Tetrahedron Letters 50 (2009) 890–892

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Unusual ring annulation during condensation of acetylacetone with pyrrole

Sanjeev P. Mahanta, Pradeepta K. Panda *

School of Chemistry, University of Hyderabad, Gachibowli, P.O. Central University, Hyderabad 500046, India

ARTICLE INFO

Article history:
Received 20 October 2008
Revised 28 November 2008
Accepted 4 December 2008
Available online 13 December 2008

ABSTRACT

During the attempted synthesis of bisdipyrromethane from acid-catalyzed condensation of acetylacetone with pyrrole, an unexpected ring annulation led to the formation of 2,3-dihydro-1*H*-pyrrolizine-bridged bipyrrole.

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Meso-functionalized dipyrromethanes are widely used as building blocks for the synthesis of porphyrins, corroles, and calixpyrroles; in particular, the strapped types that show enhanced anion binding abilities.[1–3] The synthesis of meso-substituted dipyrromethane basically involves the acid-catalyzed condensation of aldehyde/ketone with pyrrole or its derivatives. In the past two decades, the synthesis of meso-substituted dipyrromethanes has undergone several developments, the most important being the one-pot synthesis of dipyrromethane developed by Lindsay et al.,[4] and the other one (developed more recently) being an environment friendly method which uses water as the solvent.[5]

While dipyrromethanes were useful in making monomeric porphyrinoid macrocycles, the development of dimeric and oligomeric porphyrins and calixpyrroles involves a lot of tedious processes.[6] In order to simplify the above targets, it is envisaged that bisdipyrromethanes will be very good building blocks. So far, there has been only one report regarding the synthesis of bisdipyrromethane in one step from 1,4-cyclohexanedione.[7] Toward developing the chemistry of bisdipyrromethane, acetylacetone and pyrrole were condensed under acidic conditions to obtain **1** following the above two conditions (Scheme 1), after the regular work and purification by column chromatography over silica gel yielded the product (Method A—17%; Method B—21%). But to our surprise, the ^{1}H NMR spectrum was quite complicated (Fig. 1), and the mass spectrum showed a peak at 266 (*m*/*z*; for **1** *m*/*z* 332).[8] The proton NMR shows two broad NH peaks at 7.25 and 7.95 ppm along with eight multiplets between 5.95 and 6.54 ppm (seven with equal intensity, whereas the eighth one at 6.54 has approximately double the intensity of the others). Apart from this, there are two more symmetrical doublets at 2.83 and 3.18 ppm with a *J* value of 3.3 Hz indicating geminal coupling, and two signals for the methyl groups at 1.76 and 1.92 ppm. The above result confirmed that **1** has not formed and that the product is quite unsymmetrical. In order to ascertain the exact structure, a single crystal of the compound was grown from hexane/ethylacetate (90:10). While the ^{1}H NMR obtained from the crystal confirmed the above observation by ascertaining its purity, the single crystal solid-state XRD structure (Fig. 2) obtained from it revealed an unusual occurrence of ring annulation resulting in the formation of a bipyrrole moiety bridged via 2,3-dihydro-1*H*-pyrrolizine through its 1,3-position, **2**. This molecule having molecular mass 265 also confirmed the mass analysis. To the best of our knowledge, this type of ring annulation to form a pyrrolizine nucleus from simple pyrrole is unprecedented. Also, this molecule contains two chiral carbons, which highlight its potential utility as a building block to design host molecules for chiral sensing.

The pyrrolizine and its derivatives were, in general, synthesized via multi-step reactions and these bicyclic heterocycles are present in naturally occurring alkaloids. They have been attracting growing interest from synthetic chemists for their various and essential biological activities.[9] The proposed mechanism for the formation of **2** (Fig. 3) is via the formation of dipyrromethane through the general acid-catalyzed synthesis of one of the carbonyl groups of acetylacetone to form **3**, which undergoes condensation with another pyrrole molecule to form the hydroxyl derivative **4**. The protonated hydroxyl derivative **5**, undergoes the loss of a water molecule to form the carbonium ion **6**, which undergoes intramolecular nucleophilic substitution to form the ring-annulated product **7**, which upon the subsequent loss of a proton results in the formation of the 2,3-dihydro-1*H*-pyrrolizine-bridged bipyrrole **2**. Though the yield is moderate, the simplicity of the synthetic method and purification, and the presence of two unsubstituted pyrrole units having potential sites for necessary substitution (at both the 1- and 5-positions) make this molecule attractive for the desired modulation.

Presently, we are investigating the reactivity of various other diketones with pyrrole under acidic conditions. The condensation of **2** with acetone using $BF_3{\cdot}OEt_2$ led to cyclization to form a calix[4]pyrrole type macrocycle **8** (Scheme 2), having 2,3-dihydro-1*H*-pyrrolizine as a bridge between two dipyrromethane units. The formation of **8** is confirmed only on the basis of a mass spectrum. The ^{1}H NMR is quite complicated owing to the

* Corresponding author. Tel.: +91 40 2313 4818.
E-mail addresses: pkpsc@uohyd.ernet.in, pradeepta.panda@gmail.com (P.K. Panda).

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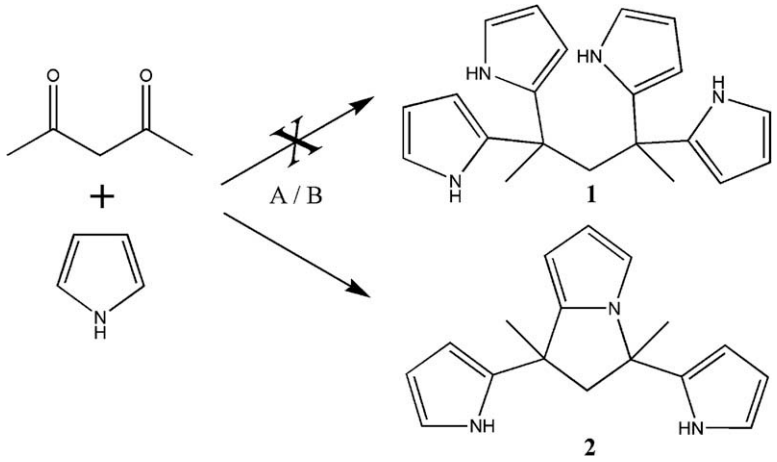
doi:10.1016/j.tetlet.2008.12.033



Scheme 1. Method A: acac (1 equiv), pyrrole (10 equiv), TFA (0.2 equiv), 5 min; Method B: acac (1 equiv), pyrrole (4 equiv), H_2O, concd HCl (0.2 equiv), 90 °C, 45 min.

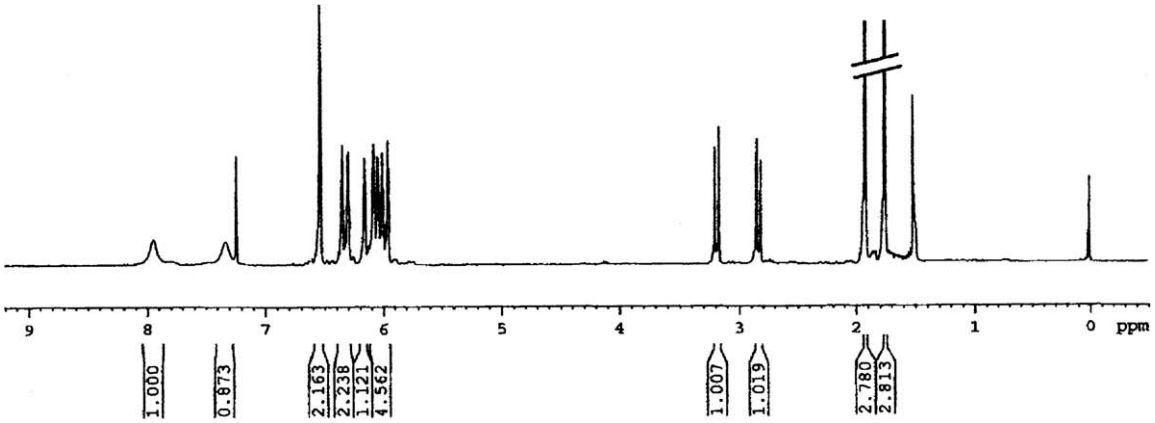


Figure 1. ^{1}H NMR spectrum of **2** in $CDCl_3$.

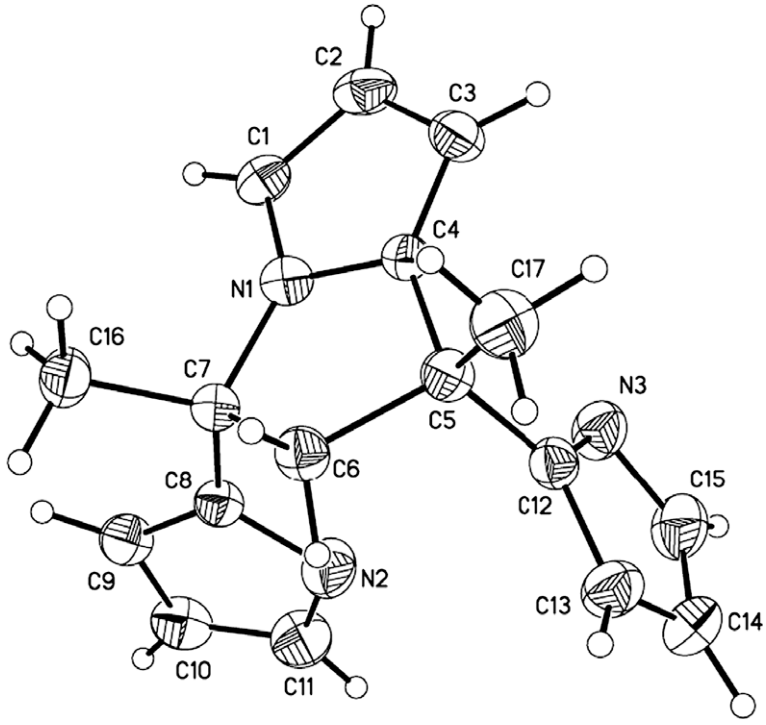


Figure 2. ORTEP diagram for **2**, 1,3-dimethyl-1,3-di(1*H*-pyrrol-2-yl)-2,3-dihydro-1*H*-pyrrolizine, with the displacement ellipsoids drawn at the 50% probability level. Crystal data: $C_{17}H_{19}N_3$, M = 265.35, triclinic, a = 9.490(3) Å, b = 9.615(3) Å, c = 9.869(3) Å, α = 80.171(5)°, β = 62.662(4)°, γ = 64.498(4)°, V = 721.6(4) Å^3, T = 298 K, space group $P\bar{1}$, Z = 2, (Mo Kα) = 0.074 mm^{-1}, 7547 reflections collected, 2821 unique (R_{int} = 0.0496), used for direct methods structure determination and full matrix least-squares refinement. The final $wR(F^2)$ was 0.1476 (for all reflections).

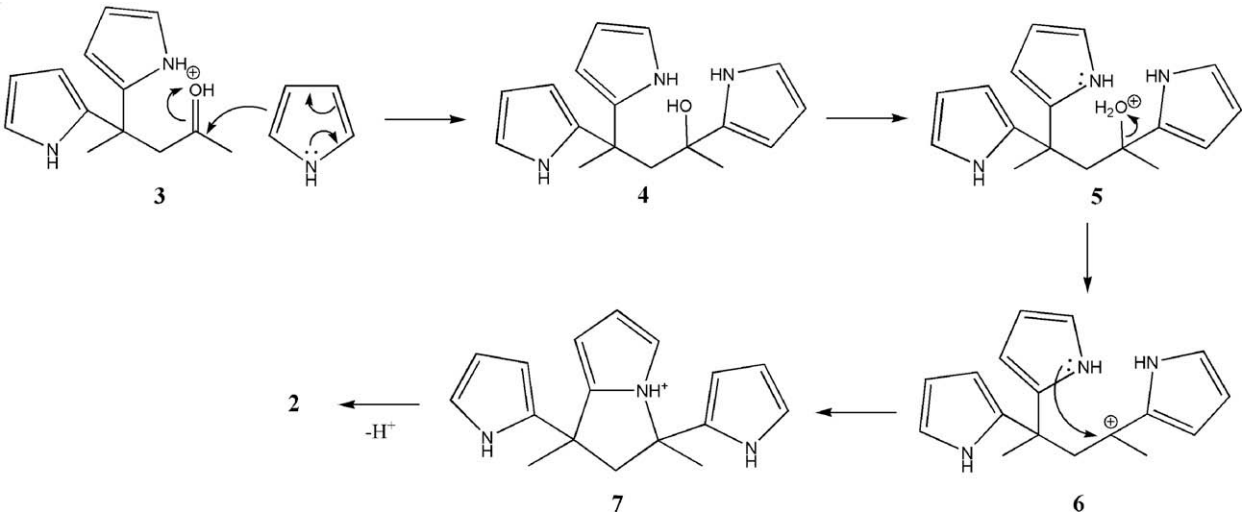
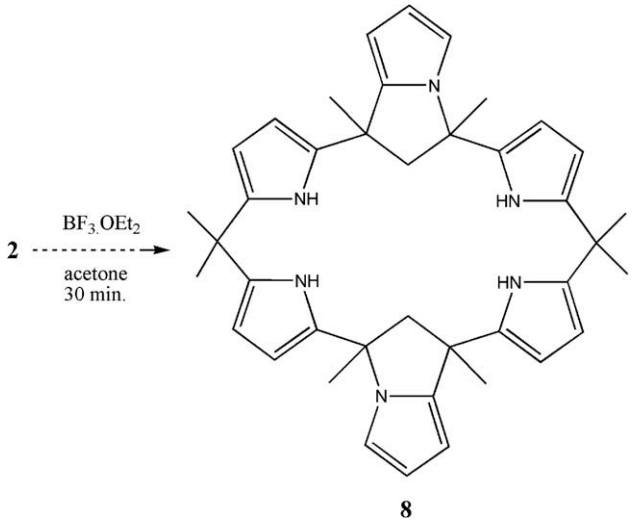


Figure 3. Proposed mechanism for the formation of **2**.



Scheme 2. Synthesis of 2,3-dihydropyrrolizine-bridged calix[4]pyrrole type macrocycle **7**.

presence of conformational isomers. Its detailed characterization along with host guest interaction studies will be reported in due course.

Crystallographic data (excluding the structure factor) for structure **2** in this Letter have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 703494. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments

This work was supported by the start-up grant provided by School of Chemistry, University of Hyderabad and the special start-up grant provided by the Vice-Chancellor, University of Hyderabad, India. SPM thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India for the Senior Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.033.

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8. *Data for compound* **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.32 (br, s, 1H), 6.53–6.54 (m, 2H), 6.34–6.35 (m, 1H), 6.29–6.31 (m, 1H), 6.14–6.17 (m, 1H), 6.07–6.09 (m, 1H), 6.04–6.05 (m, 1H), 6.00–6.02 (m, 1H), 5.95–5.97 (m, 1H), 3.18 (d, 1H, J = 3.3 Hz), 2.83 (d, 1H, J = 3.3 Hz), 1.92 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 140.66, 138.35, 135.74, 117.81, 116.22, 113.14, 111.73, 109.16, 107.82, 104.82, 103.77, 98.48, 60.97, 60.86, 41.65, 30.32 and 28.70. LCMS m/z calcd for $C_{17}H_{20}N_3$ (M+H) 266, found 266; Elemental Anal. Calcd: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.99; H, 7.17; N, 15.84.
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