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A one-pot synthesis of polysubstituted imidazo[1,2-*a*]pyridines

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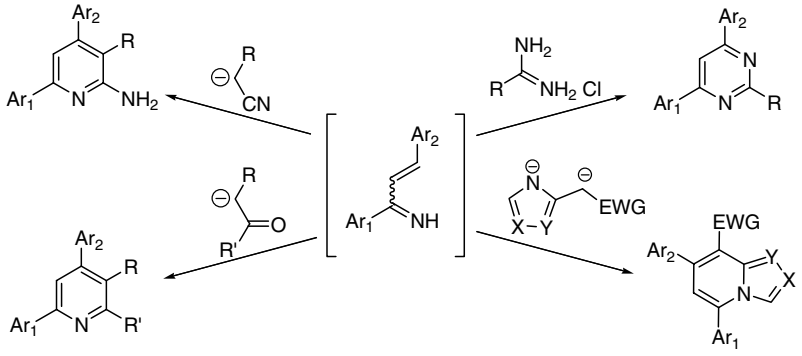
Abstract—A series of 5,7,8-polysubstituted imidazo[1,2-*a*]pyridines were synthesized regioselectively from in situ generated α,β-unsaturated imines and dianions derived from methyl azolyl acetates in a one-pot procedure. The targeted molecules were conveniently isolated in analytically pure form (ca. 50–70% yields) by trituration of the concentrated reaction mixtures with cold ether.

Synthesis of polysubstituted imidazo[1,2-*a*]pyridines received substantial attention due to their pronounced physiological activity.[1] Several reports in the literature describe the application of these substrates for the treatment of anxiety,[2] gastrointestinal diseases,[3] and neuropathy.[4] Notably, bone resorption inhibitor YM529 was efficacious in Phase III clinical trials for the treatment of osteoporosis.[5] Preclinical data from several research laboratories indicate continuing interest in polysubstituted imidazo[1,2-*a*]pyridines as selective cyclin dependent kinase inhibitors.[6] Several related compounds were reported to have pronounced phosphodiesterase V,[7] and chemokine receptor[8] inhibitory activity.

In our medicinal chemistry program geared toward identification of novel receptor tyrosine kinase inhibitors, we required a robust approach to a diverse set of the title heterocycles. Among a variety of synthetic approaches available for the assembly of imidazo[1,2-*a*]pyridine ring,[9] we have focused on α,β-unsaturated imines as starting materials.[10–12] The feasibility of these electrophilic species for the synthesis of substituted pyridines and pyrimidines,[10] *E*-allylic amines,[11] and α,β-unsaturated ketones[12] is well documented. We reasoned that the appropriate selection of bis-nucleophile for the condensation reaction would result in the targeted heterocycles (Scheme 1).

Initially, we studied the reaction of α,β-unsaturated imines with dianion derived from the methyl imidazolyl acetate (Scheme 2). This one-pot procedure yielded the anticipated imidazo[1,2-*a*]pyridines **4a**–**l** in good yields.



Scheme 1.

Keywords: One-pot reactions; Imidazo[1,2-*a*]pyridines; α,β-Unsaturated imines; Condensations.
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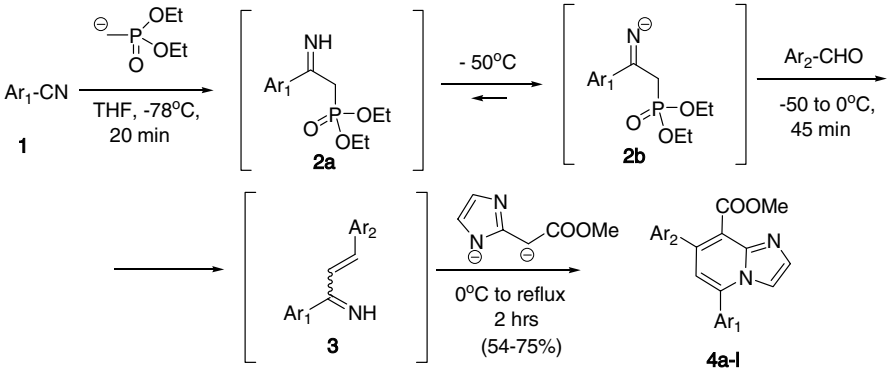
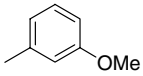
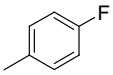
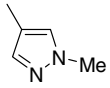
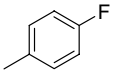
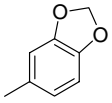
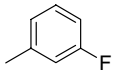
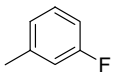
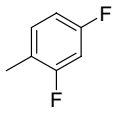
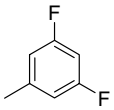
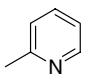
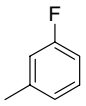
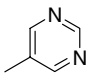
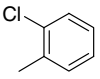


Entry, **4** (m.p., °C)	Ar_1	Ar_2	Yield, %	Entry, **4** (m.p., °C)	Ar_1	Ar_2	Yield, %
a (185-186)			54	**g** (191-193)			72
b (193-194)			61	**h** (244-246)			55
c (201-203)			64	**i** (166-167)			60
d (214-216)			62	**j** (188-190)			67
e (205-207)			71	**k** (177-178)			65
f (165-166)			75	**l** (212-214)			69

[a]Values represent combined yields of analytically pure materials **4** obtained by crystallization and column chromatography

Scheme 2.

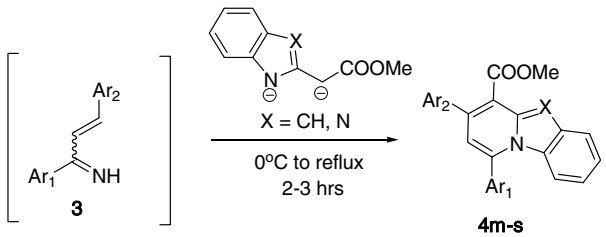
All materials were conveniently isolated in analytically pure form from the concentrated reaction mixtures by trituration with ether.[13] Additional amounts (ca. 10–15%) of heterocycles were obtained from the reaction mixtures by column chromatography on silica with hexanes/EtOAc (2:1) as eluent.

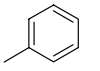
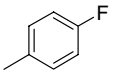
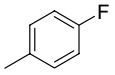
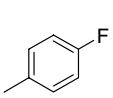
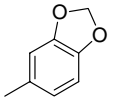
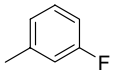
Notably, the nature of neither nitrile nor aldehyde significantly affected the reaction outcome. For example, comparable yields of **4** were obtained for both electron rich- and deficient components (see Scheme 2, entries **d** and **i**). In addition, steric hindrance (*ortho*-substituents) in both nitrile (entry **j**, product **4j**) and aldehyde (entry **l**, product **4l**) was well tolerated.

We believe that the described transformations proceed via the initial formation of respective α,β-unsaturated imines[10–12] **3** that undergo nucleophilic attack by the C-atom of 1,3-dianions. This step is then followed by cyclization and aromatization to yield the observed polysubstituted imidazo[1,2-*a*]pyridines **4a**–**l**.[14] Optimized reaction conditions include application of dry THF or dioxane as solvents, as well as thorough temperature control. The latter is particularly important at the earlier stages of reagent addition during the formation of α,β-unsaturated imines, presumably due to the high reactivity of the intermediate species **2a**/**2b** and **3**. The nature of base used for deprotonation of azolyl acetates did not affect the outcome of the condensation. For example, LDA, Li(morpholide), NaHMDS, and KHMDS all afforded comparable yields of the targeted molecules **4**, as evidenced by the LC–MS analysis of the crude reaction mixtures.

This protocol was further extended to the synthesis of fused tricyclic systems **4m**–**s** by reaction of the intermediate **3** with dianions derived from 2-indole- and 2-benzimidazole methyl acetates (Scheme 3).

Additional components of the reaction mixtures included the corresponding α,β-unsaturated ketones (25–40% by LC–MS analysis, 20–35% isolated yields) that



Entry, **4** (m.p., °C)	Ar_1	Ar_2	X	Yield, %	Entry, **4** (m.p., °C)	Ar_1	Ar_2	X	Yield, %
m (227-229)			CH	55	**q** (>250)			N	61
n (239-241)			CH	59	**r** (>250)			N	66
o (>250)			CH	64	**s** (>250)			N	62
p (>250)			CH	68	**t** (>250)			N	70

[a]Values represent combined yields of analytically pure materials **4** obtained by crystallization and column chromatography

Scheme 3.

presumably originated from the intermediate imines **3**. Our attempts to reduce formation of these side-products by thorough moisture control (dry box), increasing the temperature of the reaction (ca. 140 °C, sealed tube), microwave irradiation of the reaction mixtures or by addition of dry polar solvents at the condensation stage (NMP, DME) were unsuccessful. The regiospecific nature of the cyclization has been confirmed by NOE experiments.[15] Alternative regioisomers have not been detected in the reaction mixtures.

In summary, we have described a convenient one-pot approach to 5,7,8-polysubstituted imidazo[1,2-*a*]pyridine derivatives from in situ generated α,β-unsaturated imines and dianions derived from methyl azolyl acetates. Reaction is general with respect to all three components, namely (i) nitrile, (ii) aldehyde, and (iii) azolyl acetate reagents. Good yields (51–74%), convenient isolation of the targeted heterocycles **4a**–**t** are the distinct characteristics of the developed protocol.

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L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129.

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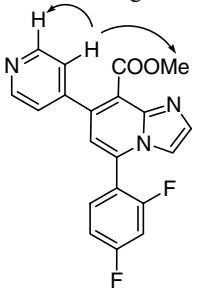
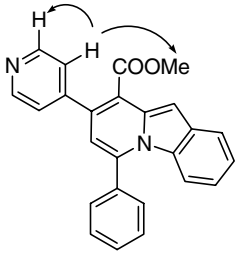
13. *General experimental procedure*: *n*-BuLi (2.5 M solution in hexanes, 4 mL, 1 mM) was added by syringe to a vigorously stirred solution of methyl phosphonate (1 mM) in dry THF or dioxane (10 mL) under Ar at −78 °C. A solution of nitrile (1 mM) in 5 mL of the same solvent was slowly added by syringe. The resulting colorless mixture was slowly warmed to −50 °C and stirred for additional 30 min. A solution of aldehyde (1 mM) in 5 mL of dry solvent (THF or dioxane) was slowly added (5 min), and the resulting mixture was allowed to warm up to room temperature (45 min). Separately, a solution of the respective methyl azolyl acetate (1 mM) in dry THF or dioxane (5 mL) was treated with freshly prepared LDA (2.25 mM) in the same solvent (5 mL) at −78 °C under Ar. The resulting pale yellow mixture was slowly (5–10 min) added via cannula to the α,β-unsaturated imine **3** generated in situ at 0 °C. The reaction mixture was slowly brought to rt (20 min) and, subsequently to reflux (20 min). Further, it was refluxed for additional 100–120 min until TLC (hexanes/ether, 1:1) or LC–MS analyses indicated absence of starting materials (nitrile and aldehyde). The mixture was then concentrated to 20 mL on rotavapor, diluted with EtOAc (50 mL), the organic extract was washed twice with brine (30 mL), dried over Na_2SO_4, concentrated to ca. 10 mL, cooled down in the freezer and triturated with cold ether. The resulting crystals were collected, washed with ether, recrystallized from EtOH and dried in vacuo to yield analytically pure imidazo[1,2-*a*]pyridines.
14. *Analytical data for representative compounds*:
Methyl 7-(benzo[*d*][1,3]dioxol-5-yl)-5-(4-fluorophenyl)*H*-imidazo[1,2-*a*]pyridine-8-carboxylate, **4c**: 64% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 3H), 5.84 (s, 2H), 6.67 (d, $J = 6.8$ Hz, 1H), 6.78 (s, 1H), 6.96 (d, $J = 6.8$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.28 (s, 1H), 7.42 (d, $J = 5.6$ Hz, 1H), 7.53 (d, $J = 5.6$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 2H); ESI MS: (M+1) 391, (M−1) 389; HR ESI MS: Exact mass calcd for $C_{22}H_{15}FN_2O_4$ 390.1016, found: 390.1009. Elemental analysis, calcd for $C_{22}H_{15}FN_2O_4$: C, 67.69; H, 3.87; N, 7.18. Found: C, 67.55; H, 3.71; N, 7.03.
Methyl 5-(2,4-difluorophenyl)-7-(pyridin-4-yl)*H*-imidazo-[1,2-*a*]pyridine-8-carboxylate, **4j**: 60% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H), 6.95 (s, 1H), 7.05 (d, $J = 7.6$ Hz, 1H), 7.22 (s, 1H), 7.40 (d, $J = 5.6$ Hz, 1H), 7.46 (d, $J = 5.6$ Hz, 1H), 7.68 (d, $J = 6.4$ Hz, 2H), 8.05 (d, $J = 7.6$ Hz, 1H), 8.72 (d, $J = 6.4$ Hz, 2H); ESI MS: (M+1) 366, (M−1) 364; HR ESI MS: Exact mass calcd for $C_{20}H_{13}F_2N_3O_2$: 365.0976, found: 365.0970. Elemental analysis, calcd for $C_{20}H_{13}F_2N_3O_2$: C, 65.75; H, 3.59; N, 11.50. Found: C, 65.57; H, 3.71; N, 11.33.
Methyl 8-(benzo[*d*][1,3]dioxol-5-yl)-6-(4-fluorophenyl)pyrido[1,2-*a*]indole-9-carboxylate, **4o**, 67% yield; 3.81 (s, 3H), 5.87 (s, 2H), 6.36 (s, 1H), 6.69 (d, $J = 6.8$ Hz, 1H), 6.81 (s, 1H), 6.86 (s, 1H), 6.93 (d, $J = 6.8$ Hz, 1H), 6.98 (m, 1H), 7.03 (m, 1H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.58 (d, $J = 7.6$ Hz, 1H), 7.95 (d, $J = 8.0$ Hz, 2H); ESI MS: (M+1) 440, (M−1) 438; HR ESI MS: Exact mass calcd for $C_{27}H_{18}FNO_4$ 439.1220, found: 439.1213. Elemental analysis, calcd for $C_{27}H_{18}FNO_4$: C, 73.80; H, 4.13; N, 3.19. Found: C, 73.57; H, 3.98; N, 3.05.
15. Observed significant NOE's for the products **4j** and **4p**.



4j



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