

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

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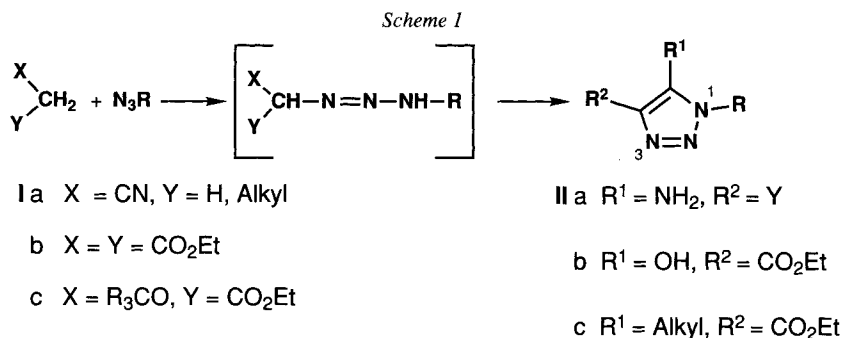
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Dedicated to Prof. Dr. Burchard Franck on the occasion of his 65th birthday

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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*).

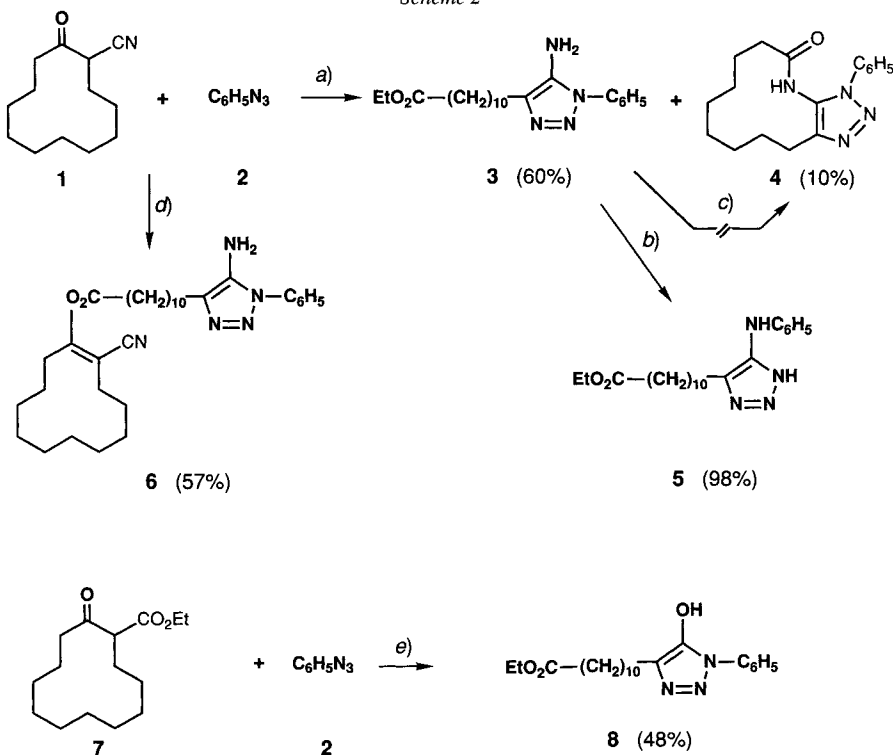


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Despite of the presence of a vast number of literature data on the *Dimroth* reaction, little is known about the reactivity of active methylene compounds substituted at the central C-atom. It was shown that the reaction of azides with alkyl- or aryl-substituted 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.

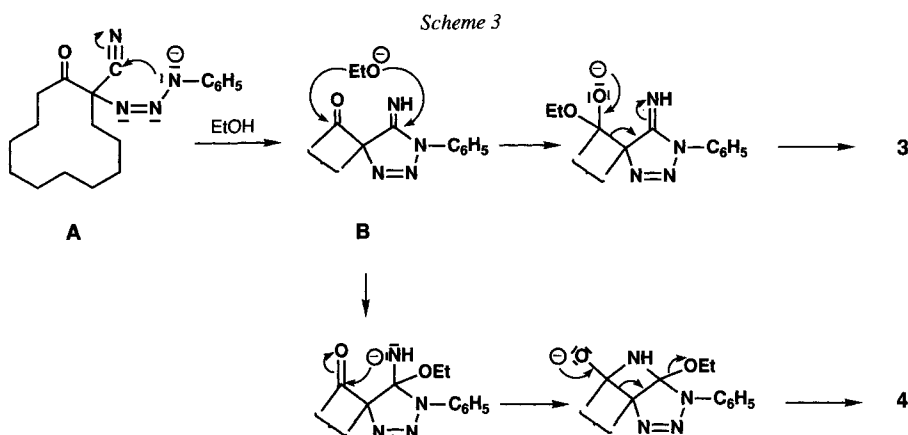
Treatment of 1-oxocyclododecane-2-carbonitrile (**1**) [8] with phenyl azide (**2**) [9] in the presence of a catalytic amount of NaOEt in EtOH/THF for four days at room temperature led to the formation of 5-amino-1-phenyl-1*H*-1,2,3-triazole **3** and lactam **4** in 60 and 10 % yield, respectively. 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 regioselective 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*).



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.

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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. ^1H -NMR spectra: in CDCl_3 ; *Brüker-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 ^1H -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-3H-1,2,3-triazolo[4,5-b]azacyclotetradecen-5(4H)-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. ^1H -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 , $\text{CH}_3\text{CH}_2\text{O}$). CI-MS: 373 ($[M + 1]^+$), 344 ($[M - \text{N}_2]^+$). Anal. calc. for $\text{C}_{21}\text{H}_{32}\text{N}_4\text{O}_2$ (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° ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$). IR: 3440, 3236, 1672, 1606. ^1H -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 ($[M - \text{N}_2]^+$). Anal. calc. for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}$ (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. ^1H -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_p); 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 , $\text{CH}_3\text{CH}_2\text{O}$). CI-MS: 373 ($[M + 1]^+$), 344 ($[M - \text{N}_2]^+$).

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. ^1H -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 $\times$ 30 ml). The aq. phase was acidified with dil. HCl soln. and extracted with CH_2Cl_2 (3 $\times$ 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. ^1H -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, CH₂O); 34.3, 29.6, 29.5 (3 CH₂); 29.3 (2 CH₂); 29.2, 29.1, 28.7, 24.9, 23.0 (5 CH₂); 14.2 (q, CH₃CH₂O). CI-MS: 347 ([M – N₂]⁺).

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