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New Scope and Limitations in the Knorr–Paal Synthesis of Pyrroles

Remir G. Kostyanovsky,* Gulnara K. Kadorkina, Anait G. Mkhitaryan, Ivan I. Chervin and Abil E. Aliev

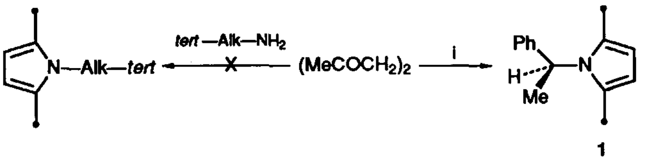
N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 117977 Moscow, Russian Federation.
Fax: + 7 095 938 2156

Newly-found steric limits for the Knorr–Paal reaction in the case of 2-methyl-1,2-propanediamine and acetonylacetone make it possible for the process to occur with only one amino group, giving aminopyrrole **2**, and with aziridines, due to dimerization under the conditions of the reaction, giving 1-(β-aziridinoalkyl)pyrroles **4a,b**.

The Knorr–Paal reaction is a classic synthesis of pyrroles from γ-diketones under the action of NH_3 or primary amines.[1]

We have shown that primary *tert*-alkylamines (*tert*-butylamine) and 1-(2-amino-2-methylpropyl)-3,3-dimethylaziridine[2] are inactive towards acetonylacetone (AA), even after 15 h refluxing of an equimolar mixture, whereas less hindered α-phenylethylamine forms pyrrole **1** under mild conditions (Scheme 1). Thus, steric hindrance is one of the limitations of the Knorr–Paal reaction.

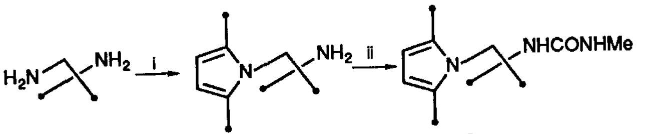
This limitation opens up the possibility of regiospecific reactions. Thus, 2-methyl-1,2-propanediamine, even with excess of AA, gives only aminopyrrole **2**, which contains an amino group susceptible to further conversion (Scheme 2).



1

acetonylacetone, AA

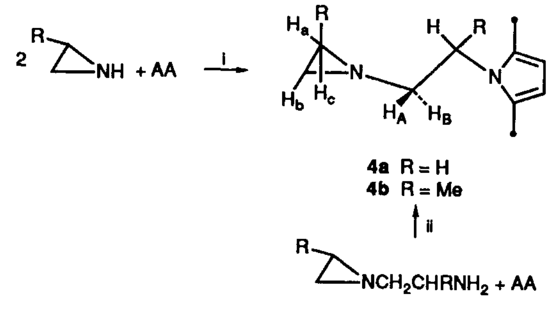
Scheme 1 *Reagents and conditions:* i, (*S*)-(−)-α-phenylethylamine, 20°C, 12 h, yield of **1** 63.4%, b.p. 96–97°C/2 mm Hg $[\alpha]_{578} = -42.35°$ (*c* 1.84, MeOH)



2 3

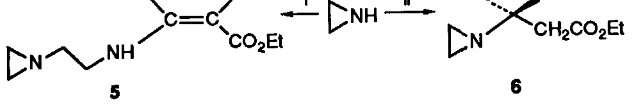
Scheme 2 *Reagents and conditions:* i, twofold excess of AA in benzene, 12 h at 20°C, yield of **2** 36.5% (without optimization), m.p. 67°C after sublimation at 30°C/1 mm Hg; ii, MeNCO in ether, 12 h at 20°C, yield of **3** 90.0%, m.p. 132–134°C (benzene–*n*-hexane, 1:1)

Under normal conditions, AA does not react with secondary amines, *e.g.* an equimolecular mixture of AA and Me_2NH does not change during 2 weeks at 20°C. However, we have found that 1-(β-aziridinoalkyl)-2,5-dimethylpyrroles **4a,b** are formed in moderate yield by heating AA with aziridine in benzene or without solvent (Scheme 3).



Scheme 3 *Reagents and conditions:* i, a mixture of aziridine with AA (ratio *ca.* 2) was heated for 18–20 h at 75–80°C, yield of **4a** 61.0%, b.p. 70°C/2 mmHg, yield of **4b** 48.0%, b.p. 68°C/2.5 mm Hg

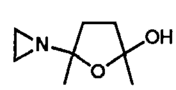
2,2-Dimethylaziridine does not react with AA under similar conditions. The structures of **4a,b** are confirmed by their alternative synthesis from aziridine and 2-methylaziridine dimers (path 2, Scheme 3). The unusual reaction (Scheme 3) may be interpreted only by the initial dimerization of aziridines. Such aziridine dimerization (Scheme 4) is caused (*cf.*[4]) by enolized acetoacetic ester (according to NMR the keto/enol ratio is *ca.* 8 in $CDCl_3$).



5 6

Scheme 4 *Reagents and conditions:* i, 0.5 equivalent of acetoacetic ester (with self-heating up to 50°C), yield of **5** 65.0%, b.p. 118–120°C/8mm Hg; ii, 0.5 equivalent of trifluoroacetoacetic ester in Et_2O, 12 h at 20°C, yield of **6** is 72.0%, b.p. 55°C/8 mm Hg

For the more electrophilic trifluoroacetoacetic ester (according to NMR the keto/enol ratio is *ca.* 6 in $CDCl_3$), in a similar fashion to hexafluoroacetone,[5] rapid aziridine addition occurs leading to stable carbinol **6**, which does not ultimately catalyse the dimerization of the excess aziridine. Aziridinocarbinol-promoted dimerization can also be excluded, since no traces of dimer were found on refluxing aziridine with methyl ethyl ketone. According to the NMR spectra of AA its mono- and di-enolic forms as well as the semiketal of the enol form have not been observed (at the 0.05% level). Hence the dimerization is more likely catalysed by the semiketal form of aziridinocarbinol, SKA (*cf.*[6]). This correlates with the observation that after 50 h refluxing of AA with 2,2-dimethylaziridine neither pyrrole nor dimer are produced; this might be interpreted in terms of the steric hindrance involved in the formation of the corresponding aziridinocarbinol and its semiketal as SKA.



SKA

The structures of all newly-synthesised compounds have been proved by NMR and elemental analysis data.†

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† *Spectroscopic data*: NMR ^1H (400 MHz), ^{13}C (100.61 MHz), δ/ppm, *J*/Hz, standard TMS.

For **1**: ^1H ($CDCl_3$) 1.88 (d, *Me*CH, ^3J 7.5), 2.09 (s, *Me*C=), 5.47 (q, *CH*Me), 5.75 (s, HC=), 7.02, 7.24 and 7.30 (*o*-, *m*-, *p*-Ph).

For **2**: ^1H (CD_3OD) 1.13 (s, Me_2C), 2.21 (s, MeC=), 3.74 (s, CH_2N), 5.72 (s, HC=); ^{13}C (CD_3OD) 14.05 (*Me*C=, ^1J 126.2), 28.57 (Me_2C, ^1J 126.2, ^3J 2.8), 53.72 ($\underline{C}Me_2$), 55.09 ($\underline{C}H_2N$, ^1J 137.3, ^3J 4.2), 107.35 (CH=, ^1J 166.5, ^3J 4.2), 129.51 (=C—N).

For **3**: ^1H ($CDCl_3$) 1.28 (s, Me_2C), 2.22 (s, *Me*C=), 2.67 (d, *Me*NH, ^3J 4.9), 4.05 (s, CH_2N), 4.66 and 4.71 (NH), 5.72 (s, HC=).

For **4a**: ^1H ($CDCl_3$) 0.99 (m) and 1.72 (m, CH_2 of ring), 2.25 (s, Me), 2.41 (t, α-CH_2, ^3J 6.75), 3.97 (t, β-CH_2), 5.78 (s, HC=); ^{13}C ($CDCl_3$) 12.02 (Me, ^1J 126.9), 26.40 (CH_2 of ring, ^1J 164.4 for H at *cis*-position with respect to the nitrogen lone pair and 175.5 for H at the *trans*-position), 42.74 (β-CH_2, ^1J 136.6, ^2J 2.8), 61.08 (α-CH_2, ^1J 135.3, ^2J 4.2), 104.98 (CH=, ^1J 167.2, ^3J 4.2), 126.47 (*C*Me, ^2J 4.2).

For **4b**: a mixture of diastereoisomers, ^1H ($CDCl_3$) 0.97 (d) and 1.18 (d, H_b, $^3J_{bc}$ 6.1), 0.98 (d) and 1.17 (d, Me of aziridine ring, ^3J 5.5), 1.09 (m) and 1.37 (m, H_c, $^3J_{ac}$ 3.7), 1.36 (d) and 1.44 (d, H_a), 1.52 (d) and 1.54 (d, *Me*CH, ^3J 7.3), 2.26 (s) and 2.28 (s, *Me*C=), 2.57 (m, α-CH_2, ABX system, $\Delta\nu_{AB} = 324$ Hz, ^2J −12.2, ^3J 6.7) and 2.56 (m, α-CH_2, ABX system, $\Delta\nu_{AB} = 180$ Hz, ^2J −12.2, ^3J 7.3), 5.73 (s) and 5.74 (s, CH=); ^{13}C ($CDCl_3$) 13.66 (*Me*CH=, ^1J 126.8), 17.41 (Me of aziridine ring, ^1J 125.6), 18.34 (*Me*CH=, ^1J 125.1), 32.91 and 32.92 (CH_2 or aziridine ring, ^1J 163.7 for C-H_b and 167.9 for C-H_a), 33.71 and 33.74 (*C*H_c of *C*Me, ^2J 4.2 aziridine ring), 51.13 and 51.19 (*C*HMe, ^1J 135.9), 64.80 (α-CH_2, ^1J 135.5), 104.95 and 105.90 (HC=, ^1J 167.0), 126.61 (*C*=CH, ^2J 4.1).

For **5**: ^1H ($CDCl_3$) 1.13 (m) and 1.75 (m, CH_2 of the ring), 1.23 (t) and 4.05 (qw, OEt, ^3J 7.0), 1.95 (s, MeC=), 2.35 (t, α-CH_2, ^3J 6.5), 3.40 (t, β-CH_2), 4.41 (s, HC=); ^{13}C ($CDCl_3$) 13.80 (*Me*CH_2O, ^1J 126.2, ^2J 2.8), 18.37 (*Me*C=, ^1J 127.6, ^3J 4.9, ^3J 5.6), 26.11 (CH_2 of the ring, ^1J 163.7 and 175.5), 42.15 (β-CH_2, ^1J 136.6, ^2J 2.8), 60.76 (α-CH_2, ^1J 135.3, ^2J 3.5), 81.70 (=CH, ^1J 165.1, ^3J 4.2, ^3J 2.8), 160.23 (*C*=CH, ^2J 2.8 and 5.6), 169.15 (*C*OOEt, ^3J 2.8).

For **6**: ^1H ($CDCl_3$) 1.57 (m), 1.68 (m) and 2.14 (m, CH_2 of the ring), 2.81 (m, *C*H_2COOEt, AB system, $\Delta\nu_{AB} = 128$ Hz, ^2J 15.9), 1.32 (t) and 4.25 (qw, OEt, ^3J 7.0); ^{13}C ($CDCl_3$) 113.64 (*Me*CH_2, ^1J 127.6, ^2J 2.8), 18.52 and 20.82 (CH_2 of the ring, ^1J 166.5 and 176.2), 37.68 (*C*H_2CO, ^1J 131.8), 61.70 (*C*H_2Me, ^1J 148.4, ^2J 4.2), 83.34 (*C*CF_3, $^2J_{CF}$ 29.1, ^2J 15.6), 123.82 (CF_3, $^1J_{CF}$ 287.1, $^3J_{CH}$ 4.2), 171.78 (*C*OOEt, ^3J 4.2).

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