Tetrahedron Letters 53 (2012) 1897–1899

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-catalysed approach to spirocyclic oxindoles via a direct C–H, Ar-H functionalisation

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ARTICLE INFO

Article history:
Received 12 December 2011
Accepted 27 January 2012
Available online 3 February 2012

Keywords:
Copper catalysis
Spirocyclic oxindoles
Radical cyclisation
C–H activation
Natural product synthesis

ABSTRACT

A practical and efficient entry to spirocyclic oxindoles from readily accessible anilide precursors, using only catalytic amounts of an inexpensive copper salt together with air as the sole re-oxidant, is described. In addition to providing access to a broad range of spiro-oxindole products, the utility of this method is demonstrated in a formal synthesis of the natural product, horsfiline.

The oxindole structure has long fascinated synthetic chemists, partly due to the synthetic challenges that many oxindole-containing targets present, and partly owing to the exciting biological profiles they exhibit and their potential as pharmaceuticals.[1]

In terms of their structure, naturally-occurring oxindoles tend to be appended with two substituents at the benzylic position (i.e., 3,3-disubstituted), with a large proportion of these having the side-chains tied together, thus giving rise to a spirocyclic junction.[2] They can range from small members, such as horsfiline (**1**),[3] to the more imposing representatives, such as the polycyclic alkaloid gelsemine (**2**),[4] which has stimulated a number of total synthesis programmes across the globe simply as a result of the attraction of its formidable and striking structure (Fig. 1).[5] More importantly, many spiro-oxindole natural products display remarkable biological properties: for example, strychnofoline (**3**) displays useful antimitotic activity against cultures of mouse melanoma,[6] and has already succumbed to a creative total synthesis by the Carreira laboratories.[7] Most notably, the prominence of the oxindole motif in naturally-occurring compounds of medicinal value has spurred the development of a valuable collection of fully synthetic clinical drugs and candidates thereof. This is well exemplified by satavaptan (**4**, SR-121463),[8] an orally-active and selective vasopressin V_2 receptor antagonist, which belongs to a new class of drugs developed for the treatment of hyponatraemia and is currently in Phase III trials.

From the synthetic viewpoint, the transition metal catalysed cyclisation of linear anilide precursors is a particularly efficient

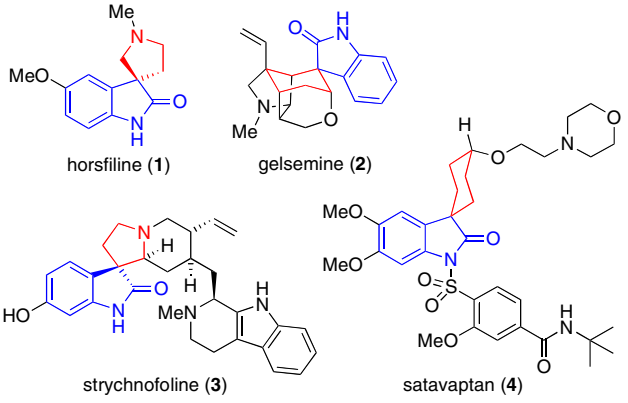
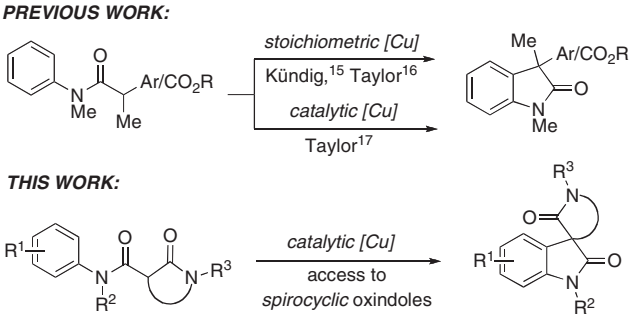


Figure 1. Examples of spirocyclic oxindoles.



Scheme 1. Copper-mediated oxindole cyclisation.

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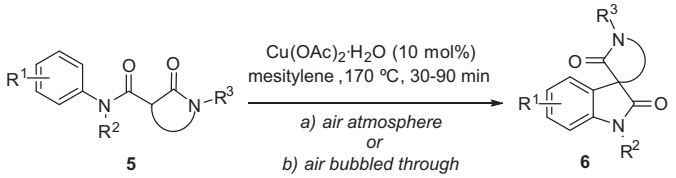
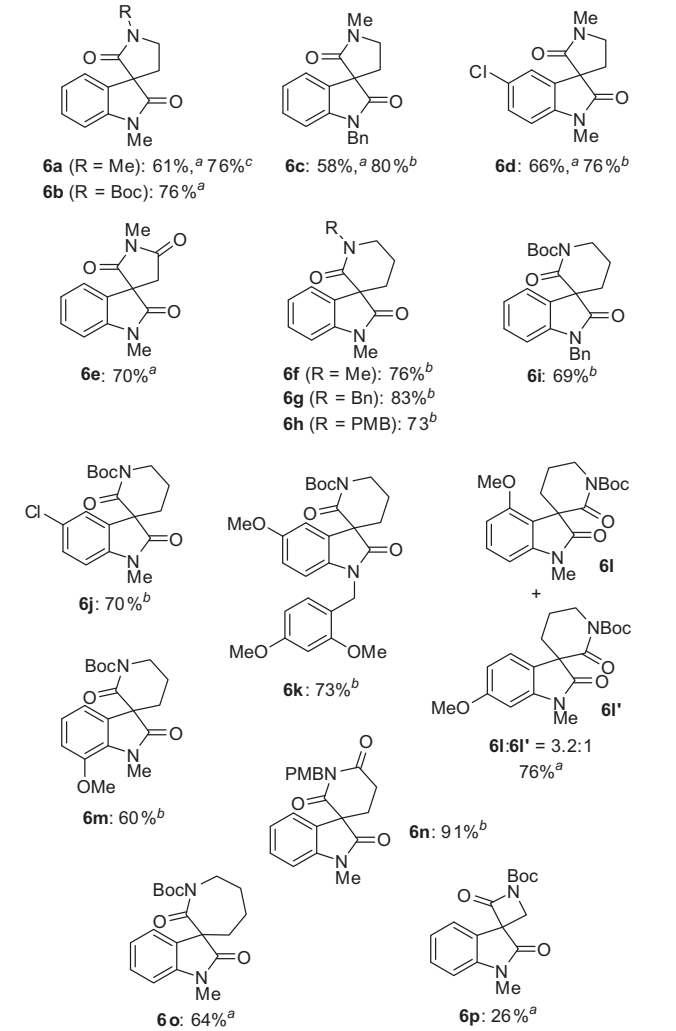
doi:10.1016/j.tetlet.2012.01.120

strategy for the synthesis of 3,3-disubstituted oxindoles.[9] Most of these methods make use of palladium catalysis, namely in Heck cyclisations,[10] C–H activation processes,[11] and enolate arylations,[12] as well as others.[13] Copper salts have also found utility as reagents for cyclisations leading to oxindoles,[14] however, it was in 2009 that Kündig and Jia,[15] as well as ourselves,[16] reported a copper-mediated cyclisation of *unfunctionalised* anilides to the 3,3-disubstituted oxindole core via a formal double C–H activation approach (Scheme 1). We subsequently disclosed an improved variant of this reaction process,[17] which utilised sub-stoichiometric amounts (5 mol %) of a copper catalyst with no loss in reaction efficiency. Herein we communicate a practical extension of this methodology for the straightforward synthesis of *spirocyclic* oxindoles, which enables the installation of a quaternary all-carbon centre via a direct C–H, Ar-H functionalisation by means of copper catalysis without the need for additional base.

Table 1
Reaction scope investigation (yields are isolated)





[a] Reaction was carried out with the reflux condenser open to air.
[b] Reaction was carried out by vigorously bubbling compressed air through the refluxing reaction mixture.
[c] Reaction was carried out in toluene at 120 °C for 15 h with the reflux condenser open to air.

In the current study, the use of just 10 mol % of the environmentally benign and inexpensive copper(II) acetate monohydrate as the catalyst and air as the stoichiometric re-oxidant enabled us to rapidly establish the broad scope of this spirocyclisation reaction (Table 1). The cyclisation precursors **5** were easily prepared in just three straightforward synthetic steps from protected lactams (see Supporting Information). All cyclisations were carried out with mesitylene as the solvent at 170 °C, thus cutting down on reaction time (30–90 min). Comparable results could also be achieved by running the reactions in refluxing toluene (120 °C), although a longer reaction time was needed in order to achieve full conversion (typically overnight). Oxygen in air was all that was required to re-oxidise the copper catalyst. In certain cases a small amount of substrate **5** was found to undergo cleavage to the corresponding aniline and lactam/imide under the reaction conditions, resulting in lower yields of the oxindole products **6**. This obstacle was eventually overcome by simply bubbling air through the refluxing reaction mixture, thus accelerating the rate of copper re-oxidation and, ultimately, oxindole cyclisation. In this way, the undesired cleavage of the starting anilides **5** was minimised and the efficiency of the cyclisation step improved.

In terms of substrate scope, anilides containing butyrolactam unit **5a–d**, appended with a range of substituents on the nitrogen atoms and the benzene ring, as well as that incorporating the succinimide motif (**5e**), all provided the cyclic products **6a–e** in good to excellent yields (Table 1). The desired oxindoles **6f–i** were also successfully obtained with six-membered valerolactam-containing anilides **5f–i** as substrates. We were able to obtain a suitable crystal of spirocyclic product **6i** for X-ray crystallographic analysis and conclusively established its identity (Fig. 2).[18]

Substitution on the benzene ring was next explored and products **6j–m** were furnished in good yields. It is noteworthy that access to aryl chlorides of type **6j** allows for further palladium-mediated manipulation to structurally more elaborate, and potentially medicinally relevant, oxindoles. The result obtained with the *meta*-methoxy-substituted example **5l** was also intriguing: a mixture of regioisomers **6l** and **6l′** was isolated,[13f] with the major isomer **6l** arising from radical addition to the position more encumbered sterically, but potentially preferred electronically, presumably due to the higher degree of stabilisation of the intermediate cyclohexadienyl radical. Glutaramide- and caprolactam-based anilides **5n** and **5o** also furnished spirocyclic oxindoles **6n** and **6o**, respectively, in good yields. Of potential medicinal interest are ß-lactam-containing oxindoles of type **6p**,[19] albeit the efficiency of the cyclisation of **5p** was found to be somewhat lower. Postulating that, mechanistically, this reaction proceeds via an intermediate enol, the lower yield of cyclic product **6p** could be attributed to the high strain associated with the enol (or the resultant radical species following oxidation of the enol), which contains three adjacent sp^2 centres within a four-membered ring. It should be noted that, to the best of our knowledge, all the oxindole products described here and accessed via the copper-catalysed cyclisation method are novel compounds.

Having established the broad scope of this cyclisation methodology we sought to demonstrate its utility in the synthesis of the natural product horsfiline (**1**, Scheme 2).[3] In this context, benzylcarboxylation of commercially available *N*-methylpyrrolidone (**7**) afforded intermediate **8** which, upon hydrogenolysis and amide coupling, swiftly furnished the linear cyclisation precursor **9** on gram scale in excellent overall yield. Ready access to anilide **9** paved the way for the application of our copper(II)-mediated cyclisation, which successfully provided the desired oxindole **10** in a

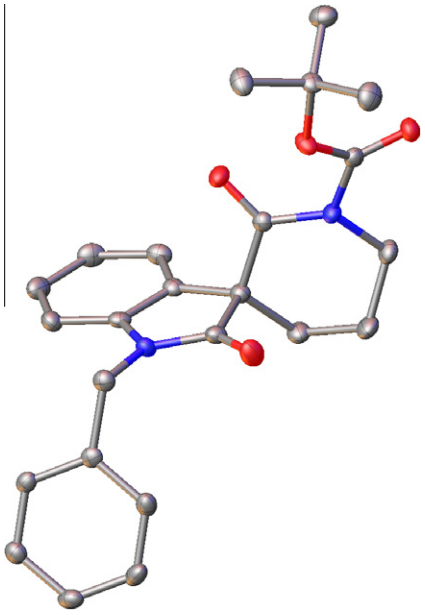
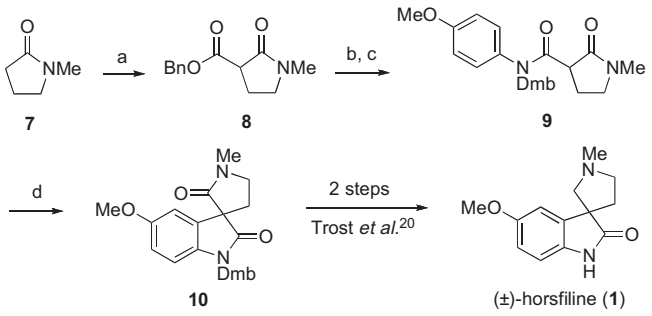


Figure 2. Crystal structure of **6i**.



Scheme 2. Formal total synthesis of horsfiline (**1**). Reagents and conditions: (a) LDA, CbzCl, THF, −78 °C, 1 h (48%); (b) H_2, Pd/C, EtOAc, rt, 1 h (97%); (c) *N*-Dmb-4-methoxyaniline, 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h (97%); (d) $Cu(OAc)_2{\cdot}H_2O$ (10 mol %), mesitylene, air bubbled through, 170 °C, 90 min (71%). LDA = lithium di-iso-propylamide; Cbz = carboxybenzyl; THF = tetrahydrofuran; Dmb = 2,4-dimethoxybenzyl.

71% yield and intercepted Trost's intermediate for the formal synthesis of horsfiline (**1**).[20]

In summary, the copper(II)-mediated cyclisation methodology enables entry to a large class of spirocyclic oxindoles via a direct C–H, Ar-H functionalisation with high efficiency from easily accessible starting materials with cheap reagents. This method allows the installation of a quaternary carbon centre at the spirocycle junction and constitutes an attractive approach for the preparation of oxindole-based natural products and their analogues. The development of a stereoselective variant of this process is currently underway in our laboratories: preliminary studies have been carried out using enantiopure additives but, to date, no significant enantioselectivity has been obtained.

Acknowledgments

We gratefully acknowledge the University of York (C.L.M., V.F., P.D., J.E.M.N.K.) and the University of York Wild Fund (P.D., J.E.M.N.K.) for generous financial support, as well as Dr. Robert Thatcher and Dr. Adrian Whitwood for help with X-ray crystallographic analysis.

Supplementary data

Supplementary data (full experimental procedures, characterisation data, ^1H NMR traces and crystallographic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.120.

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