JOC Article

Transient Azomethine-ylides from a Stable Amino-carbene and an Aldiminium Salt

Xavier Cattoën,[†,‡] Stéphane Solé,[†] Christian Pradel,[†] Heinz Gornitzka,[†] Karinne Miqueu,[†] Didier Bourissou,*[,†] and Guy Bertrand*[,†,‡]

Laboratoire d'Hétérochimie Fondamentale et Appliquée du CNRS (UMR 5069), Université Paul Sabatier, 118, route de Narbonne, F-31062 Toulouse Cedex 04, France, and UCR−CNRS Joint Research Chemistry Laboratory (UMR 2282), Department of Chemistry, University of California, Riverside, California 92521-0403

gbertran@mail.ucr.edu

Received July 19, 2002

Catalytic amounts of a protic reagent such as *tert*-butyl alcohol promote the isomerization of a stable amino-aryl-carbene into a transient azomethine ylide. Deprotonation of an alkyl-aldiminium salt also leads to a transient azomethine ylide, but labeling experiments rule out the transient formation of the corresponding amino-alkyl-carbene. The potential hypersurface between model amino-carbene, aziridine, and azomethine ylide is investigated.

Introduction

Carbenes are typical representatives of neutral reactive intermediates.[1] Their six-valence-electron shell, which defies the octet rule, is responsible for their fugacity as well as for their significant synthetic potential. In the last fifteen years, the isolation of a broad range of singlet carbenes[2,3] and the preparation of persistent triplet carbenes[4] have dramatically advanced this field of chemistry. Carbenes are not unique in this respect: 1,3-dipoles such as nitrilimines[5] or azomethine ylides[6] are routinely used transient species that have found numerous applications in organic synthesis.[7]

Herein we report the acid-promoted isomerization of a stable amino-aryl-carbene[8] into a transient azomethine ylide. In addition, it is shown that the site of deprotonation of *N*-methyl-aldiminium salts is dependent on the nature of the substituents. The results are corroborated by a theoretical study on the interconversion between a model amino-carbene, aziridine, and azomethine ylide.

Results and Discussion

The amino-aryl-carbene **2a**, obtained by deprotonation of the corresponding iminium salt **1a**,[8] is stable for months in the solid state but isomerizes within several days in tetrahydrofuran solution to afford a novel bicyclic compound **3a** in 35% yield. The structure of **3a**, unambiguously determined by multinuclear NMR spectroscopy and by a single-crystal X-ray diffraction study, is somewhat surprising since the aromaticity of the aryl group is lost. The formation of **3a** most likely results from the electrocyclization of the related azomethine ylide **4a**.[9] Indeed, 1,3-dipole **4a** can be trapped with carbon dioxide, affording adduct **5a** (Scheme 1).

Although several methods are known for the preparation of azomethine ylides,[6] the generation of such a 1,3-dipole from an amino-carbene, even as a transient species, has never been reported.[10] Therefore, we decided to investigate the mechanism of the isomerization of **2a** into **4a**.

It is conceivable that azomethine ylide **4a** might result from an intramolecular 1,3-migration of a hydrogen atom.

* To whom correspondence should be adressed.
† Université Paul Sabatier.
‡ University of California, Riverside.

(1) (a) *Carbene Chemistry*; Kirmse, W., Ed.; Academic Press: New York, 1971. (b) *Carbenes*; Jones, M., Moss, R. A., Eds.; Wiley: New York, 1975, Vols. I and II. (c) Carbene (Carbenoide). In *Methoden der Organischen Chemie (Houben-Weyl)*; Regitz, M., Ed.; Georg Thieme Verlag: Stuttgart, 1989; Vols. E19b (1−3). (d) *Advances in Carbene Chemistry*. Brinker, U. H., Ed.; Jai Press: Greenwich, CT, 1998; Vols. 1 and 2.

(2) (a) Igau, A.; Grützmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463. (b) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361. (c) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021. (d) Alder, R. W.; Buts, C. P.; Orpen, A. G. *J. Am. Chem. Soc.* **1998**, *120*, 11526. (e) Buron, C.; Gornitzka, H.; Romanenko, V.; Bertrand, G. *Science* **2000**, *288*, 834.

(3) For recent reviews on stable singlet carbenes, see: (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Herrmann, W. A *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (c) Arduengo, A. J., III. *Acc. Chem. Res.* **1999**, *32*, 913.

(4) (a) Tomioka, H. *Acc. Chem. Res.* **1997**, *30*, 315. (b) Tomioka, H.; Iwamoto, E.; Itakura, H.; Hirai, K. *Nature* **2001**, *412*, 626.

(5) (a) Bertrand, G.; Wentrup, C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 527. (b) Shawali, A. S. *Chem. Rev.* **1993**, *93*, 2731.

(6) (a) Surpateanu, G.; Lablache-Combier, A. *Heterocycles* **1984**, *22*, 2079. (b) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. L., Ed.; Academic: New York, 1989; Vol. 5, pp 231−349.

(7) (a) Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 291−392. (b) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 653−732.

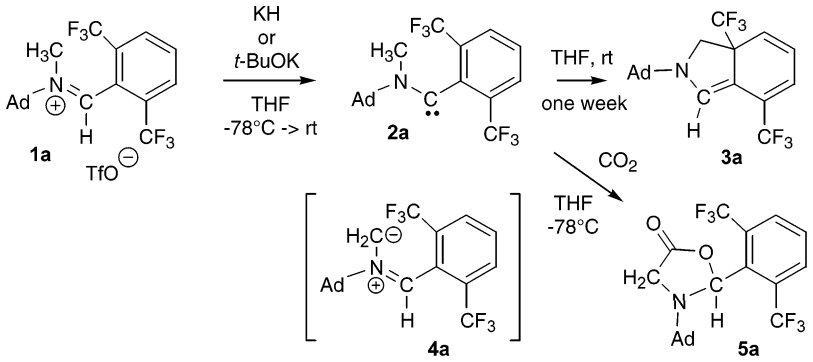
(8) Solé, S.; Gornitzka, H.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *Science* **2001**, *292*, 1901.

(9) For the rearrangement of an unsaturated azomethine ylide by a related electrocyclization process, see: Padwa, A.; Gehrlein, L. *J. Am. Chem. Soc.* **1972**, *94*, 4933.

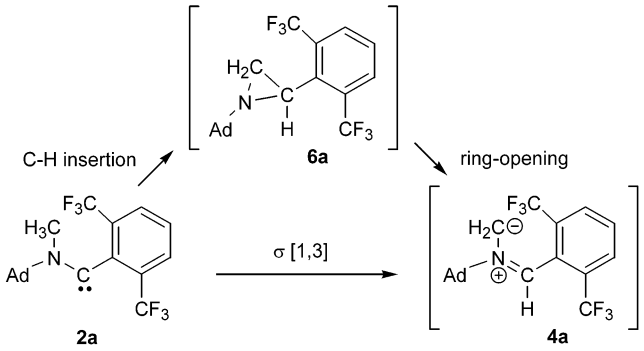
(10) The only route to azomethine ylides involving carbenes relies on the reaction of a transient difluorocarbene with a Schiff base: Novikov, M. S.; Khlebnikov, A. F.; Besedina, O. V.; Kostikov, R. R. *Tetrahedron Lett.* **2001**, *42*, 533.

10.1021/jo026214b CCC: $25.00
Published on Web 12/20/2002

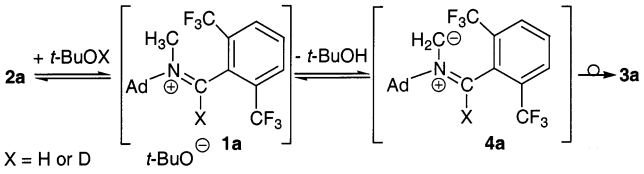
SCHEME 1



SCHEME 2



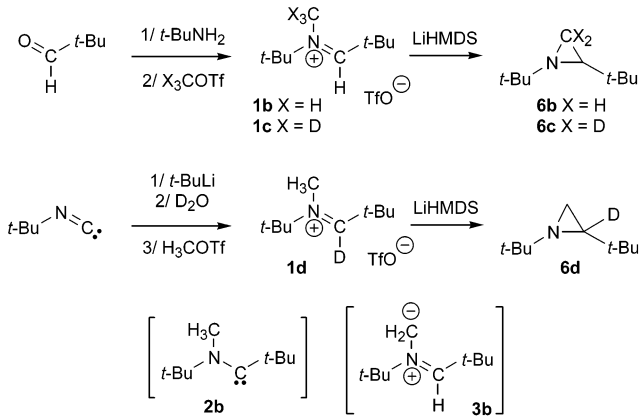
SCHEME 3



This isomerization could be either concerted or stepwise (C−H insertion/ring-opening sequence) with the transient formation of the corresponding aziridine **6a** (Scheme 2). However, we observed that protic reagents such as *t*-BuOH accelerated the rearrangement of **2a** into **3a**, which suggests an alternative mechanism involving a protonation/deprotonation sequence, the driving force being the final electrocyclization of **4a** into **3a**. This hypothesis was validated by performing the isomerization of **2a** with 1 equiv of *t*-BuOD (Scheme 3). Indeed, ca. 50% of deuterium was incorporated at the carbene carbon position,[11] as expected for a statistic exchange via a protonation/deprotonation equilibrium. Obviously, *tert*-butyl alcohol is not essential and traces of water can play the same role.

These observations suggest that competitive deprotonation reactions of *N*-methyl aldiminium salts can occur either at the CH−iminium or at the CH_3−N site of the molecule. Notably, aziridines can be obtained by deprotonation of *N*-methyl ketiminium salts but cannot be detected from aldiminium salts.[12] To favor the deprotonation at the CH_3−N site, the aldiminium salt **1b**, bearing a σ-electron donating group at the iminium carbon, was selected as a starting point. In marked contrast to that observed for aryl aldiminium salt **1a**, the amino-alkyl-carbene **2b** could not be detected when **1b** was deprotonated with the lithium salt of hexamethyldisilazane.[13] Instead, the corresponding aziridine **6b**[14] was obtained in 65% yield and subsequently fully characterized (Scheme 4). The deprotonation of the related N−CD_3 precursor **1c** (readily prepared by alkylation of the imine with deuterated methyl trifluoromethane sulfonate) and the C−D iminium salt **1d** (obtained in good yield by successive treatment of *tert*-butylisocyanide with *tert*-butyllithium, deuterated water, and methyl trifluoromethane sulfonate) was then studied (Scheme 4). Aziridines **6c** and **6d**, featuring two and one deuterium atom, respectively, were selectively obtained, which rules out the transient formation of the carbene **2b** and confirms deprotonation at the CX_3−N site.

SCHEME 4



Further information was obtained from theoretical investigations on the interconversion between aminocarbene, aziridine, and azomethine ylide. Ab initio calculations were performed at the B3LYP level with the 6-31g(d) basis set on model compounds **2***, **6***, and **3*** (Figure 1, Table 1). Despite the ring strain, aziridine **6***, the global minimum on the hypersurface, is 20.8 kcal/mol lower in energy than azomethine ylide **3***. In contrast, the amino-carbene **2*** is only 3.0 kcal/mol above **3***, thanks to the donation of the nitrogen lone pair to the carbene center. The transition state **TS1** between carbene **2*** and aziridine **6*** (intramolecular C−H insertion) features a pyramidalized nitrogen atom (ΣN =

(11) The ratio and position of deuterium incorporation were determined by ^{1}H NMR and mass spectrometry.
(12) Deyrup, J. A.; Szabo, W. A. *J. Org. Chem.* **1975**, *40*, 2048.
(13) A very bulky base is needed to perform this reaction to avoid addition reactions, as were observed with potassium *t*-butoxide.
(14) Sheehan, J. C.; Tulis, R. W. *J. Org. Chem.* **1974**, *39*, 2264.

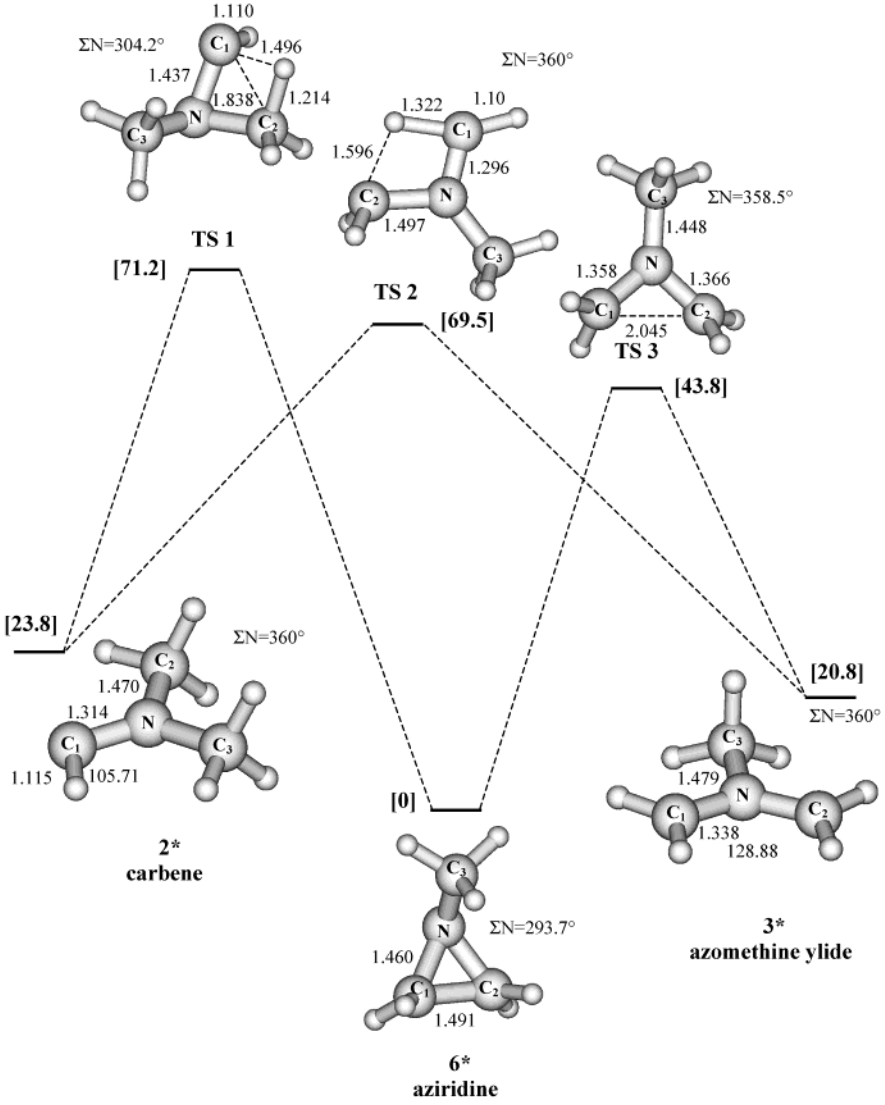


FIGURE 1. Interconversion of amino-carbene **2***, aziridine **6***, and azomethine ylide **3***. Energies (in brackets) are expressed in kcal/mol relative to the global minimum aziridine **6***. Bond lengths are given in angströms (Å) and bond angles in degrees (°).

TABLE 1. Bond Lengths in Angströms (Å) and Bond Angles in Degrees (°) for the Different Minima and Transition States

	2*	6*	3*	TS1	TS2	TS3
C_1N	1.314	1.460	1.338	1.437	1.358	1.296
C_2N	1.470	1.460	1.338	1.463	1.366	1.497
C_3N	1.477	1.457	1.479	1.472	1.448	1.461
C_1C_2	2.404	1.491	2.415	1.838	2.045	2.237
C_1NC_3	127.70	116.19	115.57	112.81	130.98	128.36
C_1NC_2	119.34	61.42	128.88	78.65	97.30	106.23
C_2NC_3	112.96	116.11	115.49	112.77	130.27	125.39
NC_1C_2	32.20	59.28	25.56	51.32	41.50	39.98
C_1C_2N	28.46	59.29	25.56	50.03	41.20	33.79

304.2°) and a three-center interaction between the C−H bond and the carbene center, while the transition state **TS2** between **2*** and azomethine ylide **3*** (1,3-H migration) retains a planar nitrogen atom and two unsymmetrically elongated C−H bonds (1.322 and 1.596 Å). The large barriers (47.4 and 45.7 kcal/mol, respectively) predicted for these intramolecular rearrangements certainly explain why carbene **2a** rearranges through an intermolecular pathway, as determined experimentally. Not surprisingly, starting from azomethine ylide **3***, the activation barrier for ring closure to afford **6**(23.0 kcal/mol) is much smaller than that of the 1,3-H migration (48.7 kcal/mol) leading to the carbene **2***. This is also in perfect agreement with the intramolecular rearrangement observed for **3b**.

Conclusion

Isomerization of a stable amino-aryl-carbene to a transient azomethine ylide was observed. An intermolecular mechanism involving a protic reagent as a catalyst is proposed on the basis of labeling experiments and ab initio calculations. The availability of stable carbenes allows for the observation of such unusual rearrangements between highly reactive species. Moreover, suitably substituted aldiminium salts appear to be convenient precursors for aziridines, which might open the way for new synthetic developments.

Experimental Section

General Methods. All manipulations were performed under an inert atmosphere of argon using standard Schlenk techniques. Dry, oxygen-free solvents were employed.

3a: A tetrahydrofuran solution of carbene **2a** was stirred for a week at room temperature. After evaporation of the solvent, bicyclic compound **3a** was isolated as yellow crystals in 35% yield by slow evaporation of a saturated diethyl ether solution. Mp: 104 °C. $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ −7.3, 11.5. ^1H NMR ($CDCl_3$): δ 1.76 (br, 6H), 1.90 (br, 6H), 2.18 (br, 3H), 3.36 (d, $^2J_{HH}$ = 11.6 Hz, 1H), 3.92 (d, $^2J_{HH}$ = 11.6 Hz, 1H), 5.67 (d, $^3J_{HH}$ = 9.3 Hz, 1H), 6.12 (d, $^3J_{HH}$ = 5.7 Hz, 1H), 6.40 (dd, $^3J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 5.7 Hz, 1H), 7.07 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.3, 36.1, 41.3, 50.6 (q, $^2J_{CF}$ = 27 Hz), 54.6, 54.8, 96.0, 114.3, 117.2, 123.8 (q, $^1J_{CF}$ = 272 Hz), 125.0 (q, $^2J_{CF}$ = 32 Hz), 126.9 (q, $^1J_{CF}$ = 289 Hz), 127.2, 140.6. MS (DCI, NH_3): 389, 320. Anal. Calcd for $C_{20}H_{21}F_6N$: C, 61.69; H, 5.44; N, 3.60. Found: C, 61.87; H, 5.67; N, 3.48.

5a: Carbon dioxide was bubbled through a tetrahydrofuran solution of carbene **2a** at −78 °C. After 1 week at this temperature, compound **5a** was obtained in 44% yield according to ^{19}F fluorine spectroscopy and characterized without further purification. $^{19}F\{^1H\}$ NMR (C_4D_8O, 193 K): δ 19.4, 20.5. ^1H NMR (C_4D_8O, 193 K): δ 1.70 (br, 6H), 1.76 (br, 6H), 1.98 (br, 3H), 3.57 (d, $^2J_{HH}$ = 15.6 Hz, 1H), 3.92 (d, $^2J_{HH}$ = 15.6 Hz, 1H), 6.52 (s, 1H), 7.96 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 8.22 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 8.32 (d, $^3J_{HH}$ = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (C_4D_8O, 193 K): δ 30.3, 36.9, 40.0, 55.1, 85.7, 124.6 (q, $^1J_{CF}$ = 275 Hz), 130.0, 133.1, 134.1, 139.4, 172.2.

General Procedure for 6b−d: A tetrahydrofuran solution (3 mL) of the iminium salt **1b−d** (0.3 mmol) was added dropwise at −78 °C to a tetrahydrofuran solution (2 mL) of the lithium salt of hexamethyldisilazane (0.4 mmol). After 30 min, the reaction mixture was allowed to warm to room temperature. The solvent was evaporated under vacuum and the crude residue purified chromatographically on neutral alumina (pentane and diethyl ether) to afford **6b−d** as pale yellow oils in 65% yield.

6b. ^1H NMR (C_6D_6): δ 0.85 (s, 9H), 0.94 (s, 9H), 1.24 (dd, 1H, J_{HH} = 6.1 and 0.6 Hz), 1.25 (dd, 1H, J_{HH} = 3.3 and 0.6 Hz), 1.41 (dd, 1H, J_{HH} = 6.1 and 3.3 Hz). $^{13}C\{^1H\}$ NMR (C_6D_6): δ 22.0, 26.5, 26.9, 30.0, 41.6, 52.0. MS (EI): 155, 140, 98. Anal. Calcd for $C_{10}H_{22}N$: C, 76.85; H, 14.19; N, 8.96. Found: C, 77.12; H, 14.48; N, 8.65.

6c. MS (EI), calcd relative abundances for the $[(M - CH_3)^+]$ signal of $C_{10}H_{20}D_2N$: 141, 4.0; 142, 100; 143, 10.7. Found: 141, 0.3; 142, 100; 143, 12.

6d. $^{13}C\{^1H\}$ NMR (C_6D_6): δ 42.0 (t, $^1J_{CD}$ = 24 Hz). MS (EI): calcd relative abundances for the $[(M - CH_3)^+]$ signal for $C_{10}H_{21}DN$: 140, 4; 141, 100; 142, 12. Found: 140, 22; 141, 100; 142, 10.

Computational Details. All calculations were carried out with the Gaussian 98 set of programs.[15] The different structures were optimized at the B3LYP level with the 6-31g(d) basis set augmented with polarization functions on the heavy atoms. This functional is built with Becke's three-parameter exchange functional[16] and the Lee−Yang−Parr correlation functional.[17] All energies were zero-point energies (ZPEs), and the temperature was corrected using unscaled density functional frequencies. All the investigated structures were characterized by corresponding vibrational analysis to identify these as energy minima or transition states (one negative eigenvalue) on the potential energy surface. The connection between each optimized transition state and the two corresponding minima was confirmed by IRC calculations.

X-ray Crystallographic Study. Crystal data for **3a**: $C_{20}H_{21}F_6N$, M = 389.38, monoclinic, space group $P2_1/n$, a = 10.6221(5), b = 13.3744(6), c = 12.7429(6) Å, β = 97.9980(10)°, V = 1792.70(14) Å^3, Z = 4, T = 193(2) K, crystal size 0.3 × 0.4 × 0.6 mm, 2.22° ≤ θ ≤ 26.37°, 3659 reflections (3659 independent, R_{int} = 0.0000), 354 parameters, R_1 [$I > 2\sigma(I)$] = 0.0433, wR_2 [all data] = 0.1033, largest electron density residue = 0.267 e/Å^3. Data were collected using an oil-coated, shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer with Mo Kα (λ = 0.71073 Å). Semiempirical absorption coefficients were employed.[18] The structure was solved by direct methods (SHELXS-97)[19] and refined using the least-squares method on F^2.[20] Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-196175 (**3a**). Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax, (+44) 1223-336-033; email, deposit@ccdc.cam.ac.uk).

Acknowledgment. Thanks are due to the CNRS, the University Paul Sabatier (France), the "Société de Secours des Amis des Sciences", and the University of California at Riverside for financial support of this work.

Supporting Information Available: Experimental and theoretical details, spectroscopic data, and X-ray crystallographic data for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026214B

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(16) (a) Becke, A. D. *Phys. Rev.* **1988**, *A38*, 3098. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(17) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785.

(18) *SADABS, Program for Data Correction*; Bruker-AXS: Madison, WI, 2001.

(19) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467.

(20) Sheldrick, G. M. *SHELXL-97, Program for Crystal Structure Refinement*; University of Göttingen, Göttingen, Germany, 1997.