85. Synthesis of 1*H*-1,2,3-Triazoles from 2-Substituted Cyclododecanones and Phenyl Azide

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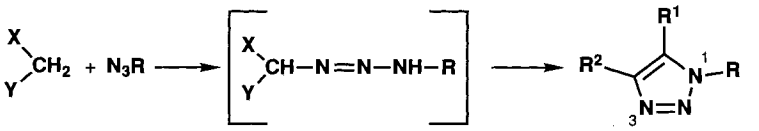
Dedicated to Prof. Dr. *Burchard Franck* on the occasion of his 65th birthday

(25.IV.91)

By reaction with phenyl azide, 2-cyano- and 2-(ethoxycarbonyl)-substituted cyclododecanones are converted into 5-amino- and 5-hydroxy-1*H*-1,2,3-triazoles, respectively. The possible reaction mechanism is discussed.

The base-catalyzed condensation of active methylene compounds **I** with azides, first described by *Dimroth* [1], is a general synthetic method for the construction of the 1*H*-1,2,3-triazole ring system [2]. The reaction proceeds through a triazene intermediate [3] formed by a nucleophilic attack of the carbanion of the active methylene compound on the terminal N-atom of the azide. Depending on the nature of the activating groups of the methylene compound, further regiospecific cyclization to a dihydrotriazole, followed by aromatization, leads to the formation of 5-amino- [4], 5-hydroxy- [1] [5] [6], or 5-alkyl-substituted [1] [6] [7] 1*H*-1,2,3-triazoles **II** (*Scheme 1*).

Scheme 1



I a X = CN, Y = H, Alkyl

b X = Y = CO_2Et

c X = R_3CO, Y = CO_2Et

II a $R^1 = NH_2$, R^2 = Y

b R^1 = OH, $R^2 = CO_2Et$

c R^1 = Alkyl, $R^2 = CO_2Et$

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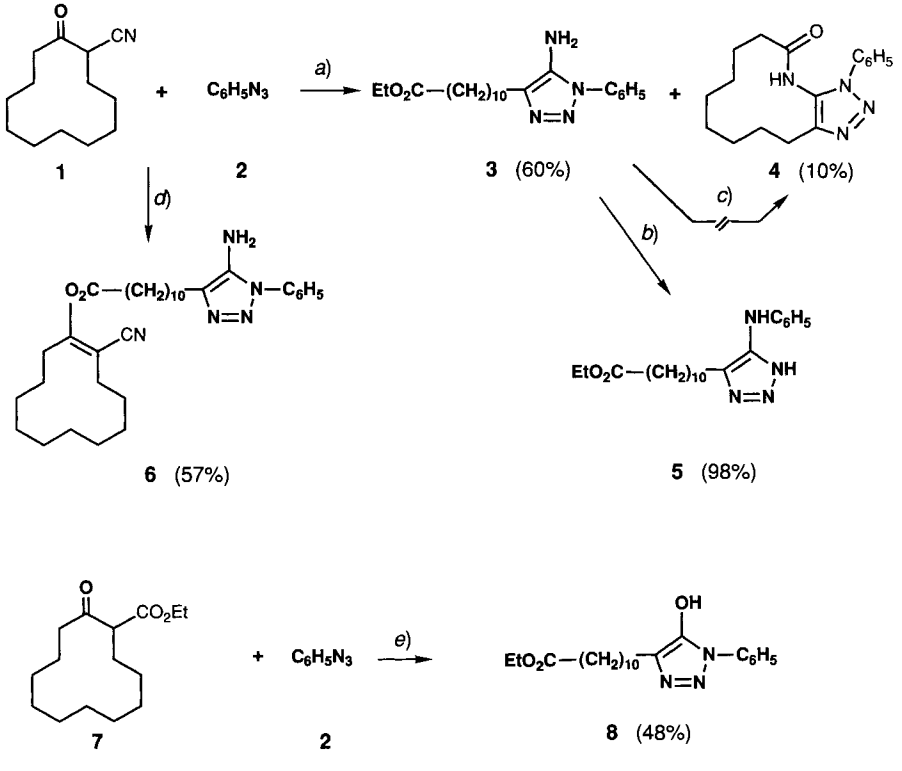
Despite of the presence of a vast number of literature data on the *Dimroth* reaction, little is known about the reactivity of active methylene compounds substituted at the central C-atom. It was shown that the reaction of azides with alkyl- or aryl-substituted malonic esters [1] [6] or ethyl acetoacetates [1] follows a different course. In both cases, the substituent is entering at C(4) of the newly formed 5-hydroxy-1*H*-1,2,3-triazole, and the reaction is accompanied by decarboxylation. Since cycloalkanones substituted at C(2) with an electron-withdrawing group could be regarded as cyclic analogues of monosubstituted active methylene compounds, we were interested to investigate their behaviour under the conditions of the *Dimroth* reaction.

Treatment of 1-oxocyclododecane-2-carbonitrile (**1**) [8] with phenyl azide (**2**) [9] in the presence of a catalytic amount of NaOEt in EtOH/THF for four days at room temperature led to the formation of 5-amino-1-phenyl-1*H*-1,2,3-triazole **3** and lactam **4** in 60 and 10 % yield, respectively. It is known that, in the presence of base, 1-substituted 5-amino-1*H*-1,2,3-triazoles undergo *Dimroth* rearrangement into 5-(arylamino)-1*H*-1,2,3-triazoles substituted at the 5-amino group [10] [11]. Rearrangement of **3** in refluxing pyridine gave the corresponding 5-(phenylamino)-1*H*-1,2,3-triazole **5** in 98 % yield, thus providing an additional confirmation of the proposed structure of **3** (*Scheme 2*).

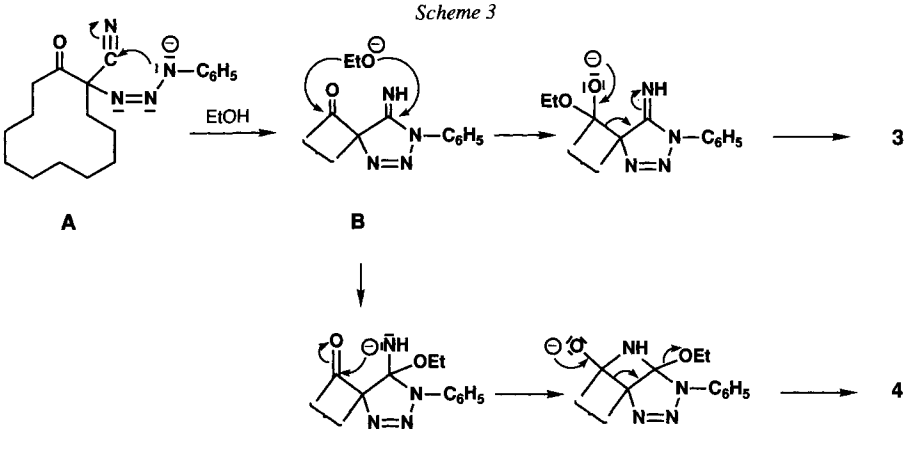
Scheme 2



a) 0.2 Equiv. of NaOEt, EtOH, THF, 20°. *b*) Py, reflux. *c*) 0.2 Equiv. of NaOEt, EtOH, 20° or reflux. *d*) 0.2 Equiv. of NaH, THF, 20°. *e*) 1 Equiv. of NaOEt, EtOH, THF, 20°.

The formation of **3** might proceed through a mechanism analogous to that of the reaction of the corresponding monosubstituted active methylene compounds with azides (see *Scheme 1*): After the initial nucleophilic attack of the carbanion of **1**, the triazene intermediate **A** undergoes regiospecific cyclization onto the CN function to dihydrotriazole intermediate **B**; nucleophilic ring opening induced by EtO^- then leads to the stable triazole **3** (*Scheme 3*). A similar ring opening of bicyclic compounds possessing an electron-withdrawing substituent serving as an anion-stabilizing group was used in our studies on the ring enlargement of cycloalkanones [12]. In the present case, the stabilization of the anion is assisted by an aromatization process. An experiment aiming at the isolation of intermediate **B** was conducted by using NaH instead of NaOEt as a base. Unfortunately, enol ester **6** was isolated as the main product, probably resulting from the nucleophilic ring opening of **B** by the sodium enolate of **1** (*Scheme 2*).

Scheme 3



The side product of the reaction of **1** with NaOEt, the 14-membered lactam **4**, could be regarded as a ring-enlarged product of **1** implying the CN function. We assume that **4** is formed by ring opening of intermediate **B**, rather than by intramolecular amidation of **3** (*Scheme 3*). Indeed, treatment of **3** with a catalytic or equivalent amount of NaOEt in EtOH at room temperature or under reflux gave a complex product mixture in which **4** could not be detected (*Scheme 2*).

Ethyl 2-oxocyclododecanecarboxylate (**7**) [13] reacted in an analogous manner with phenyl azide (**2**) in the presence of 1 equiv. NaOEt in EtOH/THF to give the corresponding 5-hydroxy-1-phenyl-1*H*-1,2,3-triazole **8** in 48% yield (*Scheme 2*).

These preliminary results show that cycloalkanones activated at C(2) with an electron-withdrawing group can be used successfully in the *Dimroth* reaction. Depending on the ring size and the type of the activating group of the cycloalkanone or the type of the azide, suitably 1,4,5-trisubstituted- 1*H*-1,2,3-triazoles could be prepared. Further investigations in this direction are in progress.

The support of this work by the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

General. If not otherwise mentioned, the following conditions were applied: the reactions were run in dry org. solvents under Ar; before evaporation, org. solns. were dried (Na_2SO_4). Column chromatography (CC): silica gel *Merck 60*, 0.040–0.063 mm. M.p.: uncorrected. IR spectra (cm^{-1}): in KBr; *Perkin-Elmer-781* instrument. ^{1}H-NMR spectra: in $CDCl_3$; *Bruker-AC-300* spectrometer; chemical shifts in ppm rel. to internal TMS (=0 ppm), coupling constants *J* in Hz. ^{13}C-NMR spectra: in $CDCl_3$; *Varian-XL-200* instrument; multiplicities from ^{1}H-decoupled or DEPT spectra. MS: *Varian-MAT-711* or *Varian-MAT-112* systems; chemical ionisation (CI); peaks in *m/z*.

1. *Ethyl 11-(5'-Amino-1'-phenyl-1'H-1',2',3'-triazol-4'-yl)undecanoate* (**3**) *and 6,7,8,9,10,11,12,13-Octahydro-3-phenyl-3*H*-1,2,3-triazolo[4,5-b]azacyclotetradecen-5(4*H*)-one* (**4**). To a soln. of **1** [8] (1.03 g, 5 mmol) and **2** [9] (0.714 g, 6 mmol) in THF (2 ml) was added 21% NaOEt soln. of in EtOH (0.32 ml, 1 mmol). After stirring at 20° for 3 days, the mixture was dissolved in Et_2O, washed with 10% aq. NaOH and sat. NaCl soln., dried, and evaporated. The residue was chromatographed (100 g of silica gel, Et_2O/hexane 3:1): **3** (more unpolar, 1.12 g, 60%) and **4** (0.16 g, 10%).

Data of **3**: M.p. 61.5–62.5° (Et_2O/hexane). IR: 3364, 3324, 3200, 1736, 1650, 1600. ^{1}H-NMR: 7.58–7.45 (*m*, 5 arom. H); 4.11 (*q*, *J* = 7.2, CH_2O); 3.67 (br. *s*, NH_2, exchangeable with D_2O); 2.59 (*t*, *J* = 7.6, 2 H–C(11)); 2.27 (*t*, *J* = 7.5, 2 H–C(2)); 1.79–1.60 (*m*, 4 H); 1.34–1.22 (*m*, 15 H), therein at 1.24 (*t*, *J* = 7.2, CH_3). ^{13}C-NMR: 173.7 (*s*, COO); 137.1 (*s*, 1 arom. C); 135.7 (*s*, C(4')); 130.6 (*s*, C(5')); 129.6, 128.7, 123.9 (3 *d*, 5 arom. C); 60.0 (*t*, CH_2O); 34.2 (CH_2); 29.3 (4 CH_2); 29.1, 29.0, 28.8, 24.8, 24.5 (5 CH_2); 14.1 (*q*, CH_3CH_2O). CI-MS: 373 ($[M + 1]^+$), 344 ($[M - N_2]^+$). Anal. calc. for $C_{21}H_{32}N_4O_2$ (372.50): C 67.71, H 8.66, N 15.04; found: C 67.98, H 8.74, N 15.32.

Data of **4**: M.p. 187.5–188.5° (CH_2Cl_2/Et_2O). IR: 3440, 3236, 1672, 1606. ^{1}H-NMR: 8.01 (*s*, NH, exchangeable with D_2O); 7.48 (*s*, 5 arom. H); 2.60 (*t*, *J* = 8.4, 2 H–C(13)); 2.34 (*t*, *J* = 6.0, 2 H–C(6)); 1.73–1.63 (*m*, 4 H); 1.4–1.21 (*m*, 12 H). ^{13}C-NMR: 173.9 (*s*, CONH); 143.6 (*s*, C (3a)); 135.7 (*s*, 1 arom. C); 129.2 (2 *d*, 3 arom. H); 128.9 (*s*, C(13a)); 123.7 (*d*, 2 arom. H); 35.7, 27.0, 26.8, 25.8 (4 CH_2); 25.6 (2 CH_2); 24.7, 24.1, 23.9, 23.2 (4 CH_2). CI-MS: 327 ($[M + 1]^+$), 298 ($[M - N_2]^+$). Anal. calc. for $C_{19}H_{26}N_4O$ (326.43): C 69.90, H 8.03, N 17.16; found: C 70.08, H 8.00, N 17.45.

2. *Ethyl 11-[5'-(Phenylamino)-1'H-1',2',3'-triazol-4'-yl]undecanoate* (**5**). A soln. of **3** (0.744 g, 2 mmol) in Py (2 ml) was heated under reflux for 6 h. After cooling, the mixture was poured into cold H_2O (100 ml), the separated oil extracted with CH_2Cl_2, the combined org. extract washed with sat. NaCl soln., dried, and evaporated, and the residue left *in vacuo* for removing traces of Py: **5** (0.73 g, 98%). Oil. IR: 3450, 3220, 1724, 1600. ^{1}H-NMR: 12.21 (br. *s*, NH, exchangeable with D_2O); 7.26 (*dd*, *J* = 7.9, 7.9, 2 arom. H_m); 7.08 (*d*, *J* = 7.8, 2 arom. H_o); 6.89 (*dd*, *J* = 7.3, 7.3, 1 arom. H_p); 5.69 (*s*, NH–C(5'), exchangeable with D_2O); 4.14 (*q*, *J* = 7.1, CH_2O); 2.60 (*t*, *J* = 7.6, 2 H–C(11)); 2.29 (*t*, *J* = 7.5, 2H–C(2)); 1.70–1.59 (*m*, 4 H); 1.56–1.22 (*m*, 15 H), therein at 1.24 (*t*, *J* = 7.1, CH_3). ^{13}C-NMR: 174.1 (*s*, COO); 144.8 (*s*); 143.5 (*s*); 129.1 (*d*, 2 arom. C); 128.1 (*s*, 1 arom. C); 119.9 (*d*, 1 arom. C); 115.2 (*d*, 2 arom. C); 60.3 (*t*, CH_2O); 34.3, 29.3, 29.2 (3 CH_2); 29.1 (3 CH_2); 29.0, 28.1, 24.9, 23.9 (4 CH_2); 14.2 (*q*, CH_3CH_2O). CI-MS: 373 ($[M + 1]^+$), 344 ($[M - N_2]^+$).

3. *2''-Cyanocyclododec-1''-en-1''-yl 11-(5'-Amino-1'-phenyl-1'H-1',2',3'-triazol-4'-yl)undecanoate* (**6**).To a soln. of **1** (1.03 g, 5 mmol) and **2** (0.714 g, 6 mmol) in THF (2 ml) was added NaH (1 mmol). After stirring at 20° for 3 days, the mixture was worked up as described in *Exper.1*: **6** (0.76 g, 57 %). Oil. IR (neat): 3420, 3328, 3194, 3054, 2218, 1760, 1630, 1600. ^{1}H-NMR: 7.60–7.47 (*m*, 5 arom. H); 3.63 (br. *s*, NH_2, exchangeable with D_2O); 2.90–1.19 (*m*, 40 H), therein at 2.61 (*t*, *J* = 7.6, 2 H–C(11)) and at 2.49 (*t*, *J* = 7.4, 2H–C(2)). ^{13}C-NMR: 169.9 (*s*, COO); 164.1 (*s*, C(1'')); 137.1 (*s*, 1 arom. C); 135.7 (*s*, C(5')); 130.6 (*s*, C(4')); 129.6 (*d*, 2 arom. C); 128.9 (*s*, 1 arom. C); 123.9 (*d*, 2 arom. C); 118.1 (*s*, CN); 106.0 (*s*, C(2'')); 34.1, 32.5 (2 CH_2); 29.3 (3 CH_2); 29.2, 29.1, 29.0, 28.9, 28.8, 26.6, 26.2, 24.9, 24.8, 24.7, 24.6, 24.5, 24.4, 24.3, 23.6 (15 CH_2). CI-MS: 327, 299, 265, 208.

4. *Ethyl 11-(5'-Hydroxy-1'-phenyl)-1'H-1',2',3'-triazol-4'-yl)undecanoate* (**8**). To a soln. of **7** [13] (1.27 g, 5 mmol) and **2** (0.714 g, 6 mmol) in THF (10 ml) was added 21% soln. of NaOEt in EtOH (1.92 ml, 6 mmol), the mixture was stirred at 20° for 3 days, and the solvent evaporated. The residue was dissolved in H_2O (100 ml) and extracted with Et_2O (3 x 30 ml). The aq. phase was acidified with dil. HCl soln. and extracted with CH_2Cl_2 (3 × 30 ml), the combined org. extract washed with H_2O, dried, and evaporated, and the residue chromatographed (100 g of silica gel, Et_2O): **8** (0.89 g, 48%). Oil. IR: 3450, 1738, 1602. ^{1}H-NMR: 7.92 (*d*, *J* = 7.5, 2 arom. H); 7.47–7.34 (*m*, 3 arom. H); 6.60 (br. *s*, OH, exchangeable with D_2O); 4.13 (*q*, *J* = 7.2, CH_2O); 2.62 (*t*, *J* = 7.7, 2H–C(11)); 2.28 (*t*, *J* = 7.5, 2 H–C(2)); 1.65–1.56 (*m*, 4 H); 1.44–1.04 (*m*, 15 H), therein at 1.26 (*t*, *J* = 7.2, CH_3). ^{13}C-NMR:

173.9 (*s*, COO); 152.2 (*s*, C(5')); 136.2 (*s*, 1 arom. C); 128.9 (*d*, 2 arom. C); 128.0 (*d*, 1 arom. C); 123.9 (*s*, C(4')); 122.1 (*d*, 2 arom. C); 60.1 (*t*, CH_2O); 34.3, 29.6, 29.5 (3 CH_2); 29.3 (2 CH_2); 29.2, 29.1, 28.7, 24.9, 23.0 (5 CH_2); 14.2 (*q*, CH_3CH_2O). CI-MS: 347 ($[M - N_2]^+$).

REFERENCES

[1] O. Dimroth, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1029, 4041.

[2] H. Wamhoff, in 'Comprehensive Heterocyclic Chemistry', Eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vol. 5, p. 669; T. L. Gilchrist, G. E. Gymer, *Adv. Heterocycl. Chem.* **1974**, *66*, 42.

[3] K. M. Baines, T. W. Rourke, K. Vaughan, D. L. Hooper, *J. Org. Chem.* **1981**, *46*, 856.

[4] H. Wamhoff, W. Wambach, *Chem.-Ztg.* **1989**, *113*, 11; G. L'abbé, L. Beenaerts, *Tetrahedron* **1989**, *45*, 749; A. Dornow, J. Helberg, *Chem. Ber.* **1960**, *93*, 2001; J. R. E. Hoover, A. R. Day, *J. Am. Chem. Soc.* **1956**, *78*, 5832.

[5] P. H. Olesen, F. E. Nielsen, E. B. Pedersen, J. Becher, *J. Heterocycl. Chem.* **1984**, *21*, 1603.

[6] M. Begtrup, C. Pedersen, *Acta Chem. Scand.* **1969**, *23*, 1091.

[7] C. Martini, W. Marrucci, A. Lucacchini, G. Biagi, O. Livi, *J. Pharm. Sci.* **1988**, *77*, 977; G. L'abbé, G. Mathys, S. Toppet, *J. Org. Chem.* **1975**, *40*, 1549.

[8] B. Föhlisch, R. Herter, E. Wolf, J. J. Stezowski, E. Eckle, *Chem. Ber.* **1982**, *115*, 355.

[9] 'Organic Syntheses', John Wiley & Sons, New York, 1955, Coll. Vol. 3, p. 710.

[10] O. Dimroth, *Liebigs Ann. Chem.* **1909**, *364*, 183.

[11] G. L'abbé, *J. Heterocycl. Chem.* **1984**, *21*, 627.

[12] St. Bienz, M. Hesse, *Helv. Chim. Acta* **1987**, *70*, 2146; M. Hesse, 'Ring Enlargement in Organic Chemistry', Verlag Chemie, Weinheim, 1991.

[13] J. Tsuji, T. Yamada, I. Shimizu, *J. Org. Chem.* **1980**, *45*, 5209.