Photocycloaddition of Six-Membered Cyclic Enones to Propen-2-yl Isocyanate

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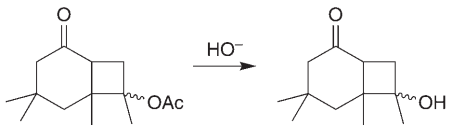
On irradiation in the presence of propen-2-yl isocyanate (**4**), six-membered cyclic enones **3** are converted into regio- and stereoisomeric mixtures of [2+2] cycloadducts **5**–**10**; the preferentially formed *HT* products, **5**–**8**, can be converted into the corresponding bicyclic amines by acid hydrolysis, whereas, under these conditions, the regioisomeric *HH*-isocyanato derivatives undergo a *retro-Mannich* reaction.

1. Introduction. – Photochemistry is a highly valuable tool for modern organic synthesis, as illustrated by one of the most important reaction types, *i.e.*, the stepwise [2+2] photocycloaddition of a cyclic unsaturated ketone to an alkene to give an (annelated) cyclobutane [1]. In this context, it is noteworthy that the synthesis of the diastereoisomeric mixture of 2-oxobicyclo[4.2.0]oct-7-yl acetates **1** by irradiation of isophorone in the presence of propenyl acetate represents one of the, unfortunately, very few procedures in *Organic Syntheses* found under the heading '*Photochemical Reaction*' [2]. Alkaline hydrolysis of these cycloadducts affords a mixture of stereoisomeric alcohols **2** (*Scheme 1*). Interestingly, up to now no such approach has been reported for the synthesis of 7-amino derivatives of these bicycles. One reason for this is that, on irradiation of cyclohexenones in the presence of enamines, electron transfer to the excited enone forestalls any cycloaddition [3]. Moreover, enamides analogous to the enol acetates mentioned before, *e.g.*, *N*-(prop-2-enyl)acetamide, are rather unstable in solution and only accessible by pyrolysis [4], albeit (intramolecular) photoisomerizations of vinylogous amides to azabicyclooctanones have been reported [5]. A very recent photochemical procedure for the synthesis of cyclobutylamines is based on the light-induced cycloaddition of uracil to ethene, followed by controlled degradation of the heterocyclic ring, *i.e.*, the N-atom stemming from the 'enone' [6].

Scheme 1



1 **2**

Here, we report that alkenyl isocyanates represent convenient 'alkene' partners for such light-induced annelation reactions.

2. Results. – Irradiation ($\lambda = 350$ nm) of a mixture of dihydropyranone **3a** and excess prop-2-enyl isocyanate (**4**) in benzene for 5 h (total enone conversion as monitored by GC) affords mixtures of cycloadducts **5a**–**10a** (*Scheme 2*). The constitution and configuration of the photoproducts can be fully assigned by NMR spectroscopy. Differentiation between regioisomers on the one side (for '*HH*'-regioisomers the C=O and NCO groups point to the same, for '*HT*'-regioisomers towards opposite directions) and defining the relative configuration (*cis*/*trans*) of the ring fusion, on the other side, directly from the product mixture becomes straightforward from the – easily detectable – splitting pattern of both bridgehead H-atoms (*Table*). The *exo*/*endo* assignment of the Me group on the cyclobutane ring stems from NOESY experiments.

Scheme 2

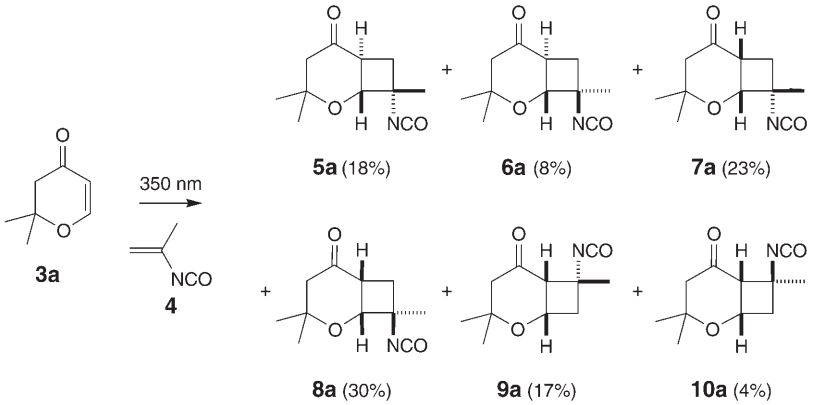
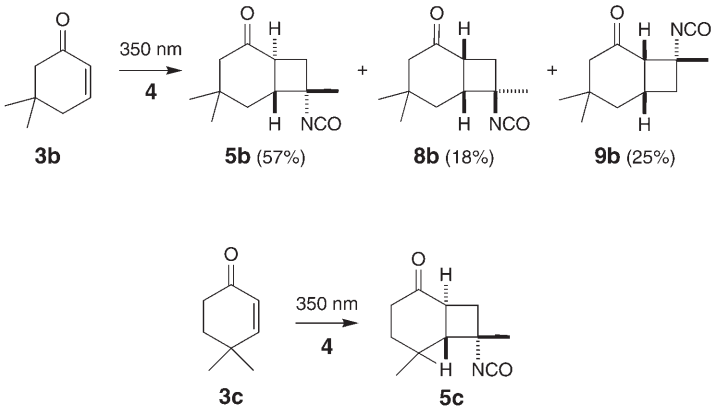


Table. *NMR Data* (chemical shifts [ppm] and coupling constants [Hz]) *of Bridgehead Atoms of Photocycloadducts from* **3a** + **4** (in $CDCl_3$)

	*H*C–C=O	*C*H–C=O	*H*C–O	*C*H–O
5a	3.24 (*ddd*, *J* = 6.8, 10.8, 11.0)	51.0	3.62 (*d*, *J* = 11.0)	80.1
6a	2.65 (*ddd*, *J*= 6.8, 10.8, 11.2)	48.2	3.82 (*d*, *J* = 11.2)	82.3
7a	2.78 (*ddd*, *J*= 4.9, 9.0, 9.5)	37.7	4.23 (*dd*, *J* = 3.3, 4.9)	76.1
8a	3.08 (*ddd*, *J* = 6.6, 7.0, 9.9)	38.4	4.43 (*dd*, *J* = 2.0, 6.6)	77.3
9a	2.86 (*d*, *J* = 5.2)	52.9	4.48 (*ddd*, *J*= 1.5, 5.2, 6.1)	64.9
10a	3.08 (*d*, *J* = 5.2)	54.9	4.55 (*ddd*, *J*= 1.3, 5.2, 6.2)	69.6

Under similar conditions, irradiation of **3b** affords a mixture of three cycloadducts, **5b**, **8b**, and **9b**, in 57, 18, and 25% relative yield, respectively. In contrast, irradiation of **3c** in the presence of excess **4** gives cycloadduct **5c** selectively, but the rate of conversion to product(s) is *ca.* 2–3 times slower than for the former two enones (*Scheme 3*).

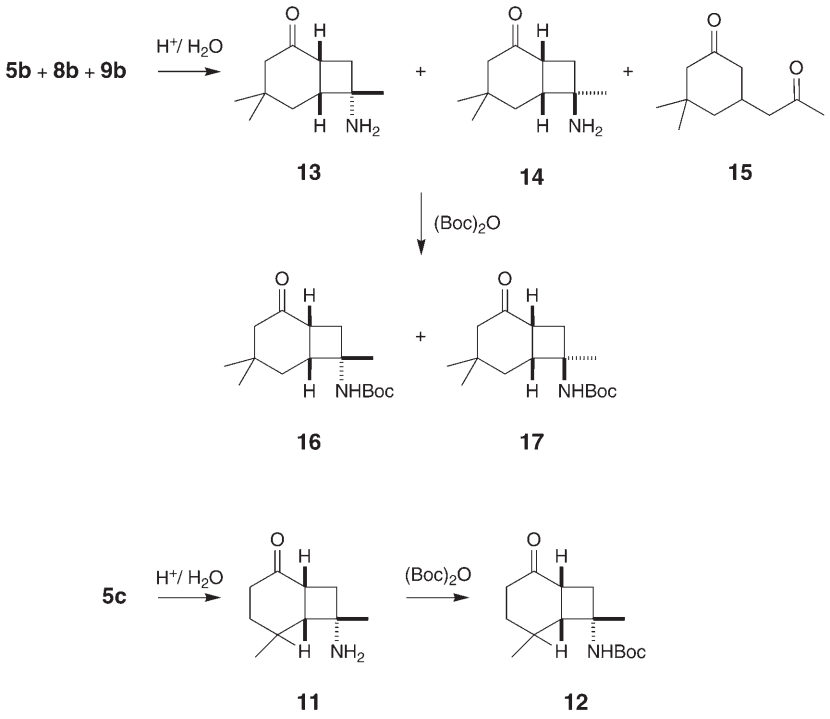
Scheme 3



Chromatographic workup of the product mixtures turns out to be cumbersome, because the isocyanates decompose on prolongued contact with SiO_2, and, therefore, the crude photoproducts themselves were hydrolyzed to the corresponding amines. On refluxing for 5 h in a mixture of concentrated HCl and benzene [7], **5c** affords the – now *cis*-fused – amine **11**, isolated by separating the organic phase, adding base to the aqueous phase, and extracting with Et_2O, and after that converted into the *N*-Boc derivative **12**. On similar treatment, the mixture of **5b**, **8b**, and **9b** affords a 2.5 : 1 mixture of amines **13** and **14**, but, in addition, evaporation of the – original – benzene phase affords a product **15** (10% overall yield), identified as 3,3-dimethyl-5-(2-oxopropyl)cyclohexanone. The amines were converted into *N*-Boc derivatives **16** and **17**, and these were then separated by chromatography (*Scheme 4*). Expectedly, the ^{1}H-NMR spectra of the *N*-Boc derivatives exhibit strong signal broadening due to the restricted rotation of the carbamate group. Under the same conditions, the isocyanates derived from pyranone **3a** afford large amounts of products resulting from tetrahydropyrane ring opening.

3. Discussion. – The overall outcome of photocycloadditions of **3** to **4** resembles that of analogous irradiations of cyclohexenones in the presence of 2-methylpropene [8][9]. Indeed, for the parent cyclohexenone itself, the *trans*-fused *HT*-cycloadduct is the major and the *cis*-fused *HH*-cycloadduct a minor product, whereas, for **3a**, *HT*-products are formed selectively, the ratio of *cis*- to *trans*-fused cycloadduct being roughly 3 : 2 [10]. Interestingly, no products stemming from H-atom transfer in a intermediate biradical, *i.e.*, so-called ene-type products [11], are observed in the reactions of **3** and **4**. The NMR data of cycloadducts **5a** – **10a** correspond fully to those observed for the photodimers of **3a** [12]. The fact that the *trans*-ring fusion in the bicyclic isocyanates is transformed into a *cis*-fusion in the corresponding amines does not come as a surprise, as epimerization of a (thermodynamically less stable) *trans*-fused bicyclo[4.2.0]octan-2-one to the less strained *cis*-fused diastereoisomer is easily achieved both by base and by acid catalysis. Finally, the conversion of **9b** into **15** can be readily explained by a sequence involving *1*) hydrolysis of the isocyanate to an amine,

Scheme 4



2) ring opening of the cylobutane *via retro-Mannich* reaction [13], and *3*) hydrolysis of the iminium ion to a C=O group.

In summary, we have shown, for the first time, that alkenyl isocyanates can be used as (photoinert) reaction component in light-induced enone–alkene cycloadditions, and that the resulting cycloadducts can be converted into the corresponding amino-bicyclooctanones.

Experimental Part

1. *General.* Photolyses were run in a *Rayonet RPR-100* photoreactor equipped with (16) 350 nm lamps and solvents of spectrophotometric grade. Column chromatography (CC): silica gel *60* (*Merck*; 230–400 mesh). ^{1}H- and ^{13}C-NMR spectra (including two-dimensional plots): in $CDCl_3$ at 500.13 and 125.8 MHz, resp., δ in ppm, J in Hz. GC/EI-MS: at 70 eV; 30 m *SE-30* capillary column.

2. *Starting Materials. 2,3-Dihydro-2,2-dimethyl-4*H*-pyran-4-one* (**3a**) [14], *5,5-dimethylcyclohex-2-enone* (**3b**) [15], *4,4-dimethylcyclohex-2-enone* (**3c**) [16], and *propen-2-yl isocyanate* (**4**) [17] were synthesized according to the references indicated.

3. *Photolyses.* Ar-Degassed solns. of **3** (2 mmol) and **4** (20 mmol) in benzene (5 ml) were irradiated for 6–8 h. Total conversion to cycloadducts for **3a** and **3b**, but only 50% conversion of **3c** was achieved, as monitored by both GC and ^{1}H-NMR. After evaporation of the solvent, the composition of the product mixture was determined by NMR spectroscopy.

3.1. *Irradiation of* **3a**. The product mixture (> 95% overall yield) consisted of the *trans*-fused *HT*-cycloadducts **5a** (18%) and **6a** (8%), of the *cis*-fused *HT*-cycloadducts **7a** (23%) and **8a** (30%), and of the *cis*-fused *HH*-cycloadducts **9a** (17%) and **10a** (4%).

Data of the Major Product (1α,6α,8α)-8-Isocyanato-3,3,8-trimethyl-2-oxabicyclo[4.2.0]octan-5-one (**8a**): ^{1}H-NMR: 4.43 (*dd*, *J* = 6.5, 2.0, H–C(1)); 3.08 (*ddd*, *J* = 10.0, 7.5, 6.5, H–C(6)); 2.51, 2.31 (*AB*, *J* = 16.7, CH_2(4)); 2.44–2.33 (*m*, CH_2(7)); 1.37, 1.36, 1.28 (3*s*, 3 Me). ^{13}C-NMR: 208.6 (*s*, C(5)); 122.5 (*s*, N=C=O); 77.3 (*d*, C(1)); 76.0 (*s*, C(3)); 59.8 (*s*, C(8)); 50.2 (*t*, C(4)); 38.6 (*d*, C(6)); 36.8 (*t*, C(7)); 30.3, 30.0, 25.3 (3*q*, Me). CI-MS: 210 (48, $[M+H]^+$), 111 (100).

3.2. *Irradiation of* **3b**. The product mixture (> 90% overall yield) consisted of the *trans*-fused *HT*-cycloadduct **5b** (57%), the *cis*-fused *HT*-cycloadduct **8b** (18%), and the *cis*-fused *HH*-cycloadduct **9b** (25%).

Data of the Major Product (1α,6β,7α)-7-Isocyanato-4,4,7-trimethylbicyclo[4.2.0]octan-2-one (**5b**): ^{1}H-NMR: 3.07 (*ddd*, *J* = 13.2, 10.8, 6.0, H–C(1)); 2.43 (*d*, *J* = 13.2, H_{ax}–C(3)); 2.30 (*ddd*, *J* = 13.2, 11.5, 3.5, H–C(6)); 2.14 (*dd*, *J* = 10.8, 10.7, H_{ax}–C(8)); 1.95 (*dd*, *J* = 10.7, 6.0, H_{eq}–C(8)); 1.83 (*dd*, *J* = 13.2, 1.0, H_{eq}–C(3)); 1.73 (*dd*, *J* = 12.3, 11.5, H_{ax}–C(5)); 1.57 (*ddd*, *J* = 12.3, 3.5, 1.0, H_{eq}–C(5)); 1.51, 1.14, 1.00 (3*s*, 3 Me). ^{13}C-NMR: 204.2 (*s*, C(2)); 123.4 (*s*, N=C=O); 63.1 (*s*, C(7)); 54.8 (*t*, C(3)); 53.7 (*d*, C(6)); 47.7 (*d*, C(1)); 38.6 (*s*, C(4)); 38.4 (*t*, C(5)); 37.2 (*t*, C(8)); 31.9, 28.0, 27.5 (3*q*, 3 Me). EI-MS: 207 (3, M^+), 68 (100).

3.3. *Irradiation of* **3c**. The product mixture consisted mainly of **5c** (40%) and of unreacted **3c** (40–50%).

Data of (1α,6β,7α)-7-Isocyanato-5,5,7-trimethylbicyclo[4.2.0]octan-2-one (**5c**): ^{1}H-NMR: 3.33 (*ddd*, *J* = 13.9, 9.7, 6.3, H–C(1)); 2.43–2.37 (*m*, CH_2(3)); 2.20 (*dd*, *J* = 10.8, 9.7, H_{ax}–C(8)); 2.03 (*dd*, *J* = 10.8, 6.3, H_{eq}–C(8)); 1.87 (*d*, *J* = 13.9, H–C(6)); 1.76–1.70 (*m*, CH_2(4)); 1.51, 1.33, 1.05 (3*s*, 3 Me). ^{13}C-NMR: 209.2 (*s*, C(2)); 123.4 (*s*, N=C=O); 64.1 (*s*, C(7)); 62.7 (*d*, C(6)); 45.5 (*t*, C(4)); 41.9 (*d*, C(1)); 38.9 (*t*, C(3)); 38.5 (*t*, C(8)); 34.0 (*s*, C(5)); 29.0, 27.4, 27.3 (3*q*, 3 Me). EI-MS: 207 (4, M^+), 125 (100).

4. *Hydrolysis of Isocyanates.* The crude isocyanates were refluxed in a mixture of benzene (1 ml) and conc. aq. HCl (1 ml) for 5 h. After separation of the aq. phase, the org. phase was extracted three times with 3N HCl (1 ml). NaOH was added to the combined aq. phases until pH *ca.* 10, which were then extracted with pentane (6 × 2 ml). The org. phase was dried (KOH), and the solvent was evaporated to afford the crude amine(s), which were further treated with $(Boc)_2O$ to afford the corresponding *N*-Boc derivatives [18].

4.1. *Hydrolysis of* **5c**. *(1α,6α,7β)-7-Amino-5,5,7-trimethylbicyclo[4.2.0]octan-2-one* (**11**; 87 mg, 50%) was obtained. ^{1}H-NMR: 2.60 (*ddd*, *J* = 8.8, 6.7, 3.8, H–C(1)); 2.50 (*dt*, *J* = 12.9, 5.3, H_{ax}–C(4)); 2.32 (*dt*, *J* = 14.5, 6.0, H_{ax}–C(3)); 2.28 (*m*, H_{eq}–C(3)); 2.13 (*dd*, *J* = 8.8, 2.0, H–C(6)); 1.89–1.88 (*m*, CH_2(8)); 1.44 (*dddd*, *J* = 12.9, 8.2, 4.4, 2.0, H_{eq}–C(4)); 1.20, 0.99, 0.97 (3*s*, 3 Me). ^{13}C-NMR: 214.0 (*s*, C(2)); 58.2 (*s*, C(7)); 55.1 (*d*, C(6)); 38.8 (*d*, C(1)); 37.1 (*t*, C(8)); 36.0 (*t*, C(3)); 35.2 (*t*, C(4)); 30.1 (*s*, C(5)); 31.9, 27.8, 24.8 (3*q*, 3 Me). EI-MS: 181 (0.4, M^+), 57 (100). The corresponding (*tert*-Butoxy)carbonyl (Boc) derivative **12** was recrystallized from AcOEt/hexane; m.p. 68–70°.

4.2. *Hydrolysis of the Mixture* **5b**, **8b**, *and* **9b**. A 2.5 : 1 mixture of the diastereoisomeric amines **16** and **17** was obtained, which were directly converted into their *N*-Boc derivatives. CC (SiO_2; Et_2O/pentane 3 : 1) afforded as a first fraction 50 mg (9%) of the minor product (R_f 0.39) *(1α,6α,7α)-7-{[(*tert*-butoxy)carbonyl]amino}-4,4,7-trimethylbicyclo[4.2.0]octan-2-one* (**17**) as a light yellow oil. The second fraction contained 129 mg (23%) of the major product (R_f 0.34) *(1α,6α,7β)-7-{[(*tert*-butoxy)carbonyl]-amino}-4,4,7-trimethylbicyclo[4.2.0]octan-2-one* (**16**).

Data of **17**: ^{1}H-NMR: 3.03 (*ddd*, *J* = 9.5, 9.0, 8.5, H–C(1)); 2.93 (br. *m*, H–C(6)); 2.38 (br. *m*, 1 H of CH_2(8)); 2.20 (*m*, CH_2(3)); 2.18 (br. *m*, 1 H of CH_2(8)); 1.71 (br. *m*, 1 H of CH_2(5)); 1.52 (br. *m*, 1 H of CH_2(5)); 1.44 (*s*, Me_3C); 1.26, 1.06, 0.95 (3*s*, 3 Me). ^{13}C-NMR: 213.4 (*s*, C(2)); 156.9 (*s*, CO of Boc); 79.3 (*s*, Me_3CO); 55.2 (*s*, C(7)); 52.8 (*t*, C(3)); 42.9 (*d*, C(6)); 38.4 (*d*, C(1)); 36.4 (*t*, C(8)); 35.8 (*t*, C(5)); 33.7 (*s*, C(4)); 32.3 (*q*, Me); 28.9 (*q*, Me_3C); 26.8 (*q*, 2 Me).

Data of **16**: M.p. 110–112°. ^{1}H-NMR: 2.80 (*ddd*, *J* = 9.5, 9.0, 8.5, H–C(1)); 2.63 (br. *m*, H–C(6)); 2.27, 2.10 (*AB*, *J* = 16.1, CH_2(3)); 2.26, 2.16 (2 br. *m*, CH_2(8)); 1.71 (br. *m*, 1 H of CH_2(5)); 1.69 (br. *m*, 1 H of CH_2(5)); 1.55 (*s*, Me); 1.44 (*s*, Me_3C); 1.02, 0.85 (2*s*, 2 Me). ^{13}C-NMR: 213.1 (*s*, C(2)); 156.9 (*s*, CO of Boc); 79.2 (*s*, Me_3CO); 52.1 (*t*, C(3)); 51.5 (*s*, C(7)); 43.4 (*d*, C(6)); 37.5 (*d*, C(1)); 36.8 (*t*, C(8)); 34.8 (*s*, C(4)); 33.9 (*t*, C(5)); 31.4 (*q*, Me); 28.9 (*q*, Me_3C); 25.2 (*q*, 2 Me).

After drying the original benzene phase ($MgSO_4$) and subsequent evaporation of the solvent, 36 mg (10%) of *3,3-dimethyl-5-(2-oxopropyl)cyclohexanone* (**15**) as colorless liquid were obtained. ^{1}H-NMR:

2.46–2.43 (*m*, H–C(5), CH_2(1′)); 2.37 (*dd*, *J* = 13.3, 6.3, H_{eq}–C(6)); 2.16 (*d*, *J* = 13.3, H_{ax}–C(2)); 2.14 (*s*, Me(3′)); 2.10 (*dd*, *J* = 13.3, 2.2, H_{eq}–C(2)); 1.92 (*dd*, *J* = 13.3, 12.6, H_{ax}–C(6)); 1.63 (*ddd*, *J* = 13.6, 5.9, 2.2, H_{eq}–C(4)); 1.31 (*dd*, *J* = 13.6, 12.6, H_{ax}–C(4)); 1.06, 0.92 (2*s*, 2 Me). ^{13}C-NMR: 210.7 (*s*, C(1)); 207.2 (*s*, C(2′)); 54.3 (*t*, C(2)); 50.4 (*t*, C(1′)); 46.6 (*t*, C(6)); 44.7 (*t*, C(4)); 35.0 (*s*, C(3)); 31.9 (*q*, Me); 30.4 (*q*, Me(3′)); 30.2 (*d*, C(5)); 25.6 (*q*, Me). EI-MS: 182 (12, M^+), 43 (100).

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