A Four-Component Synthesis of Highly Substituted Imidazole Derivatives

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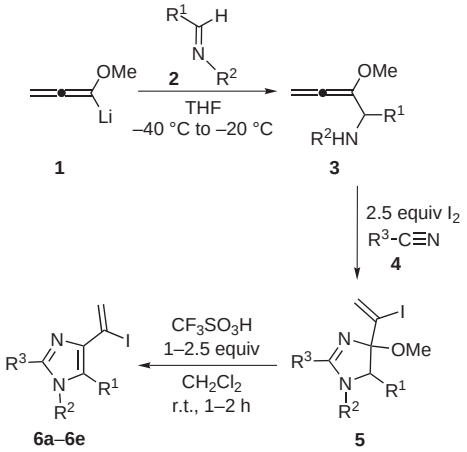
Abstract: Addition of lithiated methoxyallene **1** to imines **2** provided allenyl amines **3**, which upon reaction with iodine and nitriles furnished dihydroimidazole derivatives **5**. Treatment of these intermediates with strong acids such as trifluoromethane sulfonic acid afforded tetrasubstituted imidazole derivatives **6** in good overall yields. Subsequent base-promoted conversion of 1-iodovinyl-substituted compounds **6** into alkynyl-substituted imidazole derivatives **7** proceeded smoothly. Products **6** and **7** are versatile intermediates for further transformations such as palladium-catalyzed coupling reactions.

Key words: methoxyallene, imine, nitrile, imidazole, alkyne

In earlier publications we have reported that lithiated alkoxyallenes smoothly add to aldimines and that the resulting allenyl amines can be cyclized to produce dihydropyrrole derivatives.[1] This route has been exploited for syntheses of several natural products.[2] During attempts to prepare 4-iododihydropyrrole derivatives we detected that the reaction of allenyl amines such as **3** with iodine in acetonitrile furnished dihydroimidazole derivatives **5** in good yields (Table 1). Apparently, an allyl cation is formed by addition of the iodine cation to the central allene carbon, which is subsequently trapped by the solvent acetonitrile. Cyclization by attack of the amino group to the nitrilium carbon generated the five-membered ring. This Ritter type reaction[3] proved to be rather general allowing a new access to imidazole derivatives by a four-component process.

Addition of lithiated methoxyallene **1** (generated from methoxyallene and *n*-BuLi) to imines **2** provided allenyl amines **3**,[1c] which upon reaction with iodine in different nitriles **4** as solvent furnished dihydroimidazole derivatives **5a**–**e** as mixtures of diastereomers. Elimination of methanol to afford the 1-iodovinyl-substituted imidazoles **6a**–**e** was achieved by treatment with strong acids such as trifluoromethane sulfonic acid (Table 1).[4] Imine substituents R^1 can be aryl or alkyl, at the nitrogen R^2 = aryl and tosyl are tolerated and as typical nitriles we successfully employed acetonitrile, propionitrile, and benzonitrile. The overall yields for this three-step sequence were good to moderate (Table 1, entries a–e). It should be noted here that experiments reducing the amount of nitriles were not very successful. Thus, one drawback of our new four-component synthesis is clearly the necessity to use the corresponding nitrile in excess.

Table 1 Synthesis of 1-Iodovinylimidazole Derivatives **6** from Methoxyallene, Imines, Iodine and Nitriles



Entry	R^1	R^2	R^3	Yield (%)	Imidazole
a	Ph	Ph	Me	80	**6a**
b	Ph	Ph	Et	40	**6b**
c	Ph	Ph	Ph	40	**6c**
d	*n*-Bu	Ts	Me	63	**6d**
e	Ph	Ts	Me	35	**6e**

The 1-iodovinyl substituent of compounds **6** is a suitable handle for further diversification, the simplest one being base-induced elimination providing 4-alkynyl-substituted imidazole derivatives **7** (Table 2).[5] Whereas the reaction of *N*-phenyl-substituted compounds **6a**–**c** with potassium *tert*-butoxide in tetrahydrofuran afforded the expected alkynes **7a**–**c** the *N*-tosyl derivative **6d** suffered detosylation, thus providing imidazole derivative **7d** with a free NH group in moderate yield (Table 2, entries a–d).

Alkynes **7** are suitable substrates for Sonogashira reactions. Under standard conditions[6] precursors **7a** or **7c** reacted in the presence of iodobenzene to generate phenyl-substituted products **8a** or **8c**, respectively, in good yields (Scheme 1).

We expected that the acidic alkyne hydrogen could be used to introduce other substituents at the terminal carbon of compounds **7**. Deprotonation of **7a** with 2.2 equivalents of *n*-butyllithium followed by reaction with chlorotrimethylsilane provided the bissilylated product **9** in 72%

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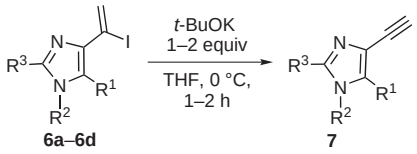
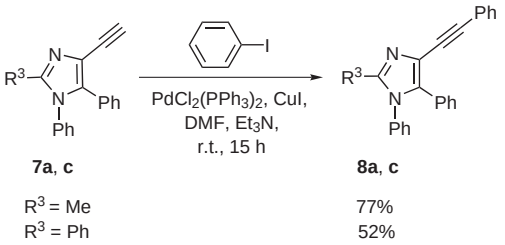
Table 2 Synthesis of 4-Alkynyl-Substituted Imidazole Derivatives **7**



6a–6d **7**

Entry	R^1	R^2	R^3	Yield (%)	Alkyne
a	Ph	Ph	Me	50	**7a**
b	Ph	Ph	Et	60	**7b**
c	Ph	Ph	Ph	72	**7c**
d	*n*-Bu	Ts	Me	54	**7d** (R^2 = H)



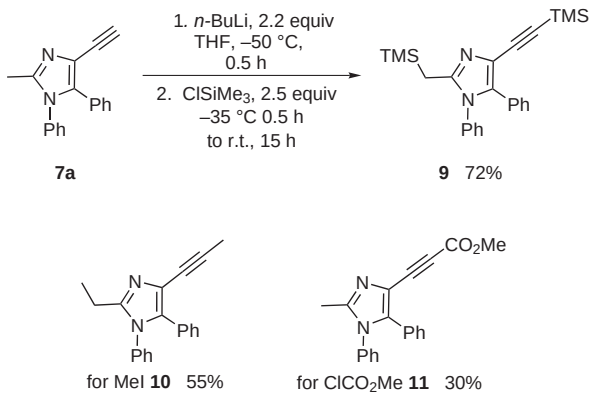
7a, **c** **8a**, **c**

R^3 = Me 77%
R^3 = Ph 52%

Scheme 1 Sonogashira reactions of **7** with iodobenzene leading to disubstituted alkynes **8**

yield (Scheme 2). Hence the base is also able to deprotonate at the C-2 methyl group. This was confirmed when methyl iodide was employed as electrophile, which furnished dimethylated compound **10** in moderate yield. Similar reaction conditions using methyl chloroformate as electrophile gave the monosubstituted product **11** in low yield.

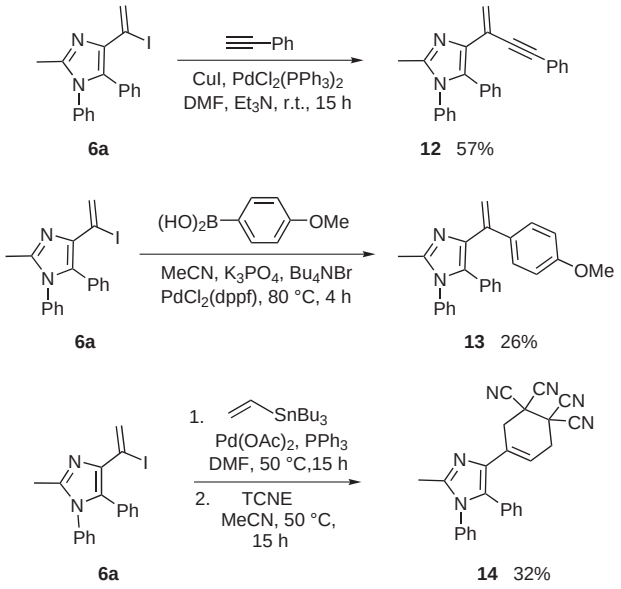
The reactivity of the 1-iodovinyl group of compound **6a** was also examined in typical palladium-catalyzed reactions. Sonogashira reaction with phenylacetylene provided coupling product **12** in acceptable yield whereas the Suzuki reaction of **6a** with an aryl boronic acid led to the expected compound **13** in lower efficacy (Scheme 3).



7a **9** 72%

Scheme 2 Deprotonation of imidazole derivative **7a** and reactions with electrophiles

Other cross-coupling experiments were even less successful. These observations may reflect the considerable steric hindrance at the reacting carbon due to the highly substituted imidazole core. We also successfully performed the Stille coupling of **6a** with tributylvinyltin, which provided the expected 2-imidazolyl-1,3-diene derivative. However, this compound rapidly polymerized and therefore it could not be completely characterized. Trapping of the crude product with tetracyanoethylene (TCNE) furnished Diels–Alder adduct **14** in 32% overall yield. Other dienophiles examined were not sufficiently reactive.



6a **12** 57%

6a **13** 26%

6a **14** 32%

Scheme 3 Cross-coupling reactions of 1-iodovinyl imidazole derivative **6a**

In this communication we present a new four-component synthesis[7] involving an alkoxyallene, an imine, a nitrile, and iodine, which furnished highly substituted imidazole derivatives in moderate to good yields.[8] Due to the functional groups these can be further transformed into several higher substituted and functionalized heterocycles. In particular, imidazole derivatives with different aryl substituents are easily accessible. Since imidazole derivatives are of considerable interest in medicinal chemistry and also in material science our new method – although restricted in scope – should establish a valuable new approach to this important class of heterocycles.[9] These results once again demonstrate the high synthetic versatility and value of lithiated alkoxyallenes,[10] which have served as an iodovinyl carbene synthon in this new application leading to imidazole derivatives.

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(4) **Typical Procedure for the Preparation of Imidazole 6a.**
A solution of methoxyallene (2.80 g, 39.9 mmol) in dry THF (50 mL) under Ar was treated at –40 °C with *n*-BuLi (2.5 M in hexane, 14.4 mL, 35.9 mmol, deprotonation time 5–10 min). Imine **2a** (5.10 g, 28.1 mmol) dissolved in dry THF (10 mL) was added within 5 min. The mixture was stirred for 2 h at –20 °C and quenched with H_2O (100 mL). Warm up to r.t. was followed by extraction with Et_2O (3 × 100 mL), drying (Na_2SO_4), and concentration in vacuo, which led to crude product **3a**, yield 7.00 g (99%).
Iodine (2.54 g, 10.0 mmol) was dissolved in freshly distilled MeCN (50 mL) at 45 °C and stirred for 10 min. A solution of crude allenyl amine **3a** (1.00 g, 3.98 mmol) dissolved in MeCN (10 mL) was added within 5 min and the mixture was stirred for 15 h at r.t. 10% $Na_2S_2O_3$ solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4 and concentrated in vacuo furnishing crude **5a** (1.95 g).
Crude **5a** was dissolved in dry CH_2Cl_2 (4 mL) under Ar, and CF_3SO_3H (0.5 mL, 5.59 mmol) was added dropwise. The mixture was stirred for 1 h at r.t., treated with dilute $NaHCO_3$ solution (30 mL), then with 10% $Na_2S_2O_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with H_2O (1 × 30 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, hexane–EtOAc = 4:1) to yield 1.22 g (80% overall yield) of **6a** as yellow crystals.
Analytical Data for 4-(1-Iodoethenyl)-2-methyl-1,5-diphenylimidazole (6a).
Mp 104–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, Me), 5.96, 6.14 (2 d, *J* = 1.4 Hz, each 1 H, $=CH_2$), 7.07–7.36 (m, 10 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1 (q, Me), 98.9 (s, =C–I), 127.8, 127.9, 128.3, 128.7, 129.4, 130.5 (6 d, Ph), 128.9 (t, $=CH_2$), 129.1 (s, Ph), 129.8 (s, C-5), 136.5 (s, Ph), 138.0 (s, C-4), 144.4 (s, C-2) ppm. IR (KBr): 3185–2870 (=CH, CH), 1600 (C=C) cm^{-1}. MS (EI, 80 eV, 40 °C): *m*/*z* (%) = 386 (17) $[M]^+$, 259 (100) $[M - I]^+$, 218 (50), 184 (18), 77 (26) $[C_6H_5]^+$, 43 (21), 28 (13). HRMS (EI, 80 eV, 40 °C): *m*/*z* calcd for $C_{18}H_{15}IN_2$: 386.0280. Found: 386.0267.

(5) **Typical Procedure for the Preparation of Alkyne 7a.**
To a solution of imidazole **6a** (152 mg, 0.39 mmol) in dry THF (2 mL) was added at 0 °C dropwise a solution of potassium *tert*-butoxide (88 mg, 0.78 mmol) in THF (1 mL). The flask was flushed with Ar, sealed and allowed to stir at 0 °C for 1 h. The mixture was quenched with sat. aq NH_4Cl solution (3 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4 and the crude product was purified by column chromatography (silica gel, hexane–EtOAc = 4:1), which provided 50 mg (50%) of **7a** as yellow crystals.
Analytical Data for 4-Ethynyl-2-methyl-1,5-diphenylimidazole (7a).
Mp 163–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, Me), 3.07 (s, 1 H, ≡CH), 7.09–7.41 (m, 10 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.2 (q, Me), 78.3 (s, ≡C), 78.4 (d, H–C≡), 127.7, 127.8, 128.2, 128.9, 129.0, 129.7 (6 d, Ph), 128.8, 137.2 (2 s, Ph), 120.3 (s, C-4), 136.6 (s, C-5), 146.0 (s, C-2) ppm. IR (KBr): 3290–2850 (C-H), 2105 (C≡C), 1595 (C=C) cm^{-1}. MS (EI, 80 eV, 40 °C): *m*/*z* (%) = 258 (71) $[M]^+$, 216 (30), 181 (5) $[M - C_6H_5]^+$, 114 (23), 91 (25), 77 (55) $[C_6H_5]^+$, 51 (28), 28 (100). HRMS (EI, 80 eV, 40 °C): *m*/*z* calcd for $C_{18}H_{14}N_2$: 258.1157. Found: 258.1163.

(6) **Typical Procedure for Sonogashira Reaction 7a → 8a.**
To a solution of Et_3N (0.8 mL) and DMF (0.4 mL) under Ar were added iodobenzene (0.08 mL, 0.69 mmol), alkyne **7a** (150 mg, 0.58 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol), and CuI (2 mg, 0.012 mmol). The mixture was stirred at r.t. for 16 h, then quenched with sat. aq NH_4Cl solution (3 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4 and the resulting crude product was purified by column chromatography (silica gel, toluene–EtOAc = 4:1) to give 150 mg (77%) of **8a** as pale yellow crystals.
Analytical Data for 4-Phenylethynyl-2-methyl-1,5-diphenylimidazole (8a).
Mp 189–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, Me), 7.11–7.46 (m, 15 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.2 (q, Me), 84.3 (s, ≡C), 90.4 (s, Ph-C≡), 127.7, 127.8, 127.9, 128.2, 128.3, 128.8, 128.9, 129.6, 131.4 (9 d, Ph), 121.4 (s, C-4), 123.7, 129.1, 136.8 (3 s, Ph), 136.4 (s, C-5), 146.3 (s, C-2) ppm. IR (KBr): 3055–2855 (=CH, CH), 2570 (C≡C), 1600 (C=C) cm^{-1}. MS (EI, 80 eV, 40 °C): *m*/*z* (%) = 335 (31), 334 (100) $[M]^+$, 333 (32), 292 (29), 291 (32), 189 (27), 167 (17), 145 (23), 139 (12), 126 (11), 125 (16), 123 (22), 105 (19), 91 (13), 57 (13). HRMS (EI, 80 eV, 40 °C): *m*/*z* calcd for $C_{24}H_{18}N_2$: 334.1470. Found: 334.1464.

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