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A New and Practical Synthesis of Indolones.

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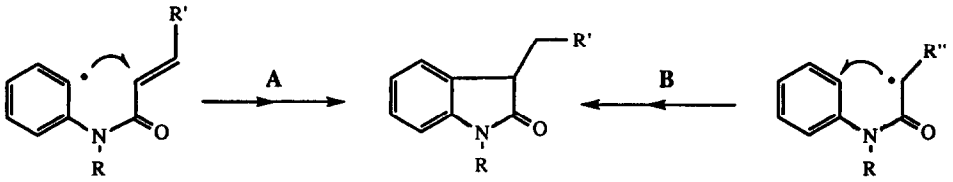
Abstract. A variety of indolones can be obtained from α-haloanilides through a radical cyclisation mediated by a combination of nickel powder and acetic acid.

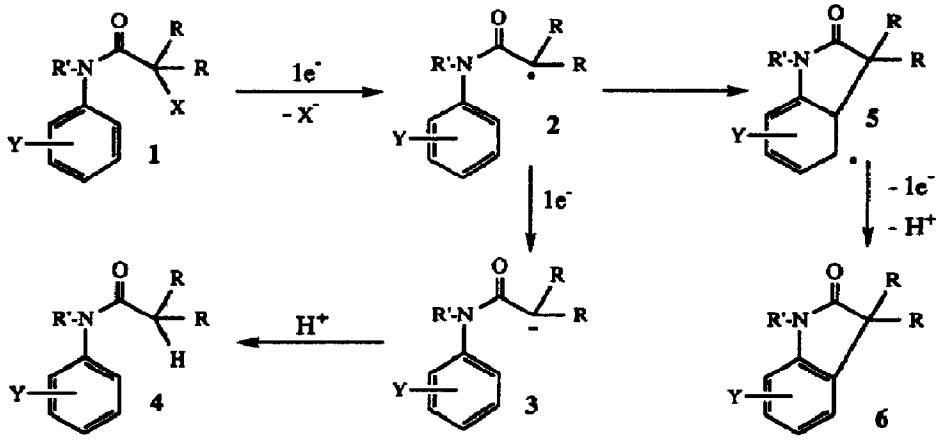
Interest in indolones (oxindoles) derives not only from the varied biological activities displayed by some members of this family but also from the fact that they are immediate precursors to indoles, an exceedingly important class of compounds.[1] Most synthetic routes to indolones rely on ionic processes, especially variants of the Friedel-Crafts reaction.[2] Radical reactions in this area have had a relatively limited impact, since practically all such approaches involve the use of ortho-bromo (or iodo-) acrylamides,[3] as depicted in scheme 1, path A. Except for the simplest members, these starting materials are of limited access. The potentially more flexible route through radical cyclisation onto the aromatic ring (path B) turns out to be quite difficult to accomplish in practice by the usual methods (e.g stannane chemistry) because the cyclisation step is relatively slow as compared with other reactions open to the radical species.[4]



Scheme 1

We recently developed a process based on xanthates[5] where the lifetime of the intermediate radical is long enough to allow it to undergo cyclisation even to an aromatic ring. This method has some weaknesses, namely long heating periods, the need to keep initiating the relatively short radical chain, and somewhat variable yields. We now wish to describe a more practical alternative based on the particular reducing properties of nickel powder, in combination with a weak organic acid such as acetic acid.

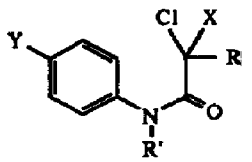
We had found that such a reducing system is capable of cleaving an oxime ester into a carboxylate ion and an iminyl radical, and this property was applied in a practical procedure for preparing 13-epi-17-ketosteroids.[6a] The same combination can reduce certain halogenated derivatives to give carbon centered radicals which may be captured in a variety of ways, one example being the construction of γ-lactams from suitable haloamides.[6b] We have now discovered that under the usual reaction conditions, the intermediate carbon radical derived from a haloanilide is sufficiently long-lived to undergo cyclisation onto the aromatic ring to give finally an indolone.



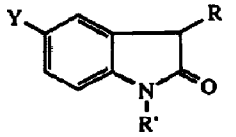
Scheme 2

The mechanistic reasoning underlying our approach is outlined in scheme 2. Thus, reduction of haloanilide **1** gives the corresponding radical **2** which, with most reducing agents, is converted into the equivalent of anion **3** (and hence to anilide **4** upon protonation) too rapidly to be of any use in a radical based synthetic process. With nickel powder / acetic acid under appropriate conditions, the second electron transfer step is sufficiently slow so that the intermediate radical can cyclise onto the aromatic ring. The cyclohexadienyl radical **5** thus produced should be easily oxidised[7] to the desired indolone **6**.

In practice this turns out to be indeed the case. For example, heating N-methyl trichloroacetanilide **1a** in isopropanol in the presence of acetic acid and nickel powder produced a mixture of two compounds: indolone **6a** in 78% yield and dichloroacetanilide **4a** in 15% yield, the latter arising from premature reduction of the first intermediate radical (i.e. **2a**). A number of other indolones bearing a variety of substituents could be prepared in the same way, as shown by the data collected in the Table.

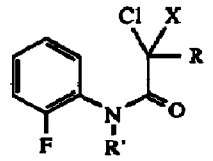


1a, R= X= Cl; R'=Me; Y= H
4a, R= Cl; R'=Me; X= Y= H
1b, R= X= Cl; R'= Bn; Y= H
4b, R= Cl; R'= Bn; X= Y= H
1c, R= R'= Me; X= Cl; Y= H
4c, R= R'= Me; X= Y= H
1d, R= X= Cl; R'= $ArCH_2$-; Y= F
4d, R= Cl; R'= $ArCH_2$-; X= H; Y= F
4'd, R= X= H; R'= $ArCH_2$-; Y= F
1f, R= X= Cl; R'= Bn; Y= I
4f, R= Cl; R'= Bn; X= H; Y= I
1g, R= X= Cl; R'= Bn; Y= OH
4g, R= Cl; R'= Bn; X= H; Y= OH

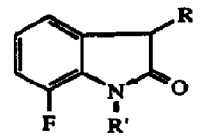


6a, R= Y= H; R'= Me
6b, R= Y= H; R'= Bn
6c, R= R'= Me; Y= H
6d, R= H; R'=$ArCH_2$-; Y=F
6f, R= H; R'=Bn ; Y= I
6g, R= H; R'=Bn; Y= OH

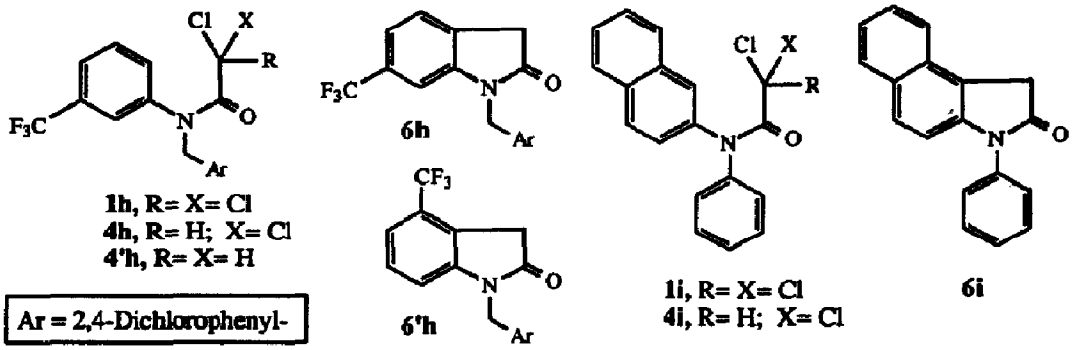
Ar = 2,4-Dichlorophenyl-



1e, R= Cl; R'=$ArCH_2$-; X= Cl
4e, R= Cl; R'=$ArCH_2$-; X= H
4'e, R= H; R'=$ArCH_2$; X= H



6e, R'=$ArCH_2$-



In principle the initial product should be the dichloroindolone (i.e. **6**, R= Cl in scheme 2). This intermediate must however be reduced faster than the starting material since upon cyclisation the carbon-chlorine bonds become benzylic. Hence all the indolones obtained are completely reduced. Uncyclised dichloroacetanilides **4a-i** were also produced in variable amounts depending on the substrate; in some cases monochloroacetanilides (i.e. **4'd,e,h**) were also isolated. Dichloroprionanilide **1c** afforded the α-methylated indolone **6c** in moderate yield. When the substituent in the aromatic ring is in the meta position, as in **1h**, reductive cyclisation gave a 3:2 mixture of isomeric indolones **6h** and **6'h** in 60% yield which in this case were not separated. N-2-naphthyl-N-phenyl trichloroacetamide **1i** underwent cyclisation exclusively on the naphthalene ring, and then only in the α-naphthyl position, in accord with previous observations.[6a,8]

Table: Formation of Indolones **6a-i** from Haloanilides **1a-i**

Entry	Starting Anilide	Reaction Time (hours)	Products (yield, %)
1	**1a**	4	**6a** (78) ; **4a** (15)
2	**1b**	6	**6b** (73) ; **4b** (23)
3	**1c**	5	**6c** (43) ; **4c** (50)
4	**1d**	4	**6d** (70) ; **4d** (7); **4'd** (10)
5	**1e**	3	**6e** (60) ; **4e** (25); **4'e** (8)
6	**1f**	10	**6f** (50) ; **4f** (30)
7	**1g**	7	**6g** (70) ; **4g** (5)
8	**1h**	6	**6h, 6'h** (60, 3:2); **4h** (20); **4'h** (10)
9	**1i**	4	**6i** (45) ; **4i** (40)

Apart for its cheapness and simplicity, [9] this method is tolerant of a wide variety of functional groups. Ordinary halides, especially when the halogen atom is attached to an aromatic ring, are not affected or only very slowly by the nickel / acetic acid system. This property allows the synthesis of various halogenated indolones which can act as springboards towards more complex derivatives by using palladium chemistry or radical based processes for example. Iodoindolones such as **6f** are especially useful in this regard. Another

important substituent is the hydroxy group which may be present unprotected. Thus indolone **6g** can serve as a starting material for the synthesis of analogues of serotonin and related substances (e.g. bufotenine) or various alkaloids containing the 5-hydroxy-indole or indolone subunit.[10] Further extensions of this process are currently under study.

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7. Cyclohexadienyl radicals are easily oxidised into the aromatic system. See for example: Cadogan, J. I. G.; Paton, R. M.; Thomson, C. *J. Chem. Soc. (B)* **1971**, 583-595. Under our conditions, oxidation could occur by reaction with nickel salts produced in the medium or by electron trasfer to the starting trichloroacetamide **1** or, even better, the intermediate dichloroindolone (**6**, R= Cl in Scheme 2); see: Fontana, F.; Kolt, R. J.; Huang, Y.; Wayner, D. D. M. *J. Org. Chem.* **1994**, *59*, 4671-4676.

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9. Typical experimental procedure: To a solution of trichloroacetanilide (1 mmole) in propan-2-ol (6 ml) was added acetic acid (30 mg) and nickel powder (Janssen, now Acros Chemicals; 1.77g) and the mixture heated to reflux with stirring until thin layer chromatograghic analysis indicated essentially complete reaction (usually several hours).The reaction mixture was then cooled, filtered on celite, washed with dilute sodium bicarbonate, and extracted with ether. The organic layer was then dried over sodium sulfate, concentrated under reduced pressure, and the residue purified by flash chromatography to give the desired indolone.

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