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SYNTHESIS OF SUBSTITUTED 1*H*-INDAZOLES BY PYRAZOLE ANNELATION TO AN ARENE

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Substituted 1H-indazoles have been synthesized by reductive intramolecular heterocyclization of 2,4-diaroyl-N-nitrosomethylanilines and 2,4-diacetyl-N-nitrosomethylaniline. The N-nitrosoanilines were obtained by nitrosation of N-methyl-2,4-diaroyl- and 2,4-diacetylanilines, the products of quaternary 3,5-diaroyl- and 3,5-diacetylpyridinium salt recyclization.

Keywords: 5-aroyl-3-aryl-1,6-dimethyl-1*H*-indazoles, 5-amino-1,3,6-trimethyl-1*H*-indazole, 3,5-bis-(cyclopropylcarbonyl)-2,6-dimethyl-1,4-dihydropyridine, 3,5-bis(cyclopropylcarbonyl)-2,6-dimethylpyridine, substituted *ortho*-aroyl-*N*-methylanilines, substituted *N*-methyl-*N*-nitrosobenzenes, Hantzsch synthesis.

Indazoles (azaindoles) are heterocyclic compounds structurally related to indoles, and can be viewed as indole (bio)isosteres [1]. Unlike indoles, indazole derivatives are rare in nature. The first alkaloids of the indazole series, nigellicine, nigellidine, and nigeglanine were isolated during the past three decades from the plants *Nigella sativa* and *Nigella glandulifera* belonging to the *Ranunculaceae* family [2-6].

Interest in the chemistry of indazoles is explained by the wide spectrum of their biological activity. In particular, indazoles display antitumor, antifungal, and anti-inflammatory activity; they possess antiseptic and antipyretic properties, and are antagonists of dopamine receptors and regulators of CNS activity [7-9].

Medications of the indazole series, bendazac, benzydamine, lonidamine, bindarit, and granisetron, are used as anticancer, anti-inflammatory, immunosuppressive, and serotoninergic agents [10-18]. In 2010, clinical trials of axitinib, a new anticancer drug of this series was completed by Pfizer. Its effectiveness in the therapy of carcinoma cells of kidney epithelium was established [19].

The classical methods of 1*H*-indazole synthesis are mainly based on closing the pyrazole ring by intramolecular heterocyclization of *ortho*-methyl-*N*-nitroso- and diazoaromatic compounds, by the reaction of *ortho*-halo- and *ortho*-hydroxyacyl benzenes, and substituted esters of 2-azidobenzoic acid with hydrazine [7, 20, 21]. The synthesis of indazoles by annelation of the benzene ring to pyrazole is limited to the cycloaddition reaction of 1-phenyl-4(5)-vinylpyrazoles and 1-aryl-3-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles with various dienophiles [22-24].

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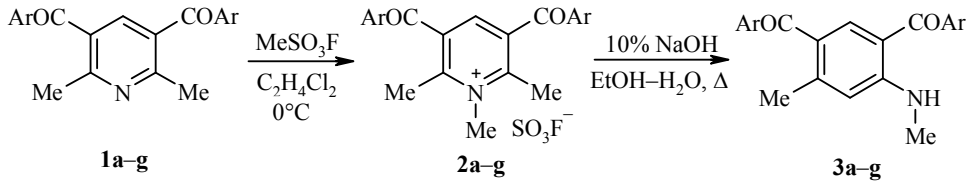
Polyfluoro-substituted indazoles, obtained by the recyclization of 5-tetrafluorophenyl-1,2,4-oxadiazoles by the action of hydrazine, are also avaible [25].

Other methods of 1*H*-indazole synthesis with lesser synthetic value are also known [7, 20].

The methods of 3-arylindazole synthesis are represented by the cycloaddition reaction of tosylhydrazones and 1,1-dialkylhydrazones to an aryne [26, 27], *N*-acetyl-4-styrylpyrazoles to *N*-methyl- and *N*-phenylmaleimide [28], the intramolecular Pd-catalyzed amination reaction of *ortho*-bromobenzophenone hydrazones [29], cyclization of *ortho*-hydroxybenzophenone hydrazones [30, 31], and by the nucleophilic substitution of hydrogen in nitroarenes by the anion of *para*-nitrobenzaldehyde hydrazone [32].

The aim of the present work was the synthesis of the previously unknown 5-aroyl-3-aryl-1*H*-indazoles and 5-acetyl-3-methyl-1*H*-indazole from 2,4-diaroyl-*N*-methylanilines and 2,4-diacetyl-*N*-methylaniline, respectively, obtained by the recyclization of quaternary 3,5-diaroylpyridinium salts and 3,5-diacetylpyridinium salts [33].

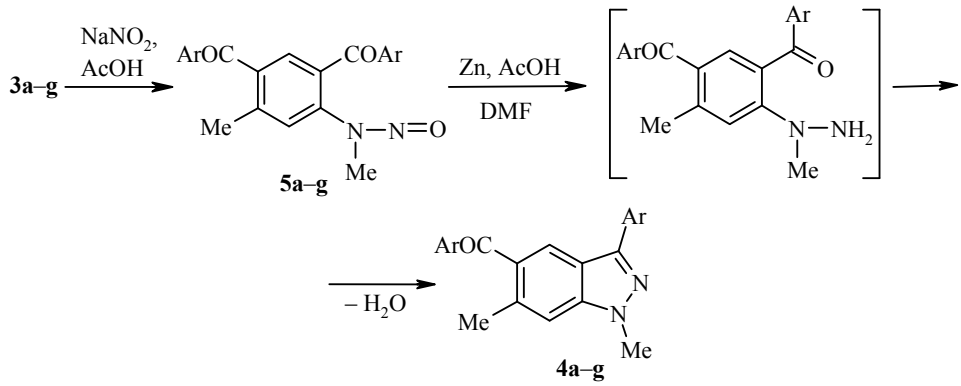
Alkylation of 3,5-diaroylpyridines **1a-g**, characterized by low basicity, was carried out using the methyl ester of fluorosulfonic acid. Rearrangement of the quaternary pyridinium salts **2a-g** on heating with an aqueous alcoholic solution of sodium hydroxide led to 2,4-diaroyl-*N*-methylanilines **3a-g**. The complete recyclization scheme for quaternary pyridinium salts **2** was presented by us previously [34].



1a–g **2a–g** **3a–g**

1–3 a Ar = Ph, **b** Ar = 4-ClC_6H_4, **c** Ar = 1-naphthyl, **d** Ar = 4-MeOC_6H_4, **e** Ar = 3-MeOC_6H_4, **f** Ar = 4-BrC_6H_4, **g** Ar = 2-naphthyl

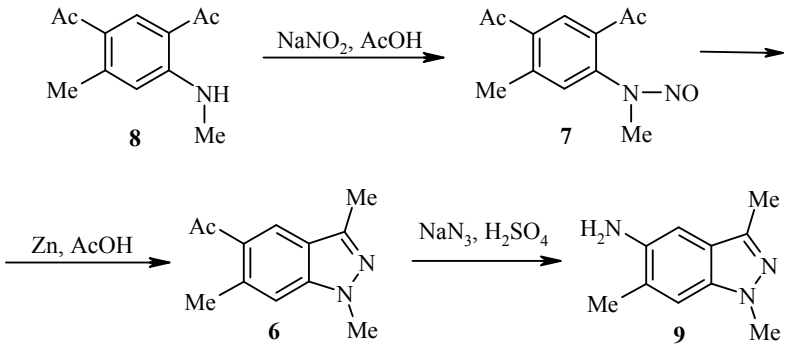
The two-stage scheme for the synthesis of substituted indazoles **4a-g** by building up the pyrazole ring involved *N*-nitrosation of *N*-methylanilines **3a-g** and a stage of intramolecular reductive heterocyclization of *N*-nitroso-*N*-methylanilines **5a-g**. The formation of the pyrazole nucleus of indazoles **4a-g** proceeded by intramolecular condensation of arylmethylhydrazine, formed *in situ* on reduction of the *N*-nitroso group, with an aroyl group. All the stages in the synthesis of indazoles were performed in preparative yields.



5a–g **4a–g**

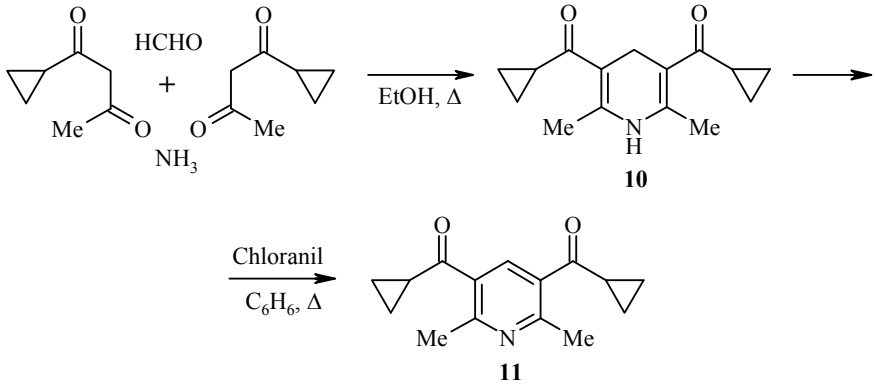
3–5 a Ar = Ph, **b** Ar = 4-ClC_6H_4, **c** Ar =1-naphtyl, **d** Ar = 4-MeOC_6H_4, **e** Ar = 3-MeOC_6H_4, **f** Ar = 4-BrC_6H_4, **g** Ar = naphtyl

Synthesized by an analogous scheme were 5-acetylindazole **6** from *N*-nitroso-*N*-methylaniline **7**, the starting material for which was 2,4-diacetyl-*N*-methylaniline **8**, itself the product of a 3,5-diacetylpyridinium salt rearrangement [33]. The 5-aminoindazole **9** was obtained in 80% yield by converting the acetyl group in position 5 of indazole **6** by the Schmidt reaction.



It should be mentioned that the two-stage synthesis of 3,5-diacetylpyridine from acetylacetone by the Hantzsch reaction was characterized by high yields both at the stage of obtaining 3,5-diacetyl-1,4-dihydropyridine (87%) and also at the stage of its aromatization (81%). The yields of the remaining compounds of the 3,5-dialkanoylpyridine series, beginning with 3,5-dipropionylpyridine, did not exceed 40% at the stage of 1,4-dihydropyridine synthesis [35]. For this reason, the syntheses of 3,5-dialkanoylpyridines and the rearrangement of their quaternary salts were stopped at 3,5-dipropionylpyridine [33].

In the present study, we have obtained for the first time 3,5-bis(cyclopropylcarbonyl)-2,6-dimethyl-1,4-dihydropyridine (**10**) by a modified Hantzsch synthesis [35]. Oxidation of the dihydropyridine **10** with sodium nitrite in acetic acid led to a complex mixture of reaction products, from which the crystalline pyridine **11** could not be isolated. Oxidation of dihydropyridine **10** with chloranil on heating in benzene led to pyridine **11** in 64% yield.



It should be noted that the recyclization of symmetrical 4-aryl-3,5-diacetylpyridinium salts into the corresponding 2,4-diacetyl-3-aryl-*N*,5-dimethylanilines occurred in yields of 19-40%, consequently we did not consider them as promising materials in the synthesis of indazoles [33].

The structures of compounds **2d-g**, **3d-g**, **4d-g**, **5d-g**, **6**, **7**, and **9-11**, which were synthesized for the first time, were confirmed by IR, ^{1}H NMR spectroscopy and by data of elemental analysis. The physicochemical and spectral characteristics of the compounds are given in Tables 1 and 2.

An effective synthesis of new substituted 1*H*-indazoles is therefore proposed, based on annelation of pyrazole ring onto the available *ortho*-aroyl-*N*-methylanilines. The obtained compounds hold promise for the study of their biological activity.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **2d-g**, **3d-g**, **4d-g**, **5d-g**, **6**, **7**, **9-11**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
2d	$C_{24}H_{24}FNO_7S$	58.80 / 58.89	4.96 / 4.94	2.85 / 2.86	230-231	91
2e	$C_{24}H_{24}FNO_7S$	58.85 / 58.89	4.90 / 4.94	2.80 / 2.86	227-228	85
2f	$C_{22}H_{18}Br_2FNO_5S$	45.07 / 45.00	3.12 / 3.09	2.43 / 2.39	266-267	92
2g	$C_{30}H_{24}FNO_5S$	68.07 / 68.04	4.55 / 4.57	2.70 / 2.64	248-249	95
3d	$C_{24}H_{23}NO_4$	74.06 / 74.02	5.98 / 5.95	3.67 / 3.60	133-134	86
3e	$C_{24}H_{23}NO_4$	74.00 / 74.02	5.94 / 5.95	3.56 / 3.60	142-143	75
3f	$C_{22}H_{17}Br_2NO_2$	54.29 / 54.24	3.55 / 3.52	2.80 / 2.88	170-171	98
3g	$C_{30}H_{23}NO_2$	83.95 / 83.89	5.36 / 5.40	3.30 / 3.26	191-192	77
4d	$C_{24}H_{22}N_2O_3$	74.63 / 74.59	5.72 / 5.74	7.30 / 7.25	157-158	63
4e	$C_{24}H_{22}N_2O_3$	74.58 / 74.59	5.77 / 5.74	7.33 / 7.25	102-103	50
4f	$C_{22}H_{16}Br_2N_2O$	54.59 / 54.57	3.30 / 3.33	5.86 / 5.79	176-177	79
4g	$C_{30}H_{22}N_2O$	84.50 / 84.48	5.23 / 5.20	6.53 / 6.57	194-195	81
5d	$C_{24}H_{22}N_2O_5$	68.93 / 68.89	5.34 / 5.30	6.73 / 6.69	158-159	86
5e	$C_{24}H_{22}N_2O_5$	68.87 / 68.89	5.33 / 5.30	6.71 / 6.69	126-127	82
5f	$C_{22}H_{16}Br_2N_2O_3$	51.22 / 51.19	3.15 / 3.12	5.48 / 5.43	207-208	93
5g	$C_{30}H_{22}N_2O_3$	78.64 / 78.59	4.80 / 4.84	6.12 / 6.11	203-204	80
6	$C_{12}H_{14}N_2O$	71.13 / 71.26	7.07 / 6.98	13.99 / 13.85	126-127	74
7	$C_{12}H_{14}N_2O_3$	61.42 / 61.53	6.04 / 6.02	12.06 / 11.96	94-95	88
9	$C_{10}H_{13}N_3$	68.62 / 68.54	7.54 / 7.48	24.08 / 23.98	183-184	80
10	$C_{15}H_{19}NO_2$	73.50 / 73.44	7.83 / 7.81	5.79 / 5.71	176-177	85
11	$C_{15}H_{17}NO_2$	74.10 / 74.05	7.09 / 7.04	5.86 / 5.76	51-52	64

EXPERIMENTAL

The IR spectra were recorded on a Simex FT-801 spectrometer (with an attachment for a frustrated total internal reflection). ^{1}H NMR spectra were recorded on a Bruker Avance DRX-400 instrument (400 MHz). Chemical shifts were measured relative to the residual signals of the solvents: $CHCl_3$ (δ 7.26 ppm), DMSO (δ 2.50 ppm). Elemental analysis was carried out on a PerkinElmer CHN analyzer. Melting points were determined on a Boetius hot stage apparatus. Column chromatography was performed on Merck 60 Å, 0.060-0.200 mm silica gel. A check on the progress of reactions and the purity of the obtained substances was effected by TLC on Silufol UV-254 plates with visualization in UV light.

TABLE 2. Spectral Characteristics of the Synthesized Compounds **2d-g**, **3d-g**, **4d-g**, **5d-g**, **6**, **7**, **9-11**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum ($CDCl_3$)*, δ, ppm (*J*, Hz)
2d	—	2.68 (6H, s, 2,6-CH_3); 3.87 (6H, s, 2OCH_3); 4.15 (3H, s, NCH_3); 7.08-7.15 (4H, m, H Ar); 7.82-7.88 (4H, m, H Ar); 8.53 (1H, s, H-4)
2e	—	2.71 (6H, s, 2,6-CH_3); 3.82 (6H, s, 2OCH_3); 4.18 (3H, s, NCH_3); 7.33-7.55 (8H, m, H Ar); 8.60 (1H, s, H-4)
2f	—	2.70 (6H, s, 2,6-CH_3); 4.16 (3H, s, NCH_3); 7.77-7.87 (8H, m, H Ar); 8.60 (1H, s, H-4)
2g	—	2.82 (6H, s, 2,6-CH_3); 4.28 (3H, s, NCH_3); 7.64-7.77 (4H, m, H Ar); 8.00-8.15 (8H, m, H Ar); 8.51 (2H, s, H-1',1'' Ar); 8.78 (1H, s, H-4)
3d	3303 (NH), 1668, 1618 (C=O)	1.94 (3H, s, 5-CH_3); 2.99 (3H, d, *J* = 5.0, NHC$\underline{H}_3$); 3.86 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 6.59 (1H, s, H-6); 6.94-7.01 (4H, m, H Ar); 7.27-7.33 (2H, m, H Ar); 7.64-7.70 (2H, m, H Ar); 8.00 (1H, s, H-3); 8.65 (1H, br. s, N$\underline{H}CH_3$)
3e	3301 (NH), 1672, 1620 (C=O)	1.94 (3H, s, 5-CH_3); 3.02 (3H, d, *J* = 4.9, NHC$\underline{H}_3$); 3.84 (3H, s, OCH_3); 3.86 (3H, s, OCH_3); 6.63 (1H, s, H-6); 6.90-6.99 (3H, m, H Ar); 7.05-7.11 (1H, m, H Ar); 7.15-7.22 (2H, m, H Ar); 7.31-7.41 (2H, m, H Ar); 8.02 (1H, s, H-3); 8.92 (1H, br. s, N$\underline{H}CH_3$)
3f	3290 (NH), 1661, 1618 (C=O)	2.01 (3H, s, 5-CH_3); 3.01 (3H, br. s, NHC$\underline{H}_3$); 6.58 (1H, s, H-6); 7.20-7.24 (2H, m, H Ar); 7.50-7.59 (4H, m, H Ar); 7.62-7.66 (2H, m, H Ar); 7.97 (1H, s, H-3); 8.30 (1H, br. s, N$\underline{H}CH_3$)
3g	3271 (NH), 1672, 1614 (C=O)	1.95 (3H, s, 5-CH_3); 3.07 (3H, br. s, NHC$\underline{H}_3$); 6.80 (1H, s, H-6); 7.48-7.64 (5H, m, H Ar); 7.77-7.82 (1H, m, H Ar); 7.88-7.99 (8H, m, H Ar); 8.16 (1H, s, H-3); 8.19 (1H, br. s, N$\underline{H}CH_3$)
4d	1678 (C=O)	2.04 (3H, s, 6-CH_3); 3.87 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 4.11 (3H, s, NCH_3); 6.97-7.07 (4H, m, H COAr, Ar); 7.30 (1H, s, H-7); 7.32-7.38 (2H, m, H Ar); 7.88-7.93 (2H, m, H COAr); 8.25 (1H, s, H-4)
4e	1670 (C=O)	2.08 (3H, s, 6-CH_3); 3.86 (3H, s, OCH_3); 3.91 (3H, s, OCH_3); 4.14 (3H, s, NCH_3); 6.94-7.02 (4H, m, H Ar); 7.33-7.46 (3H, m, H Ar, H-7); 7.50-7.59 (2H, m, H Ar); 8.29 (1H, s, H-4)
4f	1678 (C=O)	2.14 (3H, s, 6-CH_3); 4.14 (3H, s, NCH_3); 7.27-7.30 (2H, m, H Ar); 7.32 (1H, s, H-7); 7.57-7.61 (2H, m, H Ar); 7.62-7.66 (2H, m, H COAr); 7.81-7.87 (2H, m, H COAr); 8.26 (1H, s, H-4)
4g	1679 (C=O)	2.07 (3H, s, 6-CH_3); 4.21 (3H, s, NCH_3); 7.49 (1H, s, H-7); 7.51-7.60 (5H, m, H Ar); 7.88-8.02 (7H, m, H COAr, H Ar, H-4); 8.15-8.19 (1H, m, H COAr); 8.46-8.48 (1H, m, H COAr); 8.48-8.50 (1H, m, H COAr)
5d	1693, 1660 (C=O), 1443 (N-N=O)	2.07 (3H, s, 5-CH_3); 3.27 (3H, s, NCH_3); 3.85 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 6.87-6.91 (2H, m, H Ar); 6.99-7.04 (2H, m, H Ar); 7.32-7.36 (2H, m, H Ar); 7.44 (1H, s, H-6); 7.73 (1H, s, H-3); 7.74-7.77 (2H, m, H Ar)
5e	1697, 1650 (C=O), 1440 (N-N=O)	2.09 (3H, s, 5-CH_3); 3.28 (3H, s, NCH_3); 3.83 (3H, s, OCH_3); 3.86 (3H, s, OCH_3); 6.94-7.04 (3H, m, H Ar); 7.08-7.12 (1H, m, H Ar); 7.22-7.26 (1H, m, H Ar); 7.28-7.43 (3H, m, H Ar); 7.45 (1H, s, H-6); 7.79 (1H, s, H-3)
5f	1694, 1681 (C=O), 1460 (N-N=O)	2.15 (3H, s, 5-CH_3); 3.29 (3H, s, NCH_3); 7.27-7.31 (2H, m, H Ar); 7.39 (1H, s, H-6); 7.55-7.65 (6H, m, H Ar); 7.78 (1H, s, H-3)
5g	1672, 1660 (C=O), 1469 (N-N=O)	2.10 (3H, s, 5-CH_3); 3.30 (3H, s, NCH_3); 7.52-7.64 (6H, m, H Ar, H-6); 7.87-8.01 (9H, m, H Ar, H-3); 8.22-8.26 (1H, m, H Ar)
6	1690 (C=O)	2.80 (3H, s, $COCH_3$); 2.86 (3H, s, 3-CH_3); 2.90 (3H, s, 6-CH_3); 4.23 (3H, s, NCH_3); 7.30 (1H, s, H-7); 8.28 (1H, s, H-4)
7	1705, 1700 (C=O), 1490 (N-N=O)	2.76 (3H, s, 5-CH_3); 3.03 (6H, s, 2$COCH_3$); 3.88 (3H, s, NCH_3); 7.70 (1H, s, H-6); 8.46 (1H, s, H-3)
9	3495, 3382 (NH_2)	2.34 (3H, s, 6-CH_3); 2.47 (3H, s, 3-CH_3); 3.77 (2H, br. s, NH_2); 3.91 (3H, s, NCH_3); 6.88 (1H, s, H-7); 7.04 (1H, s, H-4)
10	3323 (NH), 1666 (C=O)	0.81-0.87 (4H, m, H *c*-Pr); 1.00-1.05 (4H, m, H *c*-Pr); 2.05-2.13 (2H, m, H *c*-Pr); 2.16 (6H, s, 2,6-CH_3); 3.66 (2H, s, CH_2); 5.66 (1H, br. s, NH)
11	1664 (C=O)	1.08-1.14 (4H, m, H *c*-Pr); 1.27-1.32 (4H, m, H *c*-Pr); 2.36-2.44 (2H, m, H *c*-Pr); 2.74 (6H, s, 2,6-CH_3); 8.23 (1H, s, H-4)

*Spectra of compounds **2d-g** were recorded in DMSO-d_6.

Syntheses of pyridinium salts **2a-c**, 2,4-diaroylanilines **3a-c**, and indazoles **4a-c** have been described previously [34]. The starting 3,5-diaroylpyridines **1a-g** were obtained previously by a modified Hantzsch synthesis [36]. 1-Cyclopropylbutane-1,3-dione was synthesized in 60% yield by ester condensation of methyl cyclopropyl ketone and ethyl acetate, as described in the work [37], with replacement of $NaNH_2$ and solvent methyl *tert*-butyl ether by NaH and diethyl ether.

3,5-Diaroyl-1,2,6-trimethylpyridinium Fluorosulfonates 2d-g (**General Method**). A solution of methyl fluorosulfonate (3.42 g, 30 mmol) in abs. dichloroethane (12 ml) was added dropwise with stirring to a solution of the corresponding pyridine **1d-g** [36] in abs. dichloroethane (24 ml) at 0°C. The mixture was stirred for 30 min at 0°C and for 2 days at room temperature. The precipitated solid was filtered off and recrystallized from ethanol.

2,4-Diaroyl-*N*,5-dimethylanilines 3d-g (**General Method**). A suspension of quaternary salt **2d-g** (5 mmol) in ethanol (10 ml) and 10% NaOH solution (10 ml) was heated at 80°C for 1 h, cooled, diluted with water, and yellow crystals of diaroylanilines **3d-g** were filtered off. The products were purified by column chromatography (eluent chloroform) and recrystallized from ethanol.

***N*-Nitrosoanilines 5d-g, 7** (**General Method**). $NaNO_2$ (0.97 g, 14 mmol) was added in portions at room temperature to a solution of aniline **3d-g** and **8** [33] (7 mmol) in acetic acid (14 ml). The reaction mixture was stirred for 1 h at room temperature and poured into water. White crystals of nitrosoanilines **5d-g** and **7** were filtered off and recrystallized from ethanol.

5-Aroyl-3-aryl-1,6-dimethyl-1*H*-indazoles 4d-g (**General Method**). Zinc dust (3.2 g, 50 mmol) was added in portions with stirring to a solution of nitrosoaniline **5d-g** (10 mmol) in DMF (30 ml) and acetic acid (30 ml), maintaining the temperature at or below 10°C. The mixture was stirred for 30 min at room temperature, heated to 100°C, the inorganic solids were filtered off and washed with hot acetic acid. The filtrate was cooled, diluted with water, colorless crystals of indazoles **4d-g** were filtered off and recrystallized from ethanol.

1-(1,3,6-Trimethyl-1*H*-indazol-5-yl)ethanone (6). Zinc dust (1.60 g, 25 mmol) was added in portions with stirring to a solution of nitrosoaniline **7** (1.34 g, 5 mmol) in acetic acid (10 ml), maintaining the temperature at or below 10°C. The mixture was stirred for 1 h at room temperature, the inorganic solids were filtered off, and washed with acetic acid. The filtrate was cooled, diluted with water, neutralized with potassium carbonate solution, and indazole **6** was filtered off. Yield 0.75 g (74%). Colorless crystals; mp 126-127°C (2-PrOH).

1,3,6-Trimethyl-1*H*-indazol-5-amine (9). NaN_3 (0.43 g, 6.6 mmol) was added in portions with vigorous stirring to a solution of 5-acetylindazole **6** (1.21 g, 6.0 mmol) in conc. H_2SO_4 (3 ml), so that the temperature did not exceed 40°C. (Caution! Risk of explosion!) The reaction mixture was stirred for 12 h, ice (12 g) was added, the mixture was refluxed for 12 h, cooled, diluted with water (30 ml), and neutralized with aqueous ammonia. Aminoindazole **9** was filtered off. Yield 0.65 g (80%). White crystals; mp 183-184°C (CCl_4).

3,5-Bis(cyclopropylcarbonyl)-2,6-dimethyl-1,4-dihydropyridine (10) was obtained by a modified Hantzsch synthesis [35]. Yield 74%. Yellow crystals; mp 176-177°C (EtOH).

3,5-Bis(cyclopropylcarbonyl)-2,6-dimethylpyridine (11). Oxidation of 1,4-dihydropyridine **10** with chloranil was carried out by heating in benzene according to the procedure of [38]. After purification by column chromatography (eluent chloroform–ethyl acetate, 9:1), the pyridine **11** was obtained in 64% yield as colorless crystals, mp 51-52°C (petroleum ether).

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