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Mendeleev Commun., 2017, **27**, 283–284

Mendeleev Communications

2-Aminopyrimidines in just two steps from ketones, acetylenes and guanidine *via* β,γ-enones

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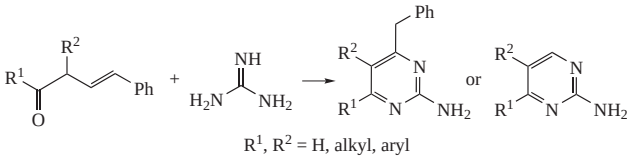
DOI: 10.1016/j.mencom.2017.05.022

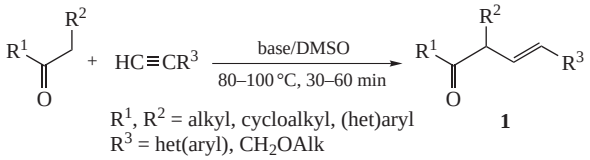
Available β,γ-enones, the products of nucleophilic addition of ketones to phenylacetylene, react with guanidine in the KOH/DMSO system at 70 °C to give 2-aminopyrimidines in up to 72% yield.



The aminopyrimidine scaffold is frequently met in pharmaceuticals including anti-atherosclerotic Aronixil®, anti-histaminic Thonzylamine®, anti-psoriatic Enazadrem®, antianxielytic Buspirone®, and many others.[1] The aminopyrimidine derivatives inhibit protein kinases and are one of the most important discoveries in aminopyrimidine chemistry.[2] Therefore, the search for a new facile and more direct access to substituted aminopyrimidines that would allow one to extend their structural diversity and hence the potential of their application, is an important challenge of modern organic synthesis.

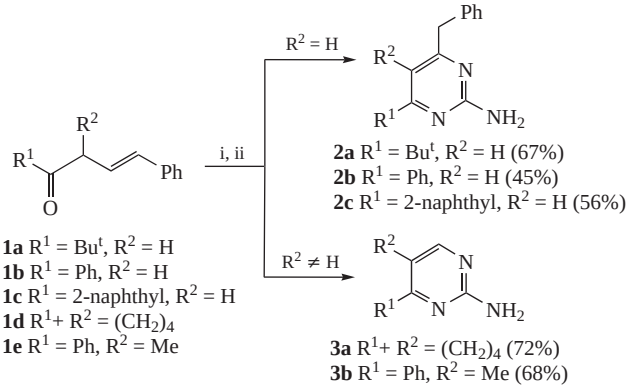
Readily accessible (*via* nucleophilic addition of ketones to acetylenes, Scheme 1)[3] diverse β,γ-enones are flexible synthons for the construction of valuable carbo- and heterocyclic compounds.[4]

Here, a one-pot synthesis of 2-aminopyrimidines **2a**–**c** and **3a**,**b** from ketones **1** and guanidinium nitrate is described (Scheme 2).† Two series of aminopyrimidines can be obtained, namely 4-benzyl substituted **2a**–**c** and unsubstituted at the 4-position **3a**,**b** that result from elimination of toluene. Products of type **3** are formed when $R^2 \neq H$ in starting ketones **1**.



Scheme 1

Obviously, the assembly of 2-aminopyrimidines **2** and **3** involves the following key transformations (Scheme 3). Ketones **1** react with guanidine in DMSO giving adducts **A**, which undergo ring



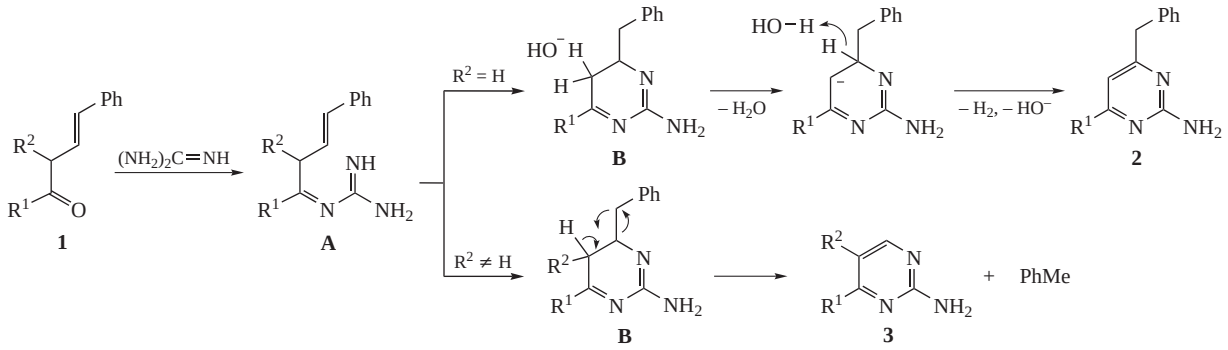
Scheme 2 *Reagents and conditions*: i, $(H_2N)_2C{=}NH{\cdot}HNO_3$, KOH/DMSO; ii, KOH, 70 °C.

† The IR spectra were recorded on a Bruker IFS25 spectrophotometer. The NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C and 40.5 MHz for ^{15}N) in $CDCl_3$. The assignment of signals was made using COSY, NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and 2D ^{1}H-^{15}N HMBC experiments. The formation of toluene was detected by GC analysis of reaction mixture using the standards [Agilent 6890N, HP-5MS column (0.25 mm × 30 m × × 0.25 μm), carrier gas – helium, constant flow].

Aminopyrimidines **2**, **3** *(typical procedure)*. A mixture of ketone **1** (5 mmol), $KOH \cdot 0.5H_2O$ (6 mmol, 390 mg) and guanidinium nitrate (6.0 mmol, 733 mg) in DMSO (10 ml) was stirred at 70 °C for 0.5 h (for **1b**,**c**), 3.0 h (for **1a**,**d**) and 4.0 h (for **1e**). Then more $KOH \cdot 0.5H_2O$ (5 mmol, 325 mg) was added and the mixture was stirred at 70 °C for 30 min. After cooling to room temperature, the mixture was diluted with H_2O (15 ml), neutralized with NH_4Cl and extracted with $CHCl_3$ (4×10 ml). The organic extract was washed with H_2O (3×5 ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (Al_2O_3, eluent C_6H_6–Et_2O, 1 : 0 → 10 : 1).

*4-Benzyl-6-(*tert*-butyl)pyrimidin-2-amine* **2a**: yield 808 mg (67%); cream oil. ^{1}H NMR, δ: 1.20 (s, 9H, 3Me), 3.87 (s, 2H, CH_2Ph), 5.02 (br. s, 2H, NH_2), 6.44 (s, 1H, H^5), 7.20–7.22 (m, 3H, *o*,*p*-H), 7.27–7.30 (m, 2H, *m*-H). ^{13}C NMR, δ: 29.5 (Me), 37.3 (*C*Me$_3$), 44.4 (*C*H$_2$Ph), 106.4 (C^5), 126.7 (*p*-C), 128.7 (2*m*-C), 129.3 (2*o*-C), 138.5 (*i*-C), 163.0 (C^4), 170.1 (C^2), 179.6 (C^6). ^{15}N NMR, δ: –138.8 (N^3), –143.0 (N^4), –306.3 (NH_2). IR (film, ν/cm^{-1}): 3487, 3398, 3325, 3317, 3062, 3028, 2962, 2928, 2870, 1953, 1885, 1811, 1613, 1577, 1552, 1487, 1448, 1396, 1359, 1237, 1201, 1174, 1155, 1076, 1029, 965, 926, 853, 804, 758, 703, 574, 552, 524. Found (%): C, 74.60; H, 7.98; N, 17.36. Calc. for $C_{15}H_{19}N_3$ (%): C, 74.65; H, 7.94; N, 17.41.

4-Benzyl-6-phenylpyrimidin-2-amine **2b**: yield 588 mg (45%); cream solid; mp 90–94 °C. ^{1}H NMR, δ: 3.90 (s, 2H, CH_2Ph), 5.41 (br. s, 2H, NH_2), 6.75 (s, 1H, H^5), 7.17–7.27 (m, 5H, Ph), 7.28–7.35 (m, 3H, Ph), 7.78–7.88 (m, 2H, Ph). ^{13}C NMR, δ: 44.3 (*C*H$_2$Ph), 107.1 (C^5), 126.8 (=CH), 127.1 (=CH), 128.7 (=CH), 129.3 (=CH), 130.4 (=CH), 137.6 (=C), 138.0 (=C), 163.4 (C^4), 165.8 (C^6), 170.9 (C^2). ^{15}N NMR, δ: –136.8 (N^3), –145.2 (N^1), –304.2 (NH_2). IR (film, ν/cm^{-1}): 3477, 3317, 3183, 3085, 3062, 3029, 2924, 2852, 1954, 1891, 1811, 1626, 1600, 1573, 1548, 1495, 1454, 1359, 1238, 1181, 1073, 1030, 1002, 909, 872, 844, 769, 733, 699, 655, 605, 532. Found (%): C, 78.31; H, 5.65; N, 15.95. Calc. for $C_{17}H_{15}N_3$ (%): C, 78.13; H, 5.79; N, 16.08.



Scheme 3

closure to dihydropyrimidines **B**. The latter further aromatize *via* the two different routes. When R^2 = H, intermediates **B** expectedly (due to tendency of dihydroheterocyclic systems to aromatization, sometimes spontaneous) lose hydride anion to afford aminopyrimidines **2** along with dihydrogen and hydroxide anion. When $R^2 \neq H$, the elimination of toluene (detected by GC) from the dihydropyrimidine ring takes place to deliver benzyl-free aminopyrimidines **3** (see Scheme 3).

Control experiment in argon atmosphere showed that air oxygen was not the reason for aromatization of dihydropyrimidine intermediates **B**. Also, DMSO (*cf*. ref. 5) and nitrate ion were not the oxidants inasmuch as Me_2S was not detected (GC-MS) and replacement of guanidinium nitrate for its chloride brought about the same results. Most probably, one should take into consideration the dehydrogenation with the hydride ion transfer commonly occurring in strongly basic media (*cf*. ref. 6).

The common aromatization (dehydrogenation) is probably initiated by the abstraction of a proton from the 5-position that is accompanied by hydride-ion loss from the 4-position, facilitated by electrophilic assistance by the proton of water (see Scheme 3). The unusual aromatization (with elimination of toluene) is likely to result from the steric hindrance at the 5-position by substituent R^2 (which prevents the hydroxide ion attack) and from a lower acidity of the C(5)–H bond due to the donor effect of this alkyl (alkylene) moiety. This promotes elimination of the benzyl substituent as a stabilized carbanionic species with simultaneous proton transfer from the 4-position.

In conclusion, a straightforward synthesis of 2-aminopyrimidines, pharmaceutically appealing precursors, has been developed *via* reaction between β,γ-enones (readily available from the base-catalyzed addition of ketones to acetylenes) and guanidine. This approach features the following synthetic advantages: inexpensive transition metal-free catalyst (KOH), environmentally benign, nontoxic solvent (DMSO), diverse structural variation in the products and operationally simple protocol.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.05.022.

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Received: 5th October 2016; Com. 16/5065

4-Benzyl-6-(2-naphthyl)pyrimidin-2-amine **2c**: yield 871 mg (56%); white solid; mp 163–168 °C. ^{1}H NMR, δ: 4.00 (s, 2H, CH_2Ph), 5.12 (br.s, 2H, NH_2), 6.98 (s, 1H, H^5), 7.20–7.38 (m, 5H, Ph), 7.47–7.52 (m, 2H, naphthyl), 7.82–7.92 (m, 3H, naphthyl), 7.98–8.01 (m, 1H, naphthyl), 8.43 (s, 1H, naphthyl). ^{13}C NMR, δ: 44.4 (*C*H_2Ph), 107.3 (C^5), 124.2 (=CH), 126.5 (*p*-C), 126.8 (=CH), 127.0 (=CH), 127.1 (=CH), 127.7 (=CH), 128.5 (=CH), 128.8 (*m*-C), 129.0 (=CH), 129.3 (*o*-C), 133.3 (=C), 134.5 (=C), 134.8 (C^7), 138.1 (*i*-C), 163.5 (C^4), 165.7 (C^6), 171.0 (C^2). ^{15}N NMR, δ: –136.6 (N^3), –144.7 (N^1), –304.9 (NH_2). IR (film, ν/cm^{-1}): 3476, 3313, 3184, 3061, 3027, 2923, 2860, 1918, 1629, 1568, 1551, 1503, 1454, 1366, 1233, 1178, 1144, 1076, 1027, 904, 852, 808, 752, 704, 568, 471. Found (%): C, 80.81; H, 5.55; N, 13.58. Calc. for $C_{21}H_{17}N_3$ (%): C, 81.00; H, 5.50; N, 13.49.

5,6,7,8-Tetrahydroquinazolin-2-amine **3a**: yield 537 mg (72%); white solid; mp 182–187 °C. ^{1}H NMR, δ: 1.75–1.77 (m, 2H, 6-CH_2), 1.81–1.83 (m, 2H, 7-CH_2), 2.55–2.58 (m, 2H, 5-CH_2), 2.64–2.67 (m, 2H, 8-CH_2), 4.94 (br.s, 2H, NH_2), 7.95 (s, 1H, H^4). ^{13}C NMR, δ: 21.9 (C^7), 22.1 (C^6), 24.4 (C^5), 31.3 (C^8), 119.4 (C^{10}), 157.7 (C^4), 160.8 (C^2), 166.3 (C^9). IR (film, ν/cm^{-1}): 3299, 3157, 2991, 2927, 2849, 2838, 2762, 1656, 1650, 1632, 1595, 1572, 1557, 1536, 1510, 1503, 1478, 1454, 1441, 1422, 1416, 1346, 1335, 1314, 1276, 1244, 1213, 1180, 1154, 1143, 1107, 1097, 1077, 1065, 959, 944, 937, 858, 822, 788, 772, 762, 749, 727, 670, 665, 637, 593, 558, 505. Found (%): C, 64.32; H, 7.49; N, 28.10. Calc. for $C_8H_{11}N_3$ (%): C, 64.40; H, 7.43; N, 28.16.

5-Methyl-6-phenylpyrimidin-2-amine **3b**: yield 629 mg (68%); cream solid; mp 122–128 °C. ^{1}H NMR, δ: 2.16 (s, 3H, Me), 5.16 (br.s, 2H, NH_2), 7.35–7.47 (m, 3H, *m*,*p*-H), 7.49–7.55 (m, 2H, *o*-H), 8.17 (s, 1H, H^4). ^{13}C NMR, δ: 15.9 (Me), 117.4 (C^5), 128.3 (*m*-C), 128.4 (*o*-C), 128.9 (*p*-C), 138.6 (*i*-C), 159.9 (C^4), 161.7 (C^2), 166.2 (C^6). ^{15}N NMR, δ: –133.8 (N^1), –135.9 (N^3), –307.1 (NH_2). IR (film, ν/cm^{-1}): 3344, 3295, 3163, 2936, 1633, 1593, 1573, 1543, 1477, 1441, 1409, 1385, 1289, 1202, 1180, 1143, 1078, 989, 913, 806, 777, 745, 710, 639, 595, 563. Found (%): C, 71.41; H, 5.93; N, 22.61. Calc. for $C_{11}H_{11}N_3$ (%): C, 71.33; H, 5.99; N, 22.69.