A Proton-Catalyzed Dimerization of a 2-Amino-1,3-diene which Ultimately Yields a 3-Aminobicyclo[4.2.0]octa-2,4-diene

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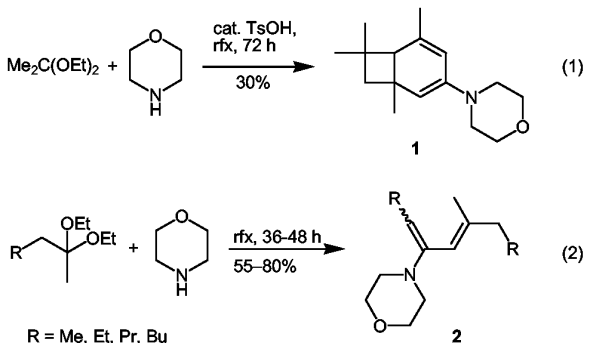
The 2-pyrrolidino-1,3-dienes (*E*)-**5** and (*Z*)-**5** are obtained by the reaction of lithium di(*tert*-butyl)cuprate with propyne iminium salt **3**. Quantitative $Z \rightarrow E$ isomerization of **5** takes place within 4 hours at 20 °C. In benzene solution, (*E*)-**5** slowly equilibrates with a [1,5]-H shift to form the 1-amino-1,3-diene derivative **6**. In concentrated chloroform solution, however, (*E*)-**5** is transformed into the 3-pyrrolidino-bicyclo[4.2.0]octa-2,4-diene **7** which is identified by X-ray crystal structure analysis. A mechanism for this transformation is proposed.

Key words: Aminoallenes, 2-Aminodienes, Electrocyclic Reaction, Iminium Salts, Organocuprates

Introduction

Fourty years ago, Bianchetti and coworkers reported that the reaction of equimolar amounts of 2,2-diethoxypropane and morpholine, catalyzed by toluenesulfonic acid, yielded a complex mixture of enamines from which the bicyclic aminodiene **1** was isolated (Scheme 1, eq. (1)) [1]. The constitution of this compound was established by NMR spectroscopy as well as derivatization and degradation reactions [1, 2]. Further experimental investigations allowed the same researchers to shed light on the formation of **1** [3]. A 2-morpholino-1,3-diene (**2**, R = H) was postulated as a reaction intermediate although it was not observed directly. In contrast to the reaction of acetone diethyl acetal, the analogous reaction of morpholine with diethylacetals of ketones different from acetone stopped at the stage of 2-aminodienes **2** (R = alkyl) (Scheme 1, eq. (2)) [4].



Scheme 1. Reaction of acetals of acetone and homologous ketones with morpholine.

In this communication, we show that the proton-catalyzed transformation of a 2-amino-1,3-pentadiene into a 3-aminobicyclo[4.2.0]octa-2,4-diene is possible, and we propose a mechanism which includes proton-induced cyclodimerization of the aminodiene followed by two different electrocyclic reactions.

Results and Discussion

The reaction of propyne iminium triflate **3** [5] with lithium di(*tert*-butyl)cuprate afforded the 2-pyrrolidino-1,3-diene **5** (Scheme 2). As in similar cases [6], this transformation proceeds via the aminoallene **4** which undergoes a spontaneous tautomerization under the reaction conditions. A ^{1}H NMR spectrum, which was recorded immediately after workup, indicated a mixture of diastereomers (*Z*)-**5** and (*E*)-**5** in a 1 : 1.3 ratio. After 4 hours at 20 °C, a complete conversion of (*Z*)-**5** into (*E*)-**5** had occurred. This facile geometrical isomerization has been observed before for related 2-amino-1,3-dienes [6, 7]. The assignment of the double bond configuration and of the *s-cis* conformation of the diene unit is based on ^{1}H NMR data as discussed earlier [6].

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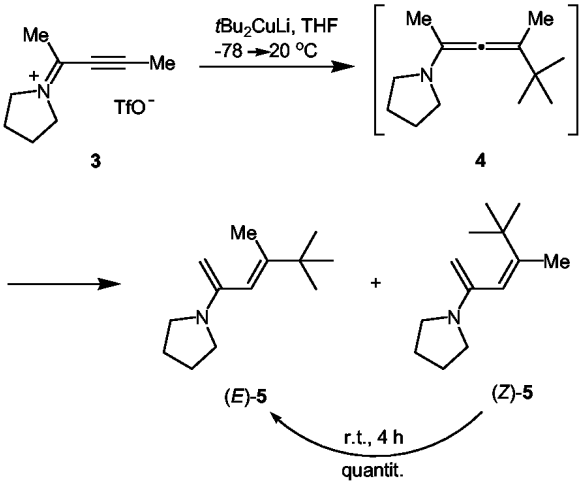
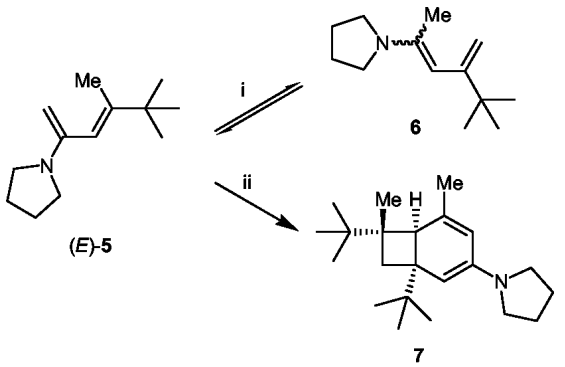


Scheme 2. Preparation of aminodienes **5**.



Scheme 3. Conditions: (i): Neat or in C_6D_6, r.t., several days. (ii) 1. $CDCl_3$, r. t., 1 day: 2. toluene, 160 °C, 1 h.

A [1,5]-sigmatropic H-shift slowly converted 2-pyrrolidino-1,3-diene (*E*)-**5** into 1-pyrrolidino-1,3-diene **6** (Scheme 3). An equilibrium mixture of (*E*)-**5** and **6** in the ratio 1 : 1.2 was obtained when (*E*)-**5** was kept either neat or in benzene solution for 5 days at *ca.* 20 °C. Only one diastereomer of **6** was observed by NMR, but its configuration could not be established firmly. Similar 2-amino-1,3-diene/1-amino-1,3-diene equilibrations or conversions by prototropic shifts have been reported occasionally [7 – 9].

In a concentrated solution of (*E*)-**5** in chloroform (we used $CDCl_3$ to monitor the disappearance of **5** by NMR), a different reaction occurred, and after one day at 20 °C, the bicyclic 2-aminodiene **7** could be isolated in 32% yield (Scheme 3). A high concentration of (*E*)-**5** was necessary to suppress the competition from the isomerization (*E*)-**5**→**6** mentioned before. The constitution and structure of **7** was established beyond

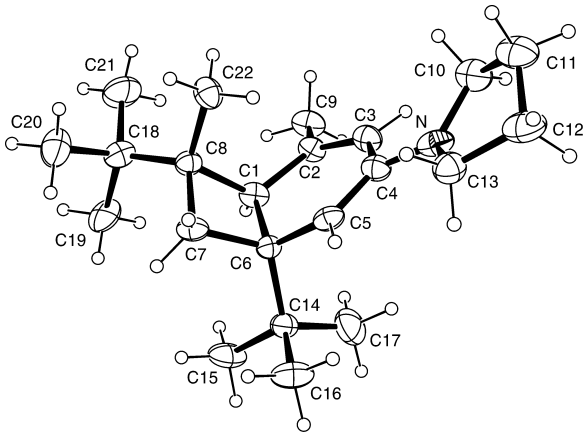
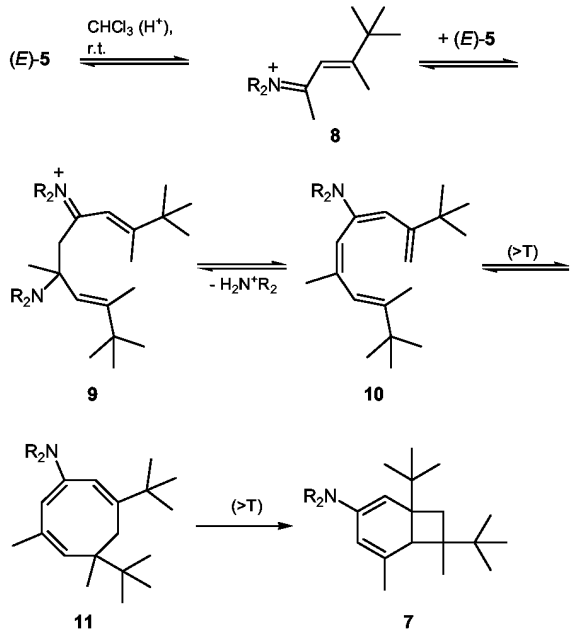


Fig. 1. Structure of **7** in the crystal (ORTEP plot, ellipsoids of thermal vibration shown at the 30% probability level). Selected bond lengths (Å): C1–C6 1.549(8), C1–C2 1.516(8), C1–C8 1.581(9), C2–C3 1.327(8), C3–C4 1.476(9), C4–C5 1.335(8), C5–C6 1.510(8).

doubt by a single-crystal X-ray diffraction analysis (Fig. 1).

To explain the formation of **7**, we assume that traces of hydrogen chloride present in chloroform first generate the conjugated iminium salt **8**, which then reacts with aminodiene (*E*)-**5** to form the dimer **9**. Elimination of pyrrolidine would lead to 1,3,5,7-octatetraene **10**, which is able to undergo an 8π electrocyclic ring closure yielding cyclooctatriene **11**. This type of valence isomerizations can occur at rather mild temperatures (0 – 80 °C) [10]. A thermally induced disrotatory 6π electrocyclic reaction converts cyclooctatriene **11** into bicyclo[4.2.0]octa-2,4-diene **7**. This type of pericyclic reactions is also well documented; typical activation energies are in the range of 22 – 27 kcal mol^{-1} and substituent-dependent equilibria of the two valence isomers are often observed [11, 12]. The latter step likely requires a higher thermal activation than the preceding ones, and therefore, we heated the reaction mixture briefly in toluene at 160 °C after it had been kept in chloroform solution for one day at 20 °C. However, the complexity of the ^{1}H NMR spectrum did not allow us to know the composition of the reaction mixture at this stage. Since the overall reaction sequence appears to be initiated by proton catalysis, we tried to improve the yield of **7** by addition of catalytic amounts of *p*-toluenesulfonic acid. However, this was not successful, perhaps because all or almost all steps shown in Scheme 4 are likely to be equilibrium reactions, so that side reactions at one or



Scheme 4. Proposed mechanism for the formation of **7**.

more of the intermediate stages cannot be excluded.

A similar reaction mechanism has been proposed by Bianchetti *et al.* [3] for the formation of **1** (see Introduction). The similarity between our aminodiene (*E*)-**5** and the proposed aminodiene intermediate **2** (R = H) is obvious; in fact, they are both of the 2-amino-1,3-pentadiene type where the presence of a C^5–H bond is necessary for the overall transformation. However, the possibility that the dimerization of aminodiene **2** (analogous to (*E*)-**5**→**10**) involved the participation of the iminium salt formed by protonation of the 2-aminodiene appears not to have been considered. There may be two reasons why aminodienes **2** (R = alkyl), derived from the higher homologues of acetone, were not transformed further under the chosen conditions: a) The initial enamine protonation, corresponding to (*E*)-**5**→**8** in Scheme 4, was not efficient (the reaction was carried by heating the acetal and morpholine without a solvent and in the absence of TsOH [4]); b) the dimerization step, corresponding to (*E*)-**5** + **8** →**9**, did not take place because a tertiary next to a quaternary center would have been formed during C–C bond formation. Since 2-amino-1,3-dienes are nowadays accessible by several methods [6, 7, 13, 14], it would be worthwile to determine the scope and limitation of the conversion of 2-amino-1,3-pentadienes into 2-aminobicyclo[4.2.0]octa-2,4-dienes.

Experimental Section

General information

The following spectroscopic and analytical instruments were used. NMR: Bruker AM 400 (^{1}H: 400.13 MHz, ^{13}C: 100.62 MHz). For ^{1}H spectra, TMS was used as internal standard. For ^{13}C NMR spectra, the solvent signal was used as internal standard [$\delta(C_6H_6) = 128.0$]. Signal assignments for ^{13}C spectra are based on proton-coupled spectra. – IR: Perkin-Elmer 1310. Elemental analyses: Perkin-Elmer EA 2400.

*1-[3,4,4-Trimethyl-1-methylenepent-2-enyl]pyrrolidine ((Z)- and (E)-**5**)*: A solution of lithium di(*tert*-butyl)cuprate was prepared by addition of cuprous bromide dimethylsulfide complex (2.448 g, 12.1 mmol) to a cooled (−15 °C) solution of *tert*-butyl lithium in hexane (1.7 M, 14.2 ml, 24.2 mmol). After cooling to −78 °C, a suspension of salt **3** [5] (3.433 g, 12.03 mmol) in THF (50 ml) was gradually added, and the mixture was kept with stirring at −78 °C for another 30 min, then at −15 °C for 1 h, then brought to 20 °C. The solvent was evaporated at 0.015 mbar, and the residue was extracted with pentane (3 × 100 ml). The pentane extracts were combined and the solvent was evaporated to leave an oil (1.524 g). A ^{1}H NMR spectrum which was taken immediately after workup indicated a 1.3 : 1 mixture of (*E*)-**5** and (*Z*)-**5**. After 4 h at 20 °C, complete conversion of (*Z*)-**5** into (*E*)-**5** had occurred. Kugelrohr distillation at 105 °C (oven temp.)/0.015 mbar yielded (*E*)-**5** as a yellow liquid (1.386 g, 60%). – IR (film): ν = 2970 (s), 2920 (s), 1590 (s) cm^{-1}. – ^{1}H NMR (C_6D_6): (*E*)-**5**: δ = 1.05 (s, 9 H, CMe_3), 1.51 (m_c, 4 H, NCH_2CH_2), 1.92 (d, $|^4J|$ = 1.2 Hz, 2 H, CH_3), 2.96 (m_c, 4 H, NCH_2), 3.90/3.93 (2 s, 2 H, $=CH_2$), 5.99 (q, $|^4J|$ = 1.2 Hz, 1 H, =CH); (*Z*)-**5**: δ = 1.24 (s, 9 H, CMe_3), 1.52 – 1.57 (m, 4 H, NCH_2CH_2), 1.69 (s, 3 H, CH_3), 2.88 – 3.00 (m, 4 H, NCH_2), 3.67/3.82 (2 s, 2 H, $=CH_2$), 5.85 (s, 1 H, =CH). ^{13}C NMR (C_6D_6): (*E*)-**5**/(*Z*)-**5**: δ = 14.5/14.5 (CH_3), 25.4/25.6 (NCH_2CH_2), 29.2/30.2 (CMe_3), 36.2/36.8 (CMe_3), 48.0/48.0 (NCH_2), 81.4/80.1 ($=CH_2$), 121.5/124.4 (=CH), 146.9/144.8 (=*C*(Me)*t*-Bu), 149.5/150.0 (=C-N). – $C_{13}H_{23}N$ (193.33): calcd. C 80.77, H 11.99, N 7.24; found C 80.1, H 11.9, N 6.9.

*Equilibration of (E)-**5** with 1-[3-tert-butyl-1-methylbuta-1,3-dienyl]pyrrolidine* (**6**): Aminodiene (*E*)-**5** was stored neat or kept as a concentrated solution in benzene for 5 days at room temp. An equilibrium mixture of (*E*)-**5** and **6** (ratio in C_6D_6: 1 : 1.2) was obtained which was not separated. – ^{1}H NMR data of **6** (C_6D_6): δ = 1.25 (s, 9 H, CMe_3), 1.47 (m_c, 4 H, NCH_2CH_2), 1.99 (d, $|^4J|$ = 0.8 Hz, 3 H, CH_3), 2.91 (m_c, 4 H, NCH_2), 4.82 (d)/4.87 (q, $|^2J|$ = 1.5 Hz, $|^4J|$ = 2.2 Hz, 2 H, $=CH_2$), 5.20 (d, $|^4J|$ = 2.3 Hz, 1 H, =CH). – ^{13}C NMR (C_6D_6): δ = 17.1 (CH_3), 25.2 (NCH_2CH_2), 29.5 (CMe_3), 36.6 (CMe_3), 47.8 (NCH_2), 107.8 ($=CH_2$), 121.5 (=CH), 143.1, 156.3.

1-[1,exo-7-Di(tert-butyl)-5,endo-7-dimethylbicyclo[4.2.0] octa-2,4-dien-3-yl]pyrrolidine (**7**): A solution of (*E*)-**5** (0.568 g, 2.94 mmol) in $CDCl_3$ (1 ml) was kept at 20 °C for 24 h. The solvent was replaced by toluene (2 ml), and this solution was heated at 160 °C for 1 h in a thick-walled Schlenk tube. The solvent was evaporated and the residue was subjected to Kugelrohr distillation at 160 °C/0.005 mbar. A viscous yellow oil was obtained which was dissolved in pentane. Crystallization at −78 °C afforded yellow crystals (0.148 g, 32%), m.p. 87 °C. – IR (KBr): $\nu = 1660$ (m), 1600 (m) $cm^{-1.}$ – ^{1}H NMR (C_6D_6): $\delta = 0.94$ (s, 9 H, CMe_3), 1.01 (s, 9 H, CMe_3), 1.36 (d, $|^2J| = 11.2$ Hz, 1 H, 8'-H_{endo}), 1.45 (s, 3 H, 7'-CH_3), 1.56 (m_c, 4 H, NCH_2CH_2), 1.70 (d, $|^4J| = 0.9$ Hz, 3 H, 5'-CH_3), 2.46 (d, $|^2J| = 11.3$ Hz, 1 H, 8'-H_{exo}), 2.91 – 3.03 (m, 4 H, NCH_2), 2.93 (s, 1 H, 6'-H), 4.29 (s, 1 H, 2-H), 5.93 (q, $|^4J| = 1.4$ Hz, 1 H, 4'-H). – ^{13}C NMR (C_6D_6): $\delta = 18.7$ (7'-CH_3), 23.6 (5'-CH_3), 24.3 (NCH_2CH_2), 25.0 (CMe_3), 26.4 (CMe_3), 36.0 (CMe_3), 37.4 (CMe_3), 39.3 (C-8'), 40.9, 41.5 (C-6'), 45.1, 48.3 (NCH_2), 100.3 (C-2'), 120.4 (C-4'), 135.1, 142.0. – $C_{22}H_{37}N$ (315.54): calcd. C 83.74, H 11.82, N 4.44; found C 83.8, H 11.5, N 4.3.

Crystal structure determination of bicyclo[4.2.0]octa-2,4-diene **7**

Suitable crystals were obtained by crystallization from pentane at 2 °C. Data collection was performed at 295 K with a four-cycle diffractometer (CAD4, Enraf-Nonius) using monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å). The structure was solved with direct methods and refined with a full-matrix least-squares procedure using F values [15]. Hydrogen atoms are in calculated positions and were only included in the structure factor calculation. *Crystal data*: $C_{22}H_{37}N$, $M = 315.5$, orthorhombic, space group $Pca2_1$ (no. 29); $a = 16.139(2)$, $b = 9.818(1)$, $c = 12.504(2)$ Å, $\alpha = \beta = \gamma = 90°$; $V = 1981.3(8)$ Å^3, $Z = 4$, $D_c = 1.058$ g cm^{-3}. *Data collection*: crystal size $0.50 \times 0.30 \times 0.25$ mm, 1680 reflections in the range $\theta = 1.50 - 23.50°$, 1680 unique reflections. *Structure refinement*: 995 reflection data ($I > 2\sigma(I)$), 207 parameters; the final R indices were $R_1 = 0.0535$, $wR_2 = 0.0471$; residual electron density between 0.18 and −0.16 e A^{-3}. The absolute structure was not determined.

Crystallographic data have been deposited as CCDC-265996. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033.

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