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A new, mild one-pot synthesis of iodinated heterocycles as suitable precursors for $N$-heterocyclic carbene complexes
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The I$_2$/AgOAc couple allows for cheap, mild, and efficient iodination of a variety of heterocycles, which can serve as useful precursors for the synthesis of $N$-heterocyclic (abnormal) carbene complexes.

Key words: $N$-heterocycles; Iodination; Ligand precursors; Abnormal carbene complexes; Palladation
A new, mild one-pot synthesis of iodinated heterocycles as suitable precursors for N-heterocyclic carbene complexes

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Abstract—The use of I₂/AgOAc in dichloromethane constitutes a cheap, mild, and efficient method for the selective iodination of a variety of heterocycles. In a number of cases, this method provides superior yields than other literature methods and affords iodinated derivatives as building blocks for carbon-carbon bond forming reactions.

N-heterocyclic carbenes (NHCs) have been shown to be versatile ligands for transition metal complexes. Most importantly, these ligands have an outstanding impact on many homogeneous catalysts, often outperforming more common phosphine ligands. Metal coordination to NHCs has been achieved by a variety of methods. Among these, oxidative addition is particularly attractive because of the typically mild reaction conditions and the high product selectivity. Moreover, oxidative addition avoids the synthesis of the corresponding free carbene or the silver carbene intermediates, which may not be easily accessible or even unfeasible due to their low stability. For the generation of N-heterocyclic carbene complexes via C–X bond oxidative addition, iodo-functionalized heterocycles serve as particularly convenient precursors. In addition, the iodination of aromatic heterocycles is a matter of continuing interest in medicinal chemistry and in modern organic chemistry, which is making extensive use of iodinated derivatives as building blocks for carbon-carbon bond forming reactions.

The synthesis of iodinated aromatic heterocycles can be achieved by direct iodination of C₆H₆–H bonds or by nucleophilic substitution of C₆H₆–X, where X is a good leaving group. The former method relies on the presence of Lewis acids or strong oxidizing agents to overcome the low electrophilicity of iodine. On the other hand, the latter method requires the pre-installation of a good leaving group. Even though the literature offers a variety of synthetic protocols for the preparation of iodinated (hetero)aromatic compounds, harsh conditions and expensive or toxic chemicals are often required. In addition, one single methodology does typically not perform well for different substrates, thus illustrating the need for the further development of efficient and reliable methodologies for the synthesis of iodinated heterocycles.

Scheme 1

Herein we report on convenient and inexpensive methods for the synthesis of a range of iodinated N-heterocycles that are suitable precursors for non-classical NHC transition metal complexes (Scheme 1). We successfully applied the iodine-iodide (I₂ and KI) methodology for the preparation of compound 2a and its N-methylated derivative 2b from the corresponding halide-free imidazoles 1a and 1b, respectively (Table 1, entries 1 and 2). However, this method failed to iodinate 3,5-dimethylisoxazole (1c) for which mainly starting material was recovered (entry 3). In contrast, the use of silver acetate and iodine afforded the desired 3,5-dimethyl-4-iodoisoxazole (2c) in almost quantitative yield (98%). In addition, better yields were obtained for the iodination of 1d under milder conditions (88% at 45 °C as compared to 67% at 100 °C using I₂/KI).
Table 1. Iodination of heterocycles 1a–g

| Entry | Substrate | Product | Yield using I₂/KI | Yield using I₂/AgOAc |
|-------|-----------|---------|-----------------|---------------------|
| 1     | 1a        | 2a      | 73%             | 58%                 |
| 2     | 1b        | 2b      | 78%             | n.d.                |
| 3     | 1c        | 2c      | <5%             | 98%                 |
| 4     | 1d        | 2d      | 67%             | 88%                 |
| 5     | 1e        | 3e      | n.d.            | 93%                 |
| 6     | 1f        | 2f, 3f  | n.d.            | 76% (3:2 ratio)     |
| 7     | 1g        | 2g      | <5%             | <5%                 |

Isolated yields of ¹H NMR pure material obtained after extraction, n.d. = not determined.

The I₂/AgOAc route is a variation of a previously reported method and involves the substitution of the Lewis acidic silver trifluoroacetate, by less expensive silver acetate. Moreover, unlike the literature procedure, I₂/AgOAc-mediated iodination was performed as a one-pot synthesis and does not require repetitive additions of silver salt or iodine. To the best of our knowledge, this is the first time that the system I₂/AgOAc has been reported as a reagent for the iodination of heterocycles.

The scope of this method is quite broad. A diverse range of heterocyclic iodides was prepared in good to excellent yields (Table 1). In all cases, a small excess of iodine was sufficient to ensure high conversions. In a typical procedure, solid iodine was added in portions to a suspension containing the heterocyclic substrate and AgOAc. After complete addition, the solution became dark red and the desired product formed as a yellow precipitate, which was isolated, washed, and dried. Selective mono-iodination was indicated specifically by the disappearance of the pertinent ¹H NMR resonance signal in the non-iodinated precursor (e.g. δH 5.8 for the C4-bound hydrogen in 1a) and was unambiguously confirmed by mass spectrometry.

The I₂/AgOAc methodology proved also efficient for the iodination of 1-ethyl-3,5-dimethyl-1H-pyrazole (1d), 2,4-dimethylimidazole (1a), 2-methylimidazole (1e), and (1f). The iodinated imidazoles 2d and 2a, and the diiodinated imidazole 3e, were obtained in good yields and high selectivity (88%, 58% and 93%, respectively). Conversely, iodination of 1-methylimidazole (1f) was not selective and afforded a mixture containing several products. Analysis using NMR spectroscopy and mass spectrometry, and comparison with authentic products obtained via different routes indicated that the product mixture includes 2,5-diido-1-methylimidazole and 1-methyl-2-iodoimidazole as the main products in an approximate 2:3 ratio. The desired
mono-iodinated heterocycle 2f was easily separated by column chromatography (SiO\textsubscript{2}, Et\textsubscript{2}O) to give the pure product in 46\% isolated yield (along with pure 3f, 30\% isolated yield). This method thus represents a more convenient alternative to the synthesis of 1-methyl-2-iodoimidazole compared to other literature methods,\textsuperscript{11} in particular because it does not require strictly anhydrous conditions nor the handling of sensitive organolithium reagents.

Attempts to iodinate 3-methylpyridine (1g) by either the I\textsubscript{2}/KI or the I\textsubscript{2}/AgOAc route failed thus far. Successful formation of 2-iodo-3-methylpyridine (2g) was accomplished, however, by reacting 2-bromo-3-methylpyridine (4) with sodium iodide and trimethylsilyl chloride in MeCN (Scheme 2).\textsuperscript{88} Long reaction times (>7 days) and high temperatures were required in order to obtain the desired iodinated pyridine 2g in good yield (82\%). The \textsuperscript{1}H and \textsuperscript{13}C NMR signals of the iodinated product barely differ from the brominated starting material, and mass spectrometry was used instead for monitoring the progress of the reaction.

Scheme 2

\[
\begin{array}{c}
\text{Br} \\
\text{Nal, Me\textsubscript{2}SiCl} \text{MeCN} \\
\begin{array}{c}
\text{4} \\
\text{2g} \\
(82\%)
\end{array}
\end{array}
\]

The potential of iodinated \(N\)-heterocycles such as 2 can be illustrated by the straightforward synthesis of the new abnormal carbene complex 5 (Scheme 3). Thus, alkylation of 4-iodoisoxazole (2c) with MeOTf followed by oxidative addition to Pd(dba)\textsubscript{2} as a palladium(0) source in the presence of pyridine afforded complex 5 in good overall yield.\textsuperscript{12} Complex 5 features a 4-isoxazolylidene ligand as a rare type of so-called abnormal carbene, and has been fully analyzed, including an X-ray structure analysis of single crystals grown from CH\textsubscript{3}Cl\textsubscript{2} and pentane.\textsuperscript{13} The Pd–C bond length is 1.974(4) Å and fits into the 1.95–2.03 Å range expected for abnormal \(N\)-heterocyclic carbene palladium bonds.\textsuperscript{82} The two hetero-cycles are almost coplanar (torsion angles are less than 8°), and they are nearly orthogonal to the palladium coordination plane (torsion angle ca. 70°). In the \textsuperscript{13}C NMR spectrum, the palladium-bound carbene carbon appears at \(\delta = 155.5\).

In conclusion, we have synthesized a variety of iodinated \(N\)-heterocycles that are suitable precursors for abnormal carbenes by using a novel protocol based on I\textsubscript{2}/AgOAc. This method is of considerably broad scope and provides convenient access to a variety of iodinated aromatic heterocycles under mild conditions. The products were isolated in good yields and with satisfactory purity after a simple extraction procedure. The procedure may prove useful for the synthesis of a wide variety of new NHC-type complexes, and also for catalytic applications which rely on in situ generated catalysts from low-valent metal precursors.

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In a typical experiment, 3,5-dimethylisoxazole (1e) (500 mg, 5 mmol) was added dropwise to a suspension of AgOAc (0.935 g, 5.5 mmol) in dry CH2Cl2 (20 mL). The resulting purple solution was filtered and washed with a saturated solution of NaCl, dried and filtered, and dried under reduced pressure to afford 3,5-dimethyl-4-isooxazolyl (56 mg, 0.25 mmol) in CH2Cl2 (5 mL) and stirred at room temperature for 3 h. The violet-colored precipitate was washed with Et2O (3 × 5 mL) and dried under reduced pressure to afford a yellow solid (98 mg, 72%).

1H NMR (360 MHz, CDCl3): δ 9.05 (dt, 2H, o-CH2), JHH = 5.2, JHI = 1.5), 7.68 (tt, 1H, p-CH2), JHH = 7.7, JHI = 1.5), 7.29 (m, 2H, m-CH2), 3.98 (s, 3H, NCH3), 2.75 (s, 3H, CH3), 2.64 (s, 3H, CH3). 13C{1H} NMR (90 MHz, CDCl3): δ 170.1 (Cox–Me), 162.6 (Cox–Me), 155.5 (C–Pd), 154.0 (o-CH3), 137.1 (p-CH3), 124.2 (m-CH3), 37.0 (NCH3), 22.2 (CH2).

Supplementary Material

Experimental details of all products from Table 1.