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ONE-STEP SYNTHESIS OF 4,5-DISUBSTITUTED PYRIMIDINES USING COMMERCIALLY AVAILABLE AND INEXPENSIVE REAGENTS

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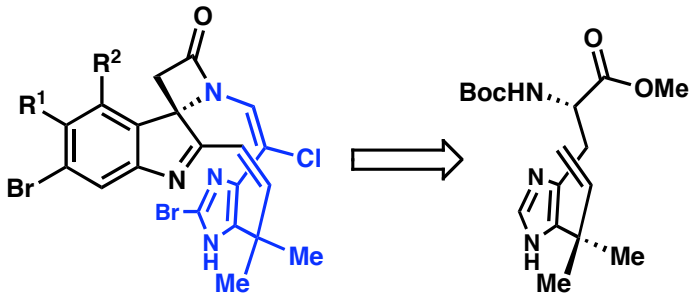
Abstract – 4,5-Disubstituted pyrimidines are synthesized from the corresponding ketone in one-step using inexpensive reagents (formamidine acetate, *n*-propanol, heat). Contrasted to other methods, this process appears quite amenable to large-scale use in industrial settings.

During the course of a program in this laboratory directed towards the total synthesis[1] of the chartelline alkaloids (**1**–**3**),[2] it was of interest to prepare the suitably protected *tert*-prenyl histidine (**4**), which was tentatively proposed as a biosynthetic precursor to these natural products.[3]

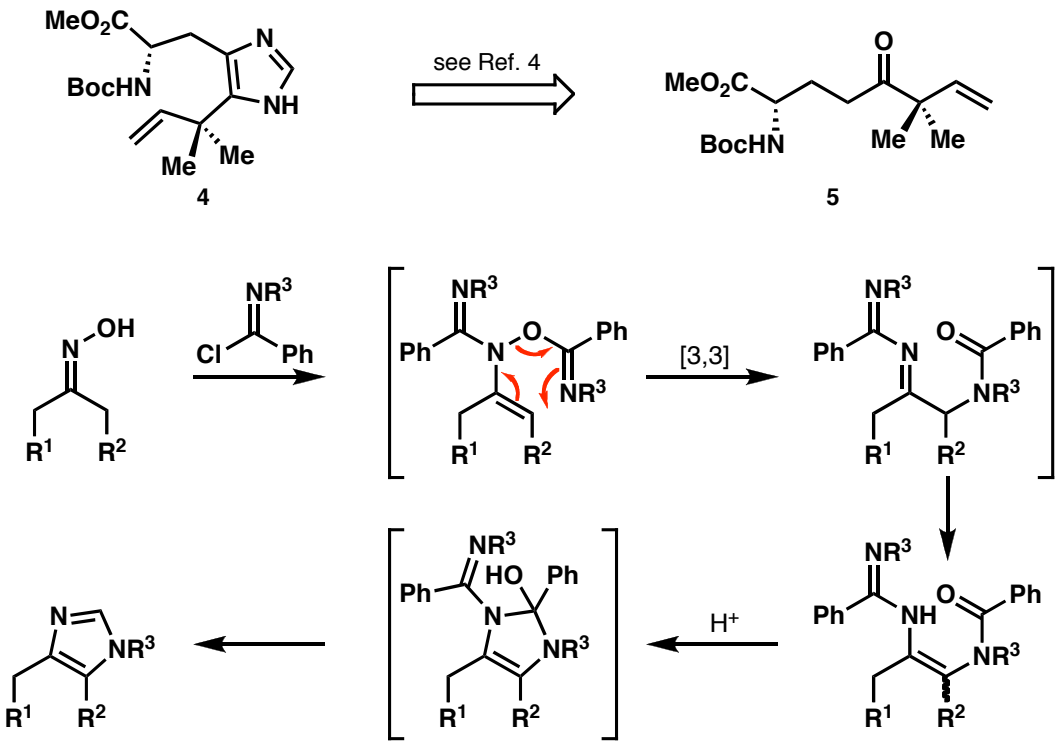


chartelline A (**1**): R^1, R^2 = Br
chartelline B (**2**): R^1 = H, R^2 = Br
chartelline C (**3**): R^1, R^2 = H

tert-prenyl histidine **4**

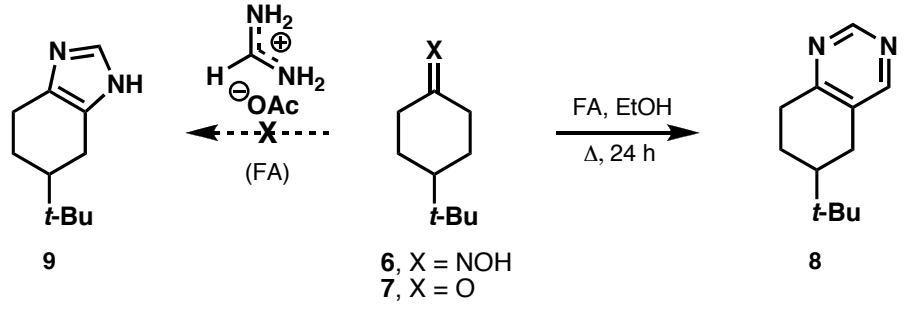
To that end, *tert*-prenyl ketone (**5**) (Scheme 1) was targeted as a reasonable synthon since numerous methods exist for the conversion of ketones (or α-functionalized ketones) to imidazoles.[4] One mode of transformation was published by Lantos and Eggleston, who demonstrated the two-step conversion of oximes to imidazoles *via* the intriguing hetero-Cope rearrangement[5] (Scheme 1).

This Note is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday and in recognition of his manifold contributions to education, organic chemistry and natural products synthesis.



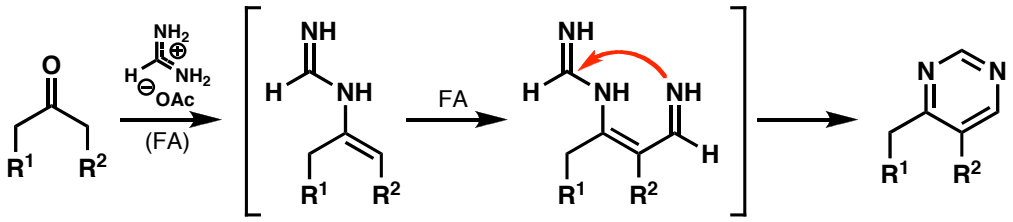
Scheme 1 Ketone synthon and the Lantos-Eggleston hetero-Cope synthesis of imidazoles

While attempting to mitigate their relatively harsh conditions for imidazole ring closure (2.5 equiv. TsOH, $PhCH_3$, Δ) and adapt the reaction to acid-labile ketone (**5**), the observation was made that model compound 4-*tert*-butylcyclohexanone oxime (**6**) (Scheme 2) very cleanly produced pyrimidine (**8**) (and no imidazole (**9**)) when refluxed in ethanol with excess formamidine acetate (FA). When investigated further, this reaction was demonstrated to be viable with the parent ketone (**7** as well, a particularly unusual finding in light of the numerous tactics for pyrimidine synthesis that already involve amidines, but transform *prefunctionalized* (α,β-unsaturated or β-carbonyl) ketones. In fact there are only two reported examples of direct ketone→pyrimidine conversion, the first of which often requires excessive temperatures (150—160 °C) and strong Lewis or Brønsted acids (*p*-TsOH, MsOH)[6]; the second utilizes a heterocyclic reagent whose multi-step synthesis renders it somewhat inaccessible and expensive.[7]



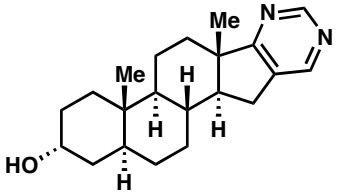
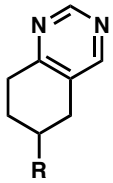
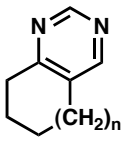
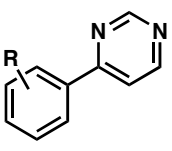
Scheme 2 Accidental discovery of a one-step pyrimidine synthesis

Formamidine acetate likely serves as both the source of the pyrimidine-amidine nitrogens *and* as the sufficiently oxidized β-methylene source (Scheme 3); these two components comprise two different reagents in most two-step pyrimidine syntheses. The FA conditions have been proven general[9] (Table 1) and particularly useful for alicyclic ketones, benzylic ketones and even the hindered androsterone (Entry 1). This reaction also proves helpful when alternative strategies fail to deliver sufficient product (Entries 2–73% and 10–70%, compare yields of 63% (two steps)[8] and 28% (two steps),[8] respectively).



Scheme 3 A possible mechanism, among many, for pyrimidine synthesis

Table 1 Application of the pyrimidine synthesis to a variety of ketones

Entry	**Product**	**Time** (h)	**Yield (%)**
1	 (**10**)	46	59
2	 R = *t*-Bu (**8**)	22	73
3	R = Ph (**11**)	47	60
4	 n = 0 (**12**)	19	42[a]
5	n = 1 (**13**)	19	35[a]
6	n = 2 (**14**)	24	72
7	n = 3 (**15**)	23	74
8	n = 5 (**16**)	20	77
9	n = 6 (**17**)	21	65
10	n = 7 (**18**)	20	70
11	n = 10 (**19**)	68	67
12	 R = H (**20**)	50	82
13	R = *o*-NO_2 (**21**)	50	28
14	R = *p*-NO_2 (**22**)	50	85

[a] Substrate volatility may have contributed to a lower yield.

In contrast to existing methods for ketone→pyrimidine conversion,[6–8] these conditions are notably 1. mild (FA is a very weak acid, pKa ~ 13[acetamidinium]), 2. inexpensive (FA = $0.23/ gram [VWR]; *n*-PrOH = $5.4/ liter [VWR]), 3. often quite efficient (Entries 2, 6, 7, 8, 10, 12, and 14), 4. operationally simple (mix substrate and reagents, stir with heating under ambient atmosphere), 5. heterogeneous at reaction temperatures, and 6. free of any prefunctionalization of the substrate ketone.

Formamidine acetate has been disclosed as a useful reagent for the one-step synthesis of pyrimidines from ketones. This reagent benefits from numerous advantages over current methods and as a consequence may see extensive use in the industrial setting.

EXPERIMENTAL

General Procedure: Formamidine acetate (20 equiv.) is added to a solution of ketone (1 equiv.) in *n*-propanol (0.01 M) at ambient temperature. The suspension is stirred in a 100°C bath until starting material is consumed. After cooling, the reaction mixture is concentrated *in vacuo* to remove the *n*-propanol. The residue is then resuspended in EtOAc (10mL), and neutralized by stirring with Et_3N (60 equiv.). The suspension is vacuum filtered over silica to remove solid impurities, and the filtrate is concentrated *in vacuo*. Flash column chromatography can be used to purify the resulting residue to provide pyrimidines (**8** and **10** – **22**).

Steroidal pyrimidine (**10**): yellow solid; R_f = 0.08 (1:1 EtOAc:hexanes); IR (neat) ν_{max} 3368, 2925, 2854, 2359, 2340, 1668, 1586, 1556, 1450, 1394, 1371, 1281, 1130, 1076, 1040, 904, 849, 795, 734, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1 H), 8.45 (s, 1 H), 3.6 – 3.4 (m, 1 H), 2.8 – 2.7 (m, 1 H), 2.5 – 2.4 (m, 1 H), 2.2 – 2.0 (m, 1 H), 1.8 – 0.9 (m, 17 H) 0.93 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ181.5, 156.7, 151.8, 134.3, 55.5, 54.8, 50.5, 46.1 44.9, 38.0, 36.8, 35.7, 34.3, 32.7, 31.6, 31.4, 28.4, 28.2, 20.7, 17.1, 12.3 ; LRMS (ESI) calcd for $C_{21}H_{30}N_2O$ $[M+H]^+$: 327.2; found: 327.2.

6-Phenyl-5,6,7,8-tetrahydroquinazoline (**11**): orange solid; R_f = 0.23 (1:1 EtOAc:hexanes); IR (neat) ν_{max} 3081, 3025, 2949, 2915, 1971, 1952, 1878, 1810, 1578, 1550, 1491, 1459, 1401, 1348, 1247, 1076, 946, 854, 802, 762, 725, 701, 604, 532 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 8.40 (s, 1 H), 7.35 – 7.31 (m, 2 H), 7.24 – 7.22 (m, 3 H), 3.05-2.97 (bm, 4 H), 2.95 – 2.84 (m, 1 H), 2.26-2.19 (bm, 1 H) 2.07 – 1.97 (bm, 2 H), 1.39 – 1.29 (bm, 4 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 156.7, 156.3, 144.7, 129.8, 128.6, 126.6, 39.5, 33.5, 32.0, 29.3; LRMS (ESI) calcd for $C_{14}H_{14}N_2$ $[M+H]^+$: 211.1; found: 211.1.

5,6,7,8,9,10-Hexahydrocycloocta[*d*]pyrimidine (**15**): yellow oil; R_f = 0.34 (1:2 EtOAc:hexanes); IR (neat) ν_{max} 3422, 2924, 2853, 1738, 1575, 1551, 1461, 1397, 1361, 1296, 1215, 1167, 1150, 1084, 927, 895, 880, 850, 833, 797, 761, 745, 720, 622, 604, 521 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 8.35 (s, 1 H), 2.87 – 2.84 (m, 2 H), 2.71 – 2.69 (m, 2 H), 1.79 – 1.74 (bm, 2 H), 1.69 – 1.64 (bm, 2 H),

1.39 – 1.29 (bm, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 156.7, 156.0, 133.8, 33.8, 31.7, 29.8, 25.6, 25.4; LRMS (ESI) calcd for $C_{10}H_{14}N_2$ $[M+H]^+$: 163.0; found: 163.0

5,6,7,8,9,10,11,12-Octahydrocyclodeca[*d*]pyrimidine (**16**): yellow oil; R_f = 0.50 (2:1 EtOAc:hexanes); IR (neat) ν_{max} 3431, 2923, 2854, 2348, 1573, 1545, 1475, 1445, 1398, 1353, 1297, 1281,1201, 173, 1157, 922, 873, 824, 789,768, 745, 727, 701, 624, 606, 504 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1 H), 8.40 (s, 1 H), 2.92 – 2.89 (m, 2 H), 2.81 – 2.79 (m, 2 H), 1.99 – 1.93 (m, 2 H), 1.79 – 1.74 (m, 2 H), 1.46 – 1.43 (bm, 4 H), 1.10 – 1.00 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 157.5, 156.1, 133.4, 31.3, 28.7, 27.6, 26.6, 26.1, 25.5, 20.9, 20.3; LRMS (ESI) calcd for $C_{12}H_{18}N_2$ $[M+H]^+$: 191.0; found: 191.0

6,7,8,9,10,11,12,13-Octahydro-5*H*-cycloundeca[*d*]pyrimidine (**17**): yellow oil; R_f = 0.45 (1:1 EtOAc:hexanes); IR (neat) ν_{max} 3434, 2925, 2862, 2349, 1573, 1542, 1467, 1444, 1398, 1345, 1293, 1165, 1147, 929, 884,852, 808, 781, 751, 727,704, 612, 592 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 8.43 (s, 1 H), 2.86 – 2.83 (m, 2 H), 2.76 – 2.73 (m, 2 H), 1.96 – 1.91 (bm, 2 H), 1.79 – 1.74 (bm, 2 H), 1.36-1.29 (bm, 4 H), 1.19 – 1.11 (bm, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 157.0, 155.9, 134.2, 31.8, 28.3, 27.3, 26.8, 26.2, 25.8, 25.6, 23.8, 23.5; LRMS (ESI) calcd for $C_{13}H_{20}N_2$ $[M+H]^+$: 205; found: 205.

6,7,8,9,10,11,12,13,14,15,16,17-Dodecahydro-5*H*-cyclopentadeca[*d*]pyrimidine (**19**): yellow oil; R_f = 0.28 (1:4 EtOAc:hexanes); IR (neat) ν_{max} 3416, 2926, 2856, 2359, 1574, 1547, 1448, 1397, 1350, 1150, 925, 754, 733, 665, 644, 613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 8.39 (s, 1 H), 2.74 – 2.71 (m, 2 H), 2.60 – 2.56 (m, 2 H), 1.76 – 1.70 (bm, 2 H), 1.63 – 1.57 (bm, 2 H), 1.55 – 1.46 (bm, 4 H), 1.42 – 1.32 (bm, 6H), 1.30 – 1.28 (bm, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 157.1, 156.3, 133.3, 34.2, 29.6, 29.1, 27.4, 27.2, 27.1, 26.8, 26.7, 26.6, 25.9, 25.8, 25.4, 25.3; LRMS (ESI) calcd for $C_{17}H_{28}N_2$ $[M+H]^+$: 261.0; found: 261.0

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