A Convenient Synthesis of Otherwise Inaccessible 3-Aminocinnoline-4-carboxylic Acid Derivatives

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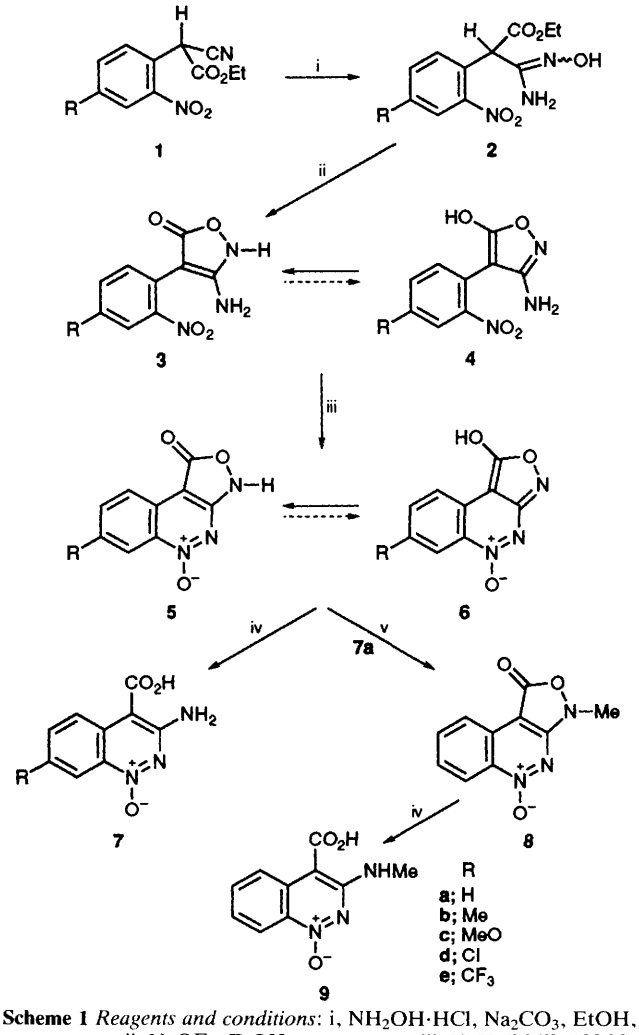
3-Amino-4-(2-nitroaryl)-2*H*-isoxazolin-5-ones, readily available by the sodium ethoxide catalysed cyclisation of amidoximes derived from ethyl 2-cyano-2-(2-nitroaryl)acetates, ring-close in the presence of sodium hydride to afford high yields of isoxazolo[3,4-*c*]cinnolin-1(3*H*)-one 5-*N*-oxides; hydrazine effects the chemoselective reductive scission of the isoxazoline ring in these heterocycles allowing simple and efficient synthetic access to erstwhile unavailable 3-aminocinnoline-4-carboxylic acid 1-*N*-oxides.

In contrast to the abundance of methods for the ring synthesis of variously functionalised benz-fused azines in general, few such methods are available for the assembly of cinnoline derivatives usefully functionalised at the 3- and 4-positions of the hetero ring.[1] In connection with an investigation of the synthesis of new antiinflammatory agents with radical scavenging capacity[2] we required access to 3-hydroxycinnoline-4-carboxylic acids or the appropriate amine precursors and their *N*-oxides. We now report a simple new strategy for the efficient general synthesis of otherwise inaccessible 3-aminocinnoline-4-carboxylic acid 1-*N*-oxides.

The strategy adopted was based on a general synthetic principle which allies aldol-like condensation reactions of aromatic nitro substituents[3] with appropriate azole ring scission to afford methods for the regiospecific synthesis of often inaccessible heterocyclic *N*-oxides and hence by de-oxygenation, the parent heterocycles. We recently described the application of this general principle in an efficient synthesis of cinnoline-4-carboxylic acid 1-*N*-oxides.[4] Pivotal to the extension of this principle to the synthesis of the required 3-aminocinnoline-4-carboxylic acid 1-*N*-oxides (Scheme 1) was the ready availability of previously undescribed 3-amino-4-(2-nitroaryl)-2*H*-isoxazolin-5-ones **3**. It was anticipated that these heterocyclic derivatives would undergo base-catalysed cyclisation through aldol-like condensation[3,4] between the amino and nitro substituents to afford the fused cinnolinone *N*-oxides **5**. Reductive cleavage of the isoxazolinone ring in the latter would then allow simple general access to the target aminocinnoline carboxylic acid derivatives **7**.



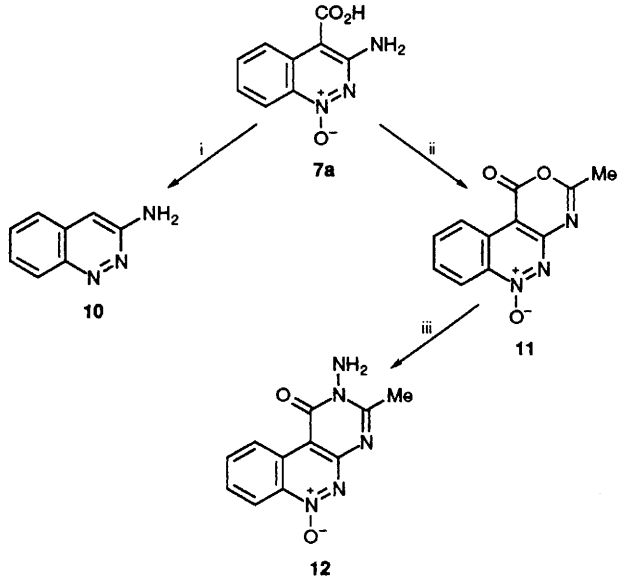
Scheme 1 *Reagents and conditions*: i, $NH_2OH{\cdot}HCl$, Na_2CO_3, EtOH, room temp.; ii, NaOEt, EtOH, room temp.; iii, NaH, DMF, 100 °C; iv, $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; v, NaH, MeI, DMF, room temp.

In practice, the isoxazolinones **3a–d** required as starting materials were readily accessible in generally high yield (Table 1) by the sodium ethoxide catalysed cyclisation of the amidoximes **2a–d** derived by the efficient reaction of the known[4] ethyl 2-cyano-2-(2-nitroaryl)acetates **1a–d** with hydroxylamine. The formulation of the isoxazole derivatives **3a–d** as isoxazolinone structures **3** rather than hydroxyisoxazoles **4** is consistent with the presence in their IR spectra of carbonyl absorption of variable frequency (1750–1690 cm^{-1}) and in the case of the parent compound **3a** by ^{13}C NMR absorption of δ 170.0 attributable to a carbonyl group. The propensity of 3,4-disubstituted 2*H*-isoxazolin-5-ones to exist in the NH rather than the OH tautomeric form has ample precedent.[5] In the case of the trifluoromethyl derivative **2e** treatment with ethanolic sodium ethoxide yielded not the expected isoxazolinone derivative **3e** but rather a low yield (Table 1) of a compound whose analytical and spectroscopic properties supported its formulation as the product of further ring-closure, namely the isoxazolocinnolinone *N*-oxide **5e**, a derivative of the hitherto unknown isoxazolo[3,4-*c*]cinnoline ring system. The analogous isoxazolo[3,4-*c*]cinnolinone *N*-oxide derivatives **5a–d** were readily obtained in largely excellent yield (Table 1) by the sodium hydride catalysed cyclisation of the isoxazolinones **3a–d** in DMF at 100 °C. The formulation of the isoxazolocinnolinone *N*-oxides **5a–e** as keto tautomers **5**

Table 1

Compound[a]	Yield (%)[b]	Mp/°C	Compound	Yield (%)[b]	Mp/°C
2a	88	153	**5d**	97	195
2b	78	153	**5e**	34	191
2c	74	141	**7a**	98	215
2d	84	154	**7b**	82	264
2e	46	117	**7c**	50	215
3a	91	175	**7d**	92	254
3b	80	159	**7e**	91	242
3c	71	100	**8**	78	204
3c	90	178	**9**	83	182
5a	97	185	**10**	48	158[d]
5b	80	201	**11**	96	260
5c	25	200	**12**	41[c]	284

[a] Satisfactory elemental combustion analyses and mass, IR, and ^1H NMR spectral data were obtained for all new compounds. [b] Yields are unoptimised. [c] **7a**, 44%, also formed. [d] Lit.,[8] 163–165 °C.



Scheme 2 *Reagents and conditions*: i, $Na_2S_2O_4$, DMF, H_2O, reflux, ii, Ac_2O, reflux; iii, $NH_2NH_2 \cdot H_2O$, dioxane, reflux

rather than hydroxy structures **6** follows from the presence of carbonyl absorption at 1780–1750 cm^{-1} in their IR spectra.

After a number of orthodox reducing agents had failed to achieve the efficient and selective reductive cleavage of the isoxazolinone ring in the isoxazolocinnolinone *N*-oxides (**5–7**) attention was turned to the use of hydrazine for this purpose. This reagent is known[6] to effect the reductive ring-opening of the hetero ring in 2,1-benzisoxazoles. Analogously, heating with 100% hydrazine hydrate in ethanol converted the isoxazolocinnolinone derivatives **5a–e** into the required 3-aminocinnoline-4-carboxylic acid 1-*N*-oxides **7a–e** in largely high yield (Table 1). The structure of the parent compound **7a** was fully substantiated (Scheme 2) by its reduction with concomitant decarboxylation[7] to give the known[8] 3-aminocinnoline **10**. In addition the aminocinnoline carboxylic acid *N*-oxide **7a** underwent ring-closure with acetic anhydride to afford the oxazinocinnoline derivative **11** whose structure in turn is supported by its reaction with hydrazine to give the pyrimidocinnolinone **12**. Reaction with carboxylic anhydrides to give fused 1,3-oxazinones is a well established[9] transformation of *ortho*-aminocarboxylic acid structures.

The precise mode of reduction involved in the ring-opening reactions (**5** to **7**) awaits the outcome of further investigation. However these processes reveal an intriguing chemoselectivity on the part of hydrazine for reduction of the N–O bond of the isoxazole ring in preference to that of the *N*-oxide substituent. In the context of mechanism it is also interesting that this apparent selectivity extends to the *N*-methyl derivative **8** of the parent isoxazolocinnolinone **7a** which is reduced to the cinnoline *N*-oxide **9** by hydrazine in high yield (Table 1).

We thank the SERC for a research studentship (M. S.) and Hoechst UK Ltd. for financial support.

Received, 30th August 1994; Com. 4/05279J

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