A New Synthethic Approach to Indazole Synthesis

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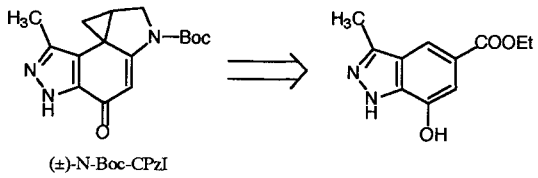
Stobbe condensation of 3-alkyl- or aryl-4-formylpyrazoles **3a–f** with diethyl succinate in the presence of potassium *t*-butoxide, followed by intramolecular ring closure (Ac_2O–NaOAc), afforded the corresponding indazole derivatives **5a–f** in 65–85% overall yield. These compounds are good starting materials for transformation to biologically active molecules, such as new pyrazole analogs of the left-hand segment of the potent natural antineoplastic agent CC-1065.

Although indazole and its derivatives have little biological significance and have not been found in natural products due to the difficulty for living organisms to construct an N–N bond, there are several examples of useful derivatives such as anti-inflammatory[1] (e.g., Bendazac and Benzydamine), antidepressant,[2] antiarthritic,[3] antispermatogenic,[4] and analgesic[5] agents.

Recently, we have reported an efficient methodology for the synthesis of a pyrazole analog of the left-hand segment of the natural antitumor agent CC-1065, named (±)-N-Boc-CpzI, using ethyl 3-methyl-7-hydroxyindazole-5-carboxylate as building block[6] (Scheme 1).



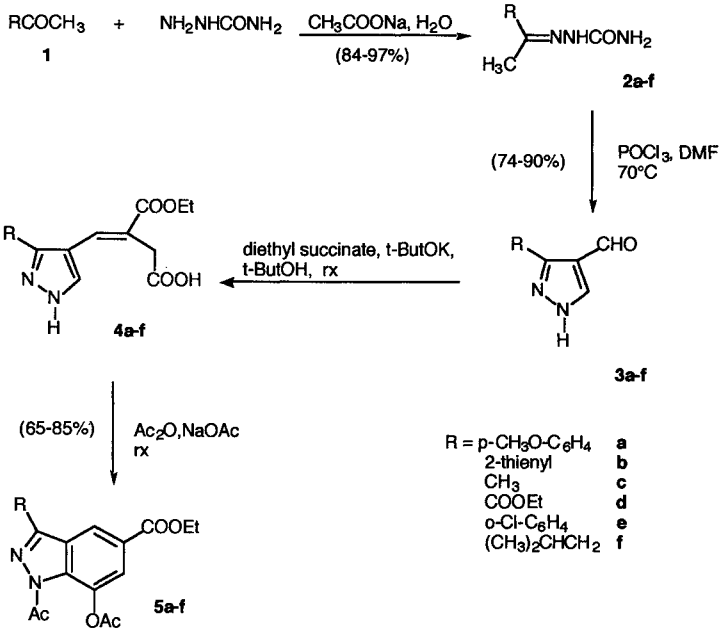
Scheme 1

In order to confirm the efficiency of our protocol, we decided to extend it to other indazole derivatives. These indazoles can be used as intermediates for the synthesis of more complex bioactive molecules, like the new CC-1065 pyrazole analogs.

Most syntheses of indazoles reported in literature proceed from benzene derivatives, where the pyrazole moiety was generated by ring closure.[7,8] Most indazole ring-closure procedures involve creating the N–N bond as the last step; nevertheless, the ring closure by creation of a C–N bond through the generation of N(2)-C(3) or N(1)-C(7a) bond is also common. But few examples are reported for the C(3)-C(3a) ring closure.[7,8]

Only two syntheses of an indazole starting with the pyrazole ring have been reported. Weygand's methodology involves an acyloin condensation between glyoxal and pyrazole-4,5-dialdehyde, with the creation of 5,6-dihydroxy-4,7-indazolequinone in poor yield,[9] while Matsugo reported an efficient one-pot synthesis of highly substituted 1*H*-indazoles, by cycloaddition of 1-aryl-4,6,6-trimethyl-3-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles with dialkyl acetylendicarboxylates.[10]

In this paper, we have extended a known, versatile procedure[11] which starts from 3-substituted 4-formylpyrazoles (prepared by the Vilsmeier–Haack reaction[12]); the benzene ring was created through Stobbe condensation[13] followed by intramolecular aromatisation. The synthetic pathway is reported in Scheme 2.



Scheme 2

The reaction of methyl ketones **1a–f** with semicarbazide in water gave the corresponding semicarbazones **2a–f**, which, after having been isolated in high yield, were submitted to cyclization by phosphoryl chloride in dimethylformamide at 0°C with the formation of related 3-substituted 4-formylpyrazoles **3a–f**.[12]

In the pyrazole, the electrophilic substitution always takes place at the 4-position.[14] The presence in this position of an electron-withdrawing group has a deactivating effect, and for this reason, further electrophilic substitution is generally not observed. When the same position is occupied by activating substituents, substitution in the 5-position can be facilitated.

The condensation of the 4-formylpyrazoles **3a–f** with diethyl succinate in the presence of potassium *t*-butoxide (as condensing agent), afforded a mixture of the half esters **4a–f**, that subsequently underwent cyclisation leading to the acetoxy esters **5a–f** by reaction with sodium acetate (0.1 M) in acetic anhydride.

Table 1. 3-Substituted 4-Formylpyrazoles Prepared

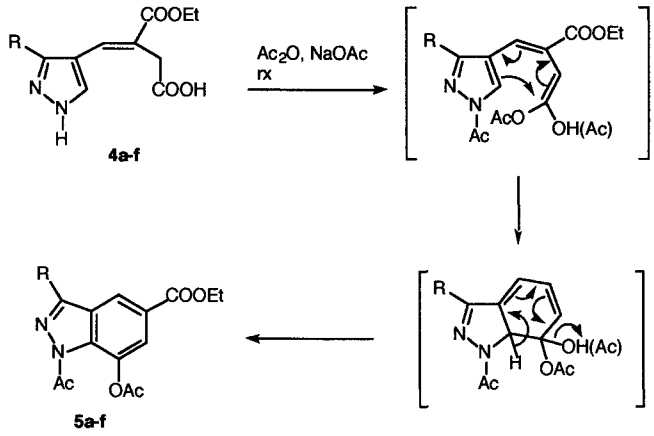
Compound	R	Yield[b] (%)	mp (°C)	^{1}H NMR ($CDCl_3$) δ, J (Hz)
3a[a]	4-$CH_3OC_6H_4$	81	143	3.92 (s, 3H), 7.01 (dd, 2H, J = 2, 6.8), 7.91 (dd, 2H, J = 2, 6.8), 8.07 (s, 1H), 10.1 (s, 1H), 12.9 (br s, 1H)
3b[a]	2-thienyl	76	63	7.72 (dd, 1H, J = 1, 3.8), 8.13 (s, 1H), 10 (s, 1H), 13.2 (br s, 1H)
3c[a]	CH_3	90	93	2.42 (s, 3H), 9.82 (s, 3H), 13.2 (br s, 3H)
3e	2-ClC_6H_4	74	64	7.47–7.58 (m, 4H), 8.01 (s, 1H), 9.75 (s, 1H), 13.1 (br s, 1H)
3f	$(CH_3)_2CHCH_2$	86	106	0.99 (d, 6H, J = 6.2), 2.05 (m, 1H), 2.84 (d, 2H, J = 7.2), 8.01 (s, 1H), 9.92 (s, 1H), 12.8 (br s, 1H)

[a] Lit.[12] Yield and mp are in full accord with the literature data.
[b] Yield of isolated, purified products after flash column chromatography (EtOAc/light petroleum).

The ring-closure step (Ac_2O/NaOAc) is likely to take place in an electrocyclic fashion after enolisation of the mixed anhydride, as reported in Scheme 3. The intramolecular Friedel–Crafts acylation is unlikely to happen under these conditions, since the formation of an acylium ion should be unfavorable.

Semicarbazones **2a–f** and the corresponding aldehydes **3a–d** have already been synthesized, and their full characterization (melting point, IR spectra) is reported in the literature.[12,15] The NMR spectra of the compounds **3a–f** (with the exception of the product **3d**,[15] with R=COOEt) are listed in Table 1.

In Table 2, we report the ^{1}H NMR spectra and the MS data of all *N'*-acetylated 3-substituted ethyl 7-acetoxyindazole-5-carboxylates **5a–f**.



Scheme 3

Table 2. 3-Substituted Ethyl 7-Acetoxy-*N*^{1}-acetylindazole-5-carboxylates Prepared

Compound	R	Yield[b] (%)	mp (°C)	Molecular Formula[b]	^{1}H NMR ($CDCl_3$) δ, J (Hz)	MS (70eV) m/z (%)
5a	4-$CH_3OC_6H_4$	65	145	$C_{21}H_{20}N_2O_6$	1.42 (t, 3H, J = 7), 2.46 (s, 3H), 2.82 (s, 3H), 3.92 (s, 3H), 4.42 (q, 2H, J = 7), 7.11 (dd, 2H, J = 2, 6.8), 7.87 (d, 1H, J = 1.4), 7.91 (dd, 2H, J = 2, 6.8), 8.53 (d, 1H, J = 1.4)	396 (M^+, 18), 354 (26), 312 (100), 284 (20)
5b	2-thienyl	68	124–126	$C_{18}H_{16}N_2O_5S$	1.43 (t, 3H, J = 7), 2.45 (s, 3H), 2.82 (s, 3H), 4.44 (q, 2H), J = 7), 7.25 (dd, 1H, J = 3.8, 5), 7.52 (dd, 1H, J = 1, 5), 7.82 (dd, 1H, J = 1, 3.8), 7.93 (d, 1H, J = 1.4), 8.25 (d, 1H, J = 1.4)	372 (M^+, 26), 330 (40), 288 (100), 260 (31)
5c	CH_3	85	125–126	$C_{15}H_{16}N_2O_5$	1.45 (t, 3H, J = 7), 2.44 (s, 3H), 2.65 (s, 3H), 2.86 (s, 3H), 4.43 (q, 2H, J = 7), 7.94 (d, 1H, J = 1.4), 8.86 (d, 1H, J = 1.4)	304 (M^+, 14), 262 (86), 220 (100), 192 (22)
5d	COOEt	73	109	$C_{17}H_{18}N_2O_7$	1.44 (t, 3H, J = 7), 1.53 (t, 3H, J = 7), 2.44 (s, 3H), 2.86 (s, 3H), 4.43 (q, 2H, J = 7), 4.56 (q, 2H, J = 7), 7.94 (d, 1H, J = 2, 1.4), 8.86 (d, 1H, J = 1.4)	362 (M^+, trace), 320 (48), 278 (100), 232 (62)
5e	2-ClC_6H_4	74	140–141	$C_{20}H_{17}N_2O_5Cl$	1.39 (t, 3H, J = 7), 2.47 (s, 3H), 2.81 (s, 3H), 4.40 (q, 2H, J = 7), 7.47–7.58 (m, 5H), 7.87 (d, 1H, J = 1.4), 8.53 (d, 1H, J = 1.4)	400 (M^+, trace), 360 (17), 358 (49), 318 (32), 316 (100), 271 (20)
5f	$(CH_3)_2CHCH_2$	69	110	$C_{18}H_{22}N_2O_5$	1.03 (d, 6H, J = 6.5), 1.43 (t, 3H, J = 7), 2.23 (m, 2H), 2.44 (d, 3H), 2.74 (s, 3H), 2.84 (d, 2H, J = 7.2), 4.42 (q, 2H, J = 7), 7.87 (d, 1H, J = 1.4), 8.25 (d, 1H, J = 1.4)	346 (M^+, 8), 304 (72), 262 (100), 220 (49)

[a] Yield of isolated, purified products after flash column chromatography (EtOAc/light petroleum).
[b] Satisfactory analyses obtained: C ± 0.25, H ± 0.22, N ± 0.10, Cl ± 0.12%.

All reactions were carried out under an inert atmosphere of anhyd nitrogen, unless otherwise described. Standard syringe techniques were applied for transferring dry solvents. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates) and visualized with aqueous $KMnO_4$. ^1H NMR spectra were recorded in $CDCl_3$ solutions on a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in ppm upfield from TMS. Mass spectra were obtained on a Fisons MD 800. Melting points were determined on a Buchi-Tottoli apparatus and are uncorrected. Chromatography was performed with Merck 60–200 mesh silica gel. All products reported showed ^1H NMR spectra in agreement with the assigned structures. Organic solutions were dried over anhyd $MgSO_4$. Anhyd *t*-BuOH was distilled from $CaCl_2$ prior to use. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

Aldehydes 3a–f; General Procedure:

To a well-stirred mixture of $POCl_3$–DMF [prepared by the slow addition of $POCl_3$ (3.43 mL, 37 mmol) to DMF (6 mL) cooled below 5 °C], the semicarbazones **2a–f** were added portionwise. The mixture was heated at 60 °C for about 4 h, and poured into crushed ice (100 g). The mixture was then neutralized with NaOH (6.8 g in 25 mL of H_2O), heated to 50–60 °C for 5 min, cooled, and acidified to pH 6 with 10 M HCl. The solution was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried and concentrated in vacuo. The crude residue was purified by chromatography to give the aldehydes **3a–f** in good yield (Table 1).

Indazoles 4a–f; General Procedure:

A solution of *t*-BuOK (0.2 mol) in *t*-BuOH (80 mL) was added to a mixture of compounds **3a–f** (63 mmol) and diethyl succinate (40 mL, 0.285 mol) and heated at reflux for 45 min. Then, an equimolar amount of diethyl succinate and *t*-BuOK in *t*-BuOH were added and the mixture refluxed for further 45 min. The mixture was cooled, acidified with aqueous 20 % HCl to pH 2, and extracted with EtOAc (3 × 50 mL). The organic layer was extracted with aqueous 5 % Na_2CO_3 (5 × 50 mL). The alkaline solution was extracted with Et_2O (2 × 50 mL) and then acidified with aqueous 20 % HCl to pH 2. This solution was extracted with EtOAc (4 × 40 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give the (*E*)-half-esters **4a–f** as a yellow oils in good yields.

A solution of crude half-ester **4a–f** (64 mmol) in Ac_2O (320 mL) and NaOAc (5.25 g, 64 mmol) was heated at reflux for 5 h. Then the Ac_2O was removed under reduced pressure and the residue was diluted with aqueous 15 % Na_2CO_3 solution (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by chromatography to give the 3-substituted ethyl 7-acetoxy-*N*-acetylindazole-5-carboxylates **5a–f** (Table 2).

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