Photocycloaddition Reactions of 2-(Alk-3-en-1-ynyl)cyclohex-2-enones

by Janne Möbius and Paul Margaretha*

Chemistry Department, University of Hamburg, Martin-Luther-King Platz 6, D-20146 Hamburg (phone: +4940428384316; fax: +4940428385592; e-mail: Paul.Margaretha@chemie.uni-hamburg.de)

The newly synthesized 2-(alk-3-en-1-ynyl)cyclohex-2-enones **4** undergo photodimerization (chemoand regio-)selectively at the exocyclic C=C bond to give diastereoisomeric mixtures of 1,2-dialkynyl-1,2dimethylcyclobutanes. On irradiation of **4** in the presence of 2-chloroacrylonitrile, cyclobutane formation occurs again (chemo- and regio-)selectively at the exocyclic C=C bond to afford diastereoisomeric mixtures of 2-alkynyl-1-chloro-2-methylcyclobutanecarbonitriles. Similarly, compounds **4** undergo photoaddition to 2,3-dimethylbuta-1,3-diene exclusively at the exocyclic C=C bond to afford mixtures of [2+2] and [4+2] cycloadducts.

1. Introduction. – Quite recently, we have reported [1] that the (photo)reactivity of 3-alkynylcyclohex-2-enones was completely altered by extending the conjugation of the side chain at C(3) by an additional C=C bond. Indeed, we observed that 5,5-dimethyl-3-(3-methylbut-3-en-1-ynyl)cyclohex-2-enone (1) *a*) undergoes photocyclodimerization selectively at this – additional – exocyclic C=C bond to afford **2**, and *b*), in the presence of 2,3-dimethylbuta-1,3-diene, affords a novel [6+4] photocycloadduct **3** containing a buta-1,2,3-triene moiety (*Scheme 1*). We have now synthesized the two cyclohex-2-enones **4a** and **4b** bearing the same alkynenyl side chain at C(2) and investigated their photochemical behavior.



© 2008 Verlag Helvetica Chimica Acta AG, Zürich

2. Results. – 2-(Alk-3-en-1-ynyl)cyclohex-2-enones **4a** and **4b** were obtained from 2iodocyclohex-2-enones **5a** and **5b** *via* a *Sonogashira*-type coupling [2] with 2-methylbut-1-en-3-yne in 28 and 61% yield, respectively (*Scheme 2*).



Irradiation (350 nm) of a 0.5M solution of **4a** in benzene affords a 2.5:1 mixture of diastereoisomeric 1,1,2,2-tetrasubstituted cyclobutanes **6a** and **7a**, respectively. Under similar conditions, **4b** affords only the *trans*-diastereoisomer **6b**. On irradiation in the presence of a 20-fold molar excess of 2-chloroacrylonitrile, both cyclohexenones **4** afford a – roughly – 1:1 diastereoisomeric mixture of 2-alkynyl-1-chloro-2-methyl-cyclobutane-1-carbonitriles **8** and **9**, respectively. On irradiation in the presence of excess 2,3-dimethylbuta-1,3-diene, again both cyclohexenones **4** behave alike, affording – roughly – 4:3 mixtures of the *trans*-1,1,2,2-tetraalkylcyclobutane **10** and the (formal) [4+2] cycloadduct **11**, respectively (*Scheme 3*). The conversion of both cyclohexenones **4** to products in all these experiments – as monitored by ¹H-NMR – is significantly slower than that of **1** in the corresponding reactions, and competing (photo)destruction of the primarily formed products begins at a much earlier stage, generally limiting the conversion of **4** to $\leq 50\%$.

3. Discussion. – Under photodimerization conditions, *i.e.*, irradiation of 0.5M solutions, cyclohexenones **4** behave very similarly to **1** by reacting almost exclusively at the exocyclic C=C bond. The assignment of the *trans*-configuration to the major-diastereoisomer **6** was based on the analysis of the vicinal coupling constants of the AA'XX' pattern of the two adjacent CH₂ groups in the cyclobutane ring [1] and the chemical shifts of the Me groups in the ¹³C-NMR spectra, in which the Me C-atoms of the *trans*-diastereoisomer resonated at lower field by *ca.* 5 ppm [3]. Interestingly, **1** gave a 1:1 mixture of diastereoisomers, whereas **4** afforded distinctly higher amounts of the *trans*-isomer **6**.

The differentiation between cyclobutanecarbonitriles **8** and **9** is straightforward from their ¹H-NMR spectra, as the four H-atoms of the adjacent CH_2 groups exhibit first order signals (and coupling constants). The relative configuration of the Me group at C(2) was deduced from NOE analysis and that of the Cl-atom at C(1) from the fact that a vicinal H-atom *trans* to the Cl-atom was shifted to lower field as compared to the corresponding *cis*-oriented H-atom [4][5]. In contrast, the *trans*-alignment of the (vicinal) alkynyl and alkenyl groups on the cyclobutane ring in **10** was based on the NOE analysis of the angular Me groups and the correspondingly adjacent H-atoms, as



here the vicinal coupling constants for the CH_2 H-atoms cannot be determined due to conformational changes in the four-membered ring occurring on the NMR-time scale.

Regarding the reaction with 2-chloroacrylonitrile, excited 1 and 4 exhibited a distinctly different behavior, as only the latter compounds cleanly underwent cyclo-addition to the unsaturated nitrile, while no such reaction was observed for 1. As for the reaction with 2,3-dimethylbuta-1,3-diene, both excited 1 and 4 underwent primary binding between the exocyclic (olefinic) CH_2 group of the enone and a diene CH_2 C-atom to afford biradicals 12 and 13, respectively. The fact that 12 then underwent a novel and unprecedented 1,10-cyclization [1], whereas 13 reacted further *via* – the expected – 1,4- and 1,6-cyclization paths is most probably due to the different position of the acyl substituent in the intermediate pentynenyl radical moiety. Whereas in 12 delocalization extends to the C-atom adjacent to the C=O group, and thus facilitates the 1,10-ring closure, this is not the case for – cross-conjugated – intermediate 13 (*Scheme 4*). In this context, the different behavior of 1 and 4 parallels that of carbonyl-substituted hexadienes [6], where 2-acylhexa-1,5-dienes were found to cyclize much

more sluggishly, *i.e.*, with quantum yields by a magnitude lower than the corresponding 1-acylhexa-1,5-dienes.



Experimental Part

1. General. Photolyses were conducted in a Rayonet RPR-100 photoreactor equipped with 350-nm lamps and solvents of spectrophotometric grade. Column chromatography (CC): silica gel 60 (Merck; 230–400 mesh). ¹H- and ¹³C-NMR spectra (including 2D plots): in CDCl₃ as solvent, Bruker WM 500; at 500.13 and 125.8 MHz, resp., δ in ppm, J in Hz. GC/EI-MS: at 70 eV. The starting materials, 2-iodocyclohex-2-enones **5a** and **5b**, were synthesized according to [7]. Coupling of **5a** and **5b** with 2-methylbut-1-en-3-yne was performed according to [2].

2. Starting Materials. 5,5-Dimethyl-2-(3-methylbut-3-en-1-ynyl)cyclohex-2-enone (4a) was obtained in 28% yield as yellow oil after purification by CC (SiO₂; AcOEt/hexane 1:6). ¹H-NMR: 7.13 (t, J = 4.5); 5.38, 5.28 (br. s); 2.36 (s, 2 H); 2.35 (d, J = 4.5, 2 H); 1.95 (br. s, 3 H); 1.06 (s, 6 H). ¹³C-NMR: 195.7 (s); 151.7 (d); 126.5 (s); 124.5 (s); 122.6 (t); 93.5 (s); 82.6 (s); 51.7 (t); 40.5 (t); 33.9 (s); 28.3 (q); 23.4 (q). EI-MS: 188 (93, M^+), 104 (100).

4,4-Dimethyl-2-(3-methylbut-3-en-1-ynyl)cyclohex-2-enone (**4b**) was obtained in 61% yield as light orange oil after purification by CC (SiO₂, AcOEt/hexane 1:6). ¹H-NMR: 6.95 (*s*); 5.37, 5.27 (br. *s*); 2.53 (*t*, J = 6.8, 2 H); 1.94 (br. *s*, 3 H); 1.88 (*t*, J = 6.8, 2 H); 1.20 (*s*, 6 H). ¹³C-NMR: 195.8 (*s*); 163.2 (*d*); 126.9 (*s*); 126.5 (*s*); 123.0 (*t*); 93.5 (*s*); 82.6 (*s*); 36.0 (*t*); 34.7 (*t*); 34.1 (*s*); 28.1 (*q*); 23.7 (*q*). EI-MS: 188 (100, M^+).

3. *Photochemical Reactions*. Ar-Degassed solns. of **4a** or **4b** were irradiated (concentration, solvent, added reaction partner, duration, degree of conversion, and workup as described).

3.1. Photodimerization of **4a**. A soln. of **4a** (188 mg, 1 mmol) in benzene (2 ml) was irradiated for 40 h up to 40% conversion; dimers **6a** and **7a** were formed in a 2.5 : 1 ratio. A first CC (SiO₂; pentane/Et₂O 1 : 1) afforded first **4a** (63 mg) and then the mixture **6a/7a**. This fraction was subjected to a second CC (SiO₂; pentane/Et₂O 2 : 1) to afford first 38 mg (10%) of trans-2,2'-[(1,2-Dimethylcyclobutane-1,2-diyl)diethyne-2,1-diyl]bis(5,5-dimethylcyclohex-2-en-1-one) **(6a)**. Light yellow oil. R_f 0.29. ¹H-NMR: 7.06 (t, J = 4.4, 2 H); 2.32 (s, 4 H); 2.31 (d, J = 4.4, 4 H); 2.30, 1.92 (AA'XX', J_{AX} = 11.0, $J_{AA'}$ = J_{XX} = 7.0, J_{AX} = 10.0, 4 H); 1.57 (s, 6 H); 1.05 (s, 12 H). ¹³C-NMR: 195.9 (s); 150.5 (d); 124.4 (s); 96.8 (s); 77.8 (s); 51.9 (t); 40.6 (t); 39.7 (s); 33.8 (t); 31.9 (t); 27.9 (q); 25.3 (q). Compound **6a** was followed by 9 mg (3%) of cis-2,2'[(1,2-dimethylcyclobutane-1,2-diyl)diethyne-2,1-diyl]bis(5,5-dimethylcyclobutane-1,2-diyl)diethyne-2,1-diyl]bis(5,5-dimethylcyclobutane-1,2-diyl)diethyne-2,1-diyl]bis(5,5-dimethylcyclobutane-1,2-diyl)diethyne-2,1-diyl]bis(5,5-dimethylcyclohex-2-en-1-one (**7a**). Light yellow oil. R_f 0.14. ¹H-NMR: 7.14 (t, J = 4.4, 2 H); 2.36, 1.91 (AA'XX', J_{AX} = 11.0, $J_{AA'}$ = J_{XX} =

 $10.0, J_{AX} = 7.0, 4 \text{ H}); 2.32 (s, 4 \text{ H}); 2.31 (d, J = 4.4, 4 \text{ H}); 1.36 (s, 6 \text{ H}); 1.04 (s, 12 \text{ H}). {}^{13}\text{C-NMR}: 196.0 (s); 51.3 (d); 124.6 (s); 98.3 (s); 77.0 (s); 51.8 (t); 40.5 (t); 39.7 (s); 34.0 (t); 32.2 (t); 28.3 (q); 21.8 (q).$

3.2 . *Photodimerization of* **4b**. A soln. of **4b** (188 mg, 1 mmol) in benzene (2 ml) was irradiated for 40 h up to 28% conversion: dimer **6b** was formed selectively. CC (SiO₂; pentane/Et₂O 1:1) afforded first **4b** (78 mg) and then 54 mg (14%) of trans-2,2'-*[*(*1*,2-*dimethylcyclobutane-1,2-diyl*)*diethyne-2,1-diyl]-bis*(*4*,*4-dimethylcyclohex-2-en-1-one*) (**6b**). Light yellow oil. R_f 0.25. ¹H-NMR: 6.87 (*s*, 2 H); 2.50 (*t*, *J* = 6.7, 4 H); 2.30, 1.92 (*AA'XX'*, *J*_{AX} = 11.0, *J*_{AA'} = *J*_{XX'} = 7.0, *J*_{AX'} = 10.0, 4 H); 1.86 (*t*, *J* = 6.7, 4 H); 1.57 (*s*, 6 H); 1.18 (*s*, 12 H). ¹³C-NMR: 195.6 (*s*); 161.8 (*d*); 122.7 (*s*); 96.7 (*s*); 78.0 (*s*); 39.8 (*s*); 35.7 (*t*); 34.3 (*t*); 33.8 (*s*); 32.2 (*t*); 27.8 (*q*); 25.2 (*q*).

3.3 Photocycloaddition of **4a** to 2-Chloroacrylonitrile. A soln. of **4a** (94 mg, 0.5 mmol) and 2-chloroacrylonitrile (870 mg, 10 mmol) in benzene (5 ml) was irradiated for 17 h up to 65% conversion. The 1:1 mixture was subjected to CC (SiO₂; pentane/Et₂O 4:3) to afford first 8 mg (7%) of cis-*1*-chloro-2-methyl-2-[(4,4-dimethyl-6-oxocyclohex-1-enyl)ethynyl]cyclobutane-1-carbonitrile (**8a**). $R_{\rm f}$ 0.29. Colorless oil. ¹H-NMR: 7.18 (t, J = 4.4); 2.82 (ddd, J = 5.2, 8.4, 12.4); 2.68 (ddd, J = 7.9, 9.5, 12.5); 2.58 (ddd, J = 5.2, 9.5, 11.1); 2.35 (s, 2 H); 2.34 (d, J = 4.4, 2 H); 2.16 (ddd, J = 7.9, 8.4, 11.1); 1.68 (s, 3 H); 1.07 (s, 6 H). ¹³C-NMR: 195.5 (s); 152.8 (d); 123.6 (s); 117.7 (CN); 92.0 (s); 81.0 (s); 57.3 (s); 52.0 (t); 46.0 (s); 40.2 (t); 34.8 (t); 33.8 (s); 32.0 (t); 28.3 (q); 24.3 (q). Compound **8a** was followed by 9 mg (7%) of trans-1-chloro-2-methyl-2-[4,4-dimethyl-6-oxocyclohex-1-enyl)ethynyl]cyclobutane-1-carbonitrile (**9a**). $R_{\rm f}$ 0.22. Colorless oil. ¹H-NMR: 7.27 (t, J = 4.6); 2.90 (ddd, J = 6.7, 8.5, 12.6); 2.55 (m, 1 H); 2.50 (m, 1 H); 2.35 (s, 2 H); 2.34 (d, J = 4.6, 2 H); 2.21 (m, 1 H); 1.59 (s, 3 H); 1.06 (s, 6 H). ¹³C-NMR: 195.5 (s); 153.5 (d); 123.7 (s); 118.4 (CN); 92.3 (s); 81.0 (s); 59.0 (s); 51.6 (t); 43.6 (s); 40.5 (t); 34.6 (t); 33.8 (s); 31.6 (t); 28.3 (q); 23.1 (q).

3.4 *Photocycloaddition of* **4b** *to* 2-*Chloroacrylonitrile*. A soln. of **4b** (188 mg, 1.0 mmol) and 2chloroacrylonitrile (1740 mg, 20 mmol) in benzene (10 ml) was irradiated for 26 h up to 62% conversion. The 1:1 mixture was subjected to CC (SiO₂, pentane/Et₂O 4:3) to afford first 32 mg (12 %) of cis-*1chloro-2-methyl-2-[(3,3-dimethyl-6-oxocyclohex-1-enyl)ethynyl]cyclobutane-1-carbonitrile* (**8b**). $R_{\rm f}$ 0.26. Colorless oil. ¹H-NMR: 6.98 (*s*); 2.82 (*ddd*, *J* = 5.2, 8.4, 12.4); 2.69 (*ddd*, *J* = 8.1, 9.7, 12.4); 2.56 (*ddd*, *J* = 5.2, 9.7, 11.1); 2.52 (*t*, *J* = 6.7, 2 H); 2.14 (*ddd*, *J* = 8.1, 8.4, 11.1); 1.88 (*t*, *J* = 6.7, 2 H); 1.68 (*s*, 3 H); 1.21 (*s*, 6 H). ¹³C-NMR: 195.2 (*s*); 163.5 (*d*); 122.0 (*s*); 117.7 (CN); 91.7 (*s*); 81.1 (*s*); 57.4 (*s*); 46.3 (*s*); 35.5 (*t*); 34.8 (*t*); 34.5 (*s*); 33.8 (*t*); 31.9 (*t*); 27.7 (*q*); 24.3 (*q*). Compound **8b** was followed by 50 mg (20%) of trans-*1-chloro-2-methyl-2-[(3,3-dimethyl-6-oxocyclohex-1-enyl)ethynyl]cyclobutane-1-carbonitrile* (**9b**). $R_{\rm f}$ 0.20. Colorless oil. ¹H-NMR: 7.06 (*s*); 2.90 (*ddd*, *J* = 4.9, 8.5, 12.5); 2.55 (*ddd*, *J* = 9.1, 9.2, 12.5); 2.51 (*t*, *J* = 6.7, 2 H); 2.50 (*m*, 1 H); 2.21 (*ddd*, *J* = 4.9, 9.2, 10.4); 1.87 (*t*, *J* = 6.7, 2 H); 1.59 (*s*, 3 H); 1.20 (*s*, 6 H). ¹³C-NMR: 195.2 (*s*); 164.1 (*d*); 121.8 (*s*); 118.3 (CN); 92.0 (*s*); 81.0 (*s*); 59.0 (*s*); 43.9 (*s*); 35.5 (*t*); 34.8 (*t*); 34.5 (*s*); 34.3 (*t*); 33.8 (*t*); 31.6 (*t*); 27.7 (*q*); 23.2 (*q*).

3.5 *Photocycloaddition of* **4a** *to* 2,3-*Dimethylbuta-1,3-diene*. A soln. of **4a** (376 mg, 2.0 mmol) and 2,3-dimethylbuta-1,3-diene (3.28 g, 40 mmol) in benzene (20 ml) was irradiated for 100 h up to 65% conversion. A first CC (SiO₂; pentane/Et₂O 4 :1) allowed the isolation of the 4 :3 mixture **10a/11a** (R_t 0.25). This mixture was subjected to a further CC (SiO₂; hexane/AcOEt 12 :1) to afford first 36.2 mg (18%) of 5,5-dimethyl-2-{2-{trans-1,2-dimethyl-2-(1-methylethynyl)cyclobutyl]ethynyl]cyclohex-2-enone (**10a**). R_t 0.29). Light yellow liquid. ¹H-NMR: 7.03 (t, J = 4.6); 4.80 (br. s); 4.63 (br. s); 2.33 (s, 2 H); 2.32 (d, J = 4.6, 2 H); 2.30 (m, 1 H); 2.28 (m, 1 H); 1.68 (s, 3 H); 1.63 (m, 1 H); 1.52 (m, 1 H); 1.42 (s, 3 H); 1.26 (s, 3 H); 1.06 (s, 6 H). ¹³C-NMR: 195.3 (s); 150.3 (d); 150.2 (s); 124.2 (s); 109.5 (t); 98.2 (s); 77.4 (s); 51.8 (t); 50.2 (s); 40.4 (t); 37.4 (s); 34.0 (s); 30.4 (t); 28.4 (q); 27.3 (t); 24.4 (q); 23.1 (q); 18.8 (q). Compound **10a** was followed by 10 mg (5%) of 5,5-dimethyl-2-[2-(1,3,4-trimethylcyclohex-3-en-1-yl)ethynyl]cyclohex-2-enone (**11a**). R_t 0.22. Colorless liquid. ¹H-NMR: 7.00 (t, J = 4.6); 2.33 (s, 2 H); 2.32 (d, J = 4.6, 2 H); 2.10 (m, 2 H); 1.79 (m, 2 H); 1.62 (s, 3 H); 1.59 (s, 3 H); 1.50 (m, 2 H); 1.26 (s, 3 H); 1.04 (s, 6 H). ¹³C-NMR: 195.5 (s); 150.3 (d); 122.9 (s); 122.7 (s); 100.2 (s); 73.9 (s); 51.3 (t); 44.8 (s); 40.3 (t); 35.3 (t); 35.2 (t); 35.1 (t); 33.6 (s); 27.7 (q); 23.1 (q); 18.2 (q).

3.6 Photocycloaddition of **4b** to 2,3-Dimethylbuta-1,3-diene. A soln. of **4b** (282 mg, 1.5 mmol) and 2,3-dimethylbuta-1,3-diene (2.46 g, 30 mmol) in benzene (15 ml) was irradiated for 74 h up to 52% conversion to afford mainly a 4:3 mixture **10b** /**11b**. CC (SiO₂; pentane/Et₂O 7:2) afforded first 25 mg (7%) of 4,4-dimethyl-2-{2-[trans-1,2-dimethyl-2-(1-methylethynyl)cyclobutyl]ethynyl]cyclohex-2-enone

HELVETICA CHIMICA ACTA - Vol. 91 (2008)

(10b). R_t 0.32. Light yellow liquid. ¹H-NMR: 6.84 (*s*); 4.80 (br. *s*); 4.63 (br. *s*); 2.50 (*t*, *J* = 6.8, 2 H); 2.30 (*m*, 1 H); 2.26 (*m*, 1 H); 1.86 (*t*, *J* = 6.8, 2 H); 1.69 (*s*, 3 H); 1.63 (*m*, 1 H); 1.52 (*m*, 1 H); 1.43 (*s*, 3 H); 1.26 (*s*, 3 H); 1.18 (*s*, 6 H). ¹³C-NMR: 195.7 (*s*); 161.1 (*d*); 150.0 (*s*); 122.9 (*s*); 109.5 (*d*); 98.0 (*s*); 76.9 (*s*); 49.8 (*s*); 37.7 (*s*); 35.7 (*t*); 34.5 (*t*); 33.6 (*s*); 30.5 (*t*); 27.8 (*q*); 27.3 (*t*); 24.4 (*q*); 23.1 (*q*); 18.8 (*q*). Compound 10b was followed by 6 mg (2.2%) of 4,4-dimethyl-2-[2'-(1,3,4-trimethylcyclohex-3-en-1-yl)ethynyl]cyclohex-2-enone (11b). R_t 0.28. Colorless liquid. ¹H-NMR: 6.82 (*s*); 2.50 (*t*, *J* = 6.6, 2 H); 2.10 (*m*, 2 H); 1.86 (*t*, *J* = 6.6, 2 H); 1.78 (*m*, 2 H); 1.63 (*s*, 3 H); 1.59 (*s*, 3 H); 1.50 (*m*, 2 H); 1.26 (*s*, 3 H); 1.18 (*s*, 6 H). ¹³C-NMR: 195.5 (*s*); 161.3 (*d*); 122.9 (*s*); 122.7 (*s*); 100.2 (*s*); 73.9 (*s*); 44.8 (*s*); 35.4 (*t*); 35.3 (*t*); 35.2 (*t*); 35.1 (*t*); 34.5 (*t*); 33.6 (*s*); 27.3 (*q*); 23.1 (*q*); 18.2 (*q*).

REFERENCES

- [1] I. Inhülsen, J. Kopf, P. Margaretha, Helv. Chim. Acta 2008, 91, 387.
- [2] M. W. Miller, C. R. Johnson, J. Org. Chem. 1997, 62, 1582.
- [3] E. L. Eliel, K. M. Pietrusewicz, Org. Magn. Reson. 1980, 13, 193.
- [4] K. B. Wiberg, D. E. Barth, W. E. Pratt, J. Am. Chem. Soc. 1977, 99, 4286.
- [5] P. Margaretha, K. Schmidt, J. Kopf, V. Sinnwell, Synthesis 2007, 1426.
- [6] W. C. Agosta, S. Wolff, Pure Appl. Chem. 1982, 54, 1579.
- [7] P. Margaretha, S. Reichow, W. C. Agosta, J. Org. Chem. 1994, 59, 5393.

Received August 4, 2008