Direct Preparation of Heteroaromatic Compounds from Alkenes

Timothy J. Donohoe,*[a] Mikhail A. Kabeshov,[a,b] Akshat H. Rathi,[a] Ian E. D. Smith[b]

[a] Department of Chemistry, University of Oxford, Chemistry Reasearch Laboratory, Mansfield Road, Oxford, OX1 3TA, UK
Fax +44(1865)275674; E-mail: timothy.donohoe@chem.ox.ac.uk

[b] GlaxoSmithKline Research and Development Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK
Fax +44(1438)764502; E-mail: ian.e.smith@gsk.com

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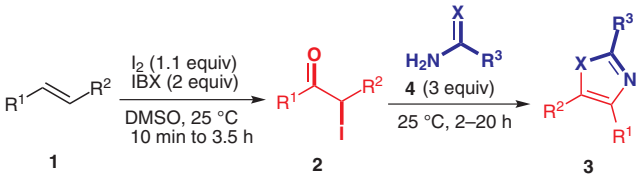
Abstract: A series of aromatic heterocycles, thiazoles, imidazoles, and dimethoxyindoles, can be synthesised directly from alkenes via a ketoiodination–cyclisation protocol. The alkene starting materials are themselves easily accessible by many different and well-established approaches, and allow access to various aromatic heterocycles with excellent yields and regioselectivity.

Key words: heterocycles, alkenes, iodine, iodo ketones, oxidation

A large proportion of modern pharmaceutical chemistry centres on aromatic heterocyclic compounds and this makes quick, general, and efficient methods for their synthesis extremely valuable. Amongst precursors to heteroaromatic compounds, α-halo- and tosyloxy ketones are important building blocks. For example, the Hantzsch thiazole synthesis from an α-halo ketone and a thioamide has been well known since the late 19th century,[1] and it is also possible to convert alcohols[2] and ketones,[3] through α-tosyloxy ketones, into a series of thiazoles, imidazoles, and imidazopyridines. Similarly, imidazoles can be obtained by employing a condensation between α-halo ketones and amidines,[4] and dimethoxyindoles can be accessed from α-halo ketones using Bischler and modified Bischler methododology.[5]

As expected, iodo ketones can be prepared from ketones[6] or their enolates[7] by iodination. However, a direct route to iodo ketones from alkenes (ketoiodination) is potentially a more potent and powerful method. Indeed, such a reaction was discovered by Cardillo et al.[8] who used the silver(I) chromate/iodine pair, although this proved to be an expensive method. Later, bis(symcollidine)iodine(I) tetrafluoroborate in DMSO was used as a reagent,[9] and recently IBX has been introduced as an oxidant for the ketoiodination of alkenes when paired with I_2[10a] and NIS.[10b]

We observed that, compared to their chloro and bromo analogues, iodo ketones have been rarely employed as electrophilic partners in aromatic heterocycle synthesis.[11] Although it is well known that iodide is easily displaced in nucleophilic substitution reactions, iodo ketones have not been used because of their limited availability. Herein, we report an efficient and succinct method for synthesising various heterocycles from readily available alkenes via iodo ketones. Scheme 1 shows the general plan, which involves ketoiodination of an alkene, followed by displacement and condensation to form a heterocycle. In addition to testing the general viability of this sequence, we also wanted to explore the range of functionality that could be incorporated into the final heterocycle, as well as addressing issues of regiochemistry that arise from the oxidation of unsymmetrical alkenes.



Scheme 1 General plan for the synthesis of aromatic heterocycles **3** from alkenes **1** via iodo ketones **2**

In our initial experiments we carried out the ketoiodination of 2-methylstyrene using a procedure developed by Moorthy et al.[10b] (1.1 equiv NIS, 2 equiv IBX, r.t., DMSO). The reaction proceeded smoothly with $\tau_{1/2} = 10$ minutes.[12] After the excess of NIS and IBX were washed out with aqueous $NaHCO_3$–$Na_2S_2O_3$, the resulting 2-iodo-1-phenyl-1-propanone[13] was reacted with thiourea (3 equiv, 25 °C, DMSO–DMF) to produce 5-methyl-4-phenyl-1,3-thiazol-2-amine (**3a**) as the only detectable product and as a single regioisomer in 71% isolated yield. However, we found that replacing NIS with I_2 (1.1 equiv) led to a substantial increase of the reaction rate: $\tau_{1/2} = 2$ min and full consumption of the starting material within 10 minutes. After condensation of the iodo ketone with thiourea the aminothiazole **3a** was isolated with a higher yield of 74% (Figure 1). Generally, we found the use of iodine/IBX superior and so used this protocol throughout.

These conditions were successfully applied to the syntheses of various thiazoles (**3a–i**, Figure 1) utilising different mono- and disubstituted alkenes as starting materials. The presence of a thiazole, pyridine, dimethylaminopyridine, or an α-methoxy group in the structure of the starting alkene **1** does not affect the efficiency of the method (**3d–f**), which can be applied to aryl-alkyl disubstituted (**3a**,**b**,**d–f**), aryl monosubstituted (**3c**,**h**,**i**) and alkyl-alkyl disubstituted alkenes (**3g**). Although regioselective heterocycle formation was not possible with unsymmetrical dialkyl substituted alkenes, it quickly emerged that the presence of an aryl group on the starting alkene led to the formation

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of a single regioisomer of the heterocyclic product, as shown. Moreover, in addition to thiourea, we showed that alkyl thioamides (**3h**) or aryl thioamides (**3i**) can be used as nucleophiles, in so doing extending the variation that is possible at R^3 (see **3**, **4**, Scheme 1). Note that iodo ketones **2** usually react with nucleophiles **4** faster than their chloro and bromo analogues, and thus it is possible to synthesise the majority of heterocycles at room temperature whereas most of the other methods described in the literature employ chloro or bromo ketones at elevated temperatures.[14,15]

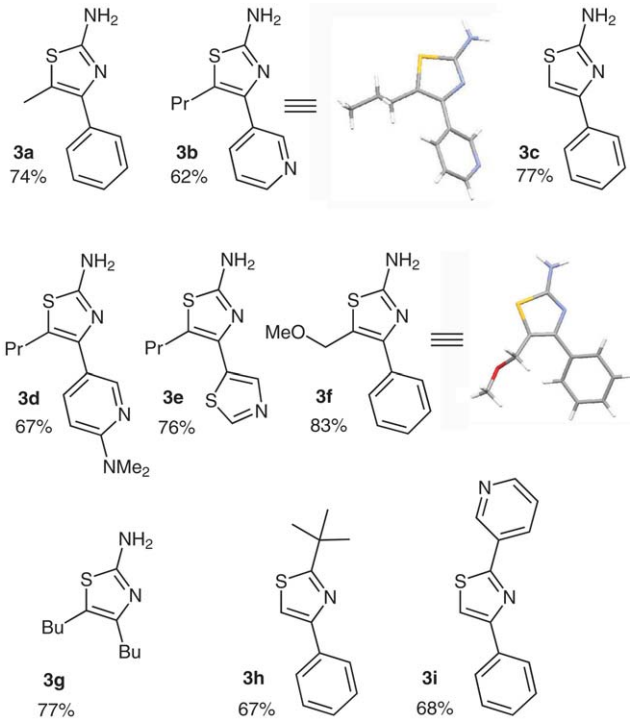

Figure 1 2-Aminothiazoles made via ketoiodination and condensation with thiourea and thioamides. X-ray structures of **3b** and **3f** are shown. Yields are based on the starting alkene.

By employing amidines or their salts as nucleophiles in this sequence, one can access the corresponding imidazoles **3j**–**n** (Figure 2). Thus, the method is applicable with alkyl amidines (**3j**,**l**), aryl amidines (**3k**), mono-N-substituted amidines (**3l**), S-alkylated pseudothioureas (**3m**), in conjunction with mono- (**3j**–**m**) or disubstituted (**3n**) alkenes. As a final example to show the versatility of this method, the dimethoxyindole (**3o**) was synthesised by using 3,5-dimethoxyaniline as a nucleophile (**4**) by a Bishler-type method.[5]

For compounds **3j**,**k**,**m**,**n** the issue of regioselectivity does not arise because of imidazole tautomerisation. However, compounds **3l** and **3o** were formed as single regioisomers, as shown.

The structures of the aromatic products **3** were proven by correlation with literature data for **3a**,**c**,**h**,**o** (see Supporting Information). To establish unambigously the regiochemistry of the sequence,[16] single crystals of **3b** and **3f** were grown and subjected to X-ray diffraction (Figure 1). Compounds **3d**,**e**,**i** were assigned by analogy and **3l** by HMBC experiments.

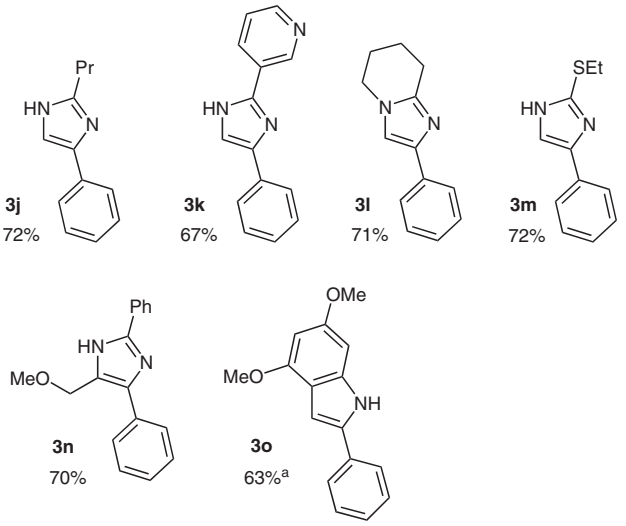

Figure 2 Synthesis of imidazoles and indoles **3** from alkenes **1** via iodo ketones **2**. Yields are based on the corresponding alkene **1**; [a] condensation with dimethoxyaniline was performed at 80 °C.

Our own studies on the mechanism of the reaction suggest that the initial ketoiodination produces the regioisomer in which the carbonyl is conjugated with the unsaturated substituent, in accordance with literature precedent. Ensuing substitution of the iodide by the most nucleophilic atom of the corresponding nucleophile, followed by condensation would explain the regiochemical outcome of the sequence.

In summary, we have demonstrated that a series of heterocycles, here thiazoles, imidazoles, and indoles, can be synthesised directly from alkenes using an efficient and succinct method. This methodology enables the preparation of heterocycles having multiple points of diversity whilst controlling the regiochemistry of unsymmetrical heterocyclic products when one substituent on the alkene is aromatic.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(11) See: Basarab, G.; Hill, P.; Zhou, F. WO 2008152418, A1 20081218, **2008**.
(12) 0.25 M solution, analysed by LCMS calibrated with nitrobenzene; see Supporting Information for details.
(13) **Analytical Data for Crude 2-Iodo-1-phenyl-1-propanone** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (d, $^3J_{CH3,CH}$ = 7.0 Hz, 3 H, CH_3), 5.47 (q, $^3J_{CH3,CH}$ = 7.0 Hz, 1 H, CHI), 7.40–7.46 (m, 2 H, Ph), 7.50–7.56 (m, 1 H), 7.92–7.98 (m, 2 H, Ph) are in agreement with the literature: Cambie, R. C.; Hayward, R. C.; Lindsay, B. G.; Phan, A. L. T.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1961.
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(15) In the reaction of 2-chloro-1-phenylpropan-1-one with benzamidine in the presence of K_2CO_3 at r.t. in DMF, only traces of the corresponding imidazole were detected after 2 h.
(16) To distinguish between two isomeric aminothiazoles: 5-propyl-4-(3-pyridinyl)-1,3-thiazol-2-amine and 4-propyl-5-(3-pyridinyl)-1,3-thiazol-2-amine.