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

Alkoxyallenes are very versatile C3-building blocks for the synthesis of heterocycles. They allow a flexible entry into functionalized furan,2 pyrane,3 pyrrole, pyrrolidine,4 pyridine,5 and 1,2-oxazine derivatives6 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 aldime 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 dihydroimidozole derivative 5. Final treatment of 5 with 1.2 equivalents of trifluoromethanesulfonic acid afforded the 1-idoethenyl-substituted imidazole derivative 6 in 80% overall yield after chromatography (Scheme 1).

This new four-component synthesis9 proceeded via (a) attack of iodine to the central allene carbon of 3, (b) Ritter-type addition10 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 1 Four-component synthesis (1 + 2 + I2 + 4) leading to dihydroimidazole derivative 5 and elimination to tetrasubstituted imidazole 6

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\(^\text{11}\) 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\(^\text{9a}\) provided the pyridine-imidazole hybrid 10 in 63% yield. Notably, 9 itself derives from yet another novel multicomponent reaction of lithiated bridged compounds at the terminal alkyne carbon or even in cycloadditions and lead to a diverse set of interesting new bicyclic 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\(^\text{13}\) as well as components for material-oriented research,\(^\text{14,15}\) thus new entries to this class of heterocycles are highly desirable.\(^\text{16,17}\)

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 leading to disubstituted alkynes 8 and 10 (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-idoethenyl 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).

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\(^\text{13}\) as well as components for material-oriented research,\(^\text{14,15}\) thus new entries to this class of heterocycles are highly desirable.\(^\text{16,17}\)

For general information concerning experimental setup and analytical methods, see ref.\(^\text{6}\).
were dried (Na₂SO₄) and the resulting crude product was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to give 50 mg (50%) of the product.

IR (KBr): 3055–2870 (=C–H, C–H), 2210 (C≡C).

HRMS (EI): m/z calcd for C₁₈H₁₅IN₂: 386 (17, [M+]⁺), 259 (100, [M – C₆H₅]⁺), 114 (23), 91 (25), 77 (55, [C₆H₅]⁺), 51 (28), 28 (100).

1H NMR (500 MHz, CDCl₃): δ = 1.38 (s, 9 H, t-C₄H₉), 2.24 (s, 3 H, CH₃), 2.34 (s, 3 H, CH₃), 3.94 (s, 3 H, OCH₃), 7.15–7.44 (m, 10 H, C₆H₅), 7.55 (s, 1 H, C-5).

13C NMR (126 MHz, CDCl₃): δ = 141 (q, CH₃), 60.8 (q, OCH₃), 28.9, 38.3 (q, C-CH₃), 84.8, 94.5 (2 s, C₆H₅), 120.2 (s, C-4), 121.4 (q, J_C,F = 273 Hz, C₆F₅), 122.7 (dq, J_C,F = 2.8 Hz, C₅–CH₃), 125.6, 128.2, 128.9, 129.1, 129.6 (6 d, C₆H₅), 128.5, 138.1 (2 s, C₆H₅), 136.2 (s, C-5′), 139.7 (q, J_C,F = 34 Hz, C₆–CH₃), 146.7, 152.4, 172.2 (3 s, C-2,3,4).

MS (EI, 80 eV, 160 °C): m/z (%) = 490 (34), 489 (100, [M+]⁺), 488 (23), 474 (27, [M’ – CH₃]⁺), 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 (13), 43 (94), 42 (24), 41 (73), 39 (24).


Anal. Calcd for C₂₃H₂ₐF₅N₂O₪: C, 71.15; H, 5.35; N, 8.85. Found: C, 71.14; H, 5.10; N, 8.47.

**Ethyl 2-Methyl-1,5-diphenylimidazo-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) and the mixture was stirred at r.t. for 30 min. Then ethyl cyanofomate (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 NH₄Cl solution (3 mL) at 0 °C under argon was added dropwise a solution of CuI (0.022 mmol, 0.05 equiv) in Et₃N (1 mL) and DMF (0.4 mL) and the mixture was stirred at r.t. for 15 h, then quenched with sat. aq NH₄Cl solution (3 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phases were dried (Na₂SO₄) and the resulting crude product was purified by column chromatography (aluminum oxide, hexane–EtOAc, 1:1) to afford 94 mg (92%) of the product.

IR (KBr): 3055–2870 (=C–H, C–H), 2210 (C≡C).

HRMS (EI): m/z calcd for C₁₈H₁₃NO₂: 258.1157; found: 258.1163.
IR (KBr): 3055–2855 (=C–H, C–H), 1600 cm–1 (C=C).

1H NMR (500 MHz, CDCl3): δ = 2.30 (s, 3 H, CH3), 5.67, 6.27 (2 d, J = 2.1 Hz, 1 H each, =CH2), 6.86–7.32 (m, 15 H, C6H5).

13C NMR (126 MHz, CDCl3): δ = 14.0 (q, CH3), 88.6, 90.3 (2 s, CsC), 121.9 (t. =CH2), 123.0, 130.2, 134.3, 136.5 (4 s, C6H5), 123.9 (s, C–4), 127.4, 127.5, 127.6, 127.7, 128.3, 129.1, 131.1, 131.4 (9 d, C6H5), 130.8 (s, C(5)), 144.8 (s, C=C).

MS (EI, 80 eV, 130 °C): J = 2.1 Hz, 1 H each, =CH2), 6.86–7.32 (m, 15 H, C6H5).

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Several of the imidazole derivatives of type 6 are highly fluorescent: Gwiazda, M.; Reissig, H.-U., unpublished results.