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One-pot synthesis of polysubstituted pyrimidines

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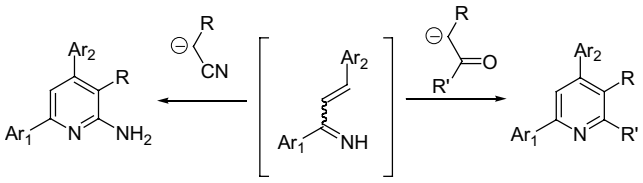
Abstract—A series of polysubstituted pyrimidines were synthesized from in situ generated α,β-unsaturated imines and the corresponding amidine or guanidine derivatives in a convenient one-pot procedure.

Synthesis of polysubstituted 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 hypoxemia,[2] neuronosis,[3] and neuropathy.[4] Notably, *bcr*-Abl kinase inhibitor Gleevec™ contains a 2,4-substituted pyrimidine core.[5] Preclinical data from several research labs indicate continuing interest in polysubstituted pyrimidines as potential anti-tumor agents.[6] Pyrimidine derivatives has been used in coordination chemistry, specifically as ligands for metal-cage complexes, in particular with lanthanides,[7] and ruthenium.[8]

In our medicinal chemistry program, we required a robust approach to a diverse set of the title heterocycles. Among wide variety of synthetic approaches available for the assembly of pyrimidine ring,[9] we have focused on α,β-unsaturated imines as starting materials.[10–12] The feasibility of generating these reactive species in situ in the synthesis of substituted pyridines,[10] *E*-allylic amines,[11] and α,β-unsaturated ketones[12] is well documented (Scheme 1).

Initially, we studied reaction of α,β-unsaturated imines with several amidines and guanidines (Table 1).[13]

We believe that the described transformations proceed via the initial formation of α,β-unsaturated imines[10–12] **3** that undergo nucleophilic attack by a bi-dentate nucleophile (amidine or guanidine). This step is then followed by elimination of ammonia and aromatization to yield the observed polysubstituted pyrimidines **4a**–**l**.[14] Optimized reaction conditions include application of dry THF or dioxane as solvents, as well as thorough temperature control of the reaction mixtures, especially at the earlier stages of reagent addition. We attribute this to the formation of unstable aza-Wittig species **2b** that undergo smooth reaction with aldehydes to result in the reactive imine species **3**. Addition of polar solvents (DMF, NMP, *N*-methyl morpholine; 20–50 vol %) to better solubilize amidine or guanidine species did not affect the outcome of the reaction.



Scheme 1.

As a further development of this protocol, we studied the effect of phosphonate substitution on the reaction (Table 2).

Application of substituted phosphonates in this reaction sequence allowed for the introduction of a substituent in the position 5 of the pyrimidine ring. However, it also reduced the overall yield of the resulting pyrimidines **5a**–**g**. For example, the best yields of the targeted pyrimidines **5** were consistently achieved with ethyl phosphonate (R′ = Me, entries **5a**–**c**). Increasing steric bulk from Me (entry **5b**) to Ph (entries **5e** and **5f**) or *i*-Bu (entry **5g**) reduced the yield of the targeted products from 57% to 22–39%, respectively. The latter reactions also resulted in a number of high-molecular weight products along with the desired compounds **5**. Identified components of the reaction mixtures included the

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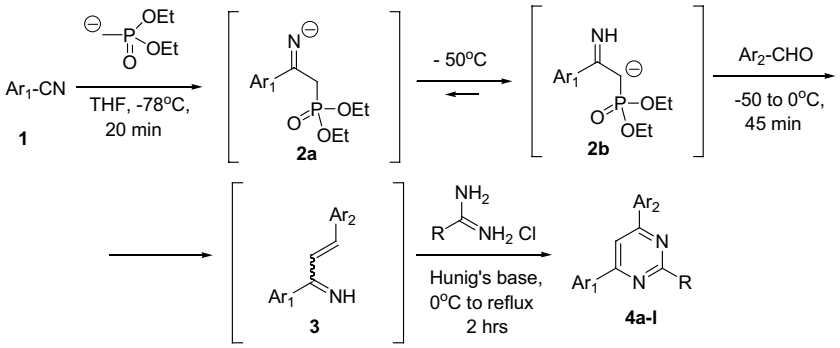
Table 1.



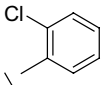
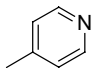
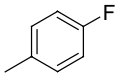
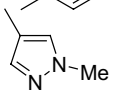
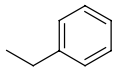
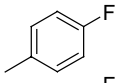
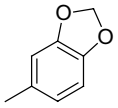
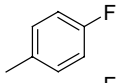
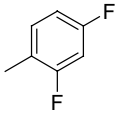
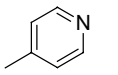
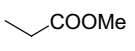
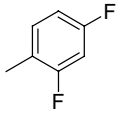
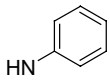
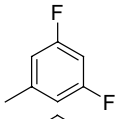
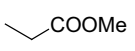
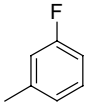
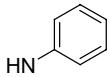
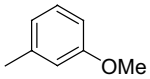
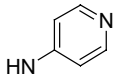
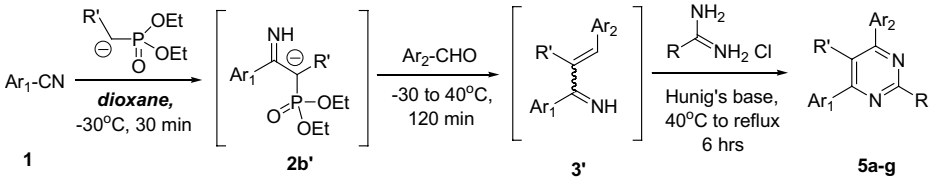
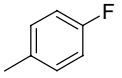
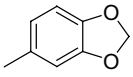
Entry, **4** (mp, °C)	Ar_1	Ar_2	R	Yield, %	Entry, **4** (mp, °C)	Ar_1	Ar_2	R	Yield, %
a (96–98)			Me	67	**g** (172–173)				58
b (108–109)			Me	71	**h** (144–145)				60
c (133–135)				73	**i** (212–214)				55
d (142–143)				64	**j** (253–255)				58
e (130–132)				61	**k** (230–232)				54
f (128–130)				68	**l** (245–247)				56

Table 2.



Entry, **5** (mp, °C)	Ar_1	Ar_2	R	R′	Yield, %
a (115–117)			Me	Me	52
b (133–135)			Me	Me	57
c (172–174)				Me	43
d (144–146)			Me		41
e (167–169)			Me		26
f (153–154)					22
g (170–172)					39

corresponding α,β-unsaturated ketones (25–40% by LC MS analysis, 20–30% isolated yields) that presumably originated from the nonreacted imines **3′**. Our attempts to improve the outcome of these reactions by further increasing the temperature of the reaction (ca. 140 °C, sealed tube), microwave irradiation of the reaction mixtures, addition of polar solvents (DMF, NMP), or by applying varying amount (2–10 equiv) of bases (Hunig's base, Bu_4NF, DABCO) were unsuccessful. In addition, no reaction was observed with phosphonates containing electron-withdrawing groups (Table 2, R′ = COOMe, CN).

In summary, we have described a convenient one-pot approach to polysubstituted pyrimidine derivatives from in situ generated α,β-unsaturated imines and the corresponding amidine or guanidine derivatives. In addition, pyrimidines with small alkyl substituents in position 5 are also accessible via this protocol by using properly substituted alkylphosphonates.

References and notes

1. (a) Dozorova, E. N.; Grizik, S. I.; Persianova, I. V.; Syubaev, R. D.; Shvarts, G. Y.; Granik, V. G. *Khim.-Pharm. Z.* **1985**, *19*, 154; (b) Buchdunger, E.; Zimmerman, J.; Mett, H.; Meyer, T.; Muller, M.; Drucker, B.; Lydon, N. *Cancer Res.* **1996**, *56*, 100.
2. Yasuji, S.; Masaichi, H.; Kataoka, K.; Hoshina, K.; Yamazaki, N.; Kadota, T.; Yamaguchi, H. Japan Patent WO 9105784.
3. Yokoyama, K.; Kato, S.; Kitahara, T.; Imuda, J.; Takei, M.; Awaya, A.; Nakano, T.; Horigome, K.; Sasaki, T. Japan Patent JP 01040469.
4. Awaya, A.; Nakano, T.; Kobayashi, H.; Tan, K.; Horikomi, K.; Sasaki, T.; Yokoyama, K.; Ohno, H.; Kato, K. Japan Patent WO 8704928.
5. (a) Nimmanapali, R.; O'Bryan, E.; Huang, M.; Bali, P.; Burnette, P. K.; Loughran, T.; Tepperberg, J.; Jove, R.; Bhalla, K. *Cancer Res.* **2002**, *62*, 5761; (b) Heinrich, M.; Griffith, D.; Drucker, B.; Wait, C.; Ott, K.; Zigler, A. *Blood* **2000**, *96*, 925; (c) Denninger, M. W. N.; Goldman, J. M.; Lydon, N.; Melo, J. V. *Blood* **1997**, *90*, 3691; (d) Buchdunger, E.; Cioffi, C. L.; Law, N.; Stover, D.; Ohno-Jones, S.; Drucker, B.; Lydon, N. B. *J. Pharmacor. Exp. Ther.* **2000**, *295*, 139.
6. (a) Maquoi, E.; Sounni, N. E.; Devy, L.; Olivier, F.; Frankenne, F.; Krell, H.-W.; Grams, F.; Foidart, J.-M.; Noel, A. *Clin. Cancer Res.* **2004**, *10*, 4038; (b) Huang, M.; Wang, Y.; Collins, M.; Mitchell, B. S.; Graves, L. M. *Mol. Pharmacol.* **2002**, *62*, 463; (c) Von Bubnoff, N.; Veach, D. R.; Miller, W. T.; Li, W.; Sanger, J.; Peschel, C.; Bornmann, W. G.; Clarkson, B.; Duyster, J. *Cancer Res.* **2003**, *63*, 6395.
7. Alpha, B.; Lehn, J. M.; Perathoner, S.; Sabbatini, N. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1266.
8. (a) Beler, P.; De Cola, L.; Von Zelewsky, A. *J. Chem. Soc., Chem. Commun.* **1988**, 1057; (b) Ziessel, R.; Lehn, J. M. *Helv. Chim. Acta* **1990**, *73*, 1149; (c) Balzani, V.; Bargmans, E.; Lehn, J. M.; Sabbatini, N.; Tetrode, R.; Zeissel, R. *Helv. Chim. Acta* **1990**, *73*, 2083.
9. (a) Brown, D. J. *The Pyrimidines*; Wiley Interscience: New York, NY, 1984; (b) Brown, D. J. *The Pyrimidines, Supplement II*; Wiley Interscience: New York, NY, 1985.
10. Kiselyov, A. S. *Tetrahedron Lett.* **1995**, *36*, 9297.
11. (a) Shin, W. S. S.; Lee, K.; Oh, D. Y. *Tetrahedron Lett.* **1995**, *36*, 281; (b) Palacios, F.; Garcia, J.; Ochoa de Retana, A. M.; Oyarzabal, J. *Heterocycles* **1995**, *41*, 1915, and references cited therein.
12. Lee, K.; Oh, D. Y. *Synthesis* **1991**, 213.
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 diethyl alkylphosphonate (1 mM) in dry THF for methyl phosphonate or dioxane (15 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 to pale-yellow 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). A mixture of amidine or guanidine (1 mM) and Hunig's base (1 mM) in dry solvent (5 mL) was introduced to the reaction vessel and the resulting heterogeneous solution was slowly brought to reflux (30 min). After this, the reaction mixture was refluxed for an additional 100–120 min until TLC (hexanes/ether, 1:1) and GC MS analyses indicated absence of starting materials (nitrile and aldehyde). The reaction mixture was then concentrated to 20 mL on rotavap, diluted with EtOAc (50 mL), 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 and recrystallized from EtOH and dried in vacuo to yield analytically pure pyrimidines.
14. Representative examples: **4b**: 71% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98 (s, 3H, Me), 6.92 (m, 3H), 7.23 (m, 2H), 7.30 (d, 2H, J = 8.0 Hz), 7.68 (d, 2H, J = 8.0 Hz), 7.98 (s, 1H). ESI MS: (M+1) 265, (M−1) 263; HR ESI MS: Exact mass calcd for $C_{17}H_{13}FN_3$ 264.1063, found: 264.1086. Elemental analysis, calcd for $C_{17}H_{13}FN_3$: C, 77.25; H, 4.96; N, 10.60. Found: C, 77.11; H, 5.11; N, 10.38; **4d**: 64% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.98 (s, 3H, Me), 3.68 (s, 2H, CH_2), 7.11 (m, 2H), 7.35 (m, 1H), 7.68 (d, 2H, J = 7.6 Hz, Py), 8.12 (s, 1H), 8.22 (d, 2H, J = 7.6 Hz, Py); ESI MS: (M+1) 342, (M−1) 340; HR ESI MS: Exact mass calcd for $C_{18}H_{13}F_2N_3O_2$: 341.0976, found: 341.0884. Elemental analysis, calcd for: $C_{18}H_{13}F_2N_3O_2$: C, 63.34; H, 3.84; N, 12.31. Found: C, 63.14; H, 3.96; N, 12.12; **5b**: 57% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95 (s, 3H, Me), 2.03 (s, 3H, Me), 2.95 (s, 2H, CH_2), 6.88 (m, 2H), 7.05 (s, 1H), 7.28 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.0 Hz); ESI MS: (M+1) 323, (M−1) 321; HR ESI MS: Exact mass calcd for $C_{19}H_{15}FN_2O_2$: 322.1118, found: 322.1128. Elemental analysis, calcd for: $C_{19}H_{15}FN_2O_2$: C, 70.80; H, 4.69; N, 8.69. Found: C, 70.62; H, 4.82; N, 6.47.