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A simple, two-step synthesis of 3-iodoindoles

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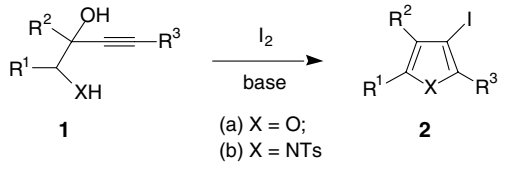
Abstract—2-Halo-anilines, protected as the corresponding sulfonamides or carbamates, can be converted very efficiently into 3-iodoindoles by sequential Sonogashira coupling with a 1-alkyne and 5-*endo*-dig iodocyclisation. Azaindoles can also be obtained using this methodology.

Haloarenes have always played a central role as intermediates in organic synthesis, a position which has been expanded enormously by the introduction of numerous palladium-catalysed methods for the substitution of halide atoms in such compounds.[1] Hence, new and efficient methods for the elaboration of these species could find sustained utility. We have recently contributed two such methods for the synthesis of β-iodofurans **2a**[2] and β-iodopyrroles **2b**[3] by 5-*endo*-dig iodocyclisations of the corresponding alkyne-diols **1a** and homopropargylic sulfonamides **1b**, respectively (Scheme 1). Clearly, a significant feature of this type of chemistry is that the heterocyclic nucleus is also elaborated during the iodination process.

Naturally, we were intrigued by the prospect of applying this methodology to the synthesis of other systems, in particular benzannulated homologues. This principle has very recently been established by the successful synthesis of 3-iodobenzofurans from the corresponding 2-alkynylphenols.[4] We speculated that such methodology could make a contribution to indole synthesis, given that the rather non-nucleophilic nitrogen centre in



1 2

Scheme 1.

2-alkynyl aniline derivatives, such as the corresponding sulfonamides or carbamates, would prove sufficiently reactive. We felt that this could well be possible, as such 5-*endo*-dig cyclisations are probably electrophile driven and hence the strength of the N–H bond to be broken is likely to be a more important factor than nitrogen nucleophilicity. The idea of carrying out cyclisations of 2-alkynylaniline derivatives is certainly not new: a number of palladium based methods have been established.[1,5] However, in most of these cases, the 3-position of the resulting indole remains unsubstituted.[6] Although subsequent functionalisation of this position is a classical feature of indole chemistry, by reason of the enamine-like character of the pyrrole residue, direct introduction of a 3-iodo group would provide alternative strategies for homologation at this site by using one of the plethora of Pd-catalysed methods alluded to earlier.[1] A very recent report from the Barluenga group[7] prompts us to report our own results on this use of 5-*endo*-dig iodocyclisations[8] to obtain 3-iodoindole derivatives.

In the light of our previous experiences with pyrrole synthesis,[3] we chose to examine cyclisations of 2-alkynylanilines **4**, in which the amine groups were protected as their tosyl derivatives. Suitable starting materials were therefore the corresponding bromo- or iodo-*N*-tosylanilines **3** (Scheme 2). In the first key step, these were homologated to the required 2-alkynyl derivatives using efficient Sonogashira couplings[9] with a 1-alkyne, which provided excellent yields (85–94%) of the *N*-tosyl-2-(alkynyl)-anilines **4**. We were delighted to find that exposure of these compounds to 3 equiv each of molecular iodine and anhydrous potassium carbonate in acetonitrile, first at 0 °C followed by warming to ambient temperature, delivered good to excellent isolated

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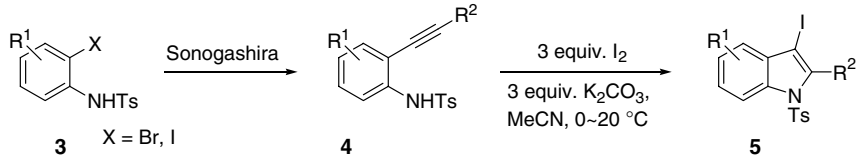


Scheme 2.

Table 1. Iodocyclisations of *N*-tosyl-*ortho*-alkynylanilines

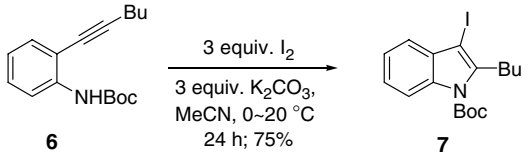
Entry	R^1	R^2	Time (h)	Yield (%)
1	H	Ph	2	95
2	H	Bu	2	82
3	H	TMS	12	81[a]
4	H	CH_2OTBS	12	96
5	5-NO_2 [in **4**]	Ph	2	93
6	5-NO_2 [in **4**]	TMS	5	91

[a] Isolated as a 70:30 mixture of the 2-silyl derivative and desilylated product.

yields of the desired 3-iodoindoles **5**. The results obtained thus far are summarised in Table 1. All yields refer to pure, isolated products **5**, whose structures have been verified by the usual criteria (^1H and ^{13}C NMR, IR, MS, micro-analysis/HRMS). The times of reaction, however, have not been fully optimised.

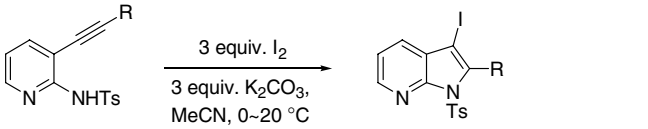
As can be seen from entries 1 and 2, both an aryl and an alkyl group, respectively, are compatible with the cyclisation and give excellent yields of the corresponding 2-substituted-3-iodoindoles **5**. A similar cyclisation of the 2-trimethylsilylethynyl derivative (entry 3), while slower, also delivered an excellent yield of the 3-iodoindole, but as a mixture of the 2-trimethylsilyl derivative ($R^2 = Me_3Si$) together with desilylated material ($R^2 = H$) in a ratio of 70:30. Subsequent complete desilylation of this mixture (TBAF, THF) gave an excellent yield of *N*-tosyl-3-iodoindole, thereby demonstrating the potential of this methodology for the synthesis of 3-monosubstituted indoles. In contrast, no loss of silicon was observed during the iodocyclisation of an *O*-silylpropargylic alcohol derivative (entry 4), which resulted in an excellent yield of the 3-iodoindole-2-methanol derivative [**5**; $R^1 = H$, $R^2 = CH_2OTBS$]. The presence of a powerful electron-withdrawing group (**4**; $R^1 = 5\text{-}NO_2$; entries 5 and 6) at the *para*-position with respect to the alkynyl group did not engender any deleterious effects on the cyclisation; both substrates also delivered excellent yields of the now expected 3-iodoindoles.

While *N*-tosyl functions are especially valuable as amine protecting groups, their very stability is naturally a potential problem when it comes to their removal. However, this is often not the case if the amine group is part of a heteroaromatic system, when removal can be readily achieved by exposure to nucleophilic reagents. These include hot methanolic hydroxide or alkoxide, by reason of the much lower pK_a value of the N–H bond in the parent heteroaromatic, when compared to aliphatic amines (see below).[10] Clearly though, alternative nitrogen protecting groups would add to the flexibility of the present methodology. We have therefore demonstrated that *N*-Boc functions are also compatible with this protocol by the efficient but somewhat slower conversion of the hexynyl derivative **6** into the *N*-Boc-3-iodoindole **7** in 75% yield (Scheme 3). The survival of this relatively sensitive protecting group suggests that other, more robust carbamate functions, for example, $NHCO_2Me$, should also survive the reaction conditions and provide the opportunity for the use of alternative deprotection methods if desired or necessary.



Scheme 3.

The method should find applications in more complex heteroaromatic synthesis as well. For example, the two pyridine derivatives **8**, obtained by Sonogashira couplings of 3-bromo-2-*N*-tosylaminopyridine with the corresponding 1-alkynes, gave excellent yields of the azaindoles **9** under the same conditions, despite requiring extended reaction times. In the former case, the product **9a** was isolated as an approximately 1:1 mixture of the 2-trimethylsilyl derivative and desilylated material (**9a**; R = H) (Scheme 4).



Scheme 4.

In summary, this methodology is both simple to perform and efficient. The alternative Barluenga protocol[7] employs 1.1 equiv of the somewhat more sophisticated iodonium source, $Ipy_2BF_4{\cdot}HBF_4$ and operates in dichloromethane at temperatures between −20 and −60 °C for 8–48 h. The present procedure is therefore more convenient, although the requirement for 3 equiv of iodine will be a disadvantage in relatively large-scale preparations, in terms of work-up and by-product disposal. Yields from the Barluenga procedure are also

quite variable and particularly poor with a combination of a carbamate and an alkyl-substituted alkyne function. Significantly, Barluenga found that a combination of an *N*-methane sulfonyl group and an alkylalkyne acceptor group led to a complex mixture when such substrates were exposed to conditions similar to those used in the present study. We have no certain explanation for this, although it is possible that we were fortunate to use *N*-toluene sulfonyl groups wherein perhaps the additional electron withdrawing power of the aryl group is sufficient to tip the balance in favour of suitably rapid N–H bond cleavage, as the cyclisation proceeds. Most likely, future applications will reveal a complementarity between the two methods when these are applied to more elaborate substrates. One notable feature of the Barluenga method[7] is that it can be applied successfully to *unprotected* 2-alkynylanilines to give directly 60–75% yields of 2-substituted-3-iodoindoles (2-Ph and 2-Bu). However, *N*-tosyl groups are relatively easy to remove from indoles, as we have recently pointed out in a report of a new method for achieving this using thioglycolate.[11]

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