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Synthesis of dibromo- and tetrabromo-bipyrrolines and their corresponding 2,6-diazasemibullvalene derivatives†

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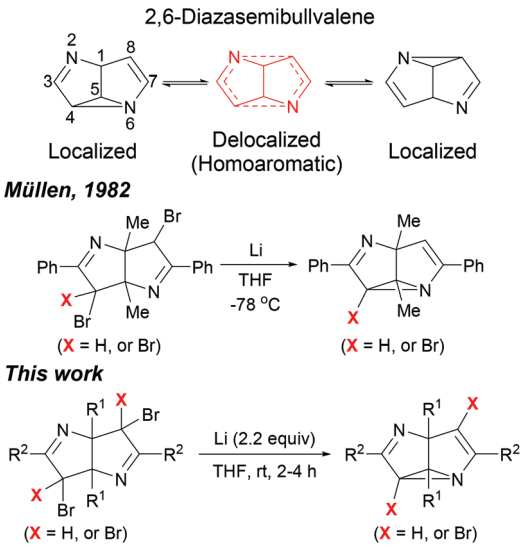
Treatment of Δ^1-dipyrrolines with NBS afforded α,α′-dibromo-Δ^1-bipyrrolines and α,α,α′,α′-tetrabromo-Δ^1-bipyrrolines respectively with excellent selectivity depending on the amount of NBS. All these multi-bromo-substituted Δ^1-bipyrrolines could be efficiently transformed into their corresponding 2,6-diaza-semibullvalene derivatives *via* reduction with lithium. An unprecedented rearrangement of 4,8-dibromo-2,6-diazasemibullvalene afforded a new type of bipyrroline derivative.

Introduction

2,6-Diazasemibullvalenes (NSBVs) have attracted fundamental interest both theoretically and experimentally for a long time because of their rapid aza-Cope rearrangement and the predicted existence of a homoaromatic delocalized structure (Scheme 1).[1–7] However, the synthesis and structural study of NSBV derivatives have been a great challenge in organic chemistry.

Müllen and co-workers reported the experimental *in situ* NMR identification of an NSBV, 1,5-dimethyl-3,7-diphenyl-2,6-diazasemibullvalene as a breakthrough in 1982 (Scheme 1).[5a] However, limited to the synthetic method of the reagent (Δ^1-bipyrroline), only one example of NSBV was obtained. 30 years later, two efficient methods for the synthesis of NSBVs were reported by our lab in 2012.[6a] A series of 3,7-dialkyl-substituted diazasemibullvalenes were synthesized and isolated from the reaction of dilithio reagents with nitriles.

Δ^1-Bipyrroline derivatives are a class of important compounds with interesting structures. An *N*-containing fused-ring is a common moiety in synthetic intermediates and biologically active compounds.[8] While synthetic methods for Δ^1-bipyrrolines are rare, we have found that the reaction of dilithio reagents with nitriles is an efficient way.[9] Herein, based on the synthetic method of Δ^1-bipyrrolines developed in our lab, we could largely expand the scope of NSBV derivatives. A number of 3,7-dialkyl-substituted and 3,7-diaryl-substituted NSBVs could be obtained in good to excellent yields.



Scheme 1 2,6-Diazasemibullvalene derivatives.

The electron-withdrawing halide substituents on NSBVs are expected to have a remarkable effect on both the rate of aza-Cope rearrangement and their further reaction chemistry.[3e,7] In our previous work, 4,8-dichloro-2,6-diazasemibullvalenes have been obtained efficiently *via* treatment of the corresponding α,α,α′,α′-tetrachloro-Δ^1-bipyrrolines with lithium.[6f] In this work, a series of α,α,α′,α′-tetrabromo-Δ^1-bipyrrolines and 4,8-dibromo-2,6-diazasemibullvalenes were synthesized *via* a similar strategy.[9a,10] Meanwhile, the skeletal rearrangements

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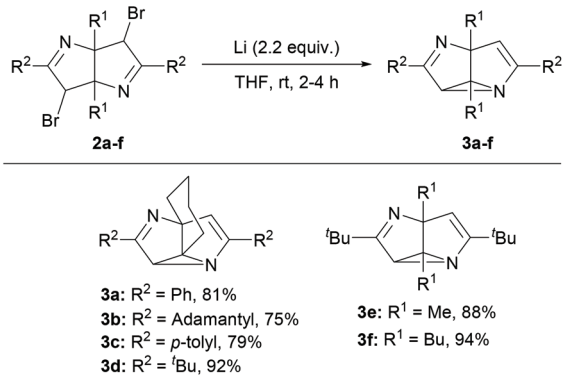
of NSBV and its derivatives are interesting, where the substituents play an important role in their thermal stability. Non-bridged NSBVs can undergo a thermal rearrangement to give 1,5-diazocine.[5b] Bridged 4,8-dichloro-2,6-diazasemibuvallenes could undergo a different skeletal rearrangement to form bipyrroline derivatives.[6f] When 4,8-dibromo-2,6-diazasemibuvallenes were synthesized and isolated, however, a new rearrangement was observed, demonstrating the different effects of halide substituents on the NSBV core skeleton.

Results and discussion

Based on our own synthetic method,[9a] the starting materials, Δ^1-bipyrroline derivatives **1a–f** used in this study were all obtained by the reaction of 1,4-dilithio-1,3-butadienes with 2 equivalents of nitriles. As shown in Scheme 2, the reaction of Δ^1-bipyrroline **1a** with 2.4 equivalents of *N*-bromosuccinimide (NBS) at 80 °C for 12 h afforded the corresponding α,α′-dibromo-Δ^1-bipyrroline **2a** in 48% isolated yield, along with a small amount of α,α,α′-tribromo Δ^1-bipyrroline as a side product.[10,11] Due to this side reaction, most α,α′-dibromo-Δ^1-bipyrrolines (**2a–2f**) could only be isolated in moderate yields (Scheme 2). Nevertheless, a range of Δ^1-bipyrrolines could be applied in this reaction, where R^2 were aryl groups (Ph, *p*-tolyl) or alkyl groups (^{t}Bu, adamantyl). Non-bridged Δ^1-bipyrrolines (**1e** and **1f**) were also applicable for this reaction and their corresponding α,α′-dibromo-Δ^1-bipyrrolines (**2e** and **2f**) were obtained in higher yields.

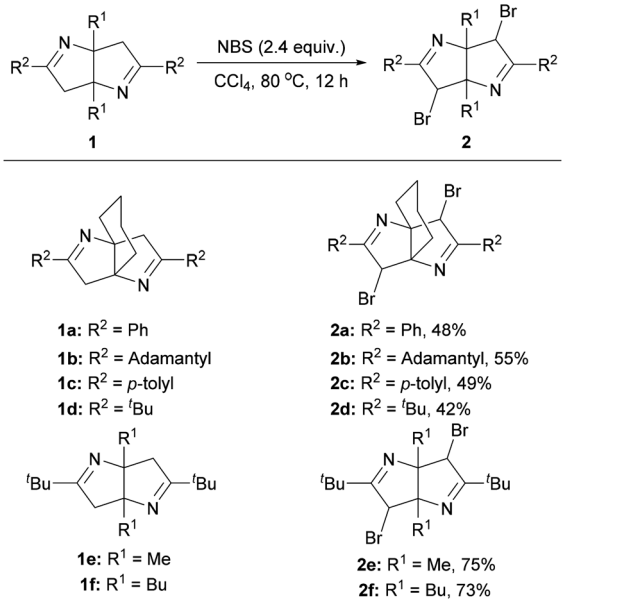
As shown in Scheme 3, 2,6-diazasemibuvallenes could be easily synthesized by the reaction of α,α′-dibromo-Δ^1-bipyrrolines with lithium in THF at room temperature. The *in situ* NMR experiment showed that α,α′-dibromo-Δ^1-bipyrroline **2a** was transformed to 2,6-diazasemibuvallene **3a** quantitatively without any side reactions. After removing LiBr, analytically pure 2,6-diazasemibuvallene **3a** could be obtained. However, due to the little solubility difference of **3a** and LiBr in the mixed solvent (hexane : Et_2O = 3 : 1), the isolated yield of **3a** was 81%. Similarly, 2,6-diazasemibuvallenes **3b–3f** were synthesized from the corresponding α,α′-dibromo-Δ^1-bipyrrolines (**2b–2f**). Higher isolated yields could be achieved for 1,5-dialkyl-substituted diazasemibuvallenes (**3e** and **3f**) because of their higher solubility than LiBr in hexane. The NMRs of **3a–3c** showed the existence of a rapid aza-Cope rearrangement of 2,6-diazasemibuvallenes, which was similar to the known 2,6-diazasemibuvallenes **3d–3f**.



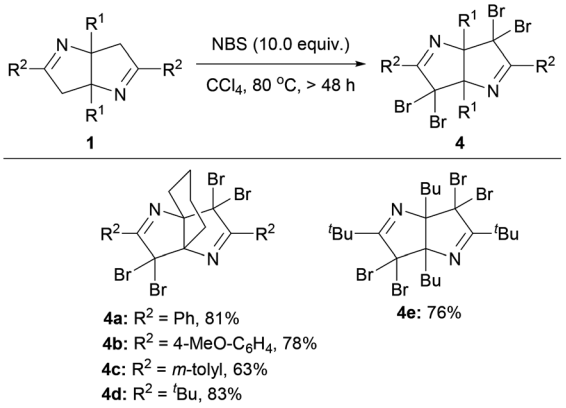
Scheme 3 The synthesis of 2,6-diazasemibuvallenes.

Tetrabromo-Δ^1-bipyrrolines **4** were obtained in moderate to high isolated yields when 10.0 equivalents of NBS were used and the reaction time was prolonged to 48 h (Scheme 4). The structure of **4a** was determined by single-crystal X-ray structural analysis (Fig. 1).

As shown in Scheme 5, 4,8-dibromo 2,6-diazasemibuvallenes **5a–c** were successfully synthesized and isolated from the reaction of α,α,α′,α′-tetrabromo-Δ^1-bipyrrolines with lithium in THF at room temperature *via* C–N bond formation. An *in situ* NMR experiment indicated that three α,α,α′,α′-tetrabromo-



Scheme 2 The synthesis of α,α′-dibromo-Δ^1-bipyrrolines.



Scheme 4 The synthesis of α,α,α′,α′-tetrabromo-Δ^1-bipyrrolines.

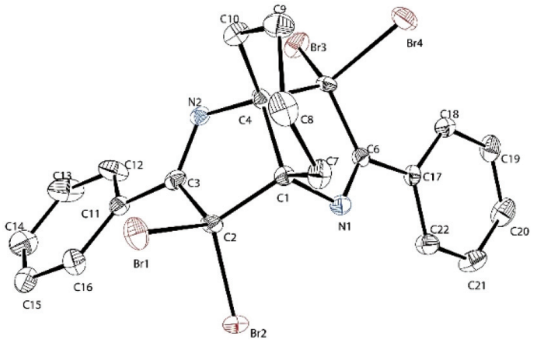
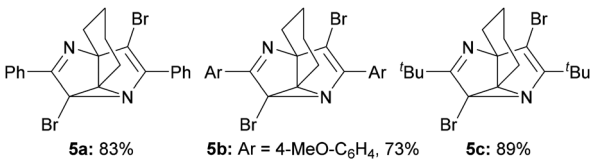


Fig. 1 ORTEP drawing of **4a** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: C(1)–N(1) 1.462(7), C(1)–C(2) 1.565(9), C(2)–C(3) 1.513(8), C(4)–N(2) 1.480(8), C(4)–C(5) 1.569(8), C(5)–C(6) 1.521(8), C(6)–N(1) 1.273(7), C(2)–Br(1) 1.965(6), C(2)–Br(2) 1.943(6), C(5)–Br(3) 1.931(6), C(5)–Br(4) 1.967(6).



Scheme 5 The synthesis of 4,8-dibromo-2,6-diazasemibuvallenes.

Δ^1-bipyrrolines could be transformed into the corresponding 4,8-dibromo-2,6-diazasemibuvallenes (**5a–c**) successfully.

The NMR spectra of all these dibromodiazasemibullvalenes showed the existence of an extremely rapid aza-Cope rearrangement in solution. The C3/C7 of **5c** displayed a singlet at 159.4 ppm in the ^{13}C NMR spectrum in THF-d_8, which is a little downfield shifted than the value of C3/C7 of the corresponding non-brominated diazasemibullvalene (163.3 ppm)

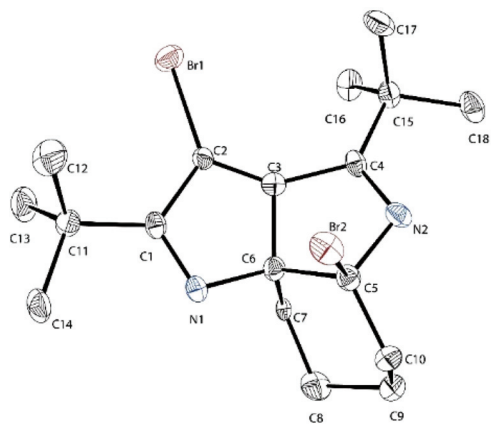
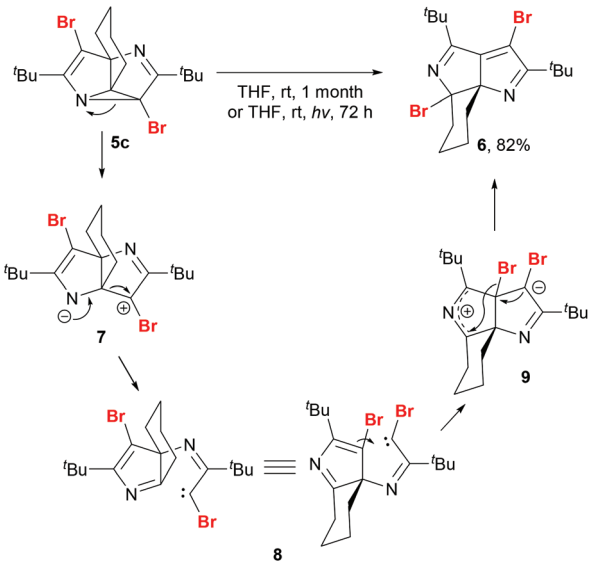


Fig. 2 ORTEP drawing of **6** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: C(1)–N(1) 1.292(7), C(1)–C(2) 1.496(7), C(2)–C(3) 1.321(7), C(3)–C(4) 1.485(7), C(4)–N(2) 1.298(6), N(2)–C(5) 1.476(7), C(5)–C(6) 1.538(7), C(6)–N(1) 1.479(6), C(2)–Br(1) 1.885(5), C(5)–Br(2) 1.969(5).



Scheme 6 Rearrangement of 4,8-dibromo-2,6-diazasemibuvallene **5c**.

and upfield shifted than that of the dichlorodiazasemibullvalene (157.2 ppm).[6a,f] Obviously, the bromide substituents had an electronic effect on the diazasemibullvalene core.

When diazasemibuvallene **5c** was kept in THF-d_8 at room temperature, a slow skeletal rearrangement took place, as monitored by NMR, until **5c** was totally transformed into a new bipyrroline derivative **6** after one month. This process could be promoted by light and completed in 3 days, and the product **6** was isolated in 82% yield. The structure of **6** was determined by single-crystal X-ray structural analysis (Fig. 2).

A similar rearrangement to that of 4,8-dichloro-2,6-diazasemibuvallene is proposed and shown in Scheme 6.[6f] The reaction was initiated *via* opening of the three-membered ring destabilized by the bromide. Then the lone pair electron of the nitrogen atom transformed to build a C=N bond, generating a carbine intermediate **8** stabilized by the bromide. An intramolecular carbine attack occurred to give the intermediate **9**, which afforded the product **6**.

Conclusions

A series of α,α′-dibromo-Δ^1-bipyrrolines and α,α,α′,α′-tetrabromo-Δ^1-bipyrrolines were synthesized and transformed into their corresponding 2,6-diazasemibuvallenes and 4,8-dibromo-2,6-diazasemibuvallenes *via* reduction with lithium. The successful synthesis of all these novel compounds should lead to further study on their chemical and physical properties.

Acknowledgements

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