehyde or *o*-halophenone hydrazones leads to 3-unsubstituted indazoles in high yields.[17]

To date, only four general methods for the synthesis of 3-arylindazoles are known. There are aryne annulation using dialkyl- and *N*-tosylhydrazones, Diels–Alder cycloaddition between 1-acetyl-4-styrylpyrazoles and *N*-methyl- or *N*-phenylmaleimide, Pd-catalyzed intramolecular amination of hydrazones of *o*-bromobenzophenones and intramolecular cyclization of *o*-hydroxybenzophenone hydrazones.[20–25] Sodium hydride-promoted interaction between arylidenehydrazines and nitroarenes in DMF affords 3-arylindazoles;[26] however, this reaction due to poor yields is of low synthetic importance.

The aim of this research was to develop a new approach to functionalized indazoles from 3,5-diaroyl-2,6-dimethylpyridines **1** by a two-step pyrazole ring formation (Schemes 1 and 2).

Apparently, transformation of pyridinium salts **2a–c** into diaroylanilines **3a–c** proceeds through the nucleophilic attack by the hydroxide ion at the most electrodeficient carbon in the pyridine ring at 2-position to form pseudo-base **A** (a neutral analogue of a σ-complex). The following base catalyzed ionic ring opening with C–N bong cleavage leads to open form **B**, which undergoes intramolecular aldol condensation involving methyl and acetyl groups in open form **C** (Scheme 1).†,[27]

At the next stage, N-nitrozation of *N*-methylanilines **3a–c** and intramolecular reductive cyclization were performed. Pyrazole ring closure took place as a result of intramolecular condensation in intermediate *N*-methyl-*N*-arylhydrazine **A** formed *in situ* upon reduction of *N*-nitroso compounds **4a–c**. Both nitrosation of compounds **3a–c** and reductive heterocyclization of compounds **4a–c** into indazoles **5a–c** proceed at room temperature in preparative yields (Scheme 2).‡



Scheme 1 *Reagents and conditions*: i, FSO_3Me/DCE, 0 °C, 30 min, then room temperature, 48 h; ii, 10% NaOH/EtOH, 80 °C, 1 h.

† Structures of compounds **2–5** were confirmed by ^{1}H NMR (Bruker Advance AC-400, 400.13 MHz) and ATR-FTIR (Simex FT-801) spectroscopy, while their composition was determined by elemental analysis (Perkin Elmer 2400).

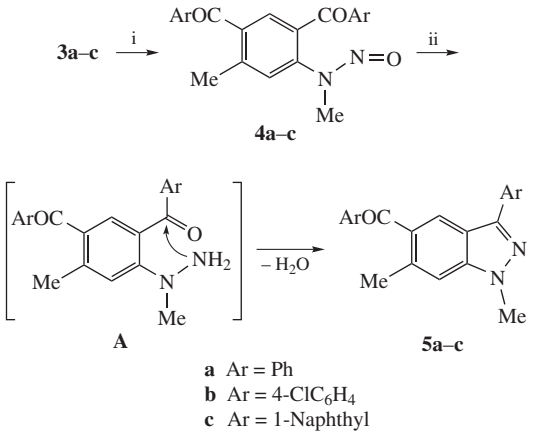
3,5-Diaroyl-1,2,6-trimethylpyridinium fluoridosulfates **2a–c** (*general procedure*). A solution of methyl fluoridosulfate (3.42 g, 30 mmol) in 1,2-dichloroethane (12 ml) was added dropwise at 0 °C to a stirred solution of the corresponding pyridine **1a–c**[28] (20 mmol) in 1,2-dichloroethane (24 ml). The reaction mixture was stirred for 30 min at 0 °C and then 2 days at room temperature. The reaction mixture was diluted with diethyl ether (30 ml). The precipitated product was filtered off and dried.

3,5-Dibenzoyl-1,2,6-trimethylpyridinium fluoridosulfate **2a**: colourless crystals, yield 95%, mp 252–253 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ: 2.70 (s, 6H, 2,6-Me), 4.18 (s, 3H, NMe), 7.59–7.64 (m, 4H, 3,5-COPh), 7.75–7.80 (m, 2H, 3,5-COPh), 7.87–7.92 (m, 4H, 3,5-COPh), 8.62 (s, 1H, 4-H). Found (%): C, 61.57; H, 4.65; N, 3.20. Calc. for $C_{22}H_{20}FNO_5S$ (%): C, 61.53; H, 4.69; N, 3.26.

2,4-Diaroyl-N,5-dimethylanilines **3a–c** (*general procedure*). A mixture of the corresponding pyridinium salt **2a–c** (5 mmol) in ethanol (10 ml) and 10% solution of sodium hydroxide in ethanol (10 ml) was heated in a water bath at 80 °C for 1 h. Cooled to room temperature reaction mixture was diluted with water (40 ml), the precipitated light-yellow crystals were filtered off and dried. The crude product was purified by LC (silica gel, $CHCl_3$) and recrystallization.

(4-Methyl-6-methylamino-1,3-phenylene)bis(phenylmethanone) **3a**: pale yellow crystals, yield 73%, mp 120–121 °C (ethanol).[29] IR (ν/cm^{-1}): 3318 (NH), 1676, 1612 (C=O). ^{1}H NMR ($CDCl_3$) δ: 1.92 (s, 3H, 4-Me), 3.02 (d, 3H, HN–*Me*, *J* 5.1 Hz), 6.63 (s, 1H, 5-H), 7.34–7.69 (m, 10H, 1,3-COPh), 8.02 (s, 1H, 2-H), 8.95 (br. s, 1H, *H*N–Me).

For characteristics of compounds **2b**,**c** and **3b**,**c**, see Online Supplementary Materials.



Scheme 2 *Reagents and conditions*: i, $NaNO_2$, AcOH, room temperature, 1 h; ii, Zn, AcOH, 5–10 °C, then room temperature, 30 min.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.05.020.

‡ *2,4-Diaroyl-N,5-dimethyl-*N*-nitrosoanilines* **4a–c** (*general procedure*). Sodium nitrite (0.97 g, 14 mmol) was added portionwise to a solution of the corresponding aniline **3a–c** (7 mmol) in glacial acetic acid (14 ml) at room temperature on stirring. After more 1 h of stirring the reaction mixture was poured into water (30 ml). The precipitated crystalline solid was filtered off and dried.

*[4-Methyl-6-(*N*-methyl-*N*-nitrosoamino)-1,3-phenylene]bis(phenylmethanone)* **4a**: colourless crystals, yield 94%, mp 173–174 °C (ethanol). IR (ν/cm^{-1}): 1680, 1670 (C=O), 1440 (N–N=O). ^{1}H NMR ($CDCl_3$) δ: 2.07 (s, 3H, 4-Me), 3.27 (s, 3H, NMe), 7.40–7.46 (m, 5H, COPh, 5-H), 7.48–7.52 (m, 3H, COPh), 7.54–7.59 (m, 1H, COPh), 7.74–7.78 (m, 2H, COPh), 7.81 (s, 1H, 2-H). Found (%): C, 73.77; H, 5.04; N, 7.80. Calc. for $C_{22}H_{18}N_2O_3$ (%): C, 73.73; H, 5.06; N, 7.82.

*[4-Methyl-6-(*N*-methyl-*N*-nitrosoamino)-1,3-phenylene]bis[(4-chlorophenyl)methanone]* **4b**: colourless crystals, yield 95%, mp 202–203 °C (ethanol). IR (ν/cm^{-1}): 1693, 1672 (C=O), 1460 (N–N=O). ^{1}H NMR ($CDCl_3$) δ: 2.14 (s, 3H, 4-Me), 3.29 (s, 3H, NMe), 7.33–7.42 (m, 5H, COAr, 5-H), 7.46–7.50 (m, 2H, COAr), 7.67–7.71 (m, 2H, COAr), 7.78 (s, 1H, 2-H). Found (%): C, 61.88; H, 3.81; N, 6.60. Calc. for $C_{22}H_{16}Cl_2N_2O_3$ (%): C, 61.84; H, 3.77; N, 6.56.

*[4-Methyl-6-(*N*-methyl-*N*-nitrosoamino)-1,3-phenylene]bis(1-naphthylmethanone)* **4c**: colourless crystals, yield 85%, mp 172–173 °C (propanol). IR (ν/cm^{-1}): 1698, 1650 (C=O), 1468 (N–N=O). ^{1}H NMR ($CDCl_3$) δ: 2.60 (s, 3H, 4-Me), 3.16 (s, 3H, NMe), 7.28–7.34 (m, 1H, 1-Naphthoyl), 7.37 (s, 1H, 5-H), 7.43–7.48 (m, 1H, 1-Naphthoyl), 7.51–7.60 (m, 6H, 1-Naphthoyl), 7.73 (s, 1H, 2-H), 7.72–7.75 (m, 1H, 1-Naphthoyl), 7.81–7.86 (m, 1H, 1-Naphthoyl), 7.89–7.95 (m, 2H, 1-Naphthoyl), 8.00–8.05 (m, 1H, 1-Naphthoyl), 8.53–8.57 (m, 1H, 1-Naphthoyl), 8.65–8.70 (m, 1H, 1-Naphthoyl). Found (%): C, 78.62; H, 4.88; N, 6.19. Calc. for $C_{30}H_{22}N_2O_3$ (%): C, 78.59; H, 4.84; N, 6.11.

*3-Aryl-5-aroyl-1,6-dimethyl-1*H*-indazoles* **5a–c** (*general procedure*). Corresponding nitrosoaniline **4a–c** (10 mmol) was dissolved in a mixture of DMF (30 ml) and glacial acetic acid (30 ml). To this solution zinc dust (3.2 g, 50 mmol) was added portionwise on stirring so that temperature of the reaction mixture did not exceed 10 °C. The mixture was stirred for additional 30 min at room temperature. Then it was heated to 100 °C, the solid residue was filtered off hot and washed on the filter with hot acetic acid (5 ml). The combined filtrate was cooled and diluted with water (30 ml). The precipitated crystalline indazole **5a–c** was filtered off and dried.

*(1,6-Dimethyl-3-phenyl-1*H*-indazol-5-yl)(phenyl)methanone* **5a**: colourless crystals, yield 62%, mp 161–162 °C (ethanol). IR (ν/cm^{-1}): 1688 (C=O). ^{1}H NMR ($CDCl_3$) δ: 2.05 (s, 3H, 6-Me), 4.15 (s, 3H, N-Me), 7.36 (s, 1H, 7-H), 7.41–7.55 (m, 8H, COPh, 3-Ph), 7.95–8.01 (m, 2H, COPh), 8.32 (s, 1H, 4-H). Found (%): C, 81.02; H, 5.60; N, 8.53. Calc. for $C_{22}H_{18}N_2O$ (%): C, 80.96; H, 5.56; N, 8.58.

*(4-Chlorophenyl)[3-(4-chlorophenyl)-1,6-dimethyl-1*H*-indazol-5-yl]methanone* **5b**: colourless crystals, yield 73%, mp 169–170 °C (ethanol). IR (ν/cm^{-1}): 1673 (C=O). ^{1}H NMR ($CDCl_3$) δ: 2.13 (s, 3H, 6-Me), 4.14 (s, 3H, NMe), 7.30–7.38 (m, 3H, 3-Ar, 7-H), 7.41–7.51 (m, 4H, COAr, 3-Ar), 7.87–7.94 (m, 2H, COAr), 8.26 (s, 1H, 4-H). Found (%): C, 66.84; H, 4.10; N, 7.15. Calc. for $C_{22}H_{16}Cl_2N_2O$ (%): C, 66.85; H, 4.08; N, 7.09.

*[1,6-Dimethyl-3-(1-naphthyl)-1*H*-indazol-5-yl](1-naphthyl)methanone* **5c**: colourless crystals, yield 76%, mp 170–171 °C (ethanol). IR (ν/cm^{-1}): 1659 (C=O). ^{1}H NMR ($CDCl_3$) δ: 2.74 (s, 3H, 4-Me), 4.23 (s, 3H, NMe), 7.30–7.63 (m, 9H, 1-Naphthoyl, 1-Naphthyl, H-7), 7.73 (s, 1H, H-2), 7.81–7.86 (m, 4H, 1-Naphthoyl), 8.15–8.20 (m, 1H, 1-Naphthoyl), 8.42–8.46 (m, 1H, 1-Naphthoyl). Found (%): C, 84.47; H, 5.17; N, 6.59. Calc. for $C_{30}H_{22}N_2O$ (%): C, 84.48; H, 5.20; N, 6.57.

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