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Note

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# A [2 + 3] Reductive Cyclodimerization of Quinoline by $SmI_2$

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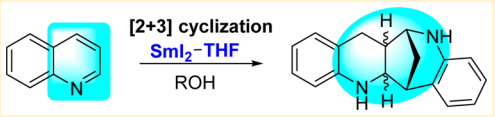
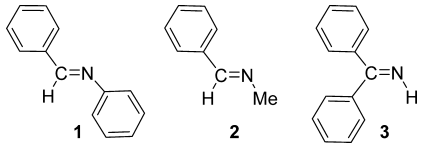
Supporting Information

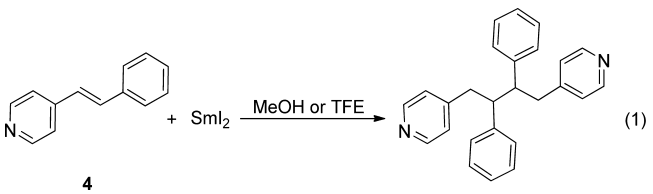
**ABSTRACT:** Pyridine and its derivatives are rather difficult to reduce, and the products often undergo a very fast reoxidation to regain aromaticity. The reduction of quinoline by $SmI_2$ results in an instantaneous [2 + 3] cyclization reaction, forming a bridged seven-membered ring within a polycyclic system.




In the last five years, we have explored the reduction of nitrogen-containing substrates by $SmI_2$. It turned out that these substrates exhibit a rich and novel behavior not observed before in any other group of substrates in the field of $SmI_2$ chemistry.[1] For example, the three compounds **1**, **2**, and **3** displayed surface catalysis and autocatalysis for the reduction of the central C═N bond.[2]




The reactivity order for these three substrates was **3** > **2** > **1**. This reactivity order is not in accord with the electron affinity of these substrates but rather with the accessibility of the lone pair on the nitrogen. Namely, it correlates with the ability of $SmI_2$ to coordinate to the substrate via the nitrogen lone pair. In the next step, we moved the nitrogen from the reaction center to the periphery.[3] Namely, we moved the nitrogen of **1** to the para position of the ring, generating a stilbene-like substrate—**4** (eq 1). Thus, this substrate retained the ability to coordinate to $SmI_2$, but in this case, the coordination site was displaced away from the reaction center.

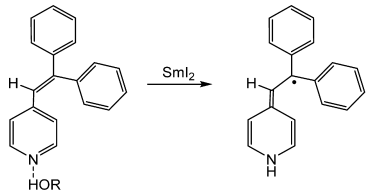



(1)

**4**

This substrate manifested another unexpected phenomenon: An unusual rate dependence on the concentration of the additives MeOH, trifluoroethanol (TFE), hexamethylphosphoramide (HMPA), and $SmI_3$. The advantage of anchoring the $SmI_2$ in the vicinity of the reaction center was recently explored also by Procter, Flowers, and co-workers in enhancing reduction of esters.[4]

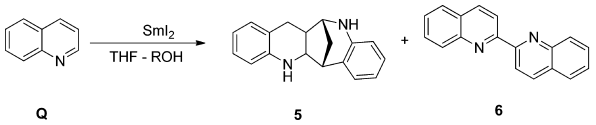
The surprises displayed by the nitrogen-containing substrates culminated in the discovery of a system where the radical produced after a proton coupled electron transfer step showed resistance to further reduction by $SmI_2$ (eq 2).[5]




(2)

The present study shows that nitrogen compounds contain even more surprises.

In this study, we simplified the system by considering an isolated aromatic nuclei containing nitrogen (pyridine derivative) with no double bond attached to it. It is well-known that partial reduction of pyridine and its derivatives is rather difficult[6] and apparently the reduced product undergoes a very fast reoxidation to regain aromaticity. Therefore, we have moved to the next simple pyridine derivative—quinoline (**Q**). The surprising result is depicted in eq 3.




(3)

**Q** **5** **6**

The formation of **5** was accompanied under all conditions by polymeric material. Attempts to optimize its yield led to the following conditions: [**Q**] = 40 mM, [$SmI_2$] = 80 mM in THF in the presence of 0.1 M TFE. The reaction was instantaneous, and the isolated yield of **5** was 45%. This was accompanied by 5% of the 2,2′ dimer **6** and polymeric material.

The major product **5** was obtained as a mixture of two diastereoisomers **7** and **8**.


**7** **8**

The structures for **7** and **8** were established by a careful analysis of their NMR spectra, which included several two-dimensional NMR techniques. The NMR data are summarized in Table 1 (for atom numbering, see **9** below). The usual

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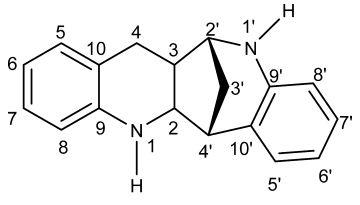
**Table 1. NMR Data for 6, 7, and 8**

| | 6 | | 7[a] (exo) | | 8 (endo) | |
|---|---|---|---|---|---|---|
| | $^1$H | $^{13}$C | $^1$H | $^{13}$C | $^1$H | $^{13}$C |
| 2 | | 156.25 | 3.74 | 65.72 | 3.83 | 62.79 |
| 3 | 8.85 | 119.43 | 2.64 | 51.39 | 2.48 | 46.31 |
| 4 | 8.33 | 136.74 | 2.28, 2.87 | 30.26 | 2.57, 2.70 | 27.62 |
| 5 | 7.89 | 127.65 | 7.04 | 127.52[b] | 7.00 | 127.35 |
| 6 | 7.58 | 126.70 | 6.77 | 119.37 | 6.68 | 119.44 |
| 7 | 7.76 | 129.55 | 7.06 | 127.65[b] | 6.90 | 126.40 |
| 8 | 8.23 | 129.94 | 6.67 | 114.55[c] | 6.52 | 115.57 |
| 9 | | 147.95 | | 146.11 | | 145.10 |
| 10 | | 128.48 | | 126.29 | | 128.00 |
| 2′ | | | 3.52 | 59.88 | 3.71 | 55.73 |
| 3′ | | | 1.80, 2.35 | 27.76 | 2.01, 2.10 | 30.68 |
| 4′ | | | 2.92 | 48.98 | 3.12 | 45.21 |
| 5′ | | | 6.98 | 126.95[b] | 6.87 | 129.10 |
| 6′ | | | 6.64 | 117.47 | 6.54 | 116.89 |
| 7′ | | | 7.01 | 127.36[b] | 6.85 | 127.86 |
| 8′ | | | 6.51 | 114.36[c] | 6.26 | 113.35 |
| 9′ | | | | 142.45 | | 142.80 |
| 10′ | | | | 126.65 | | 125.71 |

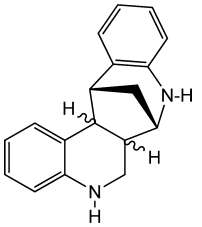
[a] $^{15}$N chemical shifts (from HMBC spectrum) −303.4 (N-1) and −300.9 (N-1′). [b] Chemical shifts with the same superscript may be interchanged. [c] Chemical shifts with the same superscript may be interchanged.

strategy for structure determination by NMR involves establishing sequences of hydrogens (and, by one-bond $^1$H × $^{13}$C correlation, HMQC, the carbons connected to them) and then connecting partial structures thus obtained by HMBC (long-range $^1$H × $^{13}$C correlation). In the case of **7**, we had the problem that the values of $^3J_{\text{H-3,H-2′}}$ and of $^3J_{\text{H-2,H-4′}}$ were very small, reflecting a dihedral angle close to 90°, and, therefore, causing a break in the proton sequence. This is a consequence of the exo stereochemistry of this diastereoisomer; for **8**, the coupling constants were 4 and 6 Hz, respectively. In the latter, NOE correlations (from a NOESY spectrum) were seen between the one of the protons on C-3′ ($\delta$ 2.01) and the bridgehead protons (H-2 and H-3), indicating that this was the endo isomer. No equivalent interactions were seen for the exo isomer (**7**). Instead, a weak, but diagnostically important, interaction was seen between H-2 and H-5′ for the latter.




**9**

A literature search for a similar structure revealed only one case where the reduction of quinoline by the Zn/AcOH method gave a [2 + 3] cyclization product.[7] However, the structure assigned to it was somewhat different from the one we obtained. Instead of the participation of carbons 2 and 3 in the cyclization, carbon atoms 3 and 4 (see structure **10**) took part in the cyclization.




**10**

In order to get unambiguous structural information regarding the structure of **5**, we carried out an X-ray analysis, which supported the structure of the two enantiomers of **5** (see ORTEP view of the endo isomer, Figure S1). It is interesting to note that the Zn/AcOH method also provides the structure of **5**, but only when C4 was methylated.

We have recently delineated the advantage of reduction by $SmI_2$ over other reducing agents, which is manifested in its versatility and enhanced chemoselectivity. Despite the difference in the products, it is instructive to compare the reaction conditions and the reaction times of the two reactions. While the Zn/AcOH method demands 15 h and reflux in THF, the $SmI_2$ reaction is instantaneous and at room temperature. Thus, another facet of the $SmI_2$ advantage is in its enhanced reactivity.

We will turn now to the mechanistic aspects of the reaction. Using ab initio calculations at the B3LYP/6-31+G* level[8] on both the radical and the radical anion of quinoline, we determined the spin densities at the 2-, 3-, and 4-positions (Figure 1).

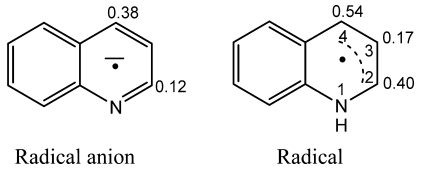



**Figure 1.** Spin densities on the relevant carbon atoms of the pyridine ring calculated at the B3LYP/6-31+G* level for the radical and the radical anion.

The spin data do not support a concerted cyclization reaction as in both, the radical and the radical anion, the spin density on C3 is miniscule. A reasonable stepwise mechanism is shown in Scheme 1. The first C2−C4′ bond could be a radical combination reaction since the spin density at both positions is high in the neutral as well as in the charged intermediate. The second C−C bond formation is somewhat more problematic since a nucleophilic attack by one ring on the other will place a negative charge on the bridge carbon. A reasonable alternative is that the allylic aza anion will undergo protonation on the carbon to become the bridge (protonation on the nitrogen is of course much faster but reversible)[9] and the nucleophilic attack by the neighboring group will take place on the carbon atom of the imine moiety, delocalizing the negative charge onto the nitrogen in a typical Michael addition reaction. This is followed by protonation on the nitrogen and a two-electron two-proton reduction by $SmI_2$ to provide the final two diastereoisomers.

A plausible mechanism for the formation of the dimer is given in eq 4.[10]





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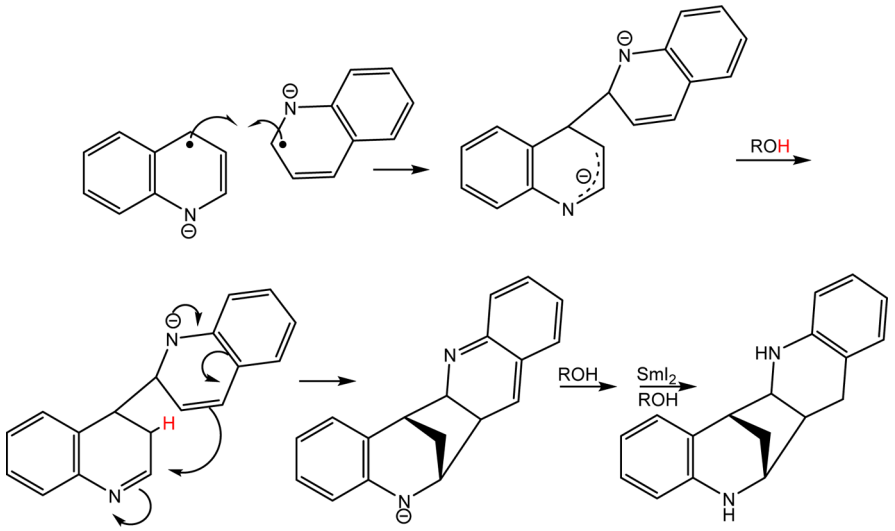
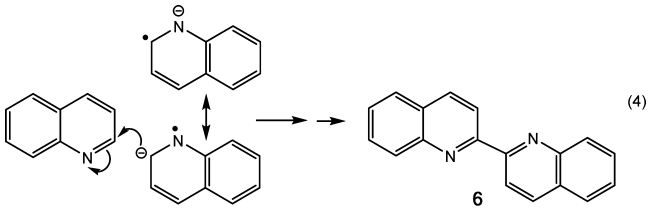
**Scheme 1**




(4)

In light of the reasonable yield of **5** and the mild conditions (short reaction times and room temperature) as opposed to 15 h reflux in the traditional methods, it is highly recommended that the scope and limitation of this reaction be explored and developed by the synthetic community.

## EXPERMENTAL SECTION

**General Information.** Reactions were performed inside the glovebox and repeated under various concentrations by changing proton donor (MeOH and TFE) concentrations to diminish the polymer formation. THF was dried over sodium/benzophenone and distilled under an argon atmosphere. MeOH and TFE were dried according to a known procedure.[11] Water content was determined and found to be lower than 20 ppm. $SmI_2$ was diluted as needed from a 0.1 M freshly prepared THF solution.[12] The concentration of the $SmI_2$ solution was spectroscopically determined ($\lambda$ = 615 nm; $\varepsilon$ = 635). Quinoline (**Q**) was used after distillation. Silica gel (60−120 mesh size) was used for column chromatography. Thick layer chromatography (silica gel 60 $F_{254}$, 0.5 mm, 20 × 20 cm) was used for separation of two diastereomers. NMR spectra were recorded on a 700 mHz instrument using $CDCl_3$ with tetramethylsilane as the internal standard for $^1$H NMR (700 MHz) and $CDCl_3$ solvent as the internal standard for $^{13}$C NMR (176 MHz).

**Experimental Procedure for Reduction of Quinoline.** To the homogeneous solution of quinoline (0.236 mL, 40 mM) and TFE (0.377 mL, 0.1 M) in dry THF (10 mL) was added a freshly prepared solution of $SmI_2$ in THF (80 mM, 40 mL) at room temperature. The final concentrations were [**Q**] = 40 mM, [$SmI_2$] = 80 mM, and [TFE] = 0.1 M. The reaction is instantaneous, and following the addition, the reaction was treated with iodine dissolved in THF and the solvent was evaporated under reduced pressure. The crude reaction mixture was redissolved in $CHCl_3$ (30 mL) and washed with saturated $NaHCO_3$ (10 mL), saturated $Na_2S_2O_3$ (10 mL), and potassium dihydrogen phosphate buffer (10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure. The pure diastereomers **5** (endo/exo, 1:1 ratio) were obtained after column chromatography (silica gel) using hexane and ethyl acetate (98:2) as eluent in 118 mg (45%) yield along with trace amounts of the dimer **6** contaminated with some polymeric material. The two diastereoisomers were separated using thick layer chromatography with hexane and ethyl acetate (98:2) as eluent. The two were crystallized from ether.

*exo-(6R,12R)-5a,6,11,12,12a,13-Hexahydro-5H-6,12-methanobenzo[6,7]azepino[4,3-b]quinoline (**7**).* Mp: 128−130 °C. $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 1.80 (d, 1H, $J$ = 11.5 Hz), 2.28 (dd, 1H, $J$ = 14, 10.5 Hz), 2.35 (dt, 1H, $J$ = 11.5, 4 Hz), 2.64 (q, 1H, $J$ = 8.5 Hz), 2.87 (dd, 1H, $J$ = 14, 7 Hz), 2.92 (d, 1H, $J$ = 3.5 Hz), 3.52 (d, 1H, $J$ = 3.5 Hz), 3.74 (d, 1H, $J$ = 8 Hz), 6.51 (d, 1H, $J$ = 8 Hz), 6.64 (td, 1H, $J$ = 7.5, 1 Hz), 6.67 (t, 1H, $J$ = 7.5 Hz), 6.77 (td, 1H, $J$ = 7.5, 1 Hz), 6.98 (dd, 1H, $J$ = 7.5, 1 Hz), 7.01 (td, 1H, $J$ = 7.5, 1.5 Hz), 7.04 (d, 1H, $J$ = 8 Hz), 7.06 (t, 1H, $J$ = 7.5 Hz); $^{13}$C NMR (175 MHz, $CDCl_3$): $\delta$ 27.8, 30.3, 49.0, 51.4, 59.9, 65.7, 114.4, 114.6, 117.5, 119.4, 126.3, 126.7, 127.0, 127.4, 127.5, 127.7, 142.5, 146.1; HRMS (ESI): $m/z$: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2$: 263.1548; found: 263.1582.

*endo-(6R,12R)-5a,6,11,12,12a,13-Hexahydro-5H-6,12-methanobenzo[6,7]azepino[4,3-b]quinoline (**8**).* Mp: 228−230 °C. $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 2.01 (dd, 1H, $J$ = 11.5, 4 Hz), 2.10 (d, 1H, $J$ = 11.5 Hz), 2.48 (dd, 1H, $J$ = 10, 5.5 Hz), 2.57 (dd, 1H, $J$ = 14, 10 Hz), 2.70 (dd, 1H, $J$ = 14, 7 Hz), 3.12 (t, 1H, $J$ = 4 Hz), 3.71 (t, 1H, $J$ = 4 Hz), 3.83 (dd, 1H, $J$ = 11, 6 Hz), 6.26 (d, 1H, $J$ = 7.5 Hz), 6.52 (d, 1H, $J$ = 7.5 Hz), 6.54 (t, 1H, $J$ = 7.5 Hz), 6.68 (t, 1H, $J$ = 7.5 Hz), 6.85 (t, 1H, $J$ = 7.5 Hz), 6.87 (d, 1H, $J$ = 7.5 Hz), 6.90 (t, 1H, $J$ = 7.5 Hz), 7.00 (d, 1H, $J$ = 7 Hz); $^{13}$C NMR (175 MHz, $CDCl_3$): $\delta$ 27.6, 30.7, 45.2, 46.3, 55.7, 62.8, 113.4, 115.6, 116.9, 119.4, 125.7, 126.4, 127.4, 127.9, 128.0, 129.1, 142.8, 145.1; HRMS (ESI): $m/z$: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2$: 263.1548; found: 263.1582.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01572.

Figure S1; $^1$H NMR, $^{13}$C NMR, DEPT of **6**; 1D and 2D NMR spectra of new compounds **7** and **8**; and coordinates for the Gaussian calculations (PDF)
Crystallographic data of **8** (CIF)

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## Notes

The authors declare no competing financial interest.

## REFERENCES


(1) For some recent reviews on $SmI_2$, see: (a) Just-Baringo, X.; Procter, D. J. *Acc. Chem. Res.* **2015**, *48*, 1263−1275. (b) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155−9183. (c) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371−3403. (d) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727−2751. (e) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745−777. (f) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (g) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.

(2) Rao, C. N.; Hoz, S. *J. Am. Chem. Soc.* **2011**, *133*, 14795−14803.

(3) Yella, R.; Hoz, S. *Org. Lett.* **2013**, *15*, 5262−5265.

(4) Szostak, M.; Spain, M.; Choquette, M. A.; Flowers, R. A.; Procter, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 15702−15705.

(5) Yella, R.; Hoz, S. *Org. Lett.* **2014**, *16*, 3876−3879.

(6) (a) Kamochi, Y.; Kudo, T. *Heterocycles* **1993**, *36*, 2383. (b) Konigs, C. D. F.; Klare, H. F. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10076−10079.

(7) Gauffre, J. C.; Grignon-Dubois, M.; Rezzonico, B.; Leger, J. M. *J. Org. Chem.* **2002**, *67*, 4696−4701.

(8) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Iiskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 09*, Revision A.01; Gaussian, Inc.: Wallingford, CT, 2009.

(9) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Chapman and Hall: London, 1973.

(10) A referee has suggested an alternative mechanism based on radical−radical coupling between two radical anions or neutral radical species. On the basis of spin densities (Figure 1), the C4−C4′ dimer should have been obtained rather than the C2−C2′ dimer. A second referee suggested a H-atom abstraction from **Q** by some other side product, and coupling of the resulting radicals was suggested by another referee.

(11) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1989.

(12) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.






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