Interesting Products Derived from the Reactions of 2,3-Diamino-2,3-dimethylbutane[1]

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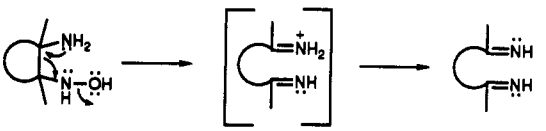
The diimine, *N,N'*-dibenzylidene-2,3-diamino-2,3-dimethylbutane (**10**), was successfully synthesized from 2,3-diamino-2,3-dimethylbutane (**3**) by reaction with excess benzaldehyde. The reaction of diimine **10** with permanganate/PTC at pH = 4.1 did not give the corresponding dinitrone **11** but unexpectedly gave 3-benzoyl-4,4,5,5-tetramethyl-2-phenylimidazoline (**13**) in 45% yield. The imidazoline **13** was independently prepared by benzoylation of 4,4,5,5-tetramethyl-2-phenylimidazoline (**9**) which had been synthesized from diamine **3** and methyl benzimidate. The cyclic α-dinitrone, 2,3-dihydro-2,2,3,3,5,6-hexamethylpyrazine 1,4-dioxide (**4**), synthesized from *N,N'*-dihydroxy-2,3-diamino-2,3-dimethylbutane (**2**) and 2,3-butanedione, underwent ozonolysis to yield the corresponding vicinal dinitro compound, 2,3-dimethyl-2,3-dinitrobutane (**1**), quantitatively.

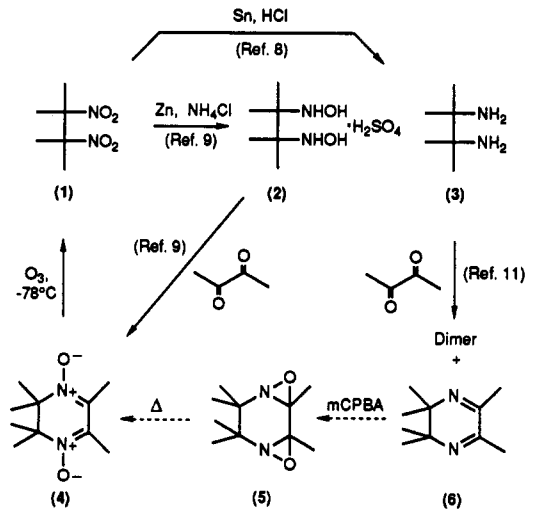
Introduction

Polynitropolycyclic cage molecules are of considerable interest because of their potential use as high-energy density materials.[2] One strategy which has proven effective for obtaining nitro groups at tertiary carbon atoms has been the oxidation of primary amine precursors.[2] Attempts to extend this methodology to strained vicinal diamines have not been as successful and products resulting from carbon–carbon bond scission have been observed in some cases.[3] The cleavage reaction is believed to occur by a mechanism reminiscent of a Grob fragmentation[4] wherein electron pair donation from the less-oxidized nitrogen toward the carbon atom can give rise to bond cleavage as the σ electrons of the carbon–carbon bond move toward the more highly oxidized nitrogen atom (Scheme I). One way to circumvent this problem of a "push-pull" mechanism operating during the oxidation would be to alter the electron donating and/or accepting abilities of the nitrogen atoms. This could be accomplished by transforming the amino groups to appropriate nitrogen-containing functionalities which could be subsequently oxidized to nitro groups. Herein we report our efforts in this area.

Scheme I



Scheme II



Results and Discussion

The reaction sequence which we sought to exploit involves the initial conversion of the amines to imines, the subsequent oxidation of the imines to nitrones, and oxidative cleavage of the nitrones with ozone[5] to provide the nitro derivatives. This strategy appeared more attractive in view of a recent report which indicated that imines could be oxidized directly to nitrones by potassium permanganate under phase-transfer catalysis (PTC) conditions.[6] This new method could be used to circumvent the more classical route which requires a somewhat unreliable thermal isomerization of an intermediate oxaziridine during the imine to nitrone conversion.[7] Because of the limited availability of cage vicinal diamines, the sequence was initially carried out using 2,3-diamino-2,3-dimethylbutane (**3**)[8] which is readily synthesized via the reduction of 2,3-dimethyl-2,3-dinitrobutane (**1**)[8] (Scheme II). The use of **3** as a model system offered the advantage that the intermediate oxidation products, *N,N'*-dihydroxy-

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(2) Marchand, A. P. *Tetrahedron.* **1988**, *44*, 2377. Eaton, P. E. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1421.

(3) Zajac, W. W., Jr., unpublished results.

(4) Grob, C. A. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 535.

(5) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. II, pp 230–231.

(6) Christensen, D.; Jorgensen, K. A. *J. Org. Chem.* **1989**, *54*, 1261.

(7) Boyd, D. R.; Coulter, P. B.; McGuckin, M. R; Sharma, N. D.; Jennings, W. B.; Wilson, V. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 301, and refs therein.

(8) Sayre, R. *J. Am. Chem. Soc.* **1955**, *77*, 6689.

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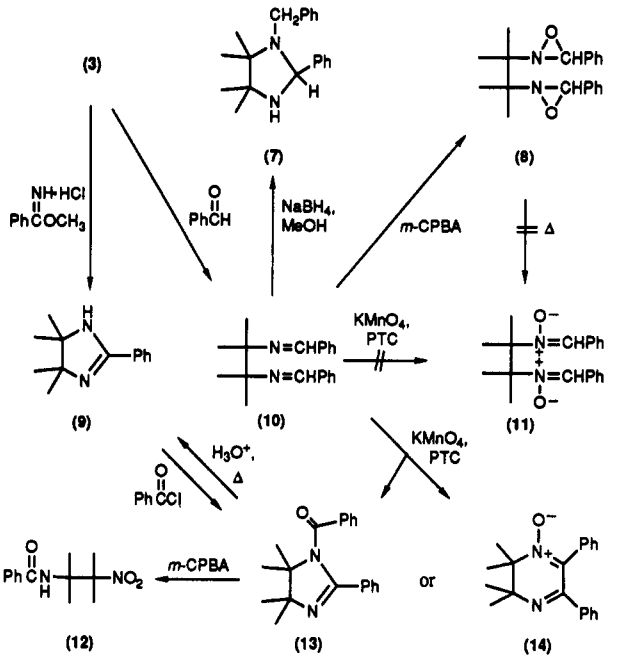
2,3-diamino-2,3-dimethylbutane (2)[9] and the intramolecular nitroso dimer, 3,3,4,4-tetramethyl-1,2-diazetine 1,2-dioxide,[10] have been characterized previously. Furthermore, a potentially useful and readily available derivative of this amine, namely 2,3-dihydro-2,2,3,3,5,6-hexamethylpyrazine 1,4-dioxide (4), has also been described.[9]

Concerned by reports detailing the diminished reactivity of α-dinitrone 4[9] relative to simple nitrones, we initiated our study by examining the reaction of 4 with ozone (Scheme II). Low-temperature ozonolysis of 4 resulted in oxidative cleavage of both nitrone moieties, to quantitatively provide the vicinal dinitro derivative 1, in a manner analogous to that of simple nitrones. Having demonstrated that the final step was viable, we attempted to synthesize the requisite diimine precursor, 4,5-dihydro-2,3,4,4,5,5-hexamethylpyrazine (6).[11] All attempts to synthesize 6 by the condensation of diamine 3 with 2,3-butanedione led to complex reaction mixtures in which the predominant product was not the desired diimine 6 but a dimeric derivative.[11] Efforts to futher exploit the potential of the dihydropyrazine ring system were abandoned after it was determined that 6, which was essential to the successful implementation of the vicinal diimine–dinitrone–dinitro strategy, was extremely sensitive toward air oxidation and hydrolysis.

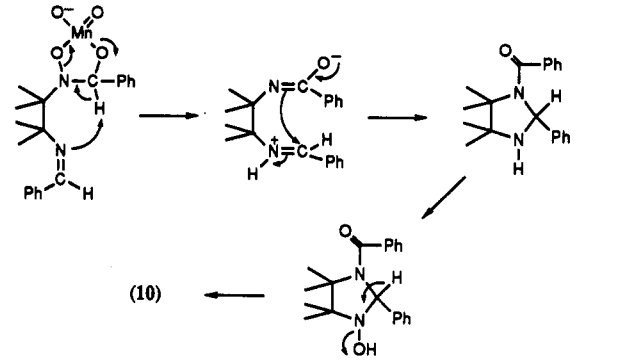
Our attention turned to an acyclic series using a diimine bearing *C*-phenyl substituents in order to stabilize the imine functions. The reaction of the diimine, *N,N'*-dibenzylidene-2,3-diamino-2,3-dimethylbutane (10), with potassium permanganate under PTC conditions gave an oily product which was determined not to be the expected dinitrone, *N,N'*-dibenzylidene-2,3-diamino-2,3-dimethylbutane *N,N'*-dioxide (11), on the basis of ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy. High-resolution mass spectrometry indicated that the product had a molecular formula of $C_{20}H_{22}N_2O$ instead of the $C_{20}H_{24}N_2O_2$ expected for 11. The data appeared to support either the imidazoline 13 or dihydropyrazine derivative 14 as the structure of the product (Scheme III). The formation of either 13 or 14 could be rationalized on mechanistic grounds (*vide infra*).

The unknown oxidation product was subjected to a series of reactions to aid us in distinguishing between structures 13 or 14. The unknown product failed to react with ozone, a result which suggested the absence of a nitrone function. Oxidation of the unidentified product with *m*-CPBA resulted in the isolation of 3-benzamido-2,3-dimethyl-2-nitrobutane (12). Hydrolysis with concentrated hydrochloric acid provided benzoic acid and a product which was determined to be 4,4,5,5-tetramethyl-2-phenylimidazoline (9) by independent synthesis (*vide infra*). All of the results supported structure 13 over 14 so an independent synthesis of 13 was undertaken. Diamine 3 was reacted with methyl benzimidate hydrochloride[12] to provide an authentic sample of 4,4,5,5-tetramethyl-2-phenylimidazoline (9) which was found to correspond to the second product of the hydrolysis reaction. Imidazoline 9 was then benzoylated to provide 3-benzoyl-4,4,5,5-tetramethyl-2-phenylimidazoline which was determined to be identical to the compound 13 previously obtained by the $KMnO_4$/PTC oxidation of diimine 7.

Scheme III



Scheme IV



While we were attempting to deduce the structure of the unexpected oxidation product by chemical methods, the compound which had been isolated as an oil eventually crystallized. The structure was confirmed to be 13 by single crystal X-ray structure determination of the 1:1 hydrate of 13.[13] One plausible mechanism which rationalizes the formation of 13 is presented in Scheme IV.

The ready availability of diimine 7 permitted us to test the viability of the more classical approach to the diimine to dinitrone conversion involving the formation of an intermediate dioxaziridine. The *m*-CPBA oxidation of the diimine 10 was sucessful in providing a mixture of isomeric dioxaziridines 8. However, our efforts were thwarted when we were unable to effect the required thermal isomerization of the dioxaziridines 8 to the dinitrone 11.

The observation that secondary amines can be oxidized directly to nitrones by Davis's reagent (2-(phenylsulfonyl)-3-phenyloxaziridine)[14] was the basis for an investigation into one final strategy for the 10 to 11 conversion. This strategy was reliant upon the successful reduction of 7 to the corresponding bis-secondary amine, *N,N'*-dibenzyl-

(9) Lamchen, M.; Mittag, T. W. *J. Chem. Soc. (C)* **1966**, 2300.
(10) Greene, F. D.; Gilbert, K. E. *J. Org. Chem.* **1975**, *40*, 1409.
(11) Lamchen, M.; Mittag, T. *Proc. Chem. Soc.* **1963**, 302.
(12) Jones, R. C. F.; Schofield, J. *J. Chem. Soc. Perkin Trans. 1* **1990**, 375.
(13) Flippen-Anderson, J.; Zajac, W. W., Jr.; Buzby, J. H.; Walters, T. R. *Acta Crystallogr. C*, in press.
(14) Zajac, W. W., Jr.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856.

2,3-diamino-2,3-dimethylbutane. The reaction of **10** with sodium borohydride in methanol resulted in the formation of a cyclized product which has been identified as N-benzyl-2-phenyl-2,3-dimethylimidazolidine (**7**).

Our current study on the freely-rotating model compound **3** suggests that the chemistry of the vicinal diamine-derived systems may be complicated by undesirable cyclizations. These side reactions may limit the utility of the aforementioned strategies to cage substrates in which similar cyclizations are precluded by geometric constraints.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ solutions at 200 and 53.3 MHz, respectively, unless specified otherwise. *J* values are given in Hertz.

2,3-Dimethyl-2,3-dinitrobutane (1). A solution of 2,3-dihydro-2,2,3,3,5,6-hexamethylpyrazine 1,4-dioxide (**4**) (700 mg, 3.54 mmol) in $CDCl_3$ (5 mL) was cooled to −78 °C and subjected to an oxygen/ozone stream until the blue color characteristic of condensed ozone was evident (~15 min). A ^{13}C NMR spectrum of the crude reaction mixture indicated that 2,3-dimethyl-2,3-dinitrobutane (**1**) and 2,3-butanedione were the only materials present in the ozonized solution. The solvent was removed and the residue chromatographed (SiO_2, EtOAc/hexanes) to provide **1** as a white solid (580 mg, 93%): mp 209–210 °C (lit.[8] 211–212 °C); ^{1}H NMR ($CDCl_3$) δ 1.75 (s); ^{13}C NMR ($CDCl_3$) δ 22.9, 91.3. This material was identical to that obtained by an alternate route.[4]

2,3-Diamino-2,3-dimethylbutane[8] (3): ^{1}H NMR ($CDCl_3$) δ 1.12 (s) ^{13}C NMR ($CDCl_3$) δ 26.1, 53.3.

***N,N'*-Dihydroxy-2,3-diamino-2,3-dimethylbutane monosulfate (2):** mp 170–173 °C (lit.[9] 172–174 °C); ^{1}H NMR (DMSO) δ 1.16 (s), 4.5–6.5 (bs); ^{13}C NMR (DMSO) δ 19.9, 63.5.

2,3-Dihydro-2,2,3,3,5,6-hexamethylpyrazine 1,4-dioxide (4): mp 131–133 °C (lit.[9] 135–138 °C); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 12H), 2.24 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.4, 72.0, 134.7.

***N,N'*-Dibenzylidene-2,3-diamino-2,3-dimethylbutane (10).** A mixture of 2,3-diamino-2,3-dimethylbutane (**3**) (630 mg, 5.43 mmol), benzaldehyde (1.17 g, 11.03 mmol), and crushed molecular sieves (120 mg) was stirred rapidly for 2 h.[15,16] The resulting suspension was diluted with $CHCl_3$ (10 mL) and filtered. The volatiles were removed under reduced pressure and the resulting residue crystallized as white needles (951 mg, 60%): mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 12H), 7.25–7.80 (m, 10H), 8.31 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 22.9, 65.0, 127.8, 128.3, 129.9, 137.4, 156.7; MS (FAB) *m/z* 293 ([M + H]$^+$). Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.56. Found: C, 82.14; H, 8.06; N, 9.32.

2,3-Dimethyl-2,3-bis(phenyloxaziridinyl)butanes (8). A solution of *m*-CPBA (631 mg of 80–85%, 2.93 mmol) in $CDCl_3$ (4 mL) was added to an ice-cold solution of *N,N'*-dibenzylidene-2,3-diamino-2,3-dimethylbutane (**10**, 290 mg, 0.99 mmol) in $CDCl_3$ (3 mL). The reaction mixture was allowed to warm to rt and stirred until the starting material was consumed (~30 min by ^{1}H NMR). The solvent was removed *in vacuo* and the residue was subjected to preparative TLC (SiO_2, CH_2Cl_2). The colorless viscous oil (77 mg, 24%) was determined to be a mixture of two isomers: ^{1}H NMR ($CDCl_3$) (major) δ 1.19 (s, 6H), 1.22 (s, 6H), 4.71 (s, 2H), 7.22–7.67 (m, 10H); (minor) 1.11 (s, 6H), 1.28 (s, 6H), 4.65 (s, 2H), 7.22–7.67 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 17.1, 17.5, 19.0, 19.5, 66.1, 66.2, 73.5, 73.9, 127.9, 128.2, 129.0, 129.6, 134.4, 135.2; MS (CI, NH_3) *m/z* 325 ([M + H]$^+$).

3-Benzoyl-4,4,5,5-tetramethyl-2-phenylimidazoline (13). Method A. Solid $KMnO_4$ (642 mg, 4.06 mmol) was added to a mixture of *N,N'*-dibenzylidene-2,3-diamino-2,3-dimethylbutane (**10**) (295 mg, 1.01 mmol), CH_2Cl_2 (2 mL), and aqueous HCl (2.0 mL, pH = 4.1), and the solution was rapidly stirred for 1 h. Tetra-*n*-butylammonium chloride (30 mg, 0.11 mmol) was added and the reaction mixture was stirred for ~3 h. Additional portions of CH_2Cl_2 (3 mL) and aqueous HCl (3 mL, pH = 4.1) were added and the flask was stoppered and stirred rapidly at rt for 24 h. The reaction was worked up by the slow addition of saturated $NaHSO_3$, with cooling. The solids were removed, and the filtrate was extracted with CH_2Cl_2 (4 × 25 mL). The combined extracts were washed sequentially with water (25 mL), aqueous KI (saturated, 4 × 25 mL), and water (25 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* to provide an oily residue. Anhydrous ether (100 mL) was added to precipitate KI. The ether layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to provide a clear yellow oil of compound **13** (138 mg, 45%) which was slowly crystallized from ethanol to yield a colorless solid which was determined to be a 1:1 hydrate by X-ray crystallographic analysis:[13] mp 77–81 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 6H), 1.54 (s, 6H), 7.0–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.6, 22.3, 70.3, 72.0, 127.8, 127.9, 128.3, 129.0, 130.4, 131.7, 132.8, 136.2, 158.9, 168.9; MS *m/z* 307 ([M + H]$^+$).

Method B. From 2,3-Diamino-2,3-dimethylbutane (3). A solution of 2,3-diamino-2,3-dimethylbutane (**3**) (476 mg, 4.10 mmol) and methyl benzimidate hydrochloride[12] (686 mg, 4.00 mmol) in anhydrous EtOH (50 mL) was refluxed for 2 h. The EtOH was removed *in vacuo*, the oily residue was suspended in $CHCl_3$, and anhydrous NH_3 was passed through the solution. The NH_4Cl was removed by filtration and the filtrate concentrated under reduced pressure to give a white solid (737 mg). The crude product was purified by flash chromatography (SiO_2, EtOAc followed by 5% MeOH/CH_2Cl_2) to give **9** (R_f = 0.02) as a white crystalline solid (341 mg, 42%): mp 154–156 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 12H), 3.8–4.5 (bs, 1H), 7.36–7.44 (m, 3H), 7.83–7.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.8, 66.8, 126.6, 128.2, 130.2, 131.0, 160.4; MS (CI, NH_3) *m/z* 203 ([M + H]$^+$). This material appeared somewhat unstable and was immediately benzoylated by the dropwise addition of a solution of benzoyl chloride (178 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (1 mL) to a solution of **9** (232 mg, 1.15 mmol) and dry Et_3N (175 mg, 1.73 mmol) in anhydrous CH_2Cl_2 (20 mL). The solution was stirred at rt for 20 h. The reaction mixture was concentrated under reduced pressure to give a white solid which was purified by flash chromatography (SiO_2, gradient 50% EtOAc/petroleum ether; EtOAc, 5% CH_3OH/CH_2Cl_2) to provide **13** (82 mg, 23%).

Hydrolysis of 3-Benzoyl-4,4,5,5-tetramethyl-2-phenylimidazoline (13). A solution of **13** (88 mg, 0.29 mmol) in aqueous HCl (concd, 5 mL) was refluxed for 5 h, allowed to cool, diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the residue was subjected to preparative TLC (SiO_2, $CHCl_3$). Recovery of the material at R_f = 0.14 afforded benzoic acid (10.3 mg, 29%, mp 119–120 °C). The original HCl solution was made basic (30% aqueous KOH) and extracted with CH_2Cl_2 (2 × 70 mL). The combined fractions were washed with water (25 mL), dried (Na_2SO_4), and concentrated to give imidazoline **9** (17.3 mg, 30%) as a white amorphous solid which was identical in all respects to the material synthesized above.

2-Benzamido-2,3-dimethyl-3-nitrobutane (12). Four portions of *m*-CPBA (110 mg of ~80%, 0.51 mmol each) were added at 30 min intervals to a 10-mm NMR tube containing a solution of **13** (150.5 mg, 0.49 mmol) in $CDCl_3$ (8 mL). The tube was warmed briefly to dissolve the contents completely and then allowed to stand at room temperature overnight (16 h). This mixture was diluted with CH_2Cl_2 (100 mL) and extracted with aqueous $NaHCO_3$ (saturated, 4 × 50 mL) and water (50 mL). The organic layer was dried (Na_2SO_4) and concentrated and the resulting residue subjected to preparative TLC (SiO_2, CH_2Cl_2). The fraction at R_f = 0.18–0.38 was collected and concentrated to give the product as a colorless oil (49.5 mg, 40%): ^{13}C NMR ($CDCl_3$) δ 24.3, 26.5, 66.7, 94.6, 128.2, 128.5, 131.7, 138.7, 174.6; MS (FAB) *m/z* 251 ([M + H]$^+$).

***N*-Benzyl-4,4,5,5-tetramethyl-2-phenylimidazolidine (7).** A mixture of $NaBH_4$ (0.15 g, 3.97 mmol) and *N,N'*-dibenzylidene-2,3-diamino-2,3-dimethylbutane (**10**) (0.60 g, 2.05 mmol) in dry MeOH (10 mL) was stirred for 1 h. The cloudy solution was diluted (CH_2Cl_2, 50 mL), extracted with NH_4Cl (10%, 50 mL),

(15) In one experiment, using highly activated 4-Å molecular sieves, 4,4,5,5-tetramethyl-2-phenylimidazolidine was isolated as the sole product: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.24 (s, 3H), 2.6 (br s, 2H), 5.24 (s, 1H), 7.25–7.39 (9m, 3H), 7.55–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.4, 25.2, 62.7, 73.2, 126.2, 127.3, 128.1, 143.6. This material was readily converted to bis-imine **10** with 1 equiv of benzaldhyde using Denmark's conditions.[16]

(16) Denmark, S. E., Stadler, H., Dorow, R. L., Kim, J. *J. Org. Chem.* 1991, *56*, 5063.

saturated $NaHCO_3$ (50 mL), and water (50 mL), and dried (Na_2SO_4), and the solvent was removed *in vacuo* to afford compound 7 (515 mg, 85%) as a clear light yellow-liquid: ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.11 (s, 6H), 1.31 (s, 3H), 1.7 (bs, 1H), 3.61 (AB_q, J = 14.6 Hz, 2H), 4.59 (s, 1H), 7.0–7.5 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.9, 24.5, 28.0, 50.3, 62.3, 64.7, 80.7, 126.0, 127.5, 128.0, 128.3, 141.1, 142.7; MS (CI, NH_3), m/z 295 ($[M + H]^+$).

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Supplementary Material Available: NMR spectra (^1H or ^{13}C) for compounds **7**, **8**, **12**, **13**, and 4,4,5,5-tetramethyl-2-phenylimidazolidine alluded to in ref 15 (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.