171. Synthesis of Macrocyclic Imides by One-Step Ring Enlargement

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By one-step ring-enlargement reaction with isocyanates, 2-cyano- and 2-(ethoxycarbonyl)-substituted cycloalkanones are converted into macrocyclic imides.

Recently, we have shown that 2-nitro- and 2-cyano-substituted cycloalkanones can undergo ring enlargement by introducing a suitably functionalized side chain at position 2, followed by intramolecular nucleophilic addition to the C=O group of the cycloalkanone. This reaction route was successfully used for the preparation of compounds with medium and large rings as carbocycles [1], lactones [2], and lactames [3].

Now, we report the preliminary results of the one-step ring enlargement of 2-cyano- and 2-(ethoxycarbonyl)-substituted cycloalkanones into macrocyclic imides. It is well known that active-methylene compounds readily react with isocyanates [4] and isothiocyanates [5] giving the corresponding 1:1 adducts. Thus, it could be expected that cycloalkanones substituted at C(2) with an electron-withdrawing group and possessing one active H-atom, would react in an analogous manner. As a model compound, we decided to use the 2-cyano-substituted cyclododecanone **1** [6]. Treatment of **1** with NaH in THF, followed by addition of the aryl isocyanates **2a**, **2b**, or **2c**, and acidic workup gave the corresponding CN-substituted cyclic imides **3a**, **3b**, and **3c** in 76, 79, and 78% yield, respectively *(Scheme 1)*. Under the same conditions from **1** and vinyl isocyanate (**4**) [7], phenyl isothiocyanate (**5**), or *p*-toluenesulfonyl isocyanate (**6**), the imides **7**, **8**, and **9** were obtained in 87, 78, and 95% yield, respectively. The physical data indicated that compounds **8** and **9** exist in the corresponding thioenol and enol forms *(Scheme 1)*.

From the structure of the reaction products, it could be assumed that the ring enlargement of **1** proceeds through the following mechanism: the initial nucleophilic addition of the sodium salt of the CN-substituted ketone into the imino function of the isocyanate leads to the 1:1 adduct **A** which undergoes ring closure to the four-membered cyclic intermediate **B**. Further ring opening gives **C**, the product of a two-membered ring enlargement *(Scheme 2)*.

In the case of 2-(alkoxycarbonyl)-substituted cycloalkanones, we found that ethyl-2-oxocyclooctanecarboxylate (**10**) [8] reacts similar to **1** with *p*-toluenesulfonyl isocyanate

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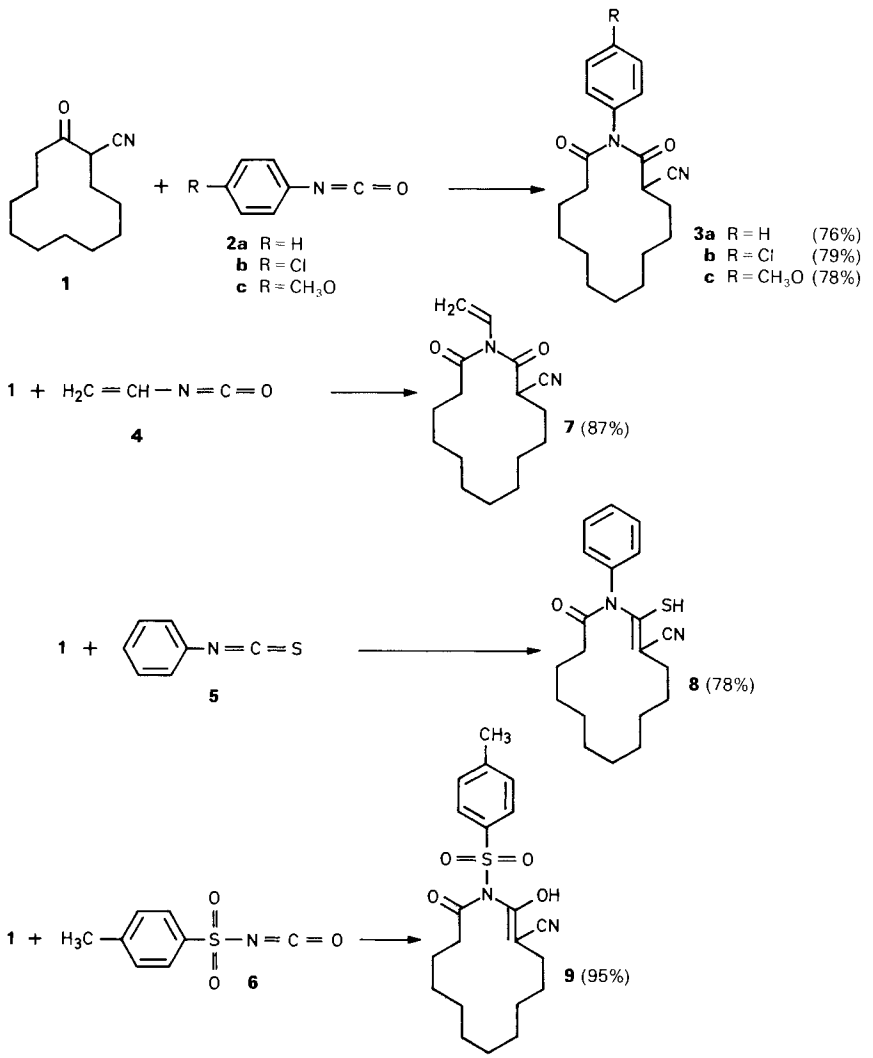
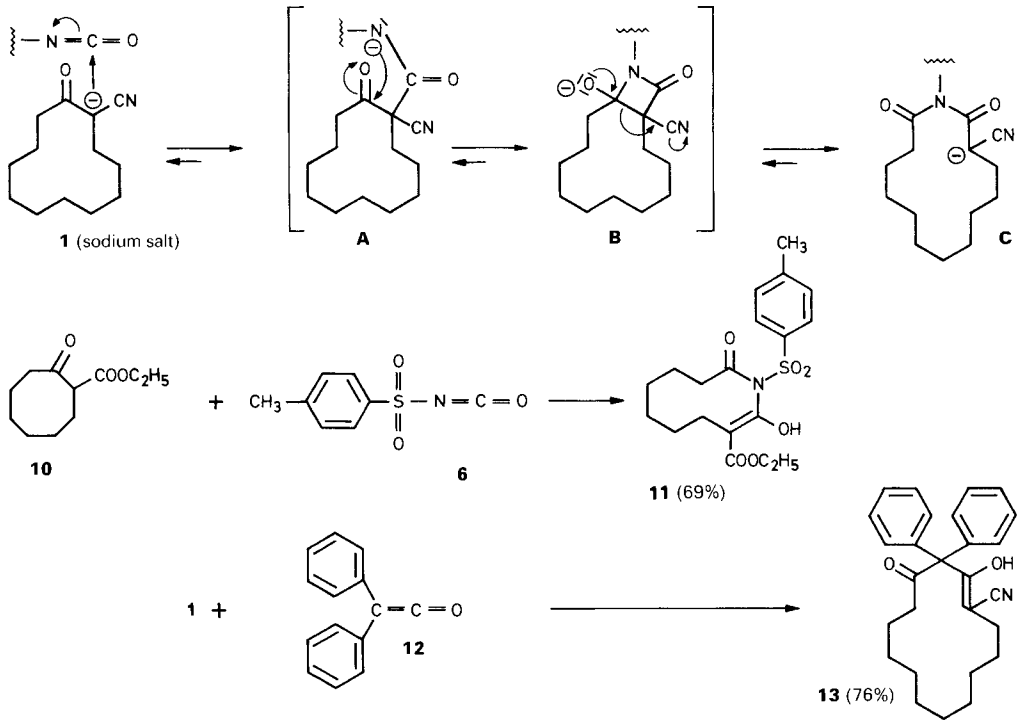
Scheme 1



(**6**). The corresponding ethoxycarbonyl-substituted imide **11**, occurring in the enol form, was obtained in 69% yield *(Scheme 2)*.

It is known that ketenes react analogously to isocyanates with active-methylene compounds giving products of *C*-acylation [9]. By taking this reactivity into account, it was suggested that the reaction of ketenes with cycloalkanones activated at C(2) with an electron-withdrawing group will lead to the formation of products of ring enlargement by two C-atoms. In a preliminary experiment, we found that the sodium salt of cyclododecanone **1** reacts with the easily available diphenyl ketene (**12**) [10] giving the expected CN-substituted diketone **13** in 76% yield as an unstable oil *(Scheme 2)*.

Scheme 2



These results indicate that ring enlargements analogous to those described in [1–3] also occur with other types of compounds containing a cumulene or heterocumulene function. Further investigations in this direction are in progress.

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Experimental Part

General. If not otherwise mentioned, the following conditions were applied: before evaporation, org. solns. were dried (Na_2SO_4). Flash chromatography: silica gel *60 PF_{254}* for prep. TLC, *Merck*. M.p.: *Mettler-FP-52* apparatus; IR [cm^{-1}]: in $CHCl_3$ on *Perkin-Elmer 297*. ^{1}H-NMR: *Varian XL-200* at 200 MHz in $CDCl_3$; δ in ppm, J in Hz; TMS as internal standard (= 0 ppm). ^{13}C-NMR: *Varian XL 200* at 50 MHz. EI-MS: *Varian MAT 112 S; m/z* (rel. intensity $\geq$ 5%). CI-MS: *Varian MAT 112* (2-methylpropane).

General Procedure for the Preparation of the Cyclic Imides **3a–c, 7–9, 11,** *and the Cyclic Diketone* **13**. To a suspension of NaH (6 mmol) in dry THF (50 ml) is added, in small portions, *2-oxocyclododecane-1-carbonitrile* (**1**; 5 mmol) or *ethyl 2-oxocyclooctane-1-carboxylate* (**10**; 5 mmol) and the resulting mixture stirred at 20° for 30 min. After addition of 6 mmol of the corresponding isocyanates **2a–c**, **4**, or **6**, *phenyl isothiocyanate* (**5**), or *diphenyl ketene* (**12**), stirring is continued for 1 h at 20° and the solvent evaporated. The residue is then dissolved in H_2O (100 ml), washed with Et_2O (3 × 30 ml), and the alkaline H_2O phase acidified with dil. HCl and extracted with Et_2O (3 × 30 ml). The combined Et_2O extracts are washed with H_2O, dried, the solvent is evaporated, and the residue purified by column chromatography or recrystallized from a suitable solvent.

2,14-Dioxo-1-phenyl-1-azacyclotetradecane-3-carbonitrile (**3a**). Yield 76%. M.p. 101–102° (EtOH). IR: 2260, 1705, 1596. ^{1}H-NMR: 7.55–7.44 (*m*, 3 arom. H); 7.15–7.10 (*m*, 2 arom. H); 4.86 (*t*, *J* = 6, H–C(3)); 2.60–1.10 (*m*, 20 H). ^{13}C-NMR: 176.4 (*s*, C(2)); 169.5 (*s*, C(14)); 137.7 (*s*, 1 arom. C); 130.1, 129.4, 128.5 (3 *d*, 5 arom. C); 116.9 (*s*, CN); 40.0 (*d*, C(3)); 36.6, 30.1, 25.9, 25.7, 25.6, 25.4, 24.6, 24.4, 24.3, 23.9 (10 *t*). CI-MS: 327 ([*M* + 1]$^+$). Anal. calc. for $C_{20}H_{26}N_2O_2$ (326.44): C 73.59, H 8.03, N 8.58; found: C 73.44, H 7.87, N 8.49.

1-(4-Chlorophenyl)-2,14-dioxo-1-azacyclotetradecane-3-carbonitrile (**3b**). Yield 79%. M.p. 144.5–145.5° (EtOH). IR: 2258, 1715, 1596. ^{1}H-NMR: 7.48, 7.07 (*AA'MM'*, 4 arom. H); 4.87 (*t*, *J* = 6, H–C(3)); 2.50–1.10 (*m*, 20 H). ^{13}C-NMR: 175.9 (*s*, C(2)); 169.4 (*s*, C(14)); 136.1, 135.5 (2 *s*, 2 arom. C); 130.4, 129.8 (2 *d*, 4 arom. C); 116.7 (*s*, CN); 40.0 (*d*, C(3)); 36.6, 30.0, 25.8, 25.7, 25.6, 25.3, 24.5, 24.4, 24.2, 23.8 (10 *t*). CI-MS: 361 ([*M* + 1]$^+$). Anal. calc. for $C_{20}H_{25}ClN_2O_2$ (360.88): C 66.56, H 6.98, N 7.76; found: C 66.47, H 6.82, N 7.85.

1-(4-Methoxyphenyl)-2,14-dioxo-1-azacyclotetradecane-3-carbonitrile (**3c**). Yield 78%. Oil. IR: 2256, 1710, 1610. ^{1}H-NMR: 7.20–6.90 (*m*, 4 arom. H); 4.83 (*t*, *J* = 6, H–C(3)); 3.84 (*s*, CH_3O); 2.66–1.10 (*m*, 20 H). ^{13}C-NMR: 176.7 (*s*, C(2)); 169.7 (*s*, C(14)); 160.0, 130.1 (2 *s*, 2 arom. C); 129.5 (*d*, 1 arom. C); 116.9 (*s*, CN); 115.3 (*d*, 1 arom. C); 55.5 (*q*, CH_3O); 39.9 (*d*, C(3)); 36.5, 30.1, 25.9, 25.7, 25.6, 25.4, 24.6, 24.4, 24.3, 23.9 (10 *t*). CI-MS: 357 ([*M* + 1]$^+$).

2,14-Dioxo-1-vinyl-1-azacyclotetradecane-3-carbonitrile (**7**). Yield 87%. M.p. 65.5–66.5° (hexane). IR: 2258, 1715, 1642. ^{1}H-NMR: 6.46 (*dd*, *J* = 15.6, 8.0, H–C(1')); 5.46 (*dd*, *J* = 8.0, 1.1, 1 H–C(2')); 5.24 (*dd*, *J* = 15.6, 1.1, 1 H–C(2')); 4.76 (*dd*, *J* = 7.5, 5.6, H–C(3)); 2.84 (*ddd*, *J* = 16, 10, 4, 1 H–C(13)); 2.54 (*ddd*, *J* = 16, 7, 4, 1 H–C(13)); 2.10–1.10 (*m*, 18 H). ^{13}C-NMR: 175.9 (*s*, C(2)); 168.7 (*s*, C(14)); 131.6 (*d*, C(1')); 117.3 (*t*, C(2')); 116.8 (*s*, CN); 39.5 (*d*, C(3)); 36.3, 29.7, 25.9, 25.7, 25.6, 25.5, 24.4, 24.3, 24.1, 23.8 (10 *t*). CI-MS: 277 ([*M* + 1]$^+$). Anal. calc. for $C_{16}H_{24}N_2O_2$ (276.37): C 69.53, H 8.75, N 10.13; found: C 69.82, H 9.00, N 10.36.

2-Mercapto-14-oxo-1-phenyl-1-azacyclotetradec-2-ene-3-carbonitrile (**8**). Yield 78%. M.p. 105–106° (CH_2Cl_2/Et_2O). IR: 2580, 2214, 1685, 1588. ^{1}H-NMR: 7.58–7.24 (*m*, 5 arom. H); 3.59 (*s*, SH, exchangeable with D_2O); 2.90–1.00 (*m*, 20 H). ^{13}C-NMR: 172.1 (*s*, C(14)); 150.5 (*s*, C(2)); 139.0 (*s*, 1 arom. H); 129.3, 127.8, 126.6 (3 *d*, 5 arom. C); 116.6 (*s*, CN); 113.7 (*s*, C(3)); 33.2, 31.6, 27.0, 26.3, 25.3, 25.2, 25.1, 23.9, 23.6, 23.5 (10 *t*). CI-MS: 343 ([*M* + 1]$^+$). Anal. calc. for $C_{20}H_{26}N_2OS$ (342.50): C 70.14, H 7.65, N 8.18; found: C 70.30, H 7.90, N 8.17.

*2-Hydroxy-14-oxo-1-(*p*-toluenesulfonyl)-1-azacyclotetradec-2-ene-3-carbonitrile* (**9**). Yield 95%. M.p. 107–109° (Et_2O/hexane). IR: 3210, 2248, 1720, 1598. ^{1}H-NMR: 9.69 (br. *s*, OH, exchangeable with D_2O); 7.96, 7.36 (*AA'MM'*, 4 arom. H); 2.88 (*ddd*, *J* = 19.2, 9.4, 3.3, 1 H–C(13)); 2.60–2.28 (*m*, 4 H), therein at 2.46 (*s*, CH_3); 2.20–1.10 (*m*, 18 H). ^{13}C-NMR: 200.2 (*s*, C(14)); 161.0 (*s*, C(2)); 145.8, 134.6 (2 *s*, 2 arom. C); 129.7, 128.8 (2 *d*, 4 arom. C); 115.3 (*s*, CN); 62.9 (*s*, C(3)); 35.5, 33.7, 26.1, 23.4, 22.6, 22.4 (6 *t*); 22.3 (2 *t*); 21.7 (*q*, CH_3); 21.2, 20.9 (2 *t*). CI-MS: 405 ([*M* + 1]$^+$). Anal. calc. for $C_{21}H_{28}N_2O_4S$ (404.52): C 62.35, H 6.98, N 6.92; found: C 62.06, H 6.96, N 7.15.

*Ethyl 2-Hydroxy-10-oxo-1-(*p*-toluenesulfonyl)-1-azacyclododec-2-ene-3-carboxylate* (**11**). Yield 69%. M.p. 95–97° (EtOH). IR: 3170, 1750, 1715, 1690, 1598. ^{1}H-NMR: 11.13 (br. *s*, OH, exchangeable with D_2O); 7.96, 7.32 (*AA'MM'*, 4 arom. H); 4.06 (*q*, *J* = 7, CH_2O), 2.90–2.26 (*m*, 8 H), therein at 2.43 (*s*, CH_3); 2.06–0.74 (*m*, 10 H), therein at 1.05 (*t*, *J* = 7, CH_3). ^{13}C-NMR: 212.0 (*s*, C(10)); 165.2 (*s*, COO); 164.7 (*s*, C(2)); 144.8, 135.5 (2 *s*, 2 arom. C); 129.3, 128.4 (2 *d*, 4 arom. C); 69.7 (*s*, C(3)); 63.0 (*t*, CH_2O); 39.1, 30.2, 29.6, 25.5, 24.3, 23.6 (6 *t*); 21.5 (*q*, CH_3); 13.4 (*q*, CH_3CH_2O). CI-MS: 396 ([*M* + 1]$^+$), 353, 307, 199. Anal. calc. for $C_{19}H_{25}NO_6S$ (395.47): C 57.71, H 6.37, N 3.54; found: C 57.87, H 6.25, N 3.47.

2-Hydroxy-4-oxo-3,3-diphenylcyclotetradec-1-ene-1-carbonitrile (**13**). Yield 76%. Oil. IR: 3510, 2224, 1712, 1602. ^{1}H-NMR: 11.52 (br. *s*, OH, exchangeable with D_2O); 7.60–7.20 (*m*, 10 arom. H); 2.50–2.30 (*m*, 4 H); 1.80–1.52 (*m*, 4 H); 1.46–1.06 (*m*, 12 H). ^{13}C-NMR: 213.0 (*s*, C(4)); 180.1 (*s*, C(2)); 133.8 (*s*, 2 arom. C); 129.1, 128.7, 128.6, 128.5, 128.4 (5*s*, 10 arom. C); 115.2 (*s*, CN); 85.1 (*s*, C(1)); 53.4 (*s*, C(3)); 34.0, 31.9, 29.3, 29.2 (4 *t*, 4 CH_2); 29.1 (*t*, 2 CH_2); 29.0, 28.6, 27.6, 24.6 (4*t*, 4 CH_2). CI-MS: 402 ([*M* + 1]$^+$). Anal. calc. for $C_{27}H_{31}NO_2$ (401.55): C 80.76, H 7.78, N 3.49; found: C 80.72, H 7.92, N 3.43.

REFERENCES

[1] Y. Nakashita, M. Hesse, *Helv. Chim. Acta* **1983,** *66,* 845; M. Süsse, J. Hájicek, M. Hesse, *ibid.* **1985,** *68,* 1986.
[2] K. Kostova, M. Hesse, *Helv. Chim. Acta* **1984,** *67,* 1713; B. Milenkov, M. Hesse, *ibid.* **1987,** *70,* 308.
[3] R. Wälchli, A. Guggisberg, M. Hesse, *Tetrahedron. Lett.* **1984,** *25,* 2205.
[4] J.H. Rigby, F.J. Burkhardt, *J. Org. Chem.* **1986,** *51,* 1374; M.M. Shoukry, M.H. Elnagdi, E.E. Mahgoub, *Ann. Chem. (Rome)* **1979,** *69,* 211; L. Capuano, P. Boschat, H.W. Heyer, G. Wachter, *Chem. Ber.* **1973,** *106,* 312.
[5] T.N. Ghosh, *J. Indian Chem. Soc.* **1935,** *12,* 692; H. Dehne, P. Krey, *Z. Chem.* **1979,** *19,* 211; R.M. Mohareb, A. Habashi, N.S. Ibrahim, S.M. Sherif, *Synthesis* **1987,** 228.
[6] B. Föhlisch, R. Herter, E. Wolf, J.J. Stezowski, E. Eckle, *Chem. Ber.* **1982,** *115,* 355.
[7] R. Hart, *Bull. Soc. Chim. Belg.* **1956,** *65,* 291.
[8] *Org. Synth. Coll. Vol.* **1973,** *5,* 198.
[9] H. Eck, H. Prigge, *Liebigs Ann. Chem.* **1970,** *731,* 12; D.O. Dean, W.B. Dickinson, O.R. Quayle, C.T. Lester, *J. Am. Chem. Soc.* **1950,** *72,* 1740; K. Yoshida, Y. Yamashita, *Tetrahedron Lett.* **1966,** 693.
[10] E.C. Taylor, A. McKillop, G.H. Hawks, *Org. Synth.* **1972,** *52,* 36.