Synthesis of chiral fused pyrimidines from (+)-3-carene- and limonene-derived isomeric β-enaminones

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10.1070/MC2000v010n03ABEH001199

New heterocyclic compounds, pyrimidines annelated with modified terpenic frames, were synthesised from positional isomers of β-enaminones derived from limonene and (+)-3-carene.

Chiral fused heterocycles (mainly pyrazoles and pyridines) were reported to be useful for the preparation of optically active complexes, chiral auxiliaries[1,2] or resolving agents.[3] Chiral heterocycles containing pyrimidine moiety are less studied although fused pyrimidines are promising chiral auxiliaries and biologically active compounds.[4] We report the preparation of new chiral fused pyrimidines with terpene-based carbon frames from readily accessible enaminones **1** and **2**[5] and new enaminones **9** and **10** prepared from diketones **4** and **7**.[3,6]

Cyclic β-hydroxymethylene ketones, including camphor derivatives, can be used in reactions with guanidine affording fused 2-aminopyrimidine derivatives.[7]

We failed to apply this method to the synthesis of pyrimidines from acetylcyclopentanone analogues **4** and **7**. The refluxing of a mixture of diketones **4** or **7** and guanidine or amidines (benzamidine, acetamidine) as free bases or as their carbonates in methanol or *n*-butanol gave only traces of pyrimidine-type compounds. Treatment of acyclic β-enaminones with cyanamide in aqueous solutions on heating was reported to be a facile method for preparation of 2-aminopyrimidines.[8] Enaminone **1**, derived from (+)-3-carene, is inert towards cyanamide under the conditions specified.[8] The inertness of compound **1** is stipulated by hindrance of an enamine fragment with one of the methyls of the cyclopropane moiety.[3] On the other hand, we found that compound **1** can be transformed into 2-aminopyrimidine **5** under more severe conditions. For example, the reaction of compound **1** with cyanamide in benzene in the presence of an equimolar amount of *p*-toluensulfonic acid under the distillation of water afforded 2-aminopyrimidine **5** in a good yield (82%)† (Scheme 1).

Analogous limonene-derived enaminone **2**, which is more reactive than compound **1**, reacted with cyanamide in hot aqueous solutions (the procedure was analogous to that described in ref. 8) for 5–6 h to give corresponding 2-aminopyrimidine derivative **8** in good yield (85%).‡

Table 1 Preparation of aminopyrimidines **5** and **8** by treatment of enaminones with cyanamide in aqueous solutions.

β-Enaminone	Reaction time/h	Final product	Yield (%)
1	12	**5**	traces
2	6	**8**	85
9	1	**5**	90
10	1	**8**	95

The synthesis of 2-(1-aminoethylidene)cyclopentanone-type enaminoketones is well documented: reaction of 2-acetylcyclopentanone with NH_3 in EtOH is known to proceed regioselectively to give 2-(1-aminoethylidene)cyclopentanone in a very good yield.[9] Our effort to apply this method to diketones **4** and **7** was unsuccessful. Under the recommended conditions, the formation of stable ammonium salts of the enols of diketones was initially observed. The prolonged treatment of the diketones with NH_3 in EtOH resulted in poor yields of the enaminones. ω-Ketoesters, products of retro-condensation of β-diketones, were the main reaction products (20–35%) accompanied by a number of unidentified by-products.

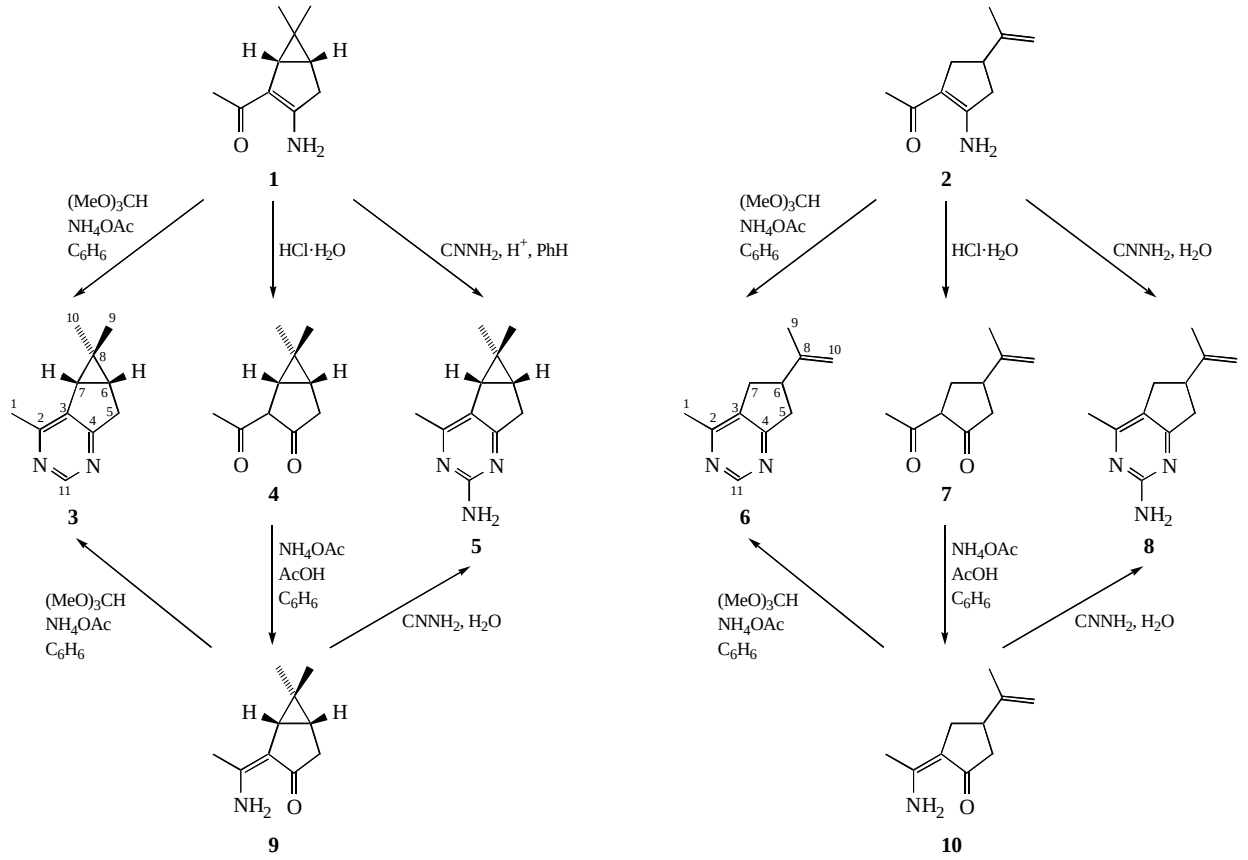
When diketones **4** and **7** were treated with a 1- to 4-molar excess of NH_4OAc in C_6H_6 under reflux (as described in ref. 10) aminoethylidene derivatives **9**§ and **10**¶ were obtained in very good yields. We found that compounds **9** and **10** are much more reactive than enaminones **1** and **2** (Table 1). Thus, the treatment of enaminones **9** and **10** with aqueous $CNNH_2$ on heating for 1 h (according to ref. 8) resulted in aminopyrimidines **5** and **8** in

† *The procedure.* A mixture of $CNNH_2$ (40.0 mmol, 1.68 g) and enaminone **1** (20.0 mmol, 3.30 g) was added in one portion to a hot solution of anhydrous *p*-TsOH (20 mmol) in dry C_6H_6 (80 ml) with stirring. The reaction mixture was vigorously stirred under azeotropic distillation of water for 20–30 min and then cooled to room temperature. The resulting solution was washed with 1 M aq. H_2SO_4 (2×20 ml), and the aqueous phase was neutralised with aq. NH_3 (30 ml) and extracted with $CHCl_3$ (4×25 ml). The organic phase was dried with anhydrous Na_2SO_4, the solvent was distilled off and the residue was chromatographed on a short silica gel column ($CHCl_3$) to give the crude product, which was then crystallised from EtOH–MeCN.

*(1a*R*,6a*R*)-1,1,2-Trimethyl-1,1a,6,6a-tetrahydro-3,5-diazacyclopropa-[a]inden-4-ylamine* **5**. $CNNH_2$ and enaminone **1** in the presence of *p*-TsOH afforded 82% of pyrimidine **5**; reaction of enaminone **9** with aqueous $CNNH_2$ afforded 90% of pyrimidine **5**. Pale yellow crystals, mp 181–183 °C (EtOH–MeCN), $[\alpha]^{20}$ +31 (*c* 1.21, EtOH). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.31 (br. s, 2H, NH_2), 2.92 (dd, 1H, H-5β, *J* 18.7 and 7.4 Hz), 2.54 (ddd, 1H, H-5α, *J* 18.7, 1.4 and 1.0 Hz), 2.21 (s, 3H, H-1), 1.94 (dd, 1H, H-7, *J* 6.9 and 1.4 Hz), 1.37 (ddd, 1H, H-6, *J* 7.4, 6.9 and 1.0 Hz), 1.06 (s, 3H, H-9), 0.56 (s, 3H, H-10). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 176.27 (s, C-4), 162.05 (s, C-2), 161.73 (s, C-3), 123.18 (s, C-11), 33.52 (t, C-5), 31.22 (d, C-7), 26.32 (q, C-9), 25.39 (d, C-6), 21.53 (s, C-8), 21.15 (q, C-1), 13.70 (q, C-10). IR ($CHCl_3$, ν/cm^{-1}): 3530, 3425, 3300, 3180, 1600, 1570, 1475, 1380, 1295, 860, 820. UV [EtOH, λ_{max}/nm (ε)]: 241 (15380), 312 (4590). MS, *m*/*z* (%): 189.1262 (M^+, 43), 174 (100), 147 (7), 146 (9), 133 (41), 118 (8), 106 (6), 91 (13), 77 (6), 65 (5).

‡ *(±)-6-Isopropenyl-4-methyl-6,7-dihydro-5*H*-cyclopentapyrimidin-2-ylamine* **8**. The reaction of enaminone **2** or enaminone **10** afforded 85% or 95% of pyrimidine **8**, respectively. Pale yellow crystals, mp 138–139 °C (MeCN–EtOH). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.51 (br. s, 2H, NH_2), 4.69 (br. s, 1H, H-10), 4.66 (br. s, 1H, H-10), 3.1–2.4 (m, 5H, H-5, H-6 and H-7), 2.14 (s, 3H, H-1), 1.66 (br. s, 3H, H-9). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 173.55 (s, C-4), 162.45 (s, C-11), 161.94 (s, C-2), 146.61 (s, C-8), 121.28 (s, C-3), 109.57 (t, C-10), 43.47 (d, C-6), 38.46 (t, C-5), 32.54 (t, C-7), 21.08 (q, C-1), 20.32 (q, C-10). IR ($CHCl_3$, ν/cm^{-1}): 3540, 3425, 3300, 3175, 1600, 1575, 1440, 1380, 940, 890. UV [EtOH, λ_{max}/nm (ε)]: 231 (5680), 253 (1010), 301 (2115). MS, *m*/*z* (%): 189.1264 (M^+, 100), 188 (93), 174 (63), 160 (8), 148 (23), 147 (24), 133 (29), 120 (5), 119 (6), 106 (16), 91 (13), 80 (7), 79 (9), 77 (10), 65 (9), 53 (12), 43 (11), 42 (9), 41 (8), 39 (12).

§ *(1*R*,5*R*)-2-(1-Aminoethylidene)-6,6-dimethylbicyclo[3.1.0]hexan-3-one* **9**. Yellow crystals, 91% yield, mp 116–118 °C (after vacuum sublimation); $[\alpha]^{19}$ –116 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.6 (br. s, 1H, NH, $W_{1/2}$ 80 Hz), 5.3 (br. s, 1H, NH, $W_{1/2}$ 80 Hz), 2.38 (dd, 1H, H-5β, *J* 19.5 and 7.5 Hz), 1.95 (d, 1H, H-5α, *J* 19.5 Hz), 1.83 (s, 3H, H-1), 1.53 (d, 1H, H-7, *J* 7.5 Hz), ~0.94 (m, 1H, H-6), 0.93 (s, 3H, H-9), 0.67 (s, 3H, H-10). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 203.89 (s, C-4), 155.89 (s, C-2), 104.63 (s, C-3), 37.69 (t, C-5), 30.04 (d, C-7), 26.32 (q, C-9), 21.34 (s, C-8), 20.90 (d, C-6), 20.19 (q, C-1), 14.08 (q, C-10). IR ($CHCl_3$, ν/cm^{-1}): 3500, 3240, 1650, 1600, 1515, 1240, 925, 860. UV [EtOH, λ_{max}/nm (ε)]: 334 (12700). MS, *m*/*z* (%): 165.1155 (M^+, 44), 150 (100), 133 (21), 122 (20), 107(5), 105 (12), 94 (10), 91 (5), 81 (6), 80 (5), 79 (9), 69 (15), 68 (14), 53 (8), 42 (45), 41 (17), 39 (12).



Scheme 1 The numbering of carbons is inconsistent with IUPAC recommendations and is given only for NMR interpretation purposes.

excellent yields (90–95%). The main reason of the greater reactivity of isomeric enaminones **9** and **10** as compared to **1** and **2** seems to be the absence of steric hindrance of the attack of a reagent on the enamine moiety.

The reaction of enaminones with trimethyl orthoformate in the presence of NH_3 was studied in order to prepare 2-unsubstituted pyrimidines. Moderate yields of pyrimidine derivatives **3** and **6** were obtained when enaminones **1**, **2**, **9** or **10** were treated with $(MeO)_3CH$ in MeCN media saturated with NH_3 in a bomb at 120 °C for 10–12 h. The other route to the above products included treatment of enaminones **1**, **2**, **9** or **10** with $(MeO)_3CH$ and NH_4OAc in C_6H_6 under the distillation of water.†† The latter method afforded better yields of pyrimidines **3**‡‡ and **6**.§§

This work was supported by the Russian Foundation for Basic Research (grant nos. 96-03-33222, 96-15-97017 and 98 03-32910), the Competitive Centre on Natural Sciences at the St. Petersburg University (grant no. 95-0-9.4-102) and INTAS (grant no. 97-0217).

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¶ *(±)-2-(1-Aminoethylidene)-4-isopropenylcyclopentanone* **10**. Yellow crystals, 84% yield, mp 68–70 °C (MeCN). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.89 (br. s, 1H, NH, $W_{1/2}$ 60 Hz), 5.75 (br. s, 1H, NH, $W_{1/2}$ 60 Hz), 4.56 (br. s, 2H, H-10), 2.7–2.4 (m, 2H, H-5), 2.3–2.0 (m, 3H, H-6 and H-7), 1.76 (s, 3H, H-1), 1.59 (br. s, 3H, H-9). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 200.88 (s, C-4), 155.75 (s, C-8), 146.92 (s, C-2), 108.96 (t, C-10), 102.22 (s, C-3), 43.12 (t, C-5), 41.05 (d, C-6), 32.19 (t, C-7), 20.29 (q, C-1), 19.78 (q, C-9). IR ($CHCl_3$, ν/cm^{-1}): 3500, 3230, 1640, 1600, 1515, 1230, 915, 870. UV [EtOH, λ_{max}/nm (ε)]: 318 (19650). MS, *m*/*z* (%): 165.1153 (M^+, 75), 150 (12), 137 (13), 123 (34), 122 (29), 108 (15), 69 (100), 68 (13), 54 (9), 43 (11), 42 (27), 41 (14).

†† $(MeO)_3CH$ (5.00 g, 51.5 mmol) and $AcONH_4$ (4.00 g, 51.9 mmol) were added to a solution of enaminone **1**, **2**, **9** or **10** (1.65 g, 10.0 mmol) in C_6H_6 (80 ml) with stirring. The reaction mixture was stirred vigorously under the azeotropic distillation of water for 4 h and then cooled to room temperature. Concentrated aq. NH_3 (10 ml) and water (50 ml) were added, and the mixture was extracted with C_6H_6 (2×20 ml). The organic extract was dried with Na_2SO_4, the solvent was distilled off and the residue was treated with an excess of AcCl (7 mmol) in a mixture of pyridine (7 mmol) and $CHCl_3$ (20 ml). The resulting mixture was stirred for 10 min, washed with water (30 ml) and treated with 1 M aq. H_2SO_4 (2×20 ml). The acidic extract was neutralised with concentrated aq. NH_3 (30 ml) and extracted with $CHCl_3$ (3×25 ml). The combined organic extracts were dried with Na_2SO_4, the solvent was distilled off and the residue was chromatographed on a short silica gel column (C_6H_6) to give crude pyrimidine **3** or **6** as yellow oil. Analytical samples were obtained by vacuum sublimation of the crude products.

‡‡ *(1a*R*,6a*R*)-1,1,2-Trimethyl-1,1a,6,6a-tetrahydro-3,5-diazacyclopropa-[*a*]indene* **3**. The reaction of enaminone **1** with trimethyl orthoformate–ammonium acetate afforded 53% of pyrimidine **3**; the reaction of enaminone **9a** afforded 58% of compound **3**. Yellow oil, $[\alpha]^{20}$ +50.5 (*c* 0.48, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.62 (s, 1H, H-11), 3.05 (dd, 2H, H-5β, *J* 19.0 and 7.4 Hz), 2.72 (ddd, 2H, H-5α, *J* 19.0, 1.6 and 1.3 Hz), 2.38 (s, 3H, H-1), 2.04 (dd, 1H, H-7, *J* 6.7 and 1.6 Hz), 1.50 (ddd, 1H, H-6, *J* 7.4, 6.7 and 1.3 Hz), 1.16 (s, 3H, H-9), 0.59 (s, 3H, H-10). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 174.23 (s, C-4), 161.13 (s, C-2), 156.34 (d, C-11), 133.14 (s, C-3), 34.08 (t, C-5), 32.53 (d, C-7), 27.22 (q, C-9), 26.70 (d, C-6), 22.35 (s, C-8), 21.68 (q, C-1), 14.36 (q, C-10). IR ($CHCl_3$, ν/cm^{-1}): 1630, 1580, 1560, 1450, 1420, 1390, 1360, 1310, 1140, 1040, 840, 820. UV [EtOH, λ_{max}/nm (ε)]: 218 (6150), 276 (3240). MS, *m*/*z* (%): 174.1152 (M^+, 50), 159 (65), 132 (19), 118 (100), 105 (5), 91 (33), 85 (5), 83 (7), 79 (6), 77 (8), 65 (8), 51 (5), 41 (7), 39 (8).

§§ *(±)-6-Isopropenyl-4-methyl-6,7-dihydro-5*H*-cyclopentapyrimidine* **6**. The reaction of enaminone **2** with trimethyl orthoformate–ammonium acetate afforded 56% of compound **6**; the reaction of enaminone **10** afforded 55% of pyrimidine **6**. Yellow crystals, mp 32–33 °C (pentane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.68 (s, 1H, H-11), 4.77 (br. s, 1H, H-10), 4.74 (br. s, 1H, H-10), 3.1–2.6 (m, 5H, H-5, H-6 and H-7), 2.32 (s, 3H, H-1), 1.73 (br. s, 3H, H-9). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.09 (s, C-4), 161.06 (s, C-2), 157.38 (d, C-8), 146.48 (s, C-11), 131.83 (s, C-3), 110.79 (t, C-10), 44.01 (d, C-6), 39.02 (t, C-7), 33.81 (t, C-5), 21.65 (q, C-1), 21.08 (q, C-9). IR ($CHCl_3$, ν/cm^{-1}): 890, 940, 1390, 1440, 1570, 1590, 1650. UV [EtOH, λ_{max}/nm (ε)]: 255 (4570), 333 (shoulder, 220). MS, *m*/*z* (%): 174.1147 (M^+, 75), 173 (100), 159 (52), 158 (5), 145 (11), 132 (25), 118 (31), 104 (12), 91 (44), 79 (9), 77 (11), 65 (10), 53 (9), 52 (9), 51 (9), 39 (13).

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Received: 18th May 1999; Com. 99/1527