Highly Substituted Imidazole Derivatives from a New Four-Component Synthesis Employing Methoxyallene

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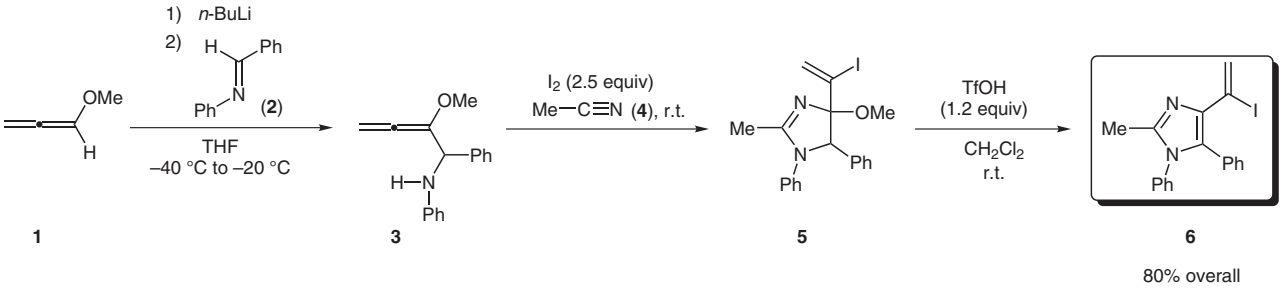
Abstract: A novel four-component reaction of alkoxyallenes with imines, iodine, and nitriles provided highly substituted imidazole derivatives in high overall yields. The simple three step protocol, exemplified by the reaction of methoxyallene (**1**) with imine **2**, acetonitrile, and iodine leading to iodoethenyl imidazole **6** is presented with full experimental detail. Imidazole **6** could be further functionalized by palladium-catalyzed couplings yet offering an entry into diversity-oriented synthesis.

Key words: allenes, imines, nitriles, imidazoles, alkynes, palladium catalysis



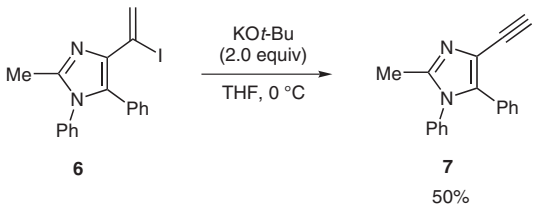
Scheme 1 Four-component synthesis (**1** + **2** + I_2 + **4**) leading to dihydroimidazole derivative **5** and elimination to tetrasubstituted imidazole **6**

Alkoxyallenes are very versatile C3-building blocks for the synthesis of heterocycles.[1] They allow a flexible entry into functionalized furan,[2] pyrane,[3] pyrrole, pyrrolidine,[4] pyridine,[5] and 1,2-oxazine derivatives[6] as well as carbocyclic compounds.[7] The addition of lithiated alkoxyallenes to imines provides α-allenyl amines and we have previously reported high-yielding cyclizations of these intermediates to dihydropyrrole derivatives.[4a,f,h–k] During our cyclization studies, we examined a number of different electrophilic reagents, for example, iodine in acetonitrile. Surprisingly, this promoter system did not lead to dihydropyrroles but to dihydroimidazole derivatives by means of a new four-component reaction.[8] The dihydroimidazole derivatives could subsequently be converted into a variety of highly substituted imidazoles. In this PSP we provide full experimental detail for some of these useful novel transformations.

Deprotonation of methoxyallene (**1**) with *n*-butyllithium in THF at –40 °C and subsequent addition of aldimine **2** furnished the α-allenyl amine **3** in high yield. Crude **3** was dissolved in acetonitrile **4** and treated with 2.5 equivalents of iodine at room temperature to give the intermediate dihydroimidazole derivative **5**. Final treatment of **5** with 1.2 equivalents of trifluoromethanesulfonic acid afforded the 1-iodoethenyl-substituted imidazole derivative **6** in 80% overall yield after chromatography (Scheme 1).

This new four-component synthesis[9] proceeded via (a) attack of iodine to the central allene carbon of **3**, (b) Ritter-type addition[10] of nitrile **4** onto the intermediate allyl cation, and (c) nucleophilic ring closure of the amino group with the nitrilium ion to provide **5**. The final elimination step leading to imidazole **6** was preferentially carried out using strong trifluoromethanesulfonic acid.

By variation of nitrile and imine components, this approach could be generalized. The highest yields of imidazoles were obtained using acetonitrile (**4**) but propionitrile and benzonitrile were also suitable. Further, the imine substituents could be varied by introducing, for example, alkyl groups at C-5 or tosyl groups at the nitrogen.[8]



Scheme 2 Preparation of 4-ethynyl-substituted imidazole derivative **7**

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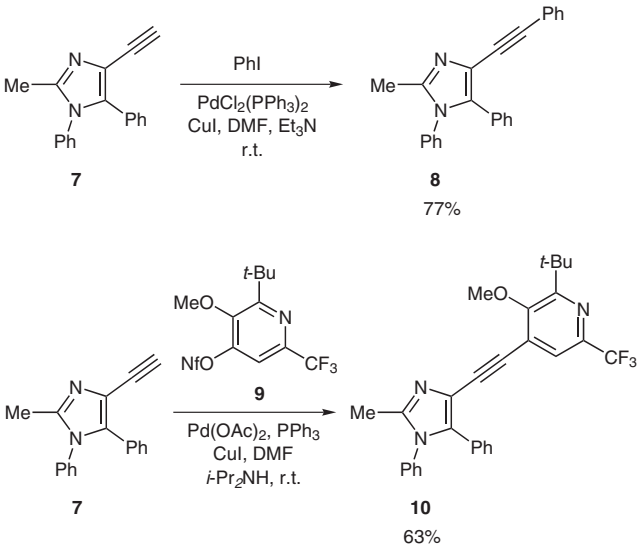
The imidazole derivatives obtained could be further elaborated by functionalizations of the 1-iodoethenyl side chain. For example, elimination of **6** by treatment with potassium *tert*-butoxide provided alkyne **7** (Scheme 2). This compound may be used in Sonogashira reactions, substitutions at the terminal alkyne carbon or even cycloadditions at the C≡C bond.

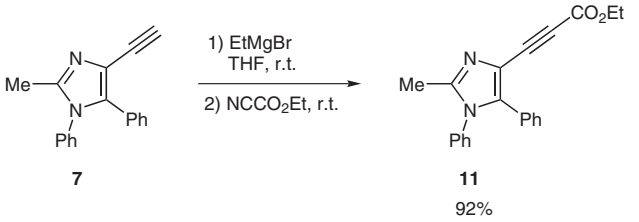
As illustrated in Scheme 3, Sonogashira reactions[11] of alkyne **7** occurred cleanly under standard conditions. Coupling with phenyl iodide gave triphenyl-substituted compound **8** in good yield and reaction with highly substituted pyridyl nonaflate **9**[5a] provided the pyridine-imidazole hybrid **10** in 63% yield. Notably, **9** itself derives from yet another novel multicomponent reaction of lithiated methoxyallene with nitriles and is accessible in just two steps from **1**, pivalonitrile and trifluoroacetic acid.[5] Alkyne **10** therefore contains six carbon atoms derived from methoxyallene (without counting the methoxy group). Disubstituted alkynes similar to **10** bearing 4-imidazolyl and 4-pyridyl substituents are potent mGluR5a receptor antagonists.[12]



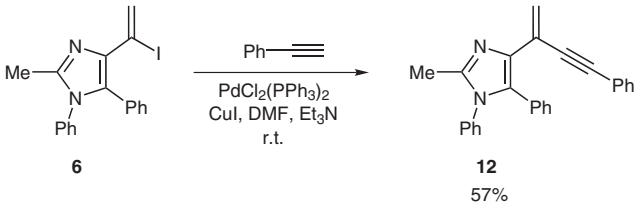
Scheme 3 Sonogashira reactions of **7** with iodobenzene and pyridyl nonaflate **9** leading to disubstituted alkynes **8** and **10**

Alkyne **7** could also be metalated at the terminus and trapped with electrophiles. For example, treatment of **7** with ethylmagnesium bromide followed by addition of ethyl cyanoformate cleanly gave carboxylic ester **11** (Scheme 4). Compounds **7** and **11** should both be of value in cycloadditions and lead to a diverse set of interesting new bicyclic derivatives.

The 1-iodoethenyl group of compound **6** was also exploited in palladium-catalyzed reactions. Whereas Suzuki and Stille couplings were not yet very efficient and further optimization is ahead, the Sonogashira reaction with phenylacetylene provided cross-conjugated imidazole derivative **12** in acceptable yield (Scheme 5).



Scheme 4 Preparation of alkynyl carboxylic ester **11**



Scheme 5 Sonogashira reaction of **6** with phenylacetylene providing coupling product **12**

The protocols presented in this PSP are simple and synthetically useful for the preparation of new imidazole derivatives. The route via our novel four-component reaction is flexible and short and should be of general interest. Imidazoles are important lead structures in medicinal chemistry[13] as well as components for material-oriented research,[14,15] thus new entries to this class of heterocycles are highly desirable.[16,17]

For general information concerning experimental setup and analytical methods, see ref.[6c]

4-(1-Iodoethenyl)-2-methyl-1,5-diphenylimidazole (6)

A solution of methoxyallene **1** (2.80 g, 39.9 mmol) in anhyd THF (50 mL) under argon 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 **2** (5.10 g, 28.1 mmol) dissolved in anhyd 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). Warming to r.t. was followed by extraction with Et_2O (3 × 100 mL), drying (Na_2SO_4), and concentration in vacuo, which led to the crude product **3**; yield: 7.00 g (99%).

I_2 (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 the crude allenylamine **3** (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. Aq 10% $Na_2S_2O_3$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo furnishing crude **5** (1.95 g).

Crude **5** was dissolved in anhyd CH_2Cl_2 (4 mL) under argon, 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% aq $Na_2S_2O_3$ (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 (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 **6** as yellow crystals; mp 104–105 °C.

IR (KBr): 3185–2870 (=C–H, C–H), 1600 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 5.96, 6.14 (2 d, *J* = 1.4 Hz, 1 H each, $=CH_2$), 7.07–7.36 (m, 10 H, C_6H_5).

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^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1 (q, CH_3), 98.9 (s, =CI), 127.8, 127.9, 128.3, 128.7, 129.4, 130.5 (6 d, C_6H_5), 128.9 (t, $=CH_2$), 129.1 (s, C_6H_5), 129.8 (s, C-5), 136.5 (s, C_6H_5), 138.0 (s, C-4), 144.4 (s, C-2).

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): *m*/*z* calcd for $C_{18}H_{15}IN_2$: 386.0280; found: 386.0267.

Anal. Calcd for $C_{18}H_{15}IN_2$ (386.2): C, 55.98; H, 3.91; N, 7.25. Found: C, 56.28; H, 3.62; N, 6.98.

4-Ethynyl-2-methyl-1,5-diphenylimidazole (7)

To a solution of imidazole **6** (152 mg, 0.39 mmol) in anhyd THF (2 mL) at 0 °C under argon was added dropwise a solution of *t*-BuOK (88 mg, 0.78 mmol, 2 equiv) in THF (1 mL). The flask was sealed and allowed to stir at 0 °C for 1 h. The mixture was quenched with sat. aq NH_4Cl (3 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the crude product was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to give 50 mg (50%) of **7** as yellow crystals; mp 163–164 °C.

IR (KBr): 3290–2850 (C–H), 2105 (C≡C), 1595 cm^{-1} (C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.07 (s, 1 H, ≡CH), 7.09–7.41 (m, 10 H, C_6H_5).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.2 (q, CH_3), 78.3 (s, ≡C), 78.4 (d, HC≡), 120.3 (s, C-4), 127.7, 127.8, 128.2, 128.9, 129.0, 129.7 (6 d, C_6H_5), 128.8, 137.2 (2 s, C_6H_5), 136.6 (s, C-5), 146.0 (s, C-2).

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): *m*/*z* calcd for $C_{18}H_{14}N_2$: 258.1157; found: 258.1163.

4-Phenylethynyl-2-methyl-1,5-diphenylimidazole (8)

To a solution of Et_3N (0.4 mL) and DMF (0.8 mL) under argon were added alkyne **7** (150 mg, 0.58 mmol), iodobenzene (0.08 mL, 0.69 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (20 mg, 0.029 mmol, 0.05 equiv), and CuI (3 mg, 0.015 mmol, 0.025 equiv). The mixture was stirred at r.t. for 15 h, then quenched with sat. aq NH_4Cl (3 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (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 **8** as pale yellow crystals; mp 189–190 °C.

IR (KBr): 3055–2855 (=C–H, C–H), 2205 (C≡C), 1600 cm^{-1} (C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 7.11–7.46 (m, 15 H, C_6H_5).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.2 (q, CH_3), 84.3 (s, ≡C), 90.4 (s, C_6H_5C≡), 127.7, 127.8, 127.9, 128.2, 128.3, 128.8, 128.9, 129.6, 131.4 (9 d, C_6H_5), 121.4 (s, C-4), 123.7, 129.1, 136.8 (3 s, C_6H_5), 136.4 (s, C-5), 146.3 (s, C-2).

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): *m*/*z* calcd for $C_{24}H_{18}N_2$: 334.1470; found: 334.1464.

2-*tert*-Butyl-3-methoxy-4-(2-methyl-1,5-diphenylimidazol-4-ylethynyl)-6-trifluoromethylpyridine (10)

To a solution of *i*-Pr_2NH (0.4 mL) and DMF (0.5 mL) containing alkyne **7** (80 mg, 0.31 mmol, 1.2 equiv), $Pd(OAc)_2$ (4 mg, 0.018 mmol, 0.07 equiv), and PPh_3 (13 mg, 0.05 mmol, 0.2 equiv) under argon was added dropwise a solution of nonaflate **9**[5a] (133 mg, 0.25 mmol, 1 equiv, dissolved in 0.5 mL of DMF). After the addition of CuI (3 mg, 0.013 mmol, 0.05 equiv), the mixture was stirred at r.t. for 15 h, then quenched with sat. aq NH_4Cl (3 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the resulting crude product was purified by column chromatography (silica gel, hexane–EtOAc, 3:2) to give 95 mg (63%) of **10** as colorless crystals; mp 178–179 °C.

IR (KBr): 3055–2870 (=C–H, C–H), 2210 (C≡C), 1600 cm^{-1} (C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, *t*-C_4H_9), 2.34 (s, 3 H, CH_3), 3.94 (s, 3 H, OCH_3), 7.15–7.44 (m, 10 H, C_6H_5), 7.55 (s, 1 H, C-5).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1 (q, CH_3), 60.8 (q, OCH_3), 28.9, 38.3 [q, s, $C(CH_3)_3$], 84.8, 94.5 (2 s, C≡C), 120.2 (s, C-4′), 121.4 (q, $J_{C,F}$ = 273 Hz, CF_3), 122.7 (dq, $J_{C,F}$ = 2.8 Hz, C-5), 127.6, 128.2, 128.3, 129.0, 129.1, 129.6 (6 d, C_6H_5), 128.5, 138.1 (2 s, C_6H_5), 136.2 (s, C-5′), 139.7 (q, $J_{C,F}$ = 34 Hz, C-6), 146.7 (s, C-2′), 124.2, 157.2, 162.2 (3 s, C-2,3,4).

MS (EI, 80 eV, 160 °C): *m*/*z* (%) = 490 (34), 489 (100, $[M^+]$), 488 (23), 474 (27, $[M^+ - CH_3]$), 458 (12), 447 (12), 446 (20), 259 (19), 246 (12), 245 (44), 180 (14), 118 (22), 97 (11), 87 (19), 85 (14), 84 (15), 83 (15), 81 (12), 77 (43), 73 (29), 71 (17), 70 (13), 69 (27), 67 (13), 60 (44), 58 (11), 57 (44), 56 (17), 55 (52), 45 (22), 44 (14), 43 (94), 42 (24), 41 (73), 39 (24).

HRMS (EI): *m*/*z* calcd for $C_{29}H_{26}F_3N_3O$: 489.2028; found: 489.2017.

Anal. Calcd for $C_{29}H_{26}F_3N_3O$ (489.5): C, 71.15; H, 5.35; N, 8.58. Found: C, 71.14; H, 5.10; N, 8.47.

Ethyl 2-Methyl-1,5-diphenylimidazol-4-ylpropynoate (11)

To a solution of alkyne **7** (80 mg, 0.31 mmol) in THF (2 mL) under argon was added dropwise a solution of EtMgBr (0.18 mL, 0.52 mmol, 1.7 equiv, 3.0 M solution in Et_2O) and the mixture was stirred at r.t. for 30 min. Then ethyl cyanoformate (0.15 mL, 0.76 mmol, 2.5 equiv) was added and the mixture was allowed to stir for 15 h at r.t. The mixture was quenched with sat. aq NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the crude product was purified by column chromatography (aluminum oxide, hexane–EtOAc, 1:1) to afford 94 mg (92%) of **11** as colorless crystals; mp 138–139 °C.

IR (KBr): 3070–2870 (=C–H, C–H), 2200 (C≡C), 1690 (C=O), 1600 cm^{-1} (C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.22 (q, *J* = 7.2 Hz, 2 H, OCH_2), 7.12–7.43 (m, 10 H, C_6H_5).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0, 14.1 (2 q, CH_3), 61.6 (t, CH_2), 82.0, 82.6 (2 s, C≡C), 118.2 (s, C-4), 127.5, 128.3, 128.4, 128.8, 129.0, 129.6 (6 d, C_6H_5), 127.6, 140.7 (2 s, C_6H_5), 136.0 (s, C-5), 146.9 (s, C-2), 154.1 (s, C=O).

Anal. Calcd for $C_{21}H_{18}N_2O_2$ (330.4): C, 76.34; H, 5.49; N, 8.48. Found: C, 76.44; H, 5.22; N, 8.56.

2-Methyl-4-(1-methylene-3-phenylprop-2-ynyl)-1,5-diphenylimidazole (12)

To a solution of iodoethenylimidazole **6** (171 mg, 0.44 mmol), phenylacetylene (54 mg, 0.53 mmol, 1.2 equiv), and $PdCl_2(PPh_3)_2$ (16 mg, 0.022 mmol, 0.05 equiv) in Et_3N (1 mL) and DMF (0.4 mL) under argon was added CuI (2 mg, 0.01 mmol, 0.025 equiv). The mixture was stirred at r.t. for 15 h, then quenched with sat. aq NH_4Cl (3 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the resulting crude product was purified by column chromatography (aluminum oxide, hexane–EtOAc, 4:1) to afford 91 mg (57%) of **12** as pale yellow crystals; mp 145–146 °C.

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IR (KBr): 3055–2855 (=C–H, C–H), 1600 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 5.67, 6.27 (2 d, *J* = 2.1 Hz, 1 H each, $=CH_2$), 6.86–7.32 (m, 15 H, C_6H_5).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0 (q, CH_3), 88.6, 90.3 (2 s, C≡C), 121.9 (t, $=CH_2$), 123.0, 130.2, 134.3, 136.5 (4 s, C_6H_5), 123.9 (s, C-4), 127.4, 127.5, 127.6, 127.7, 127.8, 128.3, 129.1, 131.1, 131.4 (9 d, C_6H_5), 130.8 (s, C-5), 144.8 (s, C-2).

MS (EI, 80 eV, 130 °C): *m/z* (%) = 361 (16), 360 (58, $[M^+]$), 359 (58), 317 (20), 215 (10), 180 (11), 118 (11), 105 (36), 86 (12), 85 (12), 84 (21), 83 (10), 77 (70, $[C_6H_5^+]$), 73 (12), 71 (15), 69 (14), 60 (19), 58 (12), 57 (18), 55 (22), 51 (19), 45 (13), 43 (43), 41 (24), 39 (11), 32 (20), 29 (19), 28 (100).

HRMS (EI): *m/z* calcd for $C_{26}H_{20}N_2$: 360.1626; found: 360.1636.

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