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A new rearrangement of fused tetracyclic heterocycles in an acidic medium in the presence of $NaBH_3CN$

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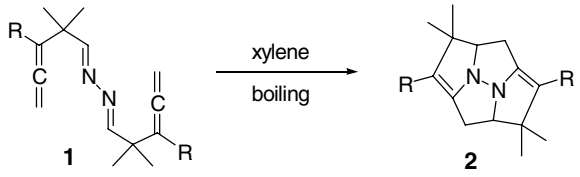
Dedicated to Professor Karel Waisser on the occasion of his birthday

Abstract—In an acidic medium the criss-cross cycloadduct **2** with four fused five-membered rings rearranges to a heterocyclic compound **3** with a completely different structure consisting of two six-membered and two five-membered rings. This newly discovered rearrangement was observed in the presence of a reducing agent ($NaBH_3CN$). The rearrangement proceeds easily and with an extremely high yield.

1. Introduction

We have been investigating criss-cross cycloaddition reactions for some time to evaluate the scope and limitations of intramolecular criss-cross reactions based on the applications of allenyl units.[1,2]

There are three types of criss-cross cycloaddition—intermolecular, intramolecular and combined intra–intermolecular cycloaddition reactions. Intermolecular criss-cross cycloadditions are the most developed and involve two sequential 1,3-dipolar cycloadditions in which an unsaturated molecule reacts with a 1,3-dipole. In 1917, Bailey published a study of the reaction of benzaldazine with phenyl isocyanate.[3] This type of reaction was later named a criss-cross cycloaddition. Huisgen predicted the success of criss-cross cycloaddition reactions involving two 1,3-dipolar cycloadditions, in 1963.[4] This prediction was confirmed by Burger in 1974 by the isolation of a stable intermediate from the reaction of hexafluoracetonazine and 2-methylpropene.[5] A combined intra–intermolecular criss-cross cycloaddition was firstly discovered in our laboratory.[6] The reaction is a combination of intra- and subsequent intermolecular cycloadditions. In intramolecular criss-cross cycloaddition reactions, both dipolarophile (allenyl group) and azine group are part of one molecule **1**. Apparently, the distance between the azine group and the multiple bonds determines whether a 'lateral' or 'central' type cyclization is preferred.[1] In our case the reaction affords a new type of compound **2** having four centrally fused five-membered heterocyclic rings (Scheme 1).



Scheme 1. Intramolecular criss-cross cycloaddition.

2. Results and discussion

Our starting compounds **2** for the transformation reported here are the products of the thermally initiated intramolecular criss-cross cycloaddition reaction of homoallenylazines **1**[1,2] prepared from homoallenyl aldehydes.[7–10] Compounds **2** are interesting because of their structure, chemical properties and rather easy method of preparation in a high yield.

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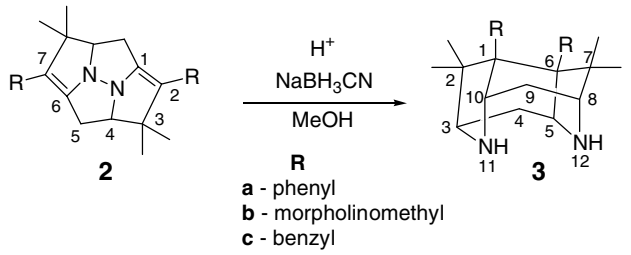


Scheme 2. Rearrangements of compounds **2**.

During our chemical investigation of products **2** we have discovered a new interesting behaviour. In an acidic medium, cycloadducts **2** rearrange to completely new structures **3** with two six-membered and two five-membered rings (Scheme 2). This new rearrangement was firstly detected in the presence of a reducing agent ($NaBH_3CN$). We suppose that the reaction begins in the acidic medium with protonation at one of the nitrogen atoms. This leads to polarization of the N–N bond and its splitting (Scheme 3). This would give a secondary enamine and a positively charged carbon atom 7. After a flip of the molecule, carbon atoms 2 and 7 can become close and the formation of a new single bond between these carbon atoms can proceed. In the last stage of the reaction, $NaBH_3CN$ reduces the newly formed C=N bonds.[11]

The course of the reaction was monitored by thin layer chromatography and the products were analyzed by NMR, IR, MS and elemental analysis. In the case of compound **3′b**, single-crystal X-ray diffraction analysis was also carried out[12] (see Figs. 1 and 2).

Due to the cage like structure we expect that the rearranged compounds **3** may serve as educts for various complex formations.

3. Experimental

3.1. General procedure for compounds 3 preparation

To the stirred solution of compound **2** (0.1 mmol) in dry methanol (10 ml) a few drops of concentrated hydrochloric acid were added. Then, $NaBH_3CN$ (0.4 mmol) was added and the mixture was stirred in an argon atmosphere for 2 h. Finally, the solvent was evaporated. After addition of water, the white precipitate was filtered off and washed with water.[13]

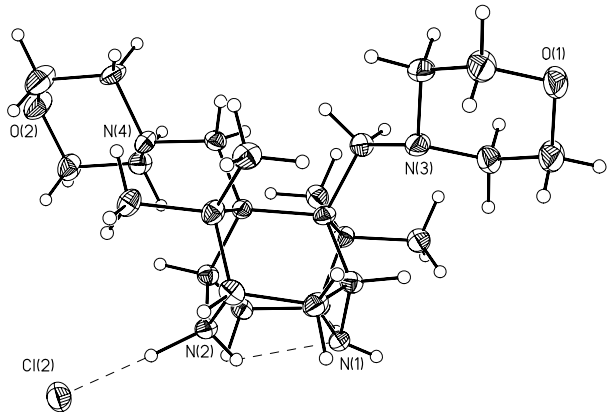


Figure 1. ORTEP representation of compound **3′b** structure.

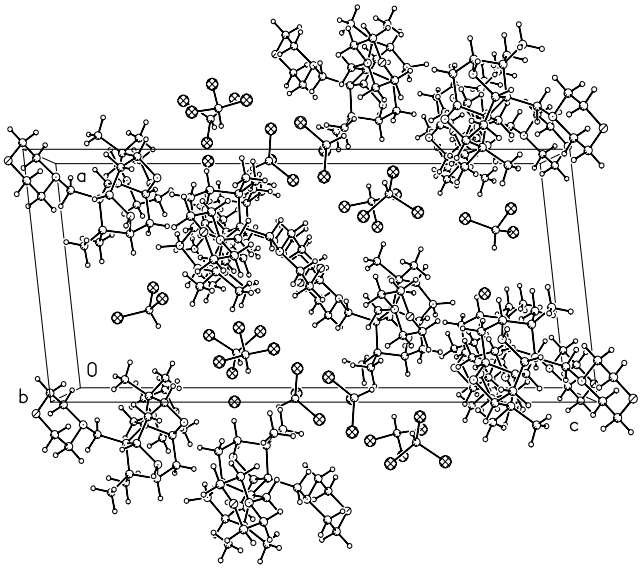
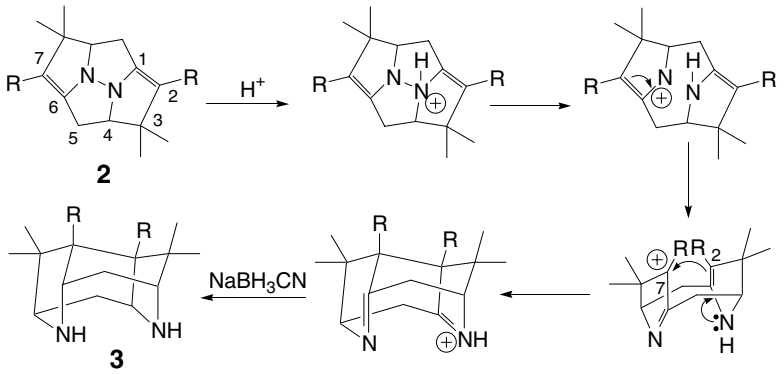


Figure 2. Crystal packing of compound **3′b**. Part of the coplanar planes oriented to *F*(101).



Scheme 3. The suggested mechanism of compounds **2** rearrangement in acidic medium with a final reduction with $NaBH_3CN$.

3.2. 1,6-Diphenyl-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane hydrochloride 3a

Compound **2a** (0.10 g, 0.27 mmol) and $NaBH_3CN$ (0.07 g, 1.1 mmol): white solid (ethanol/water = 1:4), 0.095 g (86%), mp 170–175 °C. ^{1}H NMR ($CDCl_3$):[14] δ 0.49 (s, 6H, CH_3), 1.10 (s, 6H, CH_3), 2.32 (dd, $J = 14.7$ Hz, $J = 3.0$ Hz, 2H, CH_2), 2.50 (dd, $J = 14.7$ Hz, $J = 4.4$ Hz, 2H, CH_2), 3.07 (d, $J = 3.0$ Hz, 2H, CH), 4.49 (d, $J = 4.4$ Hz, 2H, CH), 7.11 (t, 2H, H_{ar}), 7.35 (t, 4H, H_{ar}), 7.46 (d, 4H, H_{ar}) ppm. ^{13}C NMR ($CDCl_3$):[14] $\delta = 22.6$, 27.6, 33.4, 50.3, 57.3, 58.2, 65.0, 127.1, 130.1, 133.4, 142.9 ppm. IR (KBr): ν_{max} 802, 1039, 1355, 1376, 1446, 1571, 2931, 2962, 3417 cm^{-1}. MS (EI 30 eV): *m*/*z* (%) 373 (M^+, 60), 302 (15), 259 (14), 185 (75), 172 (100), 155 (50), 127 (35), 114 (30), 91 (30), 41 (10). $C_{26}H_{33}ClN_2$ (409.04): calcd: C, 76.35, H, 8.13, N, 6.85; found: C, 76.63, H, 8.22, N, 7.06.

3.3. 1,6-Di-(*N*-morpholinomethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane·3 HCl 3b

Compound **2b** (0.70 g, 1.69 mmol) and $NaBH_3CN$ (0.42 g, 6.75 mmol): white solid (chloroform), 0.73 g (82%), mp 200–205 °C. ^{1}H NMR ($CDCl_3$):[14] δ 1.16 (s, 6H, CH_3), 1.23 (s, 6H, CH_3), 2.1–2.2 (m, 4H, CH_2), 2.34 (d, $J = 15.1$ Hz, 2H, CH_2), 2.4–2.5 (m, 8H, CH_2), 2.57 (d, $J = 15.1$ Hz, 2H, CH_2), 3.24 (t, $J = 2.5$ Hz, 2H, CH), 3.6–3.7 (m, 8H, CH_2), 4.08 (t, $J = 2.9$ Hz, 2H, CH) ppm. ^{13}C NMR ($CDCl_3$):[14] $\delta = 22.0$, 27.7, 31.1, 49.3, 53.6, 55.0, 56.0, 56.8, 62.9, 67.3 ppm. IR (KBr): ν_{max} 856, 902, 1039, 1116, 1319, 1400, 1454, 1546, 2327, 2805, 2923, 2956, 3338 cm^{-1}. MS (EI 30 eV): *m*/*z* (%) 419 (M^+, 3), 361 (5), 245 (100), 229 (18), 162 (20), 99 (63), 76 (11). $C_{24}H_{45}Cl_3N_4O_2$ (528.00): calcd: C, 54.59, H, 8.59, N, 10.61; found: C, 55.01, H, 8.17, N, 10.19.

3.4. 1,6-Dibenzyl-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane·2 HCl 3c

Compound **2c** (0.1 g, 0.25 mmol) and $NaBH_3CN$ (0.064 g, 1 mmol): white solid (ethanol/water = 1:1), 0.092 g (77%), mp 280–300 °C. ^{1}H NMR ($CDCl_3$):[14] δ 0.95 (s, 6H, CH_3), 1.45 (s, 6H, CH_3), 2.17 (dd, 2H, $J = 15.1$ Hz, $J = 3.1$ Hz, CH_2), 2.35 (dd, $J = 15.1$ Hz, $J = 4.2$ Hz, 2H, CH_2), 2.95 (d, $J = 15.9$ Hz, 2H, CH_2), 3.19 (d, $J = 3.1$ Hz, 2H, CH), 3.50 (d, $J = 15.9$ Hz, 2H, CH_2), 4.07 (d, $J = 4.2$ Hz, 2H, CH), 7.2–7.3 (m, 10H, H_{ar}) ppm. ^{13}C NMR ($CDCl_3$):[14] $\delta = 22.7$, 28.5, 30.9, 34.9, 50.6, 53.4, 55.9, 63.0, 127.0, 129.0, 130.8, 139.0 ppm. IR (KBr): ν_{max} 703, 747, 1075, 1346, 1398, 1455, 1495, 1600, 2880, 2931, 3024, 3313 cm^{-1}. MS (CI): *m*/*z* (%) 401 (M^++1, 2), 214 (30), 175 (11), 123 (14), 88 (89), 63 (40), 59 (100). $C_{28}H_{38}Cl_2N_2 + H_2O$ (491.54): calcd: C, 68.42, H, 8.20, N, 5.70; found: C, 68.78, H, 8.16, N, 5.73.

Acknowledgement

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12. Crystals were obtained from chloroform solution by evaporation. The diffraction data for compound **3′b** were collected on a KUMA KM-4 CCD kappa-axis diffractometer using graphite monochromatized Mo-Kα radiation ($\lambda = 0.71069$ Å). The structure was solved by direct methods (Sheldrick G.M.: SHELX-97 program package, University of Goettingen 1997, Sheldrick G.M.: SHELXTL V 5.1, Bruker AXS GmbH.) Nonhydrogen atoms were refined anisotropically, while hydrogen atoms were inserted in calculated positions and isotropically refined assuming a 'ride-on' model (Fig. 1). In the symmetrical independent part of a unit cell there are two slightly different molecules of **3′b** and six molecules of chloroform. The crystal structure of **3′b** is without any strong H-bonding except for N–H···Cl (1.888 Å) and N–H···N (2.131 Å) contacts. The crystal packing of **3′b** contains periodically alternating coplanar planes of molecules of **3′b** (plane A) and chloroform solvent molecules (plane B). The structural motive is ABAB. The orientation of these planes is *F*(1 0 1). The crystal packing is shown in Figure 2. Crystallographic data for compound **3′b** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, under No. CCDC 601780.
13. In an alkaline medium oily products are formed, which were not easily isolable. When the crystalline products are heated dry, they readily lost HCl and formed products with a variable content of HCl.
14. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75.5 MHz.