

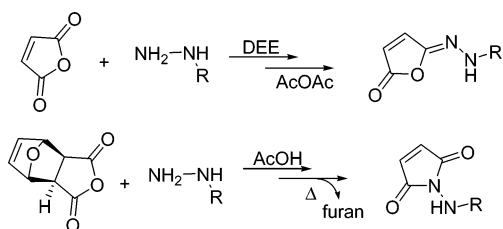
A New Synthetic Route to Authentic *N*-Substituted Aminomaleimides

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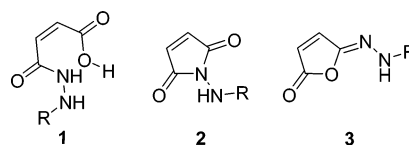
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A number of compounds reported in the literature as *N*-aminomaleimides (**2**) are, instead, isomeric *N*-aminoisomaleimides (**3**). The ubiquity of this mischaracterization and its propagation within the literature are discussed. In addition, the first general synthetic route to aliphatic and aromatic *N*-substituted aminomaleimides is described. As an illustration, the compound reported to be *N*-(4-bromophenylamino)maleimide (**2b**) was prepared and determined to be *N*-(4-bromophenylamino)isomaleimide (**3b**). The authentic compound was synthesized by the condensation of 4-bromophenylhydrazine (**7b**) and the *exo*-furan/maleic anhydride Diels–Alder adduct (**8**) in acetic acid to produce the furan-protected aminomaleimide **10b**, followed by heating to remove furan through the retro Diels–Alder reaction. The structures of **2b**, **3b**, and **10b** were established unequivocally by X-ray crystallography and other spectroscopic techniques.

Several early reports describe the reaction of maleic anhydride with a hydrazine derivative to give *N*-substituted aminomaleamic acids **1**, followed by dehydrative cyclization in acetic anhydride or thionyl chloride, as a method of preparing *N*-substituted aminomaleimides **2**,^{1–7} herein referred to as NSAMs. These initial reports have since been proven inaccurate,^{8–11} and the reported compounds are now thought to be *N*-substituted aminoisomaleimides **3**. The mischaracterization is attributable to the authors' reliance on characterization methods other

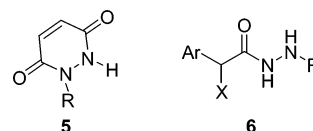
than NMR for structural assignment and the faulty assumption that **1** undergoes ring closure in a manner analogous to *N*-aminosuccinamic acids.



a: R = H
b: R = 4-bromophenyl
c: phenyl
d: R = CO₂CMe₃

The unexpected formation of aminoisomaleimide **3** may be accounted for by the mechanism shown in Scheme 1, which is analogous to the one proposed for the dehydration of *N*-arylmaleamic acids.¹² After formation of the mixed anhydride **4**, deprotonation of the amide and ejection of the acetate ion result in formation of aminoisomaleimide **3**.

The ubiquity of the aminomaleimide–aminoisomaleimide mischaracterization in the literature has resulted in a number of workers^{13–15} continuing to rely upon and cite flawed reports without knowledge of the mischaracterization. For example, in their 1988 publication describing a new method for the synthesis of NSAMs, Florac and co-workers¹³ wrote that “the *N*-amino maleimides described previously have only been prepared from the reaction of hydrazines and maleic anhydrides” and cited several erroneous reports.¹⁶ They continued by stating that “*N*-amino maleimides are useful in the synthesis of pyridazine-3,6-diones” more than a decade after Rubenstein and co-workers demonstrated that it was actually aminoisomaleimides, not NSAMs, that rearranged to pyridazinones **5** upon treatment with sulfuric acid.¹⁰



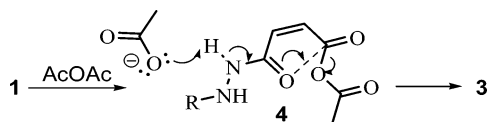
In a more spectacular example, Cheng and Comer¹⁵ recently reported the preparation of **2c** by reacting maleic anhydride with phenylhydrazine, followed by dehydration in thionyl chloride.¹⁷ It is evident from their ¹H NMR data, which shows nonequivalent olefinic protons, that they instead prepared aminoisomaleimide **3c**. Also in-

(1) Feuer, H.; Rubinstein, H. *J. Am. Chem. Soc.* **1958**, *80*, 5873.
(2) Feuer, H.; Asunskis, J. *J. Org. Chem.* **1962**, *27*, 4684.
(3) Baloniak, S. *Rocz. Chem.* **1968**, *42*, 1231.
(4) Baloniak, S.; Mroczkiewicz, A. *Rocz. Chem.* **1974**, *48*, 399–407.
(5) Baloniak, S.; Thiel, U.; Pacholczyk, M. *Acta Polon. Pharm.* **1976**, *33*, 73–9.
(6) Hageman, H. A.; Hubbard, W. L. U.S. Patent 3257414, 1966; *Chem. Abstr.* **1966**, *65*, 7066c.
(7) Krause, J. G.; Kwon, S.; George, B. *J. Org. Chem.* **1972**, *37*, 2040.
(8) Hedeya, E.; Hinman, R. L.; Theodoropoulos, S. *J. Org. Chem.* **1966**, *31*, 1311.
(9) Rubinstein, H.; Skarbek, J. E. *J. Org. Chem.* **1971**, *36*, 3372–6.
(10) Rubinstein, H.; Parnarouskis, M.; Feuer, H. *J. Org. Chem.* **1973**, *38*, 2166–9.

(11) To the best of our knowledge, we are the first to identify the method reported for the synthesis of *N*-aminomaleimide (**2a**) in ref 7 as erroneous. We repeated their procedure, which involved refluxing maleic anhydride and *tert*-butylcarbuzate in chloroform, and observed two doublets, each corresponding to one proton, in the olefinic region of the ¹H NMR spectrum (see the Supporting Information). This indicates the formation of **3d** which, upon deprotection, would yield aminoisomaleimide **3a**.

(12) Sauers, C. K. *J. Org. Chem.* **1969**, *34*, 2275–9.
(13) Florac, C.; Baudy-Floc'h, M.; Robert, A. *J. Chem. Soc., Chem. Commun.* **1988**, 1524.
(14) Mroczkiewicz, A. *Pol. J. Chem.* **1980**, *54*, 1095–9.
(15) Cheng, S.; Comer, D. D. *Tetrahedron Lett.* **2002**, *43*, 1179–81.
(16) Among others, these included refs 4 and 5.
(17) The authors were relying on erroneous refs 1 and 2.

SCHEME 1



congruous is their report of seven lines in the ^{13}C NMR spectrum; **2c** should have only six lines and **3c** should have eight. After repeating their procedure, we found that the ^{13}C NMR spectrum does in fact contain eight lines¹⁸ and the spectrum is consistent with isomaleimide **3c**. It is important to note that the other nine “*N*-(arylamino)-maleimides” that Cheng and Comer prepared are almost certainly aminoisomaleimides as well, and in light of this mischaracterization, their report of alumina-catalyzed Michael addition of mercaptans to *N*-anilino-maleimides¹⁵ must be reevaluated.

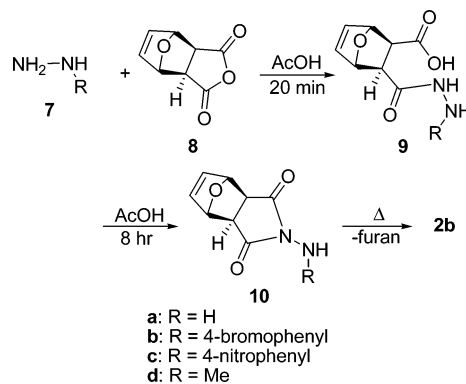
Although methods for the preparation of authentic aminomaleimides have been described, they have limitations that reduce their synthetic utility. In the method of Florac et al.,¹³ 2-aminopyridine is reacted with an α -halohyrazide (**6**) to produce an NSAM that has aryl groups at the carbon-carbon double-bond position. As a result, this method is more relevant as a route to substituted maleic anhydrides, which are obtained after hydrolysis of the NSAM, rather than synthetically useful NSAMs. A particularly interesting route to NSAM **2c** involves the dehydration of the tetracarbonyliron complex of **1c** in acetic anhydride at room temperature.¹⁹ The authors propose that the π -bound $\text{Fe}(\text{CO})_4$ group increases the nucleophilic character of the amide-like nitrogen atom in **1c**, which favors formation of **2c**. They also note that coordination of tetracarbonyliron to **1c** results in the double bond becoming closer in character to a saturated bond; this is important because, unlike maleamic acids (**1**), succinamic acids undergo cyclization to the corresponding five-membered nitrogen heterocycles. Unfortunately, the overall yield of **2c** from tetracarbonyl(maleic anhydride)iron is only 14%.

While reviewing the literature, we came across a report by Hedaya and co-workers⁸ which described the synthesis of *N,N'*-bimaleimide by the condensation of the *endo*-furan/maleic anhydride Diels-Alder adduct and hydrazine hydrate (**7a**·H₂O), followed by the retro-Diels-Alder reaction to remove furan. We investigated this synthesis to determine if it could be adapted for use with substituted hydrazines (**7**) as a general route to NSAMs (Scheme 2), particularly **2b**, a compound which we required for other work. Indeed, we were able to prepare **2b** in three steps with a 57% overall yield, thereby demonstrating a new route to the synthesis of NSAMs. The compound previously reported to be “4-bromophenylaminomaleimide”⁴ (**2b**) was also prepared and shown to be *N*-(4-bromophenylamino)isomaleimide (**3b**). The crystal structures for compounds **10b**, **2b**, and **3b**, which can be found in the Supporting Information, were consistent with the structural assignments. To demonstrate

(18) There are two closely spaced lines at 140.98 and 141.04 ppm, which could be resolved by the addition of a single drop of water to the DMSO-*d*₆. The spectrum is available as Supporting Information.

(19) Nesmeyanov, A. N.; Rybinskaya, M. I.; Rybin, L. V.; Arutyunyan, A. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1974**, *44*, 578–85.

SCHEME 2



the versatility of this new method, **10c** and **10d** were also prepared in good yield.²⁰

Experimental Section

(2Z)-4-[2-(4-Bromophenyl)hydrazino]-4-oxobut-2-enoic Acid (1b). A solution of 4-bromophenylhydrazine (**7b**, 0.250 g, 1.34 mmol) in diethyl ether (5 mL) was added dropwise to a solution of maleic anhydride (0.131 g, 1.34 mmol) in diethyl ether (5 mL). The reaction mixture was stirred for 20 min at rt and then cooled to 0 °C for 20 min. The resulting yellow precipitate was suction filtered, washed with cold diethyl ether, and dried under vacuum to give 0.295 g (77% yield) of **1b**: yellow powder; mp 175–176 °C; ^1H NMR (300 MHz, DMSO-*d*₆) δ 13.25 (br s, 1H), 10.21 (br s, 1H), 8.12 (br s, 1H), 7.33–7.25 (m, 2H), 6.76–6.69 (m, 2H), 6.53 (d, *J* = 12.3 Hz, 0.18H, minor conformer), 6.39 (d, *J* = 12.3 Hz, 0.87H, major conformer), 6.26 (d, *J* = 12.3 Hz, 0.85H, major conformer), and 6.06 (d, *J* = 12.3 Hz, 0.15H, minor conformer) [complex spectrum due to hindered rotation]; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, DMSO-*d*₆ saturated with H₂O) δ 168.6, 167.0, 148.5, 132.8, 131.8, 131.6, 115.9, and 112.0; IR (KBr) 3433, 3274, 3216, 3017, 1705, 1623, 1522, 1480, 1417, 1305, 1247, 847, and 816 cm⁻¹; MS (CI⁻) *m/z* (rel intensity) 285 ([M - H + 2]⁻; 99), 283 ([M - H]⁻; 100), 268 ([M - H₂O + 2]⁻; 96), and 266 ([M - H₂O]⁻; 99); HRMS (CI⁻) calcd for C₁₀H₉N₂O₃Br ([M - H]⁻) 282.9711, found 282.9718. Anal. Calcd for C₁₀H₉N₂O₃Br (285.09): C, 42.13; H, 3.18; N, 9.83. Found: C, 41.90; H, 3.20; N, 9.67.

(2Z)-Furan-2,5-dione (4-Bromophenyl)hydrazone (3b). To **1b** (0.116 g, 0.406 mmol) and sodium acetate (0.020 g, 0.243 mmol) was added acetic anhydride (5 mL). The reaction mixture was heated to 100 °C for 5 min under a nitrogen atmosphere, and after cooling to rt, water (10 mL) was added. The reaction mixture was stirred overnight and cooled to 0 °C, and the product was isolated by centrifugation. The solid was washed with water and dried under vacuum to give 0.082 g (76% yield) of **3b**: yellow powder; mp 222–223 °C; ^1H NMR (500 MHz, DMSO-*d*₆) δ 10.77 (s, 1H), 7.78 (d, *J* = 5.4 Hz, 1H), 7.43–7.40 (m, 2H), 7.21–7.18 (m, 2H), and 6.59 (d, *J* = 5.4 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, DMSO-*d*₆) δ 166.9, 143.1, 141.3, 140.9, 131.8, 120.4, 115.2, and 112.2; IR (KBr) 3431, 3274, 2961, 2919, 1775, 1751, 1631, 1591, 1546, 1519, 1485, 1260, 1239, 1169, 1105, 1066, 1023, 938, 886, 818, 800, 767, and 689 cm⁻¹; MS (CI⁻) *m/z* (rel intensity) 268 (M⁻ + 2; 71) and 266 (M⁻; 100); HRMS (CI⁻) calcd for C₁₀H₆N₂O₂Br ([M - H]⁻) 264.9613, found 264.9618. Anal. Calcd for C₁₀H₇N₂O₂Br (267.08): C, 44.97; H, 2.64; N, 10.49. Found: C, 44.98; H, 2.77; N, 10.44.

3-[[2-(4-Bromophenyl)hydrazino]carbonyl]-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (9b). To a solution of 4-bromophenylhydrazine (**7b**, 0.350 g, 1.87 mmol) in acetic acid (5 mL) was added a slurry of *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (**8**, 0.311 g, 1.87 mmol) in acetic acid (5 mL), and the reaction mixture was stirred for 20 min at rt. The

(20) During the reaction of **7d** with **8**, maleamic acid **9d** did not precipitate out of acetic acid, and therefore, it was not isolated.

precipitate was suction filtered, washed with diethyl ether, and dried under vacuum to afford 0.535 g (81% yield) of **9b**: colorless powder; mp 145 °C dec; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.11 (br s, 1H), 9.62 (s, 1H), 7.84 (s, 1H), 7.26–7.20 (m, 2H), 6.75–6.68 (m, 2H), 6.47 (s, 2H), 5.10 (s, 1H), 4.89 (s, 1H), 2.68 (d, *J* = 9.0 Hz, 1H), and 2.60 (d, *J* = 9.3 Hz, 1H); ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆) δ 172.5, 170.7, 148.7, 137.1, 136.5, 131.2, 114.3, 109.0, 80.8, 79.0, 46.1, and 44.5; IR (KBr) 3445, 3258, 2959, 2917, 2866, 2839, 1693, 1658, 1596, 1542, 1487, 1456, 1375, 1301, 1262, 1216, 1165, 1049, 998, 901, and 827 cm⁻¹; MS (ESI⁻) *m/z* (rel intensity) 353 ([M - H + 2]⁻; 84), 351 ([M - H]⁻; 90), 285 ([M - furan - H + 2]⁻; 97), and 283 ([M - furan - H]⁻; 100). Anal. Calcd for C₁₄H₁₃N₂O₄Br (353.17): C, 47.61; H, 3.71; N, 7.93. Found: C, 47.28; H, 3.83; N, 7.83.

exo-4-[(4-Bromophenyl)amino]-10-oxa-4-azatricyclo-[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (10b). A slurry of **9b** (3.27 g, 9.26 mmol) in acetic acid (327 mL) was stirred at rt for 8 h under a nitrogen atmosphere. The solvent was removed under vacuum, the solid was washed into a saturated solution of sodium bicarbonate (150 mL) using dichloromethane, and the mixture was stirred vigorously for 5 min. The organic layer was separated, washed with brine, treated with magnesium sulfate, and dried under vacuum. Purification of the tan crude product by flash column chromatography (silica gel, ethyl acetate/hexanes 1:1) afforded 2.28 g of **10b** (73%): colorless powder; mp 151–152 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.75 (s, 1H), 7.35–7.27 (m, 2H), 6.68–6.59 (m, 2H), 6.58 (s, 2H), 5.21 (s, 2H), and 3.00 (s, 2H); ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆) δ 174.8, 145.6, 136.2, 131.5, 114.2, 110.7, 80.3, and 45.0; IR (KBr) 3491, 3259, 2999, 1788, 1717, 1594, 1489, 1410, 1310, 1286, 1246, 1199, 1155, 1123, 1074, 1013, 1003, 957, 920, 884, 851, 827, 816, 808, 720, 658, and 643 cm⁻¹; MS (ESI⁻) *m/z* (rel intensity) 335 ([M - H + 2]⁻; 6), 333 ([M - H]⁻; 5), 268 ([M - furan + 2]⁻; 95), and 266 ([M - furan]⁻; 100); HRMS (CI⁻) calcd for C₁₄H₁₀N₂O₃Br ([M - H]⁻) 332.9875, found 332.9872. Anal. Calcd for C₁₄H₁₁N₂O₃Br (335.15): C, 50.17; H, 3.31; N, 8.36. Found: C, 49.91; H, 3.46; N, 8.19.

1-[(4-Bromophenylamino)-1H-pyrrole-2,5-dione (2b). Deprotection of **10b** (0.137 g, 0.409 mmol) was achieved by heating to 175 °C for 10 min at 5 Torr in a Kugelrohr glass oven. The starting material initially decomposed to a yellow solid and then melted to give an orange liquid with vigorous bubbling. Upon sitting for several days at rt, the resulting orange oil crystallized to give 0.105 g of **2b** (96% yield): yellow crystals; mp 152–153 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.48 (s, 1H), 7.34–7.30 (m, 2H), 7.11 (s, 2H), and 6.67–6.63 (m, 2H); ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆) δ 169.1, 146.4, 133.2, 131.6, 114.1, and 110.8; IR (KBr) 3479, 3316, 3096, 1718, 1596, 1503, 1489, 1421, 1306, 1286, 1246, 1169, 1116, 1074, 1049, 1005, 852, 820, 683, and 626 cm⁻¹; MS (CI⁻) *m/z* (rel intensity) 268 (M⁻ + 2; 96) and 266 (M⁻; 100); HRMS (CI⁻) calcd for C₁₀H₆N₂O₂Br ([M - H]⁻) 264.9613, found 264.9620. Anal. Calcd for C₁₀H₇N₂O₂Br (267.08): C, 44.97; H, 2.64; N, 10.49. Found: C, 44.74; H, 2.78; N, 10.27.

3-[[2-(4-Nitrophenyl)hydrazino]carbonyl]-7-oxabicyclo-[2.2.1]hept-5-ene-2-carboxylic Acid (9c). The title compound was prepared analogously as described for **9b** using **7c** (0.738 g, 4.82 mmol) and **8** (0.800 g, 4.82 mmol). After workup, 0.605 g (39% yield) of **9c** was obtained:²¹ brown powder; mp 135 °C dec; ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.23 (s, 1H), 9.97 (s, 1H), 9.03 (s, 1H), 8.02 (d, *J* = 9.2 Hz, 2H), 6.81 (d, *J* = 9.2 Hz, 2H), 6.49 (s, 2H), 5.12 (s, 1H), 4.95 (s, 1H), and 2.67 (s, 2H); ¹³C{¹H}

(21) As a result of its greater solubility in acetic acid, the amount of aminomaleamic acid **9c** recovered using this workup is somewhat lower than the amount of **9b**. Isolation of **9** is not required for the preparation of **10**, however.

NMR (50 MHz, DMSO-*d*₆) δ 172.6, 170.8, 155.1, 137.9, 137.2, 136.6, 125.9, 110.8, 80.8, 79.1, 46.4, and 44.5; IR (KBr) 3312, 3275, 3008, 1698, 1667, 1598, 1493, 1413, 1389, 1337, 1260, 1228, 1211, 1113, 1043, 991, 902, 845, 824, 753, 713, 632, and 504 cm⁻¹; MS (ESI⁻) *m/z* (rel intensity) 318 ([M - H]⁻; 34) and 250 ([M - furan - H]⁻; 100). Anal. Calcd for C₁₄H₁₃N₃O₆ (319.27): C, 52.67; H, 4.10; N, 13.16. Found: C, 52.73; H, 4.39; N, 13.42.

exo-4-[(4-Nitrophenyl)amino]-10-oxa-4-azatricyclo-[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (10c). A slurry of **7c** (0.738 g, 4.82 mmol) and **8** (0.800 g, 4.82 mmol) in acetic acid (55 mL) was stirred at rt for 13 h under a nitrogen atmosphere. Water (200 mL) was added, and the reaction mixture was cooled to 0 °C. The precipitate was suction filtered and washed with diethyl ether to give 0.880 g of **10c** (61%): brown powder; mp 172 °C dec; ¹H NMR (200 MHz, DMSO-*d*₆) δ 9.73 (s, 1H), 8.08 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 7.6 Hz, 2H), 6.59 (s, 2H), 5.26 (s, 2H), and 3.06 (s, 2H); ¹³C{¹H} NMR (50 MHz, DMSO-*d*₆) δ 174.5, 152.1, 139.5, 136.3, 125.8, 111.2, 80.5, and 45.2; IR (KBr) 3483, 3286, 3099, 3025, 3006, 1788, 1717, 1597, 1524, 1505, 1493, 1406, 1339, 1262, 1215, 1189, 1158, 1115, 1089, 1013, 919, 879, 850, 821, 807, 752, 701, 652, 628, and 590 cm⁻¹; MS (ESI⁺) *m/z* (rel intensity) 324 ([M + Na]⁺; 92), 256 ([M - furan + Na]⁺; 100), 302 ([M + H]⁺; 18), and 234 ([M - furan + H]⁺; 38). Anal. Calcd for C₁₄H₁₁N₃O₅ (301.25): C, 55.82; H, 3.68; N 13.94. Found: C, 55.42; H, 3.88; N, 13.79.

4-(Methylamino)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (10d). To a slurry of **8** (4.00 g, 24.1 mmol) and acetic acid (100 mL) was added **7d** (1.50 g, 1.71 mL, 32.6 mmol), and the reaction mixture was stirred for 24 h under a nitrogen atmosphere. The solvent was removed under vacuum, and the crude product was purified by flash column chromatography (silica gel, dichloromethane/methanol, 19:1), affording 3.33 g of **10d** (71%): colorless powder; mp 148–149 °C dec; ¹H NMR (200 MHz, DMSO-*d*₆) δ 6.57 (s, 2H), 5.68 (q, *J* = 5.6 Hz, 1H), 5.15 (s, 2H), 2.87 (s, 2H), and 2.47 (d, *J* = 5.6 Hz, 3H); ¹³C{¹H} NMR (50 MHz, CDCl₃) δ 173.7, 136.1, 80.4, 45.2, and 37.4; IR (KBr) 3457, 3303, 3074, 3029, 2989, 2960, 2932, 2895, 2869, 1780, 1702, 1525, 1444, 1414, 1399, 1312, 1288, 1247, 1222, 1200, 1176, 1155, 1106, 1012, 958, 920, 877, 849, 809, 717, 647, 611, and 586 cm⁻¹; MS (ESI⁺) *m/z* (rel intensity) 195 ([M + H]⁺; 65) and 127 ([M - furan + H]⁺; 100). Anal. Calcd for C₉H₁₀N₂O₃ (194.19): C, 55.67; H, 5.19; N, 14.43. Found: C, 54.98; H, 5.53; N, 13.96.

Acknowledgment. Financial support for this work by the Arnold and Mabel Beckman Foundation is gratefully acknowledged. We also thank the following people at The University of Texas at Austin: Dr. Ben Shoulders for his assistance in the interpretation of NMR spectra, Dr. Medhi Moini for advice regarding mass spectroscopic ion notation, Dr. Vince Lynch for performing the X-ray crystallographic analyses, and Estelle Garza for her assistance with a portion of the synthetic work. Near the end of this project, N.R.C.'s affiliation changed to Stanford University and he thanks Dr. Robert Waymouth at Stanford for providing the laboratory space needed to complete this work.

Supporting Information Available: ¹H NMR, ¹³C NMR, and IR spectra for all compounds described in the Experimental Section; crystal structures for **3b**, **10b**, and **2b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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