A two step route to indoles from haloarenes—a versatile variation on the Fischer indole synthesis[†]

Martyn Inman and Christopher J. Moody*

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In a new variation on the Fischer indole synthesis, readily available haloarenes are converted into a wide range of indoles in just two steps by halogen-magnesium exchange, quenching with di-*tert*-butyl azodicarboxylate, followed by reaction with ketones under acidic conditions.

Owing to the potent and wide-ranging biological activity of indoles, and the complex and unusual architectures found among their naturally occurring derivatives, this important ring system continues to hold a fascination for chemists worldwide.¹⁻⁴ As a result, useful methodologies for the synthesis of this venerable, but nonetheless ever relevant, heterocycle continue to be developed. Unfortunately, even modern methods, often transition-metal catalysed, frequently start from *ortho*-substituted anilines,^{5–7} thereby greatly restricting the availability of starting materials. A more general approach would start from a mono-functionalised arene followed by cyclisation with C-C bond formation to an unactivated C-H bond, and a few notable advances towards this goal have been reported recently. Thus Glorius and colleagues described the palladium(II)-catalysed oxidative cyclisation of N-aryl enamines derived from anilines and 1,3-dicarbonyl compounds,8 with related copper, iron and iodine(III) mediated oxidative cyclisations being subsequently reported,⁹⁻¹¹ whilst the Fagnou group conceived a complementary approach involving rhodium catalysed coupling of acetanilides with alkynes.12

However, some of the historically most important indole syntheses also fall into this reaction category, and also involve cyclisation with C-C bond formation to an unactivated C-H bond. Pre-eminent amongst these is the most famous of all indole syntheses, the Fischer reaction,13,14 that involves functionalisation of an unactivated aromatic C-H position by way of a [3,3]-sigmatropic shift (Scheme 1). Although maybe unfashionable, this celebrated reaction satisfies the requirements of a modern indole synthesis in its convenience and simplicity-coupling a mono-functionalised arene with a readily available aldehyde or ketone, the only disadvantage being the lack of availability of aryl hydrazines. Mindful of this limitation, and inspired by the mechanistic elegance of the reaction, we now present a new variation on the Fischer reaction that starts from much more readily available haloarenes and delivers a wide range of indoles in just two steps.15



Scheme 1 The Fischer indole synthesis.

In planning a straightforward route to aryl hydrazines,¹⁶ and hence indoles, we were attracted by the use of di-tert-butyl azodicarboxylate as a source of the hydrazine unit, since the resulting Boc-protecting groups would undergo concomitant cleavage under the Brønsted or Lewis acidic conditions of the Fischer cyclisation. Although azodicarboxylates have found use as electrophiles in reactions with electron rich aromatic rings,17,18 organolithiums and Grignard reagents,19,20 organozincs,²¹ or boronic acids under copper^{22,23} or palladium catalysis,²⁴ we elected to use the under utilised Grignard based procedure because of the advantages of functional group compatibility using modern methods of halogen-magnesium exchange.²⁵ Thus aryl iodides or bromides 1 underwent halogen-magnesium exchange upon treatment with isopropylmagnesium chloride in THF,²⁵ or phenylmagnesium chloride in the case of nitro containing aromatics,²⁶ followed by reaction with di-tert-butyl azodicarboxylate to give the di-Boc-protected aryl hydrazines 2 in 71-98% yield (Scheme 2, Table 1). As expected, aryl bromides underwent slower halogen-magnesium exchange than the iodides,²⁷ allowing for selective magnesiation of 2-bromoiodobenzene (entry 1), and the reaction is tolerant of a wide range of functional groups including fluoride, chloride, tosyloxy, nitro and carboxylate ester.

Reaction of hydrazines 2 with an array of ketones under acidic conditions resulted in cleavage of the protecting groups, hydrazone formation and Fischer indolisation in a single pot to give a range of indoles 3 in excellent yield

School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD. E-mail: c.j.moody@nottingham.ac.uk; Fax: +44 115 951 3564

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 Table 1
 Two-step conversion of haloarenes 1 into indoles 3 via aryl hydrazides 2



Table 1 (continued)



used in metalation step.

(Scheme 2, Table 1). A variety of acidic conditions were investigated (Table 1), but the most generally applicable were the use of concentrated hydrochloric acid in ethanol at 70 °C, although in some cases the use of acetic acid as solvent, or the use of neat TFA was found to be superior (Table 1). Indoles bearing a broad range of substituents were readily obtained by this method, the *meta*-chloro-substituted hydrazide **2f** giving, as expected,²⁸ only the 6-chloroindole **3f**. Likewise, the hydrazone derived from hydrazide **2g** gave a single indole product **3g**.

The advantages of this new variation of the classical Fischer indole synthesis, incorporating the previously little used reaction of Grignard reagents with azodicarboxylate electrophiles as a key step, lie in its simplicity and versatility. Haloarenes are appealing and readily available starting materials, and obviate the need to prepare aryl hydrazines from anilines by the oft problematic diazotisation–reduction sequence, simultaneously avoiding undesirable anilines such as naphthylamines. These features combine to make this an attractive and highly practical alternative modern protocol for the synthesis of the fundamentally important indole ring system.

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