Cycloaddition of Lewis Acid-Induced *N*-Methyleneanilines as Azadienes to 1,2-Bistrimethylsilyloxycyclobutene and Oxidative Ring Expansion to 1,2,4,5-Tetrahydro-1-benzazocine-3,6-diones[1]

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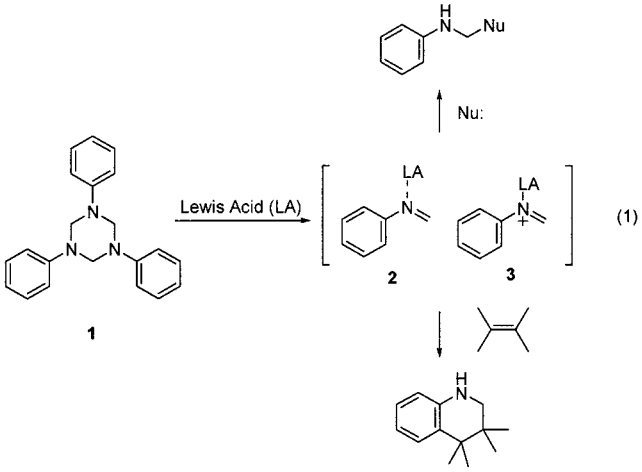
One of the simplest imines, *N*-methyleneamine (monomeric formaldehyde imine), has very limited use from a synthetic viewpoint. It has been observed only in the gas phase through flash vacuum thermolysis.[2] However, synthetically useful *N*-methyleneamine equivalents can be generated from 1,3,5-trisubstituted hexahydro-1,3,5-triazenes in the presence of a Lewis acid and used for aminomethylation reactions with various nucleophiles at the α-position of amines.[3,4]

N-Methyleneaniline equivalents, as shown by **2** and **3** (eq 1) result from the breaking of all three carbon−

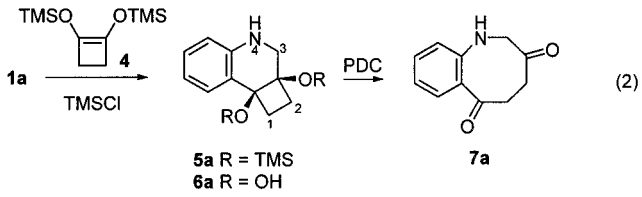


(1)

nitrogen bonds of 1,3,5-triphenylhexahydro-1,3,5-triazenes.[5] They have characteristics of imine and iminium ions similar to Mannich bases and can be used for various aminomethylation reactions. However, there have been no reports of using *N*-methyleneamine equivalents as azadienes,[6] which may react with olefins via [4π + 2π] cycloaddition to afford 1,2,3,4-tetrahydroquinolines. The possibility that *N*-methyleneamine equivalents could be used as azadienes is based on early observations using *N*-alkyl or *N*-aryliminium ions with electron-rich olefins in the presence of acids to provide *N*-alkyl-1,2,3,4-tetrahydroquinolines.[7] However, most reactions that are claimed to be [4π + 2π] cycloadditions can also be explained by a stepwise mechanism with a cationic intermediate generated from the addition of electron-rich olefins to imine or iminium ions as Mannich bases followed by electrophilic cyclization.[4]

In this report, we describe the use of *N*-methyleneamine equivalents (**2**, **3**) as azadienes in cycloaddition reactions with 1,2-bistrimethylsilyloxycyclobutene (**4**) for the synthesis of tricyclic 2a,8b-bistrimethylsilyloxy-1,2,-2a,3,4,8b-hexahydrocyclobuta[*c*]quinolines (**5**). These cycloadducts can be further transformed to the heterocycle 1,2,5,6-tetrahydro-1-benzazocine-3,6-diones (**7**).

Cycloaddition reactions with the electron-rich olefin 1,2-bistrimethylsilyloxycyclobutene (**4**) were studied using *N*-methyleneamine equivalents (**2** or **3**) generated from 1,3,5-triphenylhexahydro-1,3,5-triazine (**1a**) in the presence of various Lewis acids.[8] Most of the Lewis acids we tried gave the expected cycloadducts (**5a**) with a certain amount of diol (**6a**) resulting from the loss of the two TMS groups from the initial cycloadducts. TMSCl gave the best results; i.e., the tricyclic cycloadduct 2a,8b-bistrimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline (**5a**) was obtained in 65% isolated yield with the least amount of hydrolyzed diol.



(2)

This reaction proceeded well with 1,3,5-triphenylhexahydro-1,3,5-triazines with various substituents (Table 1) on the benzene ring, such as *p*-methoxy, *p*-fluoro, and *o*-methyl (**1b**, **1c**, and **1d**), to afford the corresponding cycloadducts (**5b**, **5c**, and **5d**) in respective yields of 55, 58, and 52% (entries 2, 3, 4). The X-ray crystal structure of **5d** shows a cis relationship between two trimethylsilyloxy groups at the ring junction. When we performed the reaction with 1,3,5-tris(2-methyphenyl)hexahydro-

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(2) Guillan, J.-C.; Denis, J.-M. *Tetrahedron* **1988**, *44*, 4431 and reference cited therein.

(3) (a) Ha, H.-J.; Nam, G.-S.; Park, K. P. *Tetrahedron Lett.* **1990**, *31*, 1567. (b) Ha, H.-J.; Nam, G.-S.; Park, K. P. *Bull. Kor. Chem. Soc.* **1990**, *11*, 485. (c) Ha, H.-J.; Nam, G.-S.; Park, K. P. *Synth. Commun.* **1991**, *21*, 155. (d) Ha, H.-J.; Ahn, Y.-G. *Synth. Commun.* **1995**, *25*, 969. (e) Ha, H.-J.; Kang, K.-H.; Suh, J.-M.; Ahn, Y.-G. *Tetrahedron Lett.* **1996**, *37*, 7069. (f) Ha, H.-J.; Ahn, Y.-G. *Synth. Commun.* **1997**, *27*, 1543. (g) Ha. H.-J.; Kang, K.-H.; Ahn, A.-G.; Oh, S.-J. *Heterocycles* **1997**, *45*, 277. (h) Ha, H.-J. Ha; Kang, K.-H.; Suh, J.-M.; Ahn, Y.-G.; Han, O. *Tetrahedron* **1998**, *54*, 851.

(4) (a) Ha, H.-J.; Ahn, Y.-G.; Chon, J.-K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2631. (b) Ha, H.-J.; Lee, Y.-S.; Ahn, A.-G. *Heterocycles* **1997**, *45*, 2357.

(5) Ha, H.-J.; Suh, J.-M.; Ahn, Y.-G.; Dong, Y.; Yun, H. *Heterocycles* **1999**, *50*, 203.

(6) (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (b) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 5, Chapter 4.3. (c) Boger, D. C. *J. Heterocycl. Chem.* **1996**, *33*, 1519. (d) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259.

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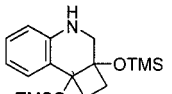
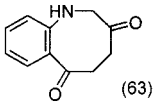
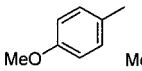
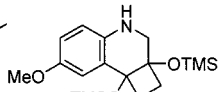
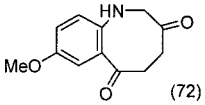
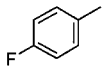
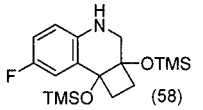
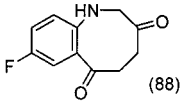
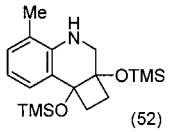
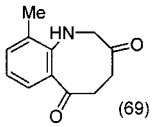
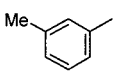
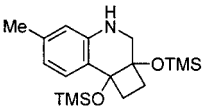
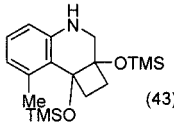
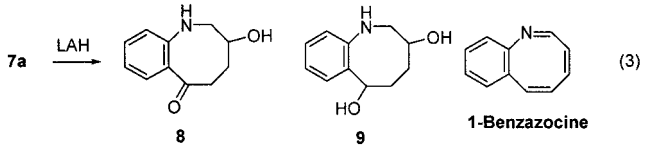
Table 1

Entry	1 (Ar)	Product (5), Yield (%)	Product (7), Yield (%)
1	 1a	 TMSO, OTMS (65) 5a	 (63) 7a
2	 MeO 1b	 MeO, TMSO, OTMS (55) 5b	 MeO (72) 7b
3	 F 1c	 F, TMSO, OTMS (58) 5c	 F (88) 7c
4	 Me 1d	 Me, TMSO, OTMS (52) 5d	 Me (69) 7d
5	 Me 1e	 Me, TMSO, OTMS 5e (79)	 Me, TMSO, OTMS (43) 5f (21)

1,3,5-triazine (**1e**), two regioisomers (**5e** and **5f**) were obtained in 43% yield in a ratio of 79:21. This discrimination may be due to steric hindrance in the approach of the diene and dienophiles (entry 5). A concerted [4π + 2π] cycloaddition route is preferred to a Mannich-type stepwise reaction. If a Mannich-type reaction occurred between an *N*-methyleneamine equivalent and 1,2-bistrimethylsilyloxycyclobutene, a trimethylsilyloxy carbonium ion intermediate would be formed. Such an intermediate would not favor electrophilic aromatic cyclization over desilylation. Therefore, aminomethylated products would be formed exclusively.[9] A similar reaction of *N*-methyleneaniline equivalents with an allyl nucleophile gave both aminomethylated and cyclized products together. Their ratios depended on the stability of the cationic intermediate and the electronic characteristics of the aromatic ring.[4a] In this case with 1,2-bistrimethylsilyloxycyclobutene, there was no detectable amount of the aminomethylated product without a significant change in the reaction regarding the electron-richness of the aromatic ring. Even though the stability of the cationic intermediate was increased with trimethylsilyloxy ketene acetals bearing an additional alkoxy group on the olefin, these reactions yielded only aminomethylated 3-anilinopropanoates without the formation of any cyclized product.[10] All of these results favor a concerted [4π + 2π] cycloaddition route of *N*-methyleneaniline equivalents as azadienes with 1,2-bistrimethylsilyloxycyclobutene as a dienophile.

The initial adduct **5a** was hydrolyzed with K_2CO_3 in MeOH to produce diol (**6a**) in quantitative yield. By further treatment with PDC in CH_2Cl_2 at room temperature, the 1,2-diol at the junction of the cyclobutane and piperidine rings was oxidatively expanded to give an eight-membered ring product, 1,2,4,5-tetrahydro-1-benzazocine-3,6-dione (**7a**), in 63% yield.[11,12] Oxidative ring expansion[13] was driven by the ring strain[14] present in the cyclobutane. Hydrolysis and oxidative ring expansion were also successful with other cycloadducts such as **5b**, **5c**, and **5d** to give the corresponding 1,2,4,5-tetrahydro-1-benzazocine-3,6-diones (**7b**, **7c**, and **7d**) in yields of 72, 88, and 69%, respectively. This may serve as an efficient way to construct 1-benzazocine skeletons,[11] some of which are biologically active.[15]

Once we had **7a** in hand, we wished to obtain free benzazocine, which has not been obtained in a pure form.[12] The sequence of reactions included reduction to diol **9** and subsequent dehydration, at which point oxidative conjugation[4b] may occur to obtain free benzazocine.



(3)

Lithium aluminum hydride reduced only one carbonyl at C-3 of **7a** to give hydroxy ketone **8**, which was not further reduced to diol **9** regardless of the amount $LiAlH_4$ used.[16] Superhydride reduction was also tried in vain and gave an unidentified complex mixture of the products. Thus, synthesis of free benzazocine remains elusive.

In summary, we have succeeded in using *N*-methyleneaniline equivalents generated from 1,3,5-triphenyl-

(7) Various reactions have been claimed to be [4π + 2π] cycloaddition from *N*-methyleneammonium ions. (a) Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753. (b) Murahashi, S.-I.; Naota, T.; Nakato, T. *Synlett* **1992**, 835. (c) Beifuss, U.; Ledderhose, S. *J. Chem. Soc. Chem. Commun.* **1995**, 2137. (d) Beifuss, U.; Kunz, O.; Ledderhose, S.; Taraschewski, M.; Tonko, C. *Synlett* **1996**, 34. (e) Caille, S.; Trimble, L.; Berthelette, C.; Lau, C. K. *Synlett* **1996**, 669. (f) Katritzky, A. R.; Zhang, G.; Qi, M.; Xie, L. *Tetrahedron Lett.* **1997**, *38*, 6959. (g) Campos, P. J.; Lamaza, I.; Rodriguez, M. A.; Canal, G. *Tetrahedron Lett.* **1997**, *38*, 6741. However, most of the tetrahydroquinoline products can also be explained by a stepwise mechanism instead of [4π + 2 π] cycloaddition with a cationic intermediate based on the addition of imine or iminium ions as a Mannich base to an olefin followed by electrophilic cyclization.[4]

(8) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, 1995.

(9) Ikeda, K.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1983**, *24*, 913.

(10) Unpublished results.

(11) (a) Naito, T.; Kaneko, C. *Chem. Pharm. Bull.* **1980**, *28*, 3150. (b) Kawahara, N.; Nakajima, T.; Itoh, T.; Ogura, H. *Heterocycles* **1981**, *16*, 729. (c) Nomura, K.; Suda, S.; Takeuchi, M.; Adachi, J.; Masuda, K. *Heterocycles* **1983**, *20*, 2051. (d) Trifonov, L. S.; Orahovats, A. S. *Heterocycles* **1984**, *22*, 355. (e) Oda, K.; Ohnuma, T.; Ban, Y. *J. Org. Chem.* **1984**, *49*, 953. (f) Cordero, F. M.; Goti, A.; De Sarlo, F.; Guarna, A.; Brandi, A. *Tetrahedron* **1989**, *45*, 5917. (g) Kobayashi, K. Suzaki, M.; Suginome, H. *J. Org. Chem.* **1992**, *57*, 599.

(12) Kurita, J.; Yamanaka, T.; Tsuchiya, T. *Heterocycles* **1991**, *32*, 2089.

(13) Oxidative ring expansion of cyclopropanol at the ring junction has been reported. See, Rubottom, G. M.; Beedle, E. C.; Kim, C.-W.; Mott, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4230.

(14) Wong, H. N. C.; Lau, K.-L.; Tam, K.-F. *Top. Curr. Chem.* **1986**, *133*, 83.

(15) Sutharchanadevi, M.; Murugan, R. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: New York, 1996; Vol. 9, Chapter 9.18.

(16) The inertness of the carbonyl at C-6 to a strong reducing agent like $LiAlH_4$ stems from possible conjugation through nonbonding electrons of the nitrogen and π-electrons of the carbonyl and the benzene ring to decrease reactivity.

hexahydro-1,3,5-triazine as azadienes with electron-rich 1,2-bistrimethylsilyloxycyclobutene to give [4π + 2π] cycloadducts 2a,8b-bis-trimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline. Two trimethylsilyl groups of the initial adduct were hydrolyzed to a diol that was subsequently treated with PDC to give oxidative ring-expanded 1,2,4,5-tetrahydro-1-benzazocine-3,6-diones.

Experimental Section

2a,8b-Bistrimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline (5a). To a stirred solution of 1,3,5-triphenylhexahydro-1,3,5-triazine[3a,b] (1.20 g, 3.8 mmol) in CH_2Cl_2 (25 mL) was slowly added TMSCl (0.41 g, 3.8 mmol) at 0 °C. After stirring for 10 min, 1,2-bistrimethylsilyloxycyclobutene (2.63 g, 11.4 mmol) was added. The resulting solution was stirred at −78 °C until all of the starting materials had disappeared on TLC, and the reaction mixture was then poured into ice−water. The resulting solution was neutralized with cold sat. $NaHCO_3$ solution. The reaction product was extracted twice with CH_2Cl_2. The organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was further purified by flash chromatography to yield 2.48 g of 2a,8b-bistrimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline in 65% yield as a white solid: mp 66−68 °C; IR (KBr) 3338, 2955, 1252, 842; ^{1}H NMR δ 0.10 (s, 9H), 0.21 (s, 9H), 1.91−2.04 (m, 3H), 2.40−2.53 (m, 1H), 3.04 (d, 1H, J = 11 Hz), 3.19 (d, 1H, J = 11 Hz), 3.78 (bs, 1H), 6.54 (d, 1H, J = 8 Hz), 6.76 (t, 1H, J = 8 Hz), 7.01 (t, 1H, J = 8 Hz), 7.35 (d, 1H, J = 8 Hz); ^{13}C NMR δ 2.2, 2.4, 26.2, 36.1, 49.5, 75.9, 80.1, 114.6, 118.6, 127.4, 128.1, 130.0, 143.8; HRMS (EI) calcd for $C_{17}H_{29}NO_2Si_2$ *m/e* 335.1737, found, 335.1731. Anal. Calcd for $C_{17}H_{29}NO_2Si_2$: C, 60.8; H, 8.71; N, 4.17. Found: C, 60.7; H, 8.82. N, 4.09.

2a,8b-Dihydroxy-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline (6a). To a stirred solution of K_2CO_3 (0.964 g, 0.697 mmol) in MeOH (10 mL) was slowly added 2a,8b-bistrimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline (468 mg, 1.40 mmol) at room temperature. After stirring for 12 h, the resulting solution was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in EtOAc. This organic solution was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated again under reduced pressure. This crude product was purified by flash chromatography to yield 263 mg of diol as a white solid: mp 104−105 °C; IR (KBr) 3330, 3272, 1492, 1309, 752; ^{1}H NMR δ 2.75 (t, 2H, J = 5.6 Hz), 3.00 (t, 2H, J = 5.6 Hz), 3.62 (d, 2H, J = 5.4 Hz), 4.53 (t, 1H, J = 5.4 Hz), 6.78 (d, 1H, J = 8.0), 6.86 (td, 1H, J = 7.4, 1.2 Hz), 7.24 (td, 1H, J = 8.0, 1.8 Hz), 7.45 (dd, 1H, J = 7.6, 1.6 Hz); ^{13}C NMR δ 27.0, 33.3, 49.2, 72.8, 75.4, 115.2, 119.5, 127.5, 127.6, 128.3, 144.4; LC-MS 214 (MNa^+, 63%), 171 (M^+ − OH, 100%). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.85; N, 7.32. Found: C, 69.0; H, 6.67; N, 7.18.

1,2,4,5-Tetrahydro-1-benzazocine-3,6-dione (7a). To a stirred solution of PDC (2.43 g, 6.30 mmol) in CH_2Cl_2 (10 mL) was added 2a,8b-dihydroxy-1,2,2a,3,4,8b-hexahydrocyclobuta-[c]quinoline (**13a**, 100 mg, 0.52 mmol) dissolved in CH_2Cl_2 (5 mL) at room temperature. After stirring for 2 h, all of the starting materials had disappeared on TLC. The reaction mixture was filtered through Celite with additional CH_2Cl_2 for washing. The solution was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the product (79 mg) in 80% yield as a white solid: mp 116−118 °C; IR (KBr) 3353, 1713, 1664, 1601, 1485, 755; ^{1}H NMR δ 2.75 (t, 2H, J = 6.6 Hz), 2.98 (t, 2H, J = 6.6 Hz), 3.62 (d, 2H, J = 5.4 Hz), 4.52 (bs, 1H), 6.80 (d, 1H, J = 8.0 Hz), 6.89 (td, 1H, J = 7.2, 1.0 Hz), 7.25 (td, 1H, J = 7.6, 1.0 Hz), 7.45 (dd, 1H, J = 7.6, 1.4 Hz); ^{13}C NMR δ 37.8, 37.9, 59.2, 118.9, 120.1, 128.0, 129.6, 132.4, 149.2, 204.8, 207.1. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.86; N, 7.40. Found: C, 69.7; H, 5.74; N, 7.27.

3-Hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazocin-6-one (8). $LiAlH_4$ (9.0 mg, 0.24 mmol) was added to **7a** (60 mg, 0.32 mmol) in THF (10 mL) at 0 °C. In 20 min, all of the starting materials had disappeared on TLC. The general workup procedure gave the crude product, which was further purified by flash chromatography to give the product (52 mg) in 86% yield as a white solid: mp 124−125 °C; IR (KBr) 3410 (br), 1668, 1472; ^{1}H NMR δ 1.88−2.04 (m, 2H), 2.49−2.62 (m, 1H), 2.78−2.99 (m, 1H), 2.92−3.07 (m, 1H), 3.26−3.91 (m, 1H), 3.85 (q, 1H, J = 5.4 Hz), 4.24 (bs, 1H), 6.64 (d, 1H, J = 8.6 Hz), 6.72 (t, 1H, J = 7.4 Hz), 7.16 (d, 1H, J = 7.0 Hz), 7.24 (td, 1H, J = 7.6, 1.4 Hz); ^{13}C NMR δ 30.7, 38.1, 51.3, 69.7, 117.7, 118.4, 125.7, 130.2, 131.9, 148.6, 207.3. HRMS (EI) calcd for $C_{11}H_{13}NO_2$ - H_2O *m/e* 173.0841, found, 173.0848. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.85; N, 7.32. Found: C, 68.9; H, 6.92; N, 7.19.

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Supporting Information Available: Spectral data including ^{1}H NMR, ^{13}C NMR, mass, and elemental analyses for all new compounds (**5b**−**f**, **6b**−**d**, **7b**−**d**), and X-ray structural data for **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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