Photoaddition of Ethyl 2,2-Dimethyl-5-oxo-5,6-dihydro-2*H*-pyridine-1-carboxylate to 2,3-Dimethylbut-2-ene

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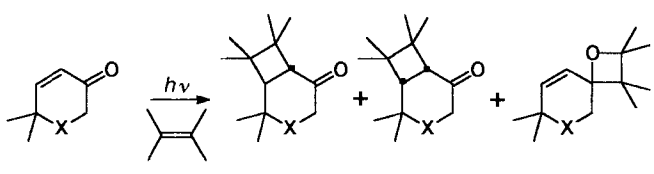
On irradiation (350 nm) in the presence of excess 2,3-dimethylbut-2-ene, the newly synthesized title compound **5** affords as main products the unexpected cyclopropylpyrrolidine **10** (50%) and the spiro-oxetane **9** (25%).

Introduction. – On irradiation in the presence of alkenes, *e.g.*, 2,3-dimethylbut-2-ene, cyclohex-2-enones typically undergo [2+2] cycloaddition at the C=C bond chemoselectively yielding bicyclo[4.2.0]octan-2-ones [1]. In contrast, 4,4-dialkylcyclohex-2-enones, *e.g.*, **1a** or its 5-oxa analogue **1b**, afford the diastereoisomeric cyclobutane derivatives **2** and **3**, *and* spiro-oxetane **4**, the alkene adding to the C=C and the C=O bond, respectively [2–4] (*Scheme 1*). Here, we report on the synthesis of an analogous aza-enone **1** (X = NCOOEt), and its novel and unprecedented behavior in such reactions.

Scheme 1



1 **2** **3** **4**

a X = CH_2, **b** X = O

Results. – The title compound **5** was synthesized in analogy to 6,6-dimethyl-2*H*,6*H*-thiin-3-one (the corresponding 5-thiacyclohex-2-enone [5]), *i.e.*, starting from the open-chain precursor **6a**, which was converted to carbamate **6b**, followed by intramolecular *Claisen* condensation to 1,3-dione **7** and subsequent $LiAlH_4$ reduction of enol ether **8**, in 15% overall yield (*Scheme 2*).

Monitoring the irradiation (350 nm) of **5** in either benzene or MeCN in the presence of excess 2,3-dimethylbut-2-ene by GC/MS indicates the formation of four products **9**–**12** (numbered according to their increasing GC retention times) in a 2:4:1:1 ratio, all being monoadducts of **5** and alkene (M^+ *m/z* 281). For preparative purposes, the irradiation was run up to 75–80% conversion of **5**, followed by chromatography of the

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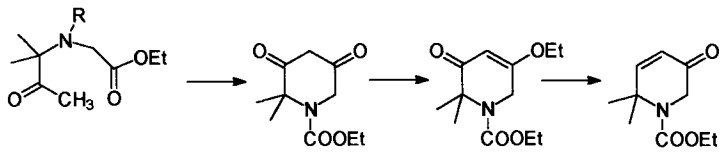
Scheme 2

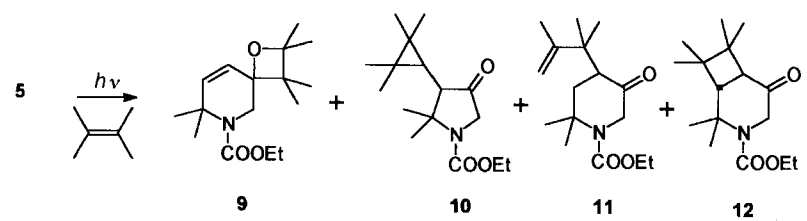


6 **7** **8** **5**

a R = H, **b** R = COOEt

crude product mixture (*A*) on SiO_2 using CH_2Cl_2/AcOEt 9:1 as eluent, which gives three main fractions, the first one (*B*) containing a 4:1 mixture **10**/**11**, the second one containing **5**, and the third one containing pure **9**. Subsequent chromatography of the first fraction (*B*) using Et_2O/pentane 1:5 as eluent affords the pure main product **10**. The spectral characteristics of **9** are very similar to those of spiro-oxetane **4b** [4]. Partial ^{1}H-NMR spectral data for azabicyclo[4.2.0]octanone **12** (cyclobutane H-atoms at 2.60 and 2.20 ppm, J = 14.5 Hz; *cf.* **2b** [4]) were obtained from product mixture *A*, and for the 5-oxopiperidine-carboxylate **11** (two olefinic H-atoms at 4.78 and 4.70 ppm, CH_2(6) at 4.50 and 3.55 ppm, J = 18.5 Hz, and the CH(4) as *dd*, J = 4.1 and 13.2 Hz at 2.35 ppm) from mixture *B*. The ^{1}H-NMR spectrum of **10** is striking due to the presence of a signal for a methine proton (*d*, J(H,H) = 11 Hz, J(C,H) = 154 Hz) resonating at very high field (0.15 ppm in $CDCl_3$ or (D_6)DMSO, 0.07 ppm in C_6D_6), *i.e.*, values typical for a cyclopropane H-atom. The proposed structures of the photoproducts are summarized in *Scheme 3* and their way of formation discussed below.

Scheme 3



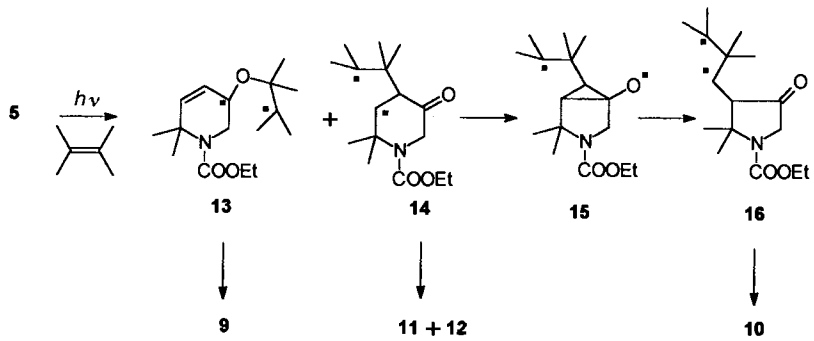
9 **10** **11** **12**

Discussion. – The formation of **10** as main product in the photoaddition of **5** to 2,3-dimethylbut-2-ene, *i.e.*, the *light-induced ring contraction of a cyclohex-2-enone adding to an alkene to afford a 2-cyclopropylcyclopentanone*, represents a novel enone + alkene photoreaction.

It is known [2][3] that the geminal dialkyl group on the allylic C-atom slows down the approach of a tetraalkylethene to the C=C bond of the excited enone, thus allowing the (slower) oxetane-forming path to become competitive. Due to steric repulsion at $C(\beta)$ binding of the alkene to the excited enone, therefore, occurs at the carbonyl O-atom and at $C(\alpha)$, the 1,4-biradical formed in this latter reaction nevertheless being able to cyclize to a cyclobutane, as illustrated for **1a** or **1b** affording **2a** and **3a** (50%), and **2b** and **3b**

(66%), respectively. In the addition of excited **5** to 2,3-dimethylbut-2-ene biradicals **13** and **14** will be formed (*Scheme 4*). While the pre-oxetane biradical **13** affords **9**, the closure of **14** to a cyclobutane, *e.g.*, **12** only represents a minor reaction path for this intermediate. Apparently the COOEt group on the ring N-atom causes additional steric hindrance in the 1,4-cyclization of **14** and, therefore, a biradical → biradical rearrangement, consisting of a *cyclization step* (formation of the cyclopropyloxy-alkyl biradical **15** by binding of the ring-alkyl radical center to the carbonyl C-atom) and a *ring opening step* (bond cleavage of the cyclopropane with restoration of the C=O group to give the 1,3-biradical **16**), becomes competitive, 1,3-cyclization of **16** then leading to the final product **10**.

Scheme 4



The overall rearrangement **14** → **16** represents an intramolecular 1,2-acyl shift. While vinyl migration in allylcarbinyl radicals (homoallylic rearrangements) are known to occur by way of cyclopropylcarbinyl radicals as discrete intermediates [6], relatively few examples of analogous carbonyl rearrangements have been reported [7].

Evidence for the proposed 'cumulative steric hindrance' of the geminal dimethyl and the carbamate groups on the one side, and the alkyl groups on the alkene on the other side, comes from the results [8][9] of irradiations of the parent aza-enone, ethyl 5-oxo-5,6-dihydro-2*H*-pyridine-1-carboxylate, in the presence of vinyl acetate, affording cyclobutanes selectively in the absence of any ring-contraction product.

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Experimental Part

General. Photolyses: *Rayonet RPR-100* photoreactor equipped with 350-nm lamps. GC: 30-m *SE-30* cap. column. UV Spectra: in nm (log ε). ^{1}H- and ^{13}C-NMR Spectra: at 500 and 100.62 MHz, resp.; chemical shifts in ppm rel. to TMS (= 0 ppm), J in Hz. MS: at 70 eV; in m/z (rel. intensity in %).

Synthesis of Ethyl 2,2-Dimethyl-5-oxo-5,6-dihydro-2H-pyridine-1-carboxylate (**5**). *Ethyl 2-[N-(2,2-Dimethyl-2-oxopropyl)amino]ethanoate* (**6a**). To a mixture of 33 g (0.2 mol) of 3-bromo-3-methylbutan-2-one and 16.8 g (0.2 mol) of $NaHCO_3$ in 200 ml of THF and 8 ml of H_2O is added dropwise at 60° during 4 h a soln. of 20.6 g (0.2 ml) of ethyl 2-aminoethanoate in 60 ml of THF. After filtration of NaBr and evaporation of the solvent, distillation affords 22.4 g (60%) of **6a**. B.p. 66°/2 Torr. ^{1}H-NMR ($CDCl_3$): 4.20 (*q*, J = 7, 2 H); 3.29 (*s*, 2 H); 2.20 (*s*, 3 H); 1.60 (*s*, 6 H); 1.29 (*t*, J = 7, 3 H). ^{13}C-NMR ($CDCl_3$): 212 (*s*); 172 (*s*); 63 (*t*); 61 (*s*); 45 (*t*); 25 (*q*); 24 (*q*); 14 (*q*). MS: 187 (0.1, M^+), *70*.

*Ethyl 2-[*N*-(2,2-Dimethyl-2-oxopropyl)-*N*-ethylamino]ethanoate* (**6b**). To a mixture of 18.7 g (0.1 mol) of **6a** and 8.4 g (0.1 mol) of $NaHCO_3$ in 100 ml of toluene is added dropwise at 60° during 2 h a soln. of 10.8 g (0.1 mol) of ethyl chloroformate in 50 ml of toluene. After filtration of NaCl and evaporation of the solvent, the residue is distilled to afford 25.0 g (97%) of **6b**. B.p. 75°/0.5 Torr. MS: 259 (0.1, M^+), *70*.

Ethyl 2,2-Dimethyl-3,5-dioxopiperidine-1-carboxylate (7). To a soln. of 22.0 g (0.096 mol) of Na in EtOH (100 ml) is added dropwise at 60° a soln. of 24.9 g (0.096 mol) of **6b** in 100 ml of EtOH and stirring continued for 6 h at 60°. After evaporation of EtOH, the residue is poured into 100 ml of 2N H_2SO_4 and extracted with Et_2O (3 ×). After washing of the org. layer with H_2O, drying ($MgSO_4$), and evaporation of the solvent, the crude residue purified by crystallization from Et_2O pentane to afford 13.8 g (67%) of 7. M.p. 117°. ^{1}H-NMR ($CDCl_3$): 4.19 (*q*, *J* = 7, 2 H); 4.11 (*s*, 2 H); 3.70 (*s*, 2 H); 1.65 (*s*, 6 H); 1.30 (*t*, *J* = 7, 3 H). ^{13}C-NMR ($CDCl_3$): 204 (*s*); 200 (*s*); 155 (*s*); 67 (*s*); 62 (*t*); 54 (*t*); 53 (*t*); 25 (*q*); 14 (*q*). MS: 213 (0.07, M^+), *70*.

*Ethyl 3-Ethoxy-6,6-dimethyl-5-oxo-5,6-dihydro-2*H*-pyridine-1-carboxylate* (**8**). A soln. of 13.7 g (0.064 mol) of 7 and TsOH (200 mg) in EtOH (100 ml) and $CHCl_3$ (400 ml) is refluxed with azeotropic removal of H_2O. After evaporation of the solvent, the residue is dissolved in CH_2Cl_2 (50 ml), washed with aq. $NaHCO_3$ and aq. NaCl solns. and dried ($MgSO_4$). The solvent is evaporated and the residue purified by chromatography (SiO_2, CH_2Cl_2/AcOEt 9:1) affording 7.8 g (50%) of **8**. Colorless oil. R_f 0.45. ^{1}H-NMR ($CDCl_3$): 6.35 (*s*); 4.19 (*q*, *J* = 7, 2 H); 4.20 (*s*, 2 H); 3.99 (*q*, *J* = 7, 2 H); 1.62 (*s*, 6 H); 1.40 (*t*, *J* = 7, 3 H); 1.30 (*t*, *J* = 7, 3 H). MS: 241 (2, M^+), *84*.

Preparation of **5**. A mixture of 7.7 g (0.032 mol) of **8** and 1.2 g (0.032 mol) of $LiAlH_4$ in Et_2O (50 ml) is refluxed for 30 min. Then, 50 ml of 2N H_2SO_4 are added and the mixture stirred for 1 h at r.t. The org. phase is separated and the aq. phase extracted with Et_2O (3 ×). The combined org. phases are washed with aq. NaCl and dried ($MgSO_4$). After evaporation of the solvent, the residue is purified by chromatography (SiO_2, pentane/Et_2O 1:1) to afford 2.8 g (45%) of **5**. M.p. 50°. UV (C_6H_{12}): 340 (1.813); 242 (3.616). ^{1}H-NMR ($CDCl_3$): 6.63, 6.01 (*d*, *J* = 10.3, 2 H); 4.16 (*q*, *J* = 7, 2 H); 4.11 (*s*, 2 H); 1.65 (*s*, 6 H); 1.29 (*t*, *J* = 7, 3 H). ^{13}C-NMR ($CDCl_3$): 193 (*s*); 158 (*d*); 155 (*s*); 123 (*d*); 62 (*t*); 56 (*s*); 51 (*t*); 26 (*q*); 14 (*q*). MS: 197 (4, M^+), *96*.

Photoaddition of **5** *to 2,3-Dimethylbut-2-ene*. An Ar-degassed soln. of 394 mg ($2 \cdot 10^{-3}$ mol) of **5** and 3.36 g ($4 \cdot 10^{-2}$ mol) of 2,3-dimethylbut-2-ene in benzene (10 ml) is irradiated for 16 h. After evaporation of the solvent and excess alkene, chromatography of the crude mixture, containing **5** (28%), **9** (18%), **10** (36%), **11** (9%) and **12** (9%), by GC analysis (SiO_2, $MeCl_2$/AcOEt 9:1) affords first a 4:1 mixture **10**/**11** (R_f 0.5; 110 mg), then aza-enone **5** (R_f 0.4; 60 mg), and finally *ethyl 2,2,3,3,7,7-hexamethyl-1-oxa-6-azaspiro[3,5]non-6-ene-1-carboxylate* (**9**). R_f 0.25; 42 mg. Colorless oil. ^{1}H-NMR (C_6D_6): 5.89 (*dd*, *J* = 1.0, 10.6); 5.13 (*d*, *J* = 10.6); 4.83 (*dd*, *J* = 1.0, 13.2); 4.12 (*m*, 1 H); 4.00 (*m*, 1 H); 2.99 (*d*, *J* = 13.2); 1.59, 1.31, 1.28, 1.23, 1.19, 0.96 (*s*, Me); 1.01 (*t*, *J* = 7.0, 3 H). MS: 281 (0.1, M^+), *84*.

The first fraction is rechromatographed using pentane/Et_2O 5:1 to afford *ethyl 2,2-dimethyl-3-(2,2,3,3-tetramethylcyclopropyl)-4-oxopyrrolidine-1-carboxylate* (**10**). R_f 0.45; 31 mg. Colorless oil. ^{1}H-NMR (C_6D_6, 333 °K): 4.00 (*m*, 2 H); 3.68 (*dd*, *J* = 0.5, 19.3); 3.58 (*d*, *J* = 19.3); 1.80 (*dd*, *J* = 0.5, 11.2); 1.48, 1.21, 1.15, 1.02, 0.92, 0.77 (*s*, Me); 1.00 (*t*, *J* = 7, 3 H); 0.07 (*d*, *J* = 11.2). ^{13}C-NMR ($CDCl_3$): 207 (*s*); 164 (*s*); 63 (*s*); 61 (*t*); 58 (*d*); 53 (*t*); 31 (*d*); 27 (*s*); 26 (*s*); 23.6, 23.4, 21.6, 19.8, 18.7, 17.7 (*q*, Me); 14.6 (*q*). MS: 281 (0.9, M^+), *97* ($[Me_2CCHCMe_2]^+$).

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