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Novel one pot synthesis of polysubstituted pyrazolo[1,5-*a*]- and imidazo[1,2-*a*]pyrimidines

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Abstract—We have described a convenient regioselective one-pot approach to pyrazolo[1,5-*a*]- and imidazo[1,2-*a*]pyrimidine derivatives from α,β-unsaturated imines generated in situ and amino heterocycles. Reaction is general with respect to all three components, namely (i) nitrile, (ii) aldehyde, and (iii) amino heterocycle reagents. Good yields (52–77%), convenient isolation of the targeted molecules are the distinct characteristics of the developed protocol.

Synthesis of polysubstituted pyrazolo[1,5-*a*]- and imidazo[1,2-*a*]pyrimidines 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 labs indicate continuing interest in these templates 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 the two ring systems,[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. Two regioisomers were possible as a result of this latter step (Scheme 1).

In order to investigate the regioselectivity, we studied the reaction of α,β-unsaturated imines with 5-amino pyrazoles (Scheme 2, entries **a**–**d**). This one-pot procedure yielded the anticipated pyrazolo[1,5-*a*]pyrimidines **4a**–**d**. A single isomer has been detected in the crude reaction mixtures (LC MS and TLC analyses) and the targeted molecules were obtained in good yields (54–75%). The protocol was further extended to the synthesis of imidazo[1,2-*a*]pyrimidines **4e**–**l**. All materials were conveniently isolated in analytically pure form as a single regioisomer from the concentrated reaction mixtures by trituration with ether.[13] Additional amounts (ca. 10–15%) of heterocycles were obtained from the mother liquor by column chromatography on Silica with hexanes/EtOAc (2:1) as an 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 entries **b** and **c**, **f** and **i**, Scheme 2).

In our hands, the addition of the oxidizing agents at the last step of the transformation decreased the yields of the desired products **4**. Specifically, bubbling dry O_2 through the refluxing mixture of amino heterocycle and α,β-unsaturated imine **3** for entries **a** and **b** (Scheme 2) resulted in 23% and 25% yields of heterocycles **4a** and **4b**. Similarly, addition of DDQ to the reaction mixtures yielded **4a** and **4b** in a 19% and 26% yields along with a number of side products based on the HPLC analysis.

Keywords: One-pot reactions; Pyrazolo[1,5-*a*]pyrimidines; Imidazo[1,2-*a*]-pyrimidines; α,β-Unsaturated imines; Condensations.
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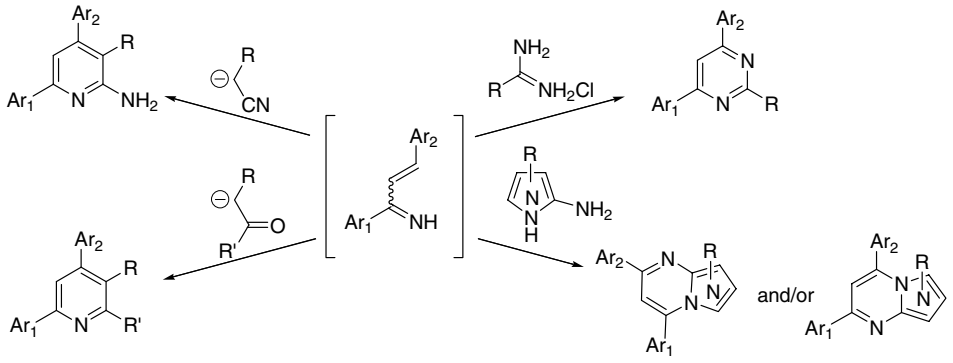
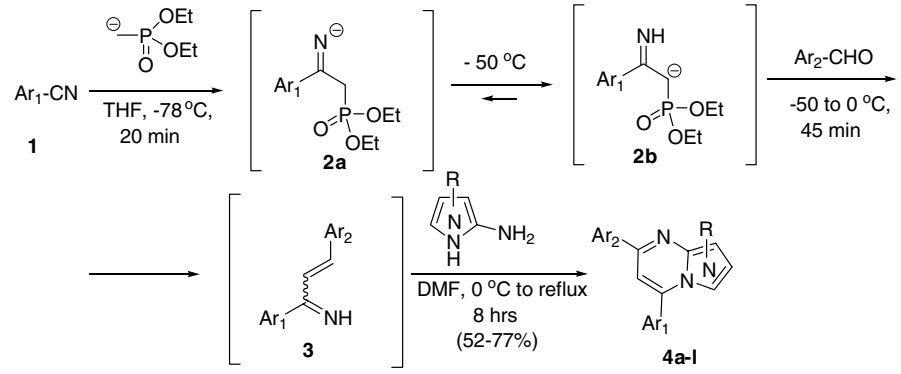


Scheme 1.



Entry, **4** (m.p., °C)	Ar$_1$	Ar$_2$	Yield, %[a]	Entry, **4** (m.p., °C)	Ar$_1$	Ar$_2$	Yield, %[a]
a (224-226)	Ph	Ph	54	**g** (241-243)	2-pyridyl	4-F-Ph	72
b (231-233)	4-F-Ph	Ph	64	**h** (>250)	Ph	1-Me-pyrazol-4-yl	52
c (211-213)	4-F-Ph	3,4-methylenedioxyphenyl	68	**i** (>250)	4-F-Ph	2-pyridyl	77
d (>250)	4-F-Ph	3-pyridyl	75	**j** (>250)	2,4-diF-Ph	3-pyridyl	71
e (208-210)	4-F-Ph	Ph	67	**k** (>250)	2-pyridyl	4-F-Ph	73
f (237-239)	4-F-Ph	3,4-methylenedioxyphenyl	69	**l** (>250)	2-pyridyl	2-F-Ph	76[b]

[a]Values represent combined yields of analytically pure materials **4** obtained by crystallization and column chromatography; [b]Single regioisomer was detected in the reaction mixture by NMR and HPLC methods.

Scheme 2.

The described transformations is likely to proceed via the initial formation of the respective α,β-unsaturated imines[10–12] **3** that undergo nucleophilic attack at *C*3 by the exocyclic amino group of the heterocycle. This step is then followed by cyclization and aromatization to yield the observed products **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. The reason could be high reactivity of the intermediate species **2a/2b** and **3**. Addition of dry freshly distilled DMF (ca. 20%) to the reaction mixtures at the heterocyclization stage was found to increase the overall yields of the targeted molecules by ca. 25–30%. This is presumably due to the increased solubility of the amino heterocycle component and higher reaction temperature that both facilitate condensation and aromatization steps. We further extended the described procedure to the synthesis of fused tricyclic systems **4j–l** by reaction of the intermediate **3** with 2-amino benzimidazole derivatives (Scheme 2).

Additional components of the reaction mixtures included the corresponding α,β-unsaturated ketones (25–40% by LC MS analysis, 20–35% isolated yields) that likely 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 an alternative polar solvents at the condensation stage (*N*-methylpyrrolidone, dimethoxyethane) were unsuccessful. Regioselective nature of the cyclization has been confirmed by NOE experiments.[13]

In summary, we have described a convenient regiospecific one-pot approach to pyrazolo[1,5-*a*]- and imidazo[1,2-*a*]pyrimidine derivatives from α,β-unsaturated imines generated in situ and amino heterocycles. Reaction is general with respect to all three components, namely (i) nitrile, (ii) aldehyde, and (iii) amino heterocycle reagents. Good yields (52–77%), convenient isolation of the targeted heterocycles **4a–l** are the distinct characteristics of the developed protocol. Currently, we are in the process of investigating both scope and limitations of the procedure.

References and notes

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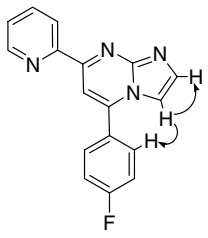
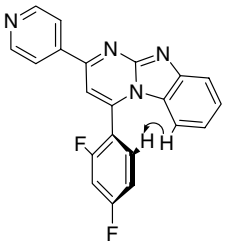
13. *General experimental procedure*: *n*-BuLi (2.5 M solution in hexanes, 4 mL, 10 mmol) was added by syringe to a vigorously stirred solution of methyl phosphonate (10 mmol) in dry THF or dioxane (10 mL) under Ar at −78 °C. A solution of nitrile (10 mmol) in 5 mL of the same solvent was slowly added by syringe. The resulting colorless mixture was slowly warmed to −50 °C and stirred for additional 30 min. A solution of aldehyde (10 mmol) 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). A solution of amino heterocycle (10 mmol) in freshly distilled dry DMF (5 mL) was added to the α,β-unsaturated imine **3** generated in situ at 0 °C. The reaction mixture was brought to rt (20 min) and, subsequently to reflux (20 min). Further, it was refluxed for additional 8 h until TLC (hexanes/ether, 1:1) or LC MS analyses indicated absence of starting materials (nitrile and aldehyde). The mixture was then concentrated on rotavap, the residue was re-dissolved in EtOAc (50 mL) and filtered. The organic

phase 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.

Observed significant NOE's for the products **4i** and **4j**:



4i



4j

14. *Analytical data for representative compounds*:

Compound **4b**: 64% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.68 (d, $J = 5.6$ Hz, 2H), 7.01 (d, $J = 7.6$ Hz, 1H), 7.21–7.24 (m, 3H), 7.50 (d, $J = 7.6$ Hz, 2H), 7.56 (d, $J = 7.2$ Hz, 2H), 7.64 (d, $J = 5.6$ Hz, 1H), 7.75 (s, 1H). ESI MS: (M+1) 290, (M−1) 288; HR ESI MS: Exact mass calcd for $C_{18}H_{12}FN_3$: 289.1015, found: 289.1007. Elemental analysis, calcd for $C_{18}H_{12}FN_3$: C, 74.73; H, 4.18; N, 14.52. Found: C, 74.56; H, 4.29; N, 14.01.

Compound **4i**: 77% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.95 (d, $J = 7.2$ Hz, 2H), 7.18 (d, $J = 4.8$ Hz, 1H), 7.31 (dd, $J_1 = 7.2$ Hz, $J_2 = 4.8$ Hz, 1H), 7.50 (d, $J = 4.8$ Hz, 1H), 7.57 (d, $J = 7.2$ Hz, 2H), 7.66 (d, $J = 6.8$ Hz, 1H), 7.79 (dd, $J_1 = 7.2$ Hz, $J_2 = 6.8$ Hz, 1H), 8.44 (s, 1H), 8.72 (d, $J = 4.8$ Hz, 1H); ESI MS: (M+1) 291, (M−1) 289; HR ESI MS: Exact mass calcd for $C_{17}H_{12}FN_4$: 290.0968, found: 290.0962. Elemental analysis, calcd for $C_{17}H_{12}FN_4$: C, 70.34; H, 3.82; N, 19.30. Found: C, 10.29; H, 3.64; N, 19.11.

Compound **4j**: 71% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.92 (s, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 7.22–7.24 (m, 2H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.62 (d, $J = 6.4$ Hz, 2H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.81 (s, 1H), 8.74 (d, $J = 6.4$ Hz, 2H); ESI MS: (M+1) 359, (M−1) 357; HR ESI MS: Exact mass calcd for $C_{21}H_{12}F_2N_4$: 358.1030, found: 358.1021. Elemental analysis, calcd for: $C_{21}H_{12}F_2N_4$: C, 70.39; H, 3.38; N, 15.63. Found: C, 70.13; H, 3.19; N, 15.45.