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A short and efficient synthesis of *N*-substituted indol-2-ones (oxindoles)

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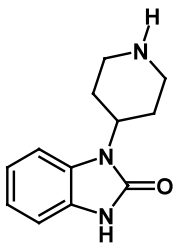
Abstract—A short and high yielding process has been developed for the synthesis of *N*-(4-piperidinyl)-indol-2-ones. This strategy also constitutes a general route to *N*-substituted indol-2-ones. © 2001 Elsevier Science Ltd. All rights reserved.

The 1-piperidin-4-yl-1,3-dihydro-benzimidazol-2-one ring system **1** is well known in pharmaceutical research as a template for ligands at numerous G-protein coupled receptors, e.g. dopamine receptors and 5-hydroxytrypamine (5-HT) receptor subtypes.[1] Indeed, various derivatives of **1** are currently marketed as drugs for the treatment of psychiatric and/or gastrointestinal disorders.[2] In-house calculations on various structures containing the template **1** indicated potential low brain penetration for these compounds, due primarily to the presence of the polar benzimidazolone NH group.[3] Thus, we became interested in the less polar O and CH_2 isosteres, **2** and **3**, which were predicted to confer greater brain penetration in a wide range of analogues. There are numerous high yielding syntheses of the benzoxazol-2-one **2**,[4] but very few references to the corresponding 1,3-dihydro-indol-2-one (oxindole) **3a**.[5,6] We have developed a simple, flexible, and high yielding synthetic route to **3a**, as well as substituted analogues **3b** and **3c** (Scheme 3). This methodology also constitutes a general syntheses of *N*-substituted indol-2-ones as it is capable of introducing a wide variety of substituents onto the indolone nitrogen atom.

Literature routes to **3a** involve either a Friedel–Crafts cyclisation step[5] or involve reductive alkylation of an *ortho*-aminophenylacetic acid or *ortho*-aminophenylacetamide followed by cyclisation (Scheme 1).[6] In our hands, the Friedel–Crafts approach was low yielding and not reproducible, while the main disadvantages of the other (also low yielding) approaches were unwanted cyclisation to the indol-2-one prior to reductive alkylation, or the harsh conditions required for complete cyclisation onto the primary amide.[6]

We envisaged that the general process outlined in Scheme 2 would offer numerous advantages to existing routes. The *t*-butyl ester of *ortho*-aminophenylacetic acid, **4**, is a stable compound,[7] which should readily allow reductive amination, prior to effecting ring closure.

In practice, we developed the route summarised in Scheme 3. Addition of di-*t*-butyl malonate, under basic conditions, to the *ortho*-fluoronitrobenzene derivatives **5** afforded the adducts **6**. The use of di-*t*-butyl malonate serves two functions: it allows facile anion forma-



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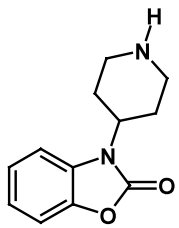

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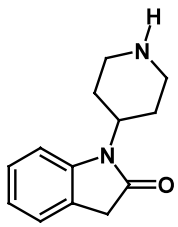

3a

Keywords: heterocyclic compounds; indol-2-ones; oxindoles; synthesis.

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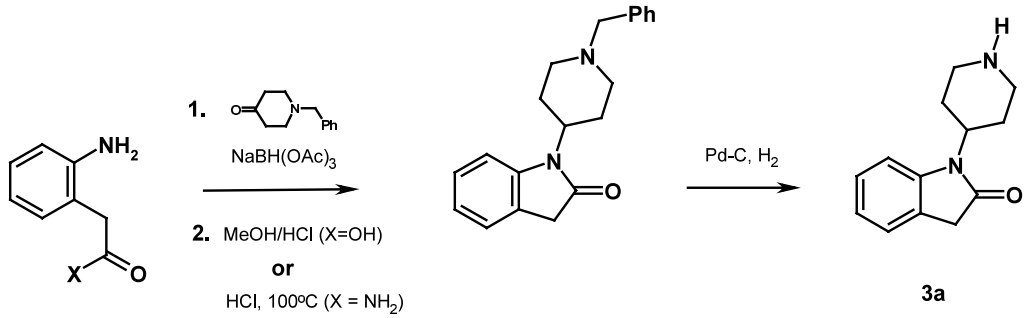
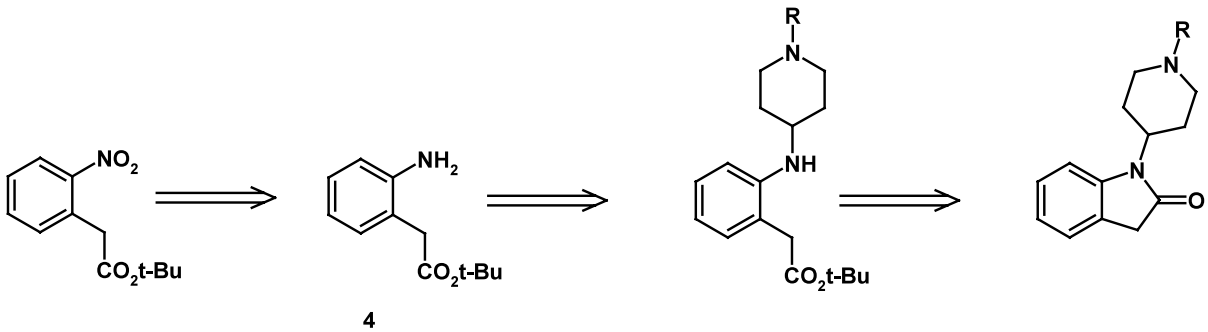
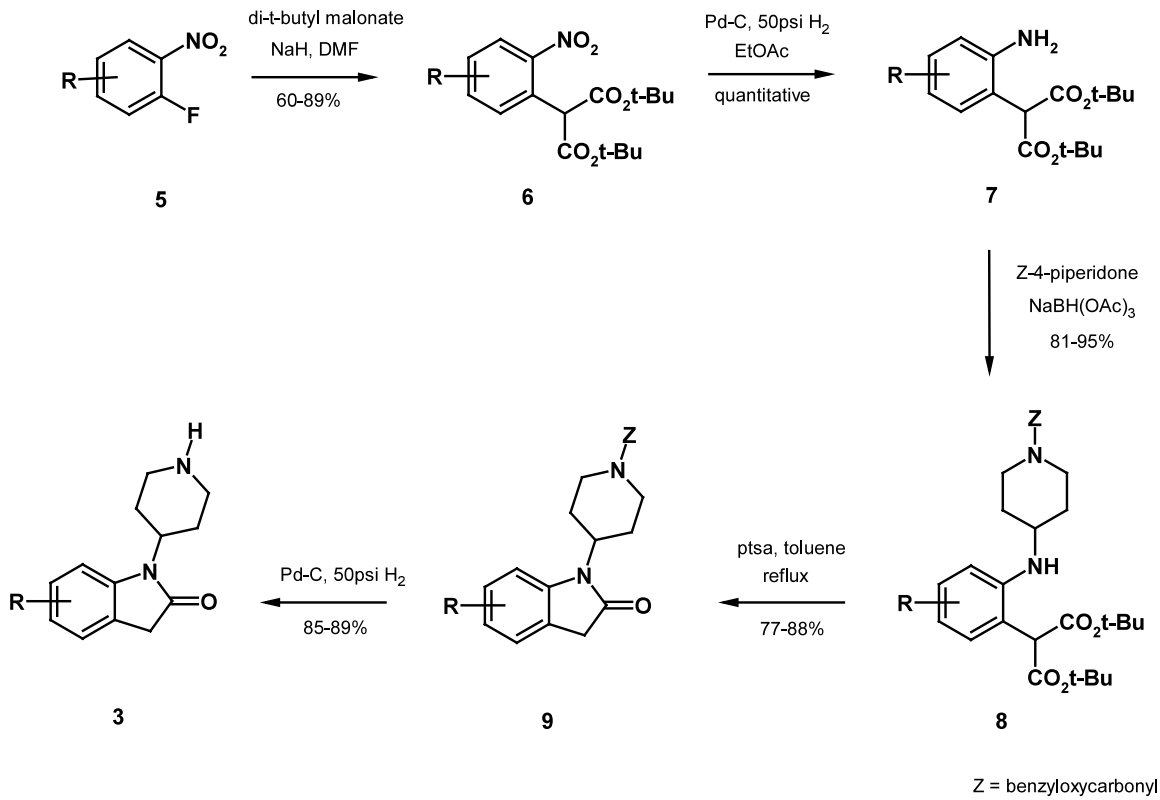


Scheme 1. Literature routes to **3**.



Scheme 2. Outline of synthetic strategy.



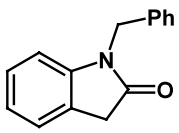
Scheme 3. Synthetic route to substituted indol-2-ones: (a) R = H; (b) R = 5-F, (c) R = 6-F.

tion prior to nucleophilic aromatic substitution, and use of the *t*-butyl esters prevents unwanted cyclisation at the next stage. Thus, the nitro adducts **6** were hydrogenated in quantitative yield to the anilines **7**, which gratifyingly showed no propensity to cyclise. Reductive alkylation of **7** using *N*-benzyloxycarbonyl-4-piperidone proceeded under standard literature conditions[8] to provide the key di-esters **8**. In a highly efficient manner,

the di-esters **8** were converted into the desired indol-2-ones **9**, by treatment with 4-toluenesulfonic acid (ptsa) in refluxing toluene for 1 h. Thus, in a single step, the di-*t*-butyl esters **8** were deprotected, allowing concomitant intramolecular cyclisation to the indol-2-one to occur, in addition to the facile decarboxylation of the redundant carboxyl group. Removal of the benzyloxycarbonyl protecting group on the piperidine nitrogen was accomplished by standard hydrogenation, affording compounds of generic structure **3**.[9]

A wide range of substituted *ortho*-fluoro and *ortho*-chloro nitrobenzenes are commercially available, in addition to various heteroaryl analogues, thus opening up pathways to the synthesis of a wide range of substituted and heterocyclic indol-2-ones. Additionally, this route is also a versatile process for the synthesis of indol-2-ones having a diverse range of *N*-substituents, by appropriate choice of aldehyde or ketone in the reductive alkylation of **7**.

For example, reductive alkylation of **7a** with benzaldehyde followed by treatment with ptsa in refluxing toluene afforded the *N*-benzylindol-2-one **10** in 70% overall yield.

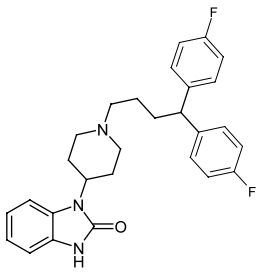


10

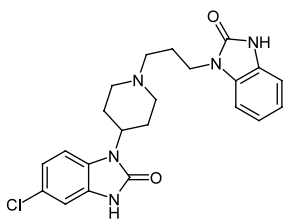
In summary, a short, versatile and high yielding process for the synthesis of *N*-substituted 1,3-dihydroindol-2-ones has been developed. The high yields and ready availability of starting materials distinguish this approach from other routes to *N*-substituted indol-2-ones.[10]

References

1. A search of Chemical Abstracts gave ~6,000 references to substituted 1-piperidin-4-yl-1,3-dihydro-benzimidazol-2-ones mainly in the patent literature. For examples see WO 0127104, WO 0125200, WO 9955694, WO 9936421, US 5789402, EP 739891.
2. For example, Pimozide is marketed as a neuroleptic and Domperidone is marketed as an antiemetic agent.



Pimozide



Domperidone

3. GlaxoSmithkline, unpublished data.
4. For examples see WO 9932481, US 5665719, WO 9502405.
5. US 3325499.
6. (a) US 5665719; (b) Klein, W.; Back, W.; Mutschler, E. *Arch. Pharm. (Weinheim, Ger.)* **1975**, *308*, 910–916.
7. (a) Flitsch, W.; Russkamp, P. *Liebigs Ann. Chem.* **1985**, *7*, 1398–1412; (b) Orlemans, E. O. M.; Schreuder, A. H.; Conti, P. G. M.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1987**, *43*, 3817–3826.
8. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
9. NMR and mass spectra of all compounds were fully consistent with the structures shown.
10. *Comprehensive Heterocyclic Chemistry* **1984**, *4*, 364–366; *Comprehensive Heterocyclic Chemistry* II **1996**, *2*, 146.