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Unusual Reactions of 2,3,5-Trichloro-4,4-dimethoxy-5-allylcyclopent-2-en-1-one with Amines

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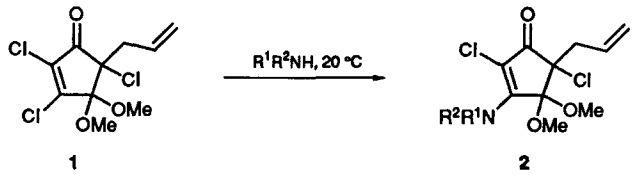
The transformation of enaminochlorovinyl ketone **2** *via* the diketone **3** into a mixture of keto–enol tautomers **4** and **5**, synthons for 13-azaprostanoids, is described; reactions of compound **1** with amine derivatives of different types leading to abnormal products have also been studied.

As reported recently,[1] 2,3,5-trichloro-4,4-dimethoxy-5-allylcyclopent-2-en-1-one **1**[2] reacts readily with primary and secondary amines to form enamino ketones **2** in high yields (Scheme 1).

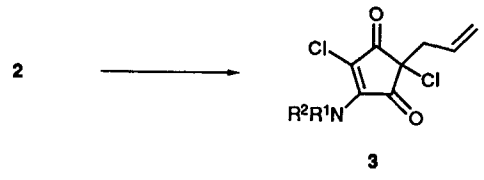
Polyheterofunctionalized cyclopentane derivatives **1** and **2** are hyperconjugated systems which are overloaded with substituents of different types, and their reactivity and chemical transformations are of great interest. The series of examples described below confirms this fact.

First of all, the unusual hydrolytic stability of the enamino vinyl ketone fragment in **2** surprised us. All our attempts to carry out a comprehensive hydrolysis of compound **2** under the influence of aqueous mineral acids failed and only a partial hydrolysis leading to dione **3** took place (Scheme 2).



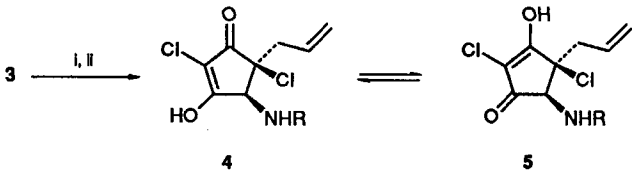
R^1, R^2 = alkyl, cycloalkyl, heterocycle

Scheme 1



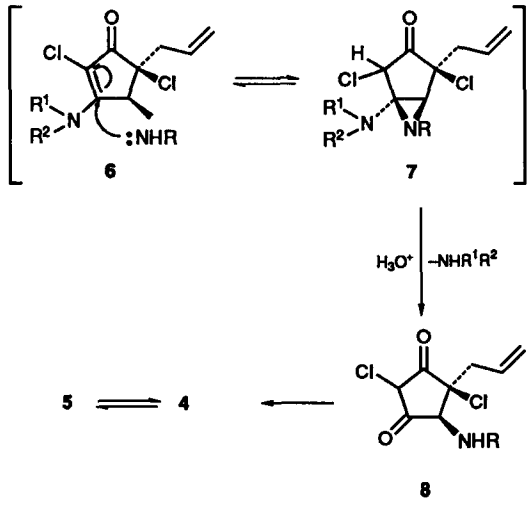
Scheme 2 *Reagents and conditions*: 10% HCl, reflux, or 50% H_2SO_4, 25°C

At the same time, we needed to develop a simple method suitable to hydrolyse the enaminochlorovinyl ketone fragment mentioned above in model compounds of 13-azaprostanoids. This was carried out by a process which may involve anchimeric assistance. Thus, a normal transition 'ketone→imine→amine'[3] in the presence of the C–O group in position 1 of the enaminochloro ketones **3** led to a mixture of keto–enol tautomers **4** and **5** in approximately equal ratios in high yields (70–90%) (Scheme 3).†

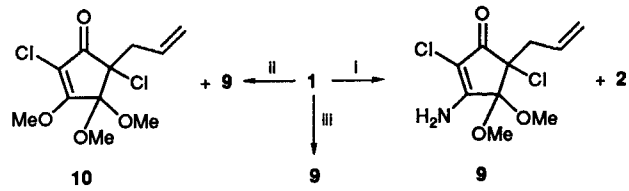


Scheme 3 *Reagents and conditions*: i. NH_2R^3(R^3 = heptyl, dodecyl), molecular sieves 3 Å, MeOH, 20°C; ii, $NaBH_4$, MeOH, −40°C

A possible mechanism for the reaction described may involve imine formation followed by reduction to the corresponding amine **6** which then cyclizes *via* a 3-*exo-trig* process to give aziridine **7** which, being an aminal, is easily hydrolysed to give the observed 1,3-diketone **8** (Scheme 4).



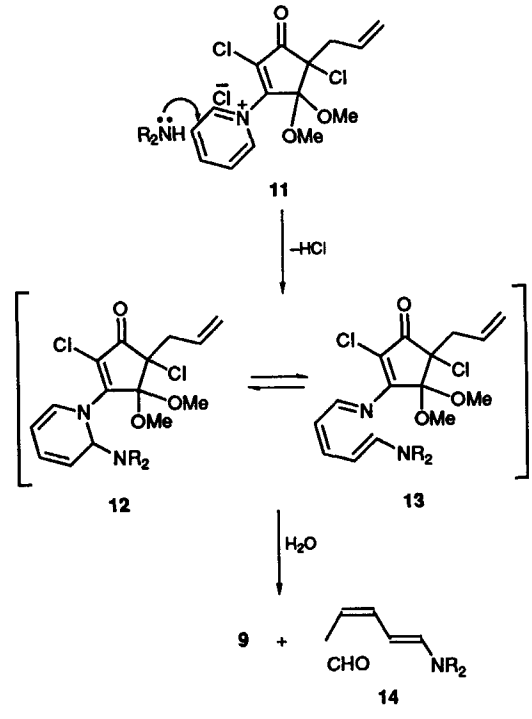
Scheme 4



Scheme 5 *Reagents and conditions*: i, R_2NH, Py, MeOH, 20°C; ii, R_2NH·HCl, Py, MeOH, 20°C; iii, NH_3, MeOH, 20°C

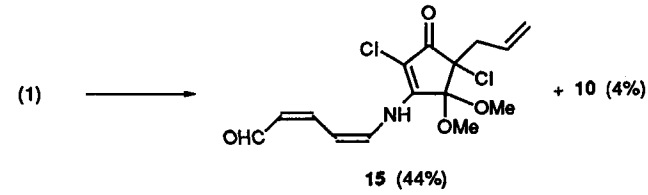
The reaction of compound **1** with amines in the presence of three equivalents of pyridine gave an unexpected, more polar product, together with the expected enaminoketones **2**. Structure **9** was assigned to this compound according to its spectroscopic data and to an alternative synthesis. It should be noted that, on using hydrochlorides instead of secondary amines, compound **9** (65%) was formed predominantly along with a minor product (8%) **10** resulting from methanol substitution into **9**.

In the absence of amine and in a methanol medium, pyridine reacted easily with chlorovinyl ketone **1** to form a water-soluble brown coloured ionic complex. The elemental composition and ^1H and ^{13}C NMR data correspond to structure **11** (m.p. 97–98°C). Evidently, the transformation cycle **1**→**9** proceeds in the presence of pyridine, and a possible mechanism is shown in Scheme 6.



Scheme 6

It is interesting to note that the use of hydrochlorides of sterically loaded dicyclohexyl- and diisopropyl-amines in this reaction produced *N*-dienal **15** and the methoxy derivative **10** as a minor product (Scheme 7). The mechanism of this trans-



Scheme 7 *Reagents and conditions*: R_2NH·HCl (R = Ph or Pr^i), Py, MeOH, 20°C

formation is not absolutely clear. It should be noted that there are some similarities in the ring-opening of analogous pyridinates according to Hafner, which leads to Zinke bases.[4]

The second unusual transformation of ketone **1** was observed during boiling triethylamine containing 1–2 equiv. of water. Thus, enamino ketones **16** and **17** were formed in a 2:3 ratio, respectively, in a total yield of 55%. The spectroscopic and chromatographic data of compound **17** are identical with those of an authentic sample, prepared by the interaction of **1** with Bu^nNH_2 (Scheme 8).†

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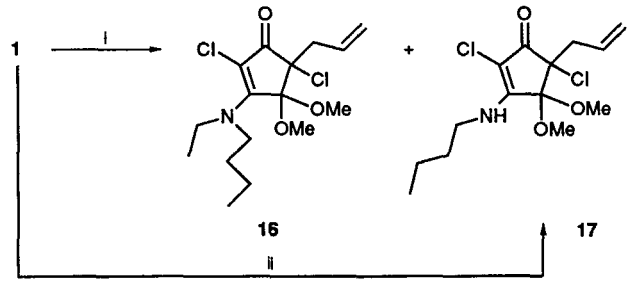

Scheme 8 *Reagents and conditions*: i, NEt_3, H_2O (55%); ii, Bu^nNH_2, MeOH, 20°C

† *Spectroscopic data* for **4**⇌**5** (R = heptyl): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.80 (t, 3H, Me, *J* 6.48 Hz), 1.35 (m, 8H, $4CH_2$), 1.70 (m, 2H, CH_2), 2.80 (m, 2H, $CH_2CH{=}CH_2$), 3.70 (m, 2H, NCH_2), 4.75 (s, 1H, C^4H), 4.85 (s, 1H, C^4H), 5.13–5.30 (m, 2H, CH_2 $CH{=}CH_2$), 5.60–5.80 (m, 1H, $CH_2CH{=}CH_2$), 6.25 (br s, 1H, NH), 6.80 (br s, 1H, C^2H); ^{13}C NMR (67.5 MHz, $CDCl_3$, 25 °C) δ_C 189.02 (s, C=O), 186.38 (s, C–O), 166.63 (s, =C–OH), 165.48 (s, =C–OH), 131.62 (d, CH=), 131.28 (d, CH=), 120.68 (t, CH_2=), 120.56 (t, CH_2=), 100.38 (s, C^2), 96.65 (s, C^2), 73.60 (s, C^5), 71.02 (s, C^5), 71.02 (d, C^4), 69.46 (d, C^4), 44.97 (t, CH_2N), 44.16 (t, CH_2N), 42.61 (t, $CH_2CH{=}CH_2$), 41.38 (t, $CH_2CH{=}CH_2$), 31.65 (t, CH_2), 30.73 (t, CH_2), 28.85 (t, CH_2), 26.44 (t, CH_2), 22.53 (t, CH_2), 14.02 (q, Me).

16: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.96 (t, 3 H, Me, *J* 7.30 Hz), 1.26 (t, 3H, Me, *J* 7.04 Hz), 1.34 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.75 (d, 2H, CH_2, *J* 7.16 Hz), 3.22 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.76 (m, 4H, $2CH_2N$), 5.03–5.09 (m, 2H, CH_2=), 5.70–5.82 (m, 1H, CH=); ^{13}C NMR (67.5 MHz, $CDCl_3$, 25 °C) δ_C 186.62 (c, C=O), 158.31 (s, C^3), 132.44 (d, CH=), 118.63 (t, CH_2=), 104.85 (s, C^4), 102.19 (s, C^2), 75.13 (s, C^5), 53.22 (q, OMe), 51.34 (q, OMe), 50.32 (t, CH_2N), 45.84 (t, CH_2N), 44.83 (t, CH_2), 30.99 (t, CH_2), 19.94 (t, CH_2), 13.95 (q, Me), 13.87 (q, Me); *m/z* 349 (M^+, 66%), 314 (M – Cl, 82), 334 (M – Me, 53), 318 (M – OMe, 77), 278 (M – Cl – HCl, 33) (Calc.: M^+ 350).

17: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.98 (t, 3H, Me, *J* 7.29 Hz), 1.41 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 2.75 (dd, 2H, CH_2, *J* 7.08 and 1.04 Hz), 3.38 (s, 3H, OMe), 3.52 (s, OMe), 3.75 (m, 2H, CH_2), 5.04–5.15 (m, 2H, CH_2=), 5.73–5.95 (M, 1H, CH= and 1H, NH); ^{13}C NMR (67.5 MHz, $CDCl_3$, 25 °C) δ_C 187.49 (c, C=O), 159.76 (s, C^3), 132.44 (d, CH=), 118.75 (t, CH_2=), 101.90 (s, C^4), 98.01 (s, C^2), 74.74 (s, C^5), 52.26 (q, OMe), 51.93 (q, OMe), 43.65 (t, CH_2N), 41.97 (t, CH_2), 32.91 (t, CH_2), 19.74 (t, CH_2), 13.70 (q, Me); *m/z* 321 (M^+, 78%), 286 (M – Cl, 100), 306 (M – Me, 48), 290 (M – OMe, 65), 278 (M – C_3H_7, 75) (Calc.: M^+ 322).

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