A New Strategy for the Synthesis of Cinnoline Derivatives

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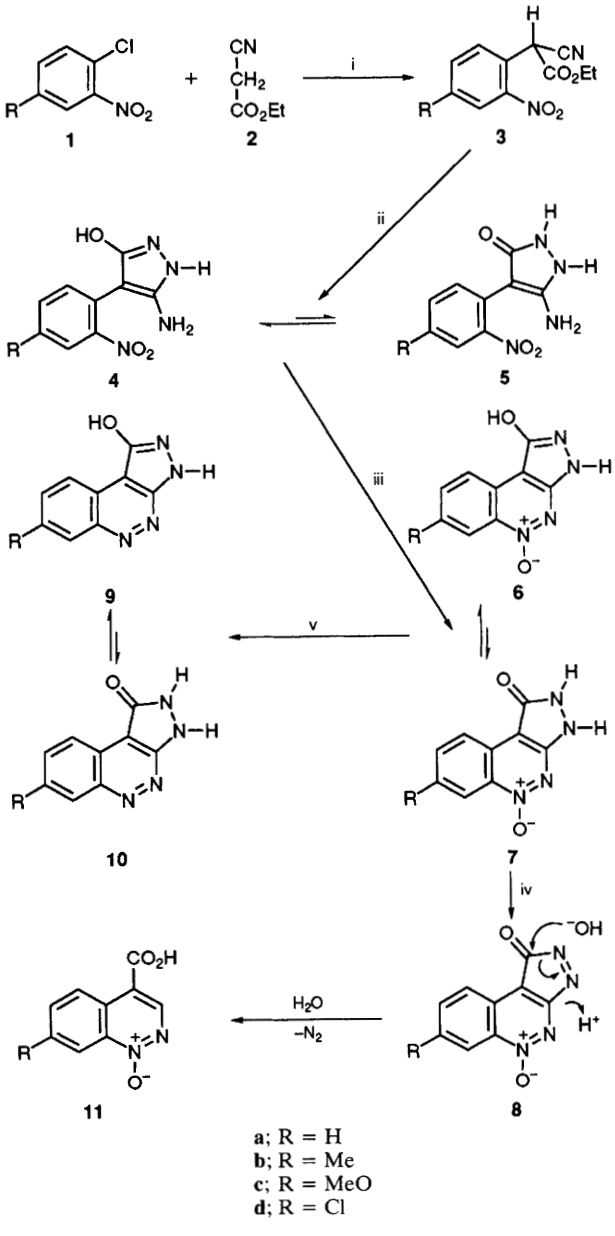
Readily accessible 3-amino-5-hydroxy-4-(2-nitroaryl)pyrazoles undergo efficient base-catalysed cyclisation to afford 7-substituted 1-hydroxy-3*H*-pyrazolo[3,4-*c*]cinnoline 5-*N*-oxides, hypochlorite oxidation of which provides a viable synthetic route to hitherto inaccessible cinnoline-4-carboxylic acid 1-*N*-oxides.

As part of an investigation concerned with the design of new radical scavenging agents having anti-inflammatory activity we required efficient and unambiguous synthetic access to cinnoline 1-*N*-oxides containing exploitable functionality at the 3- and/or 4-positions. There is no simple method for the synthesis of cinnoline *N*-oxides other than direct peracid oxidation of the parent heterocycles.[1] Moreover this approach in practice is often ambiguous in regard to the site of mono-oxidation, inefficient owing to the formation of mixtures of 1- and 2-*N*-oxides, and incompatible with existing functionality sensitive to oxidation. These potentially undesirable features precluded the use of direct peracid oxidation for the synthesis of the cinnoline *N*-oxides in question and prompted the development of an alternative synthetic route based on a new strategy for the construction of the cinnoline ring system. This incorporates two novel synthetic procedures. Firstly the regiospecific formation of a cyclic azoxy nucleus using the known[2] but little explored base-catalysed aldol-type condensation of an amino substituent with a suitably positioned aromatic nitro group, and secondly the previously unexploited oxidative transformation of a fused pyrazolone ring into a carboxy substituent.[3] Application of the new strategy is now shown to provide a viable synthetic route to otherwise inaccessible cinnoline-4-carboxylic acid 1-*N*-oxides.



Scheme 1 *Reagents and conditions*: i, NaH, DMF, 100 °C; ii, $NH_2NH_2 \cdot H_2O$, EtOH, reflux; iii, 2 mol l^{-1} NaOH, reflux; iv, 14% NaOCl aq., 2 mol l^{-1} NaOH, room temp.; v, $Na_2S_2O_4$, DMF, H_2O, reflux

The key starting materials for the new synthetic route to cinnoline 1-*N*-oxide derivatives (Scheme 1) were 3-amino-5-hydroxy-4-(2-nitroaryl)-1*H*-pyrazoles **4a–d**. These previously undescribed pyrazole derivatives were readily obtained (Scheme 1) by the condensation of easily accessible (Table 1) ethyl 2-cyano-2-(2-nitroaryl)acetates **3a–d** with hydrazine under standard conditions. The lack of carbonyl absorption in the IR spectra of the products **4a–d** supports their formulation as hydroxypyrazoles rather than the alternative tautomeric pyrazolinones **5a–d**.[4] However the unusual behaviour of the hydroxypyrazole derivatives **4a–d** at their melting points (Table 1), the reason for which is not yet clear, may indicate their tautomeric conversion into the pyrazolinones **5a–d** at elevated temperature.

Heating the amino-nitropyrazoles **4a–d** with 2 mol l^{-1} aqueous sodium hydroxide under reflux (2 h) resulted in their clean cyclisation to the expected pyrazolo[3,4-*c*]cinnoline *N*-oxides **6a–d** in good to excellent yields (Table 1). The gross structures of these derivatives of the previously undescribed pyrazolo[3,4-*c*]cinnoline ring system are supported by their simple reduction to the parent heterocycles **9a–d** in high yield (Table 1) using sodium dithionite in aqueous dimethylformamide (DMF). The existence of the pyrazolocinnoline derivatives **6a–d** and **9a–d** predominantly in the hydroxy rather than the keto tautomeric forms **7a–d** and **10a–d** respectively is, as for the hydroxypyrazoles **4a–d**, indicated by the absence of carbonyl absorption in their IR spectra.

Table 1

Compound[a]	Yield (%)[b]	Mp (*t*/°C)	Compound[a]	Yield (%)[b]	Mp (*t*/°C)
3a	92	60	**6c**	53	>320
3b	83	oil	**6d**	75	>320
3c	62	oil	**9a**	97	330[f]
3d	97	82	**9b**	77	>320
4a	64	178[c]	**9c**	88	>320
4b	53	124[d]	**9d**	63	>320
4c	81	224	**11a**	100	222
4d	22	135[e]	**11b**	83	250
6a	80	320[f]	**11c**	90	320[f]
6b	56	>320	**11d**	73	252

[a] Satisfactory elemental combustion analyses and mass, IR and ^1H NMR spectral data were obtained for all new compounds. [b] Yields are unoptimised. [c] Monohydrate. [d] With resolidification and remelting at 213 °C. [e] With resolidification and remelting at 221 °C. [f] Decomp.

Exposure of the pyrazolocinnoline *N*-oxides **6a–d** to aqueous alkaline sodium hypochlorite at room temperature for 0.5 h resulted in their smooth conversion in high yield (Table 1) into the corresponding previously unknown cinnoline-4-carboxylic acid 1-*N*-oxides **11a–d**. These processes are readily explained (Scheme 1) in terms of the oxidative transformation of the pyrazolocinnoline *N*-oxides **6a–d** (presumably reacting in the pyrazolinone tautomeric forms **7a–d**) into transient pyrazolone structures **8a–d** which suffer spontaneous hydrolytic ring cleavage with loss of nitrogen, in the alkaline medium. The efficiency of these transformations demonstrates that the apparent existence of the pyrazolocinnoline *N*-oxides largely as the hydroxy tautomers **6a–d** does not preclude their ability to react in the pyrazolinone tautomeric forms **7a–d** when the occasion demands. Preliminary investigations indicate that the analogous oxidative cleavage reactions of the parent pyrazolocinnolines **9a–d** are not so straightforward.

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