Graphical Abstract

A new, mild one-pot synthesis of iodinated heterocycles as suitable precursors for *N*-heterocyclic carbene complexes

Manuel Iglesias, Oliver Schuster, and Martin Albrecht

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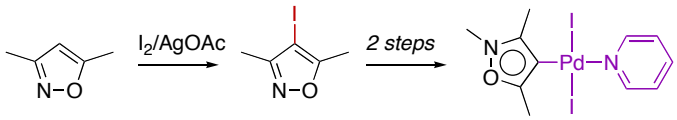
The I_2/AgOAc couple allows for cheap, mild, and efficient iodination of a variety of heterocycles, which can serve as useful precursors for the synthesis of *N*-heterocyclic (abnormal) carbene complexes.



Key words: *N*-heterocycles; Iodination; Ligand precursors; Abnormal carbene complexes; Palladation

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LETTERS

A new, mild one-pot synthesis of iodinated heterocycles as suitable precursors for *N*-heterocyclic carbene complexes

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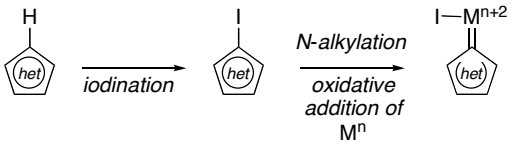
Abstract— The use of I_2/AgOAc in dichloromethane constitutes a cheap, mild, and efficient method for the selective iodination of a variety of heterocycles. In a number of cases, this method provides superior yields than other literature methods and affords iodo-functionalized heterocycles that are suitable precursors for carbene complexes.

N-heterocyclic carbenes (NHCs) have been shown to be versatile ligands for transition metal complexes.[1] Most importantly, these ligands have an outstanding impact on many homogeneous catalysts, often outperforming more common phosphine ligands.[2] 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.[3] For the generation of *N*-heterocyclic carbene complexes *via* C–X bond oxidative addition, iodo-functionalized heterocycles serve as particularly convenient precursors.[4] In addition, the iodination of aromatic heterocycles is a matter of continuing interest in medicinal chemistry[5] and in modern organic chemistry, which is making extensive use of iodinated derivatives as building blocks for carbon-carbon bond forming reactions.[6]

The synthesis of iodinated aromatic heterocycles can be achieved by direct iodination of C_{Het}–H bonds[7] or by nucleophilic substitution of C_{Het}–X,[8] 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 (I_2 and KI) methodology[4b] 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 I_2/KI).

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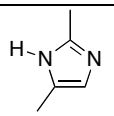
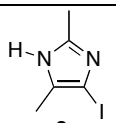
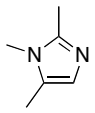
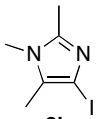
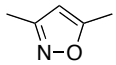
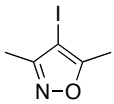
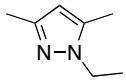
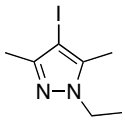
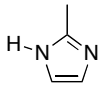
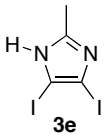
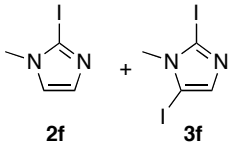
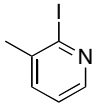
Table 1. Iodination of heterocycles **1a–g**

Entry	Substrate	Product	Yield using I_2/KI [a]	Yield using I_2/AgOAc [a]
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%

[a] Isolated yields of ^{1}H NMR pure material obtained after extraction, n.d. = not determined.

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The I_2/AgOAc route is a variation of a previously reported method[9] and involves the substitution of the Lewis acidic silver trifluoroacetate, by less expensive silver acetate. Moreover, unlike the literature procedure, I_2/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 I_2/AgOAc has been reported as a reagent for the iodination of heterocycles.

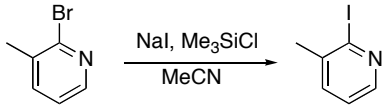
The scope of this method is quite broad. A diverse range of heterocyclic iodides was prepared in good to excellent yields (Table 1). In all cases, a small excess of iodine was sufficient to ensure high conversions. In a typical procedure,[10] solid iodine was added in portions to a suspension containing 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 ^{1}H NMR resonance signal in the non-iodinated precursor (*e.g.* δ_H 5.8 for the C4-bound hydrogen in **1**) and was unambiguously confirmed by mass spectrometry.

The I_2/AgOAc methodology proved also efficient for the iodination of 1-ethyl-3,5-dimethyl-1*H*-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-diiodo-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_2, Et_2O) 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,[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_2/KI or the I_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).[8b] Long reaction times (>7 days) and high temperatures were required in order to obtain the desired iodinated pyridine **2g** in good yield (82%). The ^1H and ^{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.

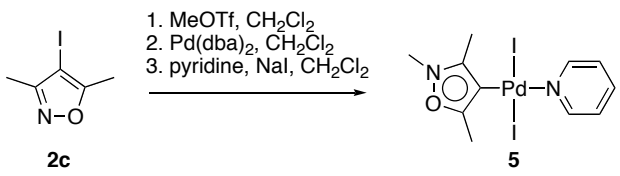
Scheme 2



4 **2g** (82%)

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 $Pd(dba)_2$ as a palladium(0) source in the presence of pyridine afforded complex **5** in good overall yield.[12] Complex **5** features a 4-isoxazolylidene ligand as a rare type of so-called abnormal carbenes, and has been fully analyzed, including an X-ray structure analysis of single crystals grown from CH_2Cl_2 and pentane.[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.[3d] 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 ^{13}C NMR spectrum, the palladium-bound carbene carbon appears at δ_C 155.5.

Scheme 3



2c **5**

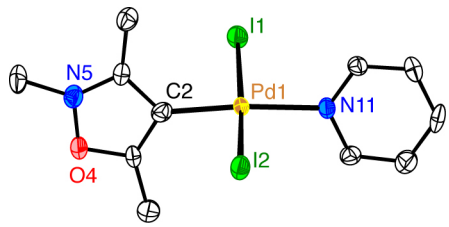


Figure 1. ORTEP representation of the molecular structure of **5** (50% probability, H-atoms omitted). Selected bond lengths (Å): Pd1–C2 1.974(4), Pd1–N11 2.121(3), Pd1–I1 2.6063(6), Pd1–I2 2.5936(7).

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_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.

Acknowledgements

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10. In a typical experiment, 3,5-dimethylisoxazole (**1c**) (500 mg, 5 mmol) was added dropwise to a suspension of AgOAc (0.935 g, 5.5 mmol) in dry CH_2Cl_2 (20 mL). Subsequently, I_2 (1.500 g, 6.4 mmol) was added in portions under N_2 and the reaction mixture was stirred at 50 °C for 16 h. The resulting purple solution was filtered and washed with a saturated solution of $Na_2S_2O_3$ (30 mL). The aqueous layer was basified to pH 9 with KOH_{aq} and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were then washed with saturated $NaHCO_3$ (40 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and dried under reduced pressure to afford 3,5-dimethyl-4-iodoisoxazole (**2c**) (476 mg, 98%). ^{1}H NMR (360 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$): δ 169.0 (C_{isox}–Me), 160.5 (C_{isox}–Me), 59.1 (C_{isox}–I), 11.5 (CH_3), 11.2 (CH_3). HR-MS: 223.9578 (calcd for C_5H_7INO 223.9572).
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12. In a typical experiment, MeOTf (0.034 mL, 0.30 mmol) was added dropwise to a solution of 3,5-dimethyl-4-iodoisoxazole (**2c**) (56 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) and stirred at room temperature for 3 h. The volatiles were distilled under reduced pressure and the residue rinsed with Et_2O (3 × 5 mL). The white solid thus obtained was dissolved in CH_2Cl_2 (10 mL) and stirred for 15 min at room temperature with $Pd(dba)_2$ (75 mg, 0.25 mmol), subsequently, an excess of NaI (75 mg, 0.50 mmol) and pyridine (0.025 mL, 0.25 mmol) were added and the reaction mixture was stirred overnight at room temperature. The resulting suspension was filtered through a short pad of Celite and the solution concentrated to ca. 2 mL. Addition of Et_2O induced precipitation of a yellow solid which was collected by decantation, rinsed with Et_2O (3 × 10 mL) and dried under reduced pressure to afford **5** as a yellow solid (98 mg, 72%). ^{1}H NMR (360 MHz, $CDCl_3$): δ 9.05 (dt, 2H, *o*-CH_{Py}, $^3J_{HH}$ = 5.2, $^4J_{HH}$ = 1.5), 7.68 (tt, 1H, *p*-CH_{Py}, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.5), 7.29 (m, 2H, *m*-CH_{Py}), 3.98 (s, 3H, NCH_3), 2.75 (s, 3H, CH_3), 2.64 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$): δ 170.1 (C_{isox}–Me), 162.6 (C_{isox}–Me), 155.5 (C–Pd), 154.0 (*o*-C_{Py}), 137.1 (*p*-C_{Py}), 124.2 (*m*-C_{Py}), 37.0 (NCH_3), 16.9 (CH_3), 15.7 (CH_3). Anal. Calcd for $C_{11}H_{14}I_2N_2OPd$ (550.47): C 24.00, H 2.56, N 5.09; found: C 23.85, H 2.70, N 4.85.
13. Crystal data for **5**: $C_{11}H_{14}I_2N_2OPd$, M = 550.46, monoclinic, a = 8.9614(18), b = 14.124(3), c = 12.544(3) Å, V = 1559.4(6) Å, β = 100.83(3)°, T = 130(2) K, space group Cc (No. 9), Z = 4, ρ_{calcd} 2.345 g cm^{-3}, μ (Mo-K$_\alpha$) = 5.137 cm^{-1}, 9631 total reflections, 2891 unique (R_{int} = 0.031), R_1 = 0.0150, wR_2 = 0.0320, S = 1.13 for $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 781506. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary Material

Experimental details of all products from Table 1.