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# SYNTHESES OF 2-ARYL-3-CINNOLINONES BY CYCLISATION OF DIARYLAZO COMPOUNDS

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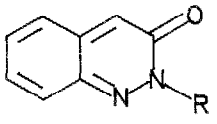
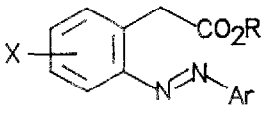
Abstract: Cyclisation of 2-arylazophenylacetic acid with oxalyl chloride gives novel 2-aryl-3-cinnolinones in good yield. Mixed ketene acetals derived from the corresponding phenylacetate esters also give the same product, sometimes with 2-arylindazoles, on treatment with titanium tetrachloride.

The parent 3-cinnolinone (1a) and its N-alkylated derivatives (1b) are well-documented species.[1] In contrast, the corresponding N-aryl analogues (1c) are almost unknown,[2] and no rational synthesis is available. We now report two new reactions of 2-arylazophenylacetic acids (2) or their esters (3). One of these reactions can be applied to a range of substituted diarylazo compounds (2), and provides the first convenient synthetic access to 2-aryl-3-cinnolinones (1c).

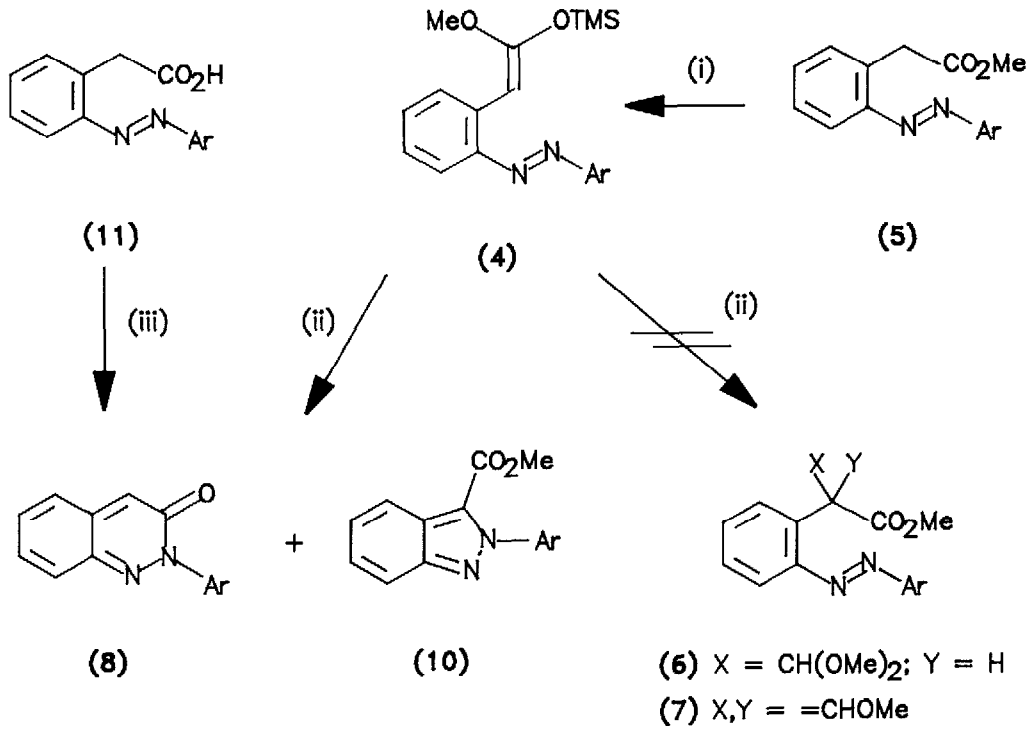


(1a) R = H
(1b) R = alkyl
(1c) R = aryl



(2) R = H
(3) R = $CH_3$

Attempted Mukaiyama alkylation of the mixed ketene acetal[3] (4), derived from the corresponding ester (5), with $TiCl_4$ and $(MeO)_3CH$ under conditions previously described[4] (-70°C, $CH_2Cl_2$) led to isolation of a yellow crystalline material which fluoresced strongly on a silica tlc plate under UV irradiation (Scheme). However, this was not the desired acetal (6) or its elimination product, methoxyacrylate ester (7).[4] Rather, it was assigned the N-arylcinnolinone structure (8), initially on the basis of microanalytical and spectroscopic information.[5] In particular, only one methoxy group was observed in the $^1H$ and $^{13}C$ nmr spectra; an AA'BB' pattern was evident for the <u>para</u>-disubstituted pendant 2-aryl group; four other tightly coupled aromatic protons were observed in the $^1H$ nmr spectrum, along with a broadened singlet at $\delta$ 7.55 ppm; the ir spectrum showed a resonance consistent with an amide-like carbonyl at 1659 $cm^{-1}$; two low field resonances corresponding to carbon doubly bonded to an electronegative atom occurred in the $^{13}C$ nmr spectrum; a molecular ion consistent with the assigned formula was observed in the mass spectrum, as well as a prominent ion resulting from loss of a fragment with m/z = 28 (CO) analogous to that observed for the parent cinnolinone (1a).[6] Subsequent single crystal X-ray structure determination of the analogue (9; see Table) has confirmed the structure assignment.[7]




**SCHEME** Ar = 4–$MeOC_6H_4$

(i) $Me_3SiO_3SCF_3$, $Et_3N$, $CH_2Cl_2$; (ii) $TiCl_4$, $(MeO)_3CH$; (iii) $(COCl)_2$, $CH_2Cl_2$, 20°C.

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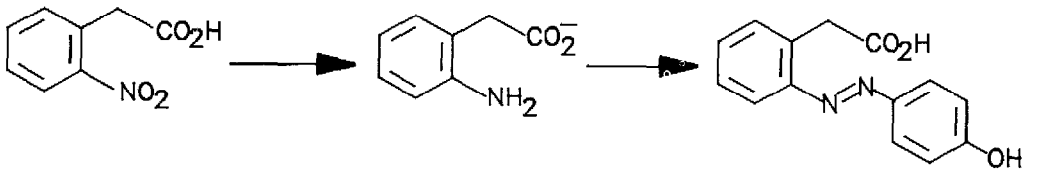
The cyclisation of (4) could be induced equally effectively by $TiCl_4$ in the absence of $(MeO)_3CH$. If the reaction was carried out at room temperature rather than -70°C, a second product, previously only observed in trace amounts, increased at the expense of (8). This was assigned the 2-arylindazole structure (10),[8] resulting from an alternative ring-closure mode.

Although the reaction could be applied to at least one other example (3; Ar = 4-$Me_2NC_6H_4$, X = H), it failed in the case of diester (3; Ar = 4-$AcOC_6H_4$, X = H). In these instances, the presence of indazoles corresponding to (10) was not investigated.

Attempts to by-pass the inconvenient intermediate mixed ketene acetal (4) by direct cyclisation of diarylazo ester precursor (5) were unsuccessful. None of a range of Lewis or protic acids, tertiary amines, or $SOCl_2$ gave any cinnolinone (8).

Fortunately, an alternative more convenient and general reaction based on the carboxylic acid (11) was discovered which gave 2-arylcinnolinones in good yield. Simply treating the acid (11) with an acid chloride (AcCl, $SOCl_2$, $(COCl)_2$) or anhydride ($Ac_2O$) led directly to (8). Best results were achieved when two equivalents of oxalyl chloride were used in $CH_2Cl_2$ at room temperature (Scheme). No indazole (10) was detected by tlc. The generality of these conditions was demonstrated by application to a variety of readily prepared diarylazo compounds, giving a range of cinnolinone derivatives in good yields (Table).[5] Methylation of hydroxy-substituted cinnolinones (12) and (14) gave ethers (8) and (15), respectively (Table).

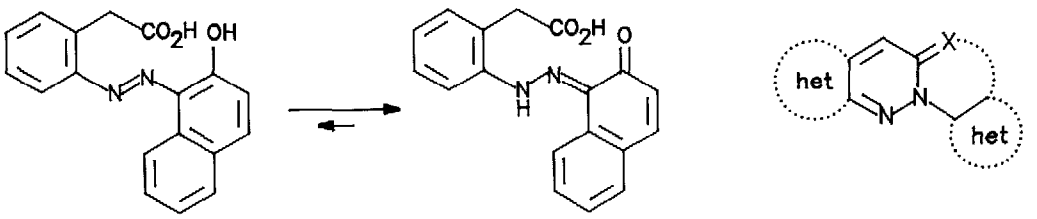
The scope of the reaction is limited by the availability of suitable diarylazo precursors (2). This in turn is dependent on the functionality necessary to enable the azo coupling reaction, including availability of suitable anilines. In general, one of the aryl groups present must be relatively electron rich, and the substituents which ensure this property will limit the substitution patterns present in the cinnolinone products. The examples in the Table include cases where the arylacetic acid precursor is either diazo or coupling component. In the former case, aniline (16), which is most conveniently stored as an aqueous solution of the anion, was derived from the commercially available nitro compound (17) by Pd/C catalysed hydrogenolysis under basic conditions. In the latter case, m-hydroxyphenylacetic acid, which is also commercially available, was coupled with diazotised p-nitroaniline, to give an azo compound which was readily cyclised to cinnolinone (14) (Table). Most of the other diarylazo acetic acids (2) were derived by straightforward diazotisation of (16) and coupling with a suitable coupling component (dialkylaniline or phenol). The exception was anisylazophenylacetic acid (11; Scheme), which was most conveniently prepared by hydrolysis of the corresponding ester (5). This in turn was derived from the phenolic diarylazo acetic acid (18) by double methylation.




(17) (16) (18)

We have yet to demonstrate that the cyclisation reaction occurs efficiently for diarylazo compounds (2) which exist predominantly as hydrazo tautomers, although preliminary experiments on the beta-naphthol derivative (19) indicate cinnolinone formation. (Although the azophenol precursors to cinnolinones (12) and (14) have the formal possibility to exist as hydrazo tautomers, the azo form is likely to predominate.[9])

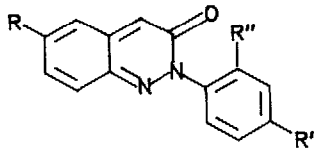
Despite these obvious limitations, the new reaction offers promise of easy, high-yield access to a wide range of cinnolinones which themselves could be further modified to new classes of molecules. For example, further intramolecular cyclisation reactions are being investigated for suitably substituted cinnolinones (e.g. (13) Table), leading to derivatives of the general type (20). The variety of potential cyclisation modes, as well as substitution of heterocyclic units for one or both of the benzenoid rings in (2), suggest a rich source of novel polycondensed heterocycles.




(19) (20)

We thank Dr GV Garner (Manchester Polytechnic) for helpful advice.

Table. 2-Aryl-3-cinnolinones prepared

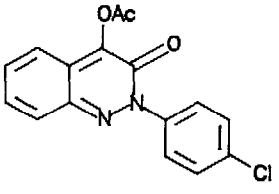


| Compound | Substituents[a] | Reaction conditions | % yield[b] | m.p.°C |
|---|---|---|---|---|
| (8) | R' = $OCH_3$ | [c] | 95 (77) | 183-84 |
| (8) | " | (12) + MeI | 95 | |
| (8) | " | (4) + $TiCl_4$ | (39) | |
| (9) | R' = $N(CH_3)_2$ | [c] | 73 (43) | 197-201 |
| (9) | " | acetal + $TiCl_4$ | 74 | |
| (12) | R' = OH | [c] | 75 (49) | 274-76 |
| (13) | R' = $N(C_2H_5)_2$, R" = $NHCOCH_3$ | [c] | 74 (29) | 263-64 |
| (14) | R = OH, R' = $NO_2$ | [c] | (74) | >300 |
| (15) | R = $OCH_3$, R' = $NO_2$ | (14) + MeI | 75 (30) | 271-72 |

[a] R,R',R" = H unless otherwise noted. [b] Crude (recrystallised). In most cases, crude material from the oxalyl chloride route, or methylation, was spectroscopically and chromatographically pure. [c] Oxalyl chloride (2 equivs) in $CH_2Cl_2$ at room temperature, either for 15 mins or overnight.

References and footnotes


1. G.M.Singerman in "Condensed Pyridazines Including Cinnolines and Phthalazines", ed. R.N.Castle, vol.27 of "The Chemistry of Heterocyclic Compounds", ed. A.Weissberger and E.C.Taylor, John Wiley and Sons, New York, 1973, p.1.
2. A single example (21) has been found in the literature. This is an ill-characterised reaction product found alongside many others. F.A.Mendelvich and M.M.Shemyakin, Dokl.Akad.Nauk SSSR, 1961, 141, 1380.
3. H.Emde and G.Simchen, Annalen, 1983, 1-6, 816.
4. M.G.Hutchings, A.M.Chippendale, and I.Ferguson, Tetrahedron, 1988, 44, 3727.
5. All new compounds had satisfactory microanalytical and spectroscopic data.
6. M.T.Williams, J.Chem.Res.(S), 1986, 136.
7. M.McPartlin, unpublished results.
8. For (10): mp 136-42°C; ir (KBr) 1723 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ 3.89 (s, 3H, OMe), 3.93 (s, 3H, OMe), 8 aromatic protons including AA'BB' pattern; $^{13}C$ nmr ($CDCl_3$) δ 51.9, 55.58, and 6 unique aromatic CH; m/z 282 (100%, $M^+$), 251 (28%, $[M - OMe]^+$).
9. P.Ball and C.H.Nicholls, Dyes and Pigments, 1982, 3, 5, and references cited.

(21)

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