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SYNTHESIS OF 1-(3-ISOXAZOLYL)- AND 1-(3-PYRAZOLYL)AZULENE DERIVATIVES *VIA* METHYL 1-(3-DIMETHYLAMINO-2-PROPENOYL)AZULENE-3-CARBOXYLATE

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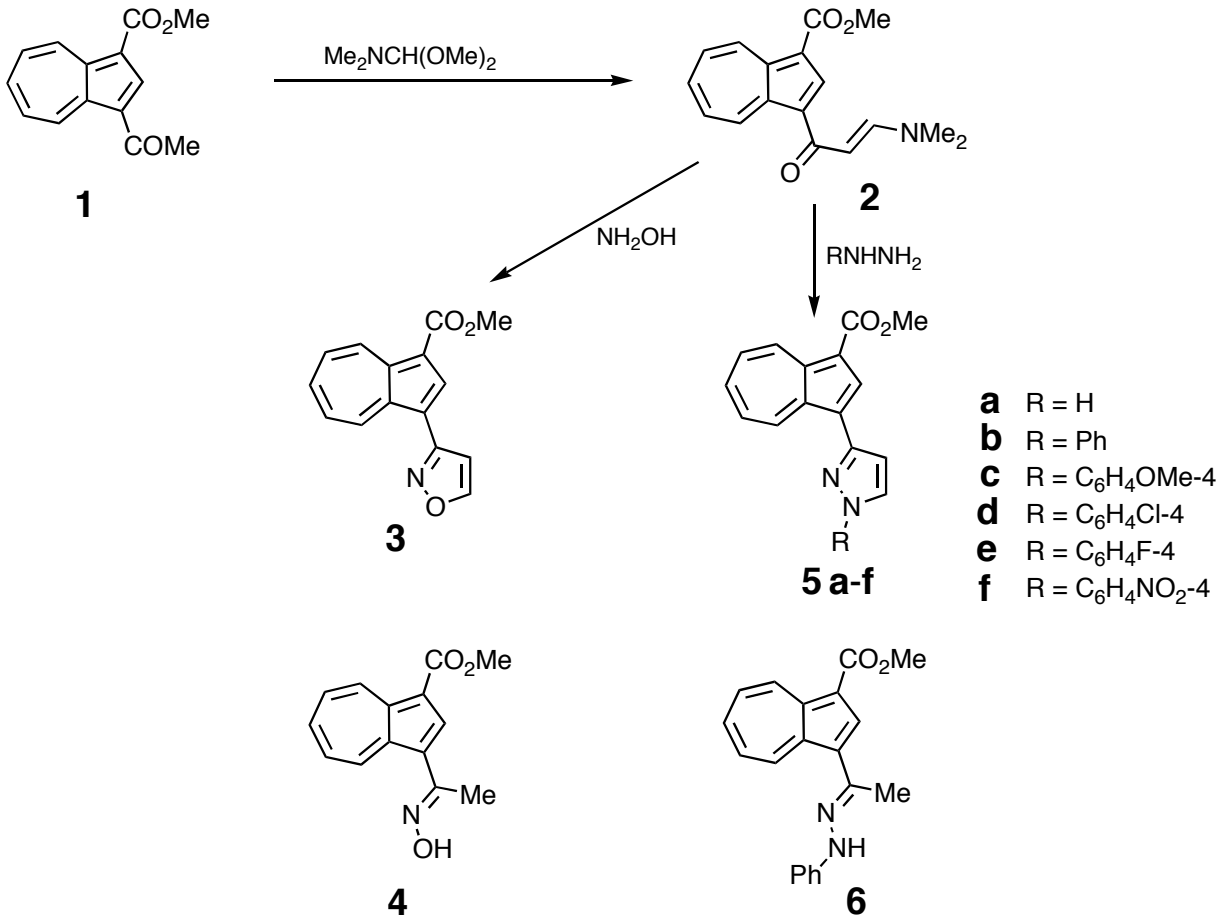
Abstract – Methyl 1-acetylazulene-3-carboxylate (**1**) reacted with *N,N*-dimethylformamide dimethylacetal (DMFDMA) to give enaminone (**2**), which reacted with hydroxylamine and hydrazines to yield methyl 1-(3-isoxazolyl)azulene-3-carboxylate (**3**) and methyl 1-(3-pyrazolyl)azulene-3-carboxylates (**5a**-**f**), respectively. Compound (**1**) was also gave the products (**3** and **5b**) via oxime (**4**) and phenylhydrazone (**6**).

It is well-known that enaminones are versatile synthetic precursors and their utilities in heterocyclic synthesis have recently received a considerable attention.[1-4] Nitrogen heterocycles are found in a large number of commonly used drugs which have diverse pharmacological activities. On the other hand, azulene is theoretically and chemically interesting compound with many unusual properties. Physiological activities have been found in azulene derivatives.[5a-c] In conjunction with our interest in synthesis of heteroaryl-substituted azulene derivatives, such as 1-(2-pyridyl)- and 1-(4-pyridyl)azulenes,[6] 1- and 2-(2-quinolyl)azulenes,[7] 1-(benzofurancarbonyl)azulenes,[8] 1-(2-imidazo[1,2-*b*]pyridyl)azulene,[9] and 1-(4-thiazolyl)azulenes.[10] In this communication, we wish to report an efficient synthesis of a variety of target molecules from methyl 1-acetylazulene-3-carboxylate (**1**)[11] via its enaminone (**2**).

Methyl 1-acetylazulene-3-carboxylate (**1**) was treated with *N,N*-dimethylformamide dimethylacetal (DMFDMA) in refluxing *N,N*-dimethylformamide (DMF) to yield enaminone, methyl 1-(3-dimethylamino-2-propenoyl)azulene-3-carboxylate (**2**). The ^{1}H NMR spectrum of **2** shows that *trans* isomer was formed exclusively based on coupled olefinic protons at δ 5.89 and 7.80 with J = 15 Hz.



Scheme 1

The enaminone (**2**) reacted with hydroxylamine hydrochloride in ethanol in the presence of pyridine to yield isoxazolyl-substituted azulene. Its structure was established to be methyl 1-(3-isoxazolyl)azulene-3-carboxylate (**3**) on the basis of elemental analysis and spectral data. The IR spectrum showed the ester carbonyl absorption at ν 1701 cm^{-1}. In the ^1H NMR spectrum, characteristic signals for the isoxazole and azulene rings were observed at δ 6.56 (1H, d, *J* = 1.6 Hz, 4'-H), 7.62-7.67 (3H, m, 5',6-H + 5- or 7-H), 7.91 (1H, dd, *J* = 9.6, 10.0 Hz, 5- or 7-H), 8.35 (1H, s, 2-H), 9.23 (1H, d, *J* = 10.0 Hz, 8-H), and 9.73 (1H, d, *J* = 10.0 Hz, 4-H). Compound (**1**) reacted with hydroxylamine to afford oxime (**4**) which was also converted to the isoxazolyl-substituted azulene (**3**).

Similarly, the enaminone (**2**) reacted with hydrazine hydrate and with arylhydrazines to give the pyrazolyl-substituted azulenes (**5a**-**f**). Their structures were confirmed on the basis of elemental analysis and spectral data. As an example, the IR spectrum of compound (**6b**) showed the ester carbonyl absorption at ν 1692 cm^{-1}. The ^1H NMR spectrum exhibited characteristic signals at δ 6.64 (1H, d, *J* = 1.6 Hz, 4'-H), 7.38 (1H, dd, *J* = 9.6, 10.0 Hz, 5- or 7-H), 7.47 (1H, dd, *J* = 9.6, 10.0 Hz, 5- or 7-H), 7.67 (1H, d, *J* = 1.6 Hz, 5'-H), 7.74 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.47 (1H, s, 2-H), 9.10 (1H, d, *J* = 10.0 Hz, 8-H), and 9.56 (1H, d, *J* = 10.0 Hz, 4-H). The phenylhydrazone (**6**) also formed the

pyrazolyl-substituted azulene (**5b**).

In conclusion, it was found that the reactions of the enaminone (**2**) with hydroxylamine and hydrazines provided a simple and efficient method for synthesis of 1-(3-isoxazolyl)azulene (**3**) and 1-(3-pyrazolyl)azulenes (**5a**-**f**) in moderate yields, respectively.

EXPERIMENTAL

All the melting points were determined with a Yanaco MP JP-3 apparatus and are uncorrected. The elemental analyses were performed on a LECO CHNS-932 apparatus. The IR spectra were measured on a JASCO A-102 and a Shimadzu IR-740 spectrophotometer. The ^{1}H NMR were recorded with a JEOL JNM-EX 300 spectrometer. The MS spectra were run on a GS-MS INCOS XL Finnigan MAT.

Preparation of Methyl 1-(3-Dimethylamino-2-propenoyl)azulene-3-carboxylate (2).

A mixture of methyl 1-acetylazulene-3-carboxylate (**1**) (2.28 g, 10 mmol) and DMFDMA (2.52 g, 20 mmol) in DMF (30 mL) was heated under refluxing for 6 h. After the solvent was removed under reduced pressure, the residue was chromatographed on a silica gel column with benzene as an eluent to give methyl 1-(3-dimethylamino-2-propenoyl)azulene-3-carboxylate (**2**) was obtained as dark green crystals (from benzene); yield 2.15 g (76%), mp 130-131 ºC; IR (KBr): ν 1695 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.01 (6H, s, NCH_3 x 2), 3.98 (3H, s, CO_2CH_3), 5.89 (1H, d, *J* = 15.0 Hz, 2'-H), 7.65-7.72 (2H, m, 6-H + 5- or 7-H), 7.80 (1H, d, *J* = 15.0 Hz, 3'-H), 7.91 (1H, dd, *J* = 9.6, 10.0 Hz, 5- or 7-H), 8.74 (1H, s, 2-H), 9.71 (1H, d, *J* = 10.0 Hz, 8-H), 10.08 (1H, d, *J* = 10.0 Hz, 4-H); MS: *m/z* 283 (M^+). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.13; H, 6.23; N, 4.81.

Methyl 1-(3-Isoxazolyl)azulene-3-carboxylate (3).

A solution of the enaminone (**2**) (100 mg, 0.35 mmol) and hydroxylamine hydrochloride (70 mg, 0.80 mmol) in ethanol (30 mL) was refluxed for 6 h in the presence of pyridine (60 mg, 0.80 mmol). After removal of the sovent, the residue was chromatographed on a silica gel column with benzene to afford methyl 1-(3-isoxazolyl)azulene-3-carboxylate (**3**) was obtained as dark green crystals (from benzene); yield 51 mg (58%), mp 126-127 ºC; IR (KBr): ν 1701 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.96 (3H, CO_2CH_3), 6.56 (1H, d, *J* = 1.6 Hz, 4'-H), 7.62-7.67 (3H, m, 5',6-H + 5- or 7-H), 7.91 (1H, dd, *J* = 9.6, 10.0 Hz, 5- or 7-H), 8.35 (1H, s, 2-H), 9.23 (1H, d, *J* = 10.0 Hz, 8-H), 9.73 (1H, d, *J* = 10.0 Hz, 4-H); MS: *m/z* 253 (M^+). *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.19; H, 4.23; N, 5.71.

Methyl 1-Acetylazulene-3-carboxylate Oxime (4).

A mixed solution of methyl 1-acetylazulene-3-carboxylate (**1**) (57 mg, 0.25 mmol) and hydroxylamine hydrochloride (35 mg, 0.50 mmol) in methanol (20 mL) was refluxed for 2 h. The evaporation residue was chromatographed on a silica gel column with benzene to give methyl 1-acetylazulene-3-carboxylate oxime (**4**) as dark green crystals (from benzene); yield 53 mg (88%), mp 140-142 ºC; IR (KBr): ν 3413 (OH), 1707 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 2.47 (3H, s, CH_3), 3.96 (3H, s, CO_2CH_3), 7.52 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.58 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.82 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.46 (1H, s, 2-H), 9.41 (1H, d, *J* = 9.6 Hz, 8-H), 9.66 (1H, d, *J* = 9.6 Hz, 4-H); MS: *m/z* 243 (M^+). *Anal*. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.19; H, 5.63; N, 5.71.

Reaction of Methyl 1-Acetylazulene-3-carboxylate Oxime (4) with DMFDMA.

A mixture of the oxime (**4**) (48 mg, 0.2 mmol) and DMFDMA (39 mg, 0.3 mmol) in DMF (15 mL) was heated under refluxing for 2 h. After removal of the solvent, the residue was chromatographed on a silica gel column with benzene to give compound (**3**); yield 30 mg (59%), mp 126-127 ºC.

Reactions of the Enaminone (2) with Hydrazines.

General Procedure: To a solution of the enaminone (**2**) (57 mg, 0.2 mmol) in ethanol (30 mL), hydrazine (0.3 mmol) was added. The reaction mixture was heated under refluxing for 6-12 h under monitoring by TLC. The solvent was removed and the residue was purified by chromatography on a silica gel column to yield methyl 1-(3-pyrazolyl)azulene-3-carboxylates (**5a**-**f**).

Methyl 1-(3-Pyrazolyl)azulene-3-carboxylate (5a): Bluish green crystals (from benzene), yield 68%, mp 123-125 ºC; IR (KBr): ν 1703 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.96 (3H, s, CO_2CH_3), 6.64 (1H, d, *J* = 1.6 Hz, 4'-H), 7.38 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.47 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.67 (1H, d, *J* = 1.6 Hz, 5'-H), 7.74 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.47 (1H, s, 2-H), 9.10 (1H, d, *J* = 9.6 Hz, 8-H), 9.56 (1H, d, *J* = 9.6 Hz, 4-H); MS: *m/z* 252 (M^+). *Anal*. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.29; H, 4.63; N, 11.03.

Methyl 1-(1-Phenylpyrazol-3-yl)azulene-3-carboxylate (5b): Bluish green crystals (from benzene), yield 64%, mp 120-121 ºC; IR (KBr): ν 1703 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H, CO_2CH_3), 6.58 (1H, d, *J* = 1.7 Hz, 4'-H), 7.19-7.22 (5H, m, Ph), 7.39 (1H, dd, *J* = 9.6, 10.0 Hz, 5- or 7-H), 7.81 (1H, dd, *J* = 9.6, 10.0 Hz, 5- or 7-H), 7.84 (1H, d, *J* = 1.7 Hz, 5'-H), 8.07 (1H, s, 2-H), 8.42 (1H, d, *J* = 10.0 Hz, 8-H), 9.66 (1H, d, *J* = 10.0 Hz, 4-H); MS: *m/z* 328 (M^+). *Anal*. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.69; H, 4.73; N, 8.43.

Methyl 1-[1-(4-Methoxyphenyl)pyrazol-3-yl]azulene-3-carboxylate (5c): Bluish green crystals (from benzene), yield 72%, mp 118-120 ºC; IR (KBr): ν 1696 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 3.73 (3H, s, CH_3), 3.90 (3H, s, CO_2CH_3), 6.55 (1H, d, *J* = 1.8 Hz, 4'-H), 6.72 (2H, d, *J* = 8.7 Hz, 3",5"-H), 7.13 (2H, d, *J* = 8.7 Hz, 2",6"-H), 7.41 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.58 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.79-7.84 (2H, m, 5',6-H), 8.07 (1H, s, 2-H), 8.44 (1H, d, *J* = 9.6 Hz, 8-H), 9.65 (1H, d, *J* = 9.6 Hz, 4-H); MS: *m/z* 358 (M^+). *Anal.* Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.69; H, 5.23; N, 7.63.

Methyl 1-[1-(4-Chlorophenyl)pyrazol-3-yl]azulene-3-carboxylate (5d): Bluish green crystals (from benzene), yield 61%, mp 130-131 ºC; IR (KBr): ν 1687 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 3.92 (3H, s, CO_2CH_3), 6.57 (1H, d, *J* = 1.6 Hz, 4'-H), 7.17-7.19 (4H, m, Ar-H), 7.43 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.62 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.82-7.87 (2H, m, 5',6-H), 8.08 (1H, s, 2-H), 8.41 (1H, d, *J* = 9.6 Hz, 8-H), 9.69 (1H, d, *J* = 9.6 Hz, 4-H); MS: *m/z* 362 (M^+). *Anal.* Calcd for $C_{21}H_{15}ClN_2O_2$: C, 69.52; H, 4.17; N, 7.72. Found: C, 69.69; H, 4.23; N, 7.53.

Methyl 1-[1-(4-Fluorophenyl)pyrazol-3-yl]azulene-3-carboxylate (5e): Bluish green crystals (from benzene), yield 55%, mp 147-148 ºC; IR (KBr): ν 1698 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 3.90 (3H, s, CO_2CH_3), 6.75 (1H, d, *J* = 1.7 Hz, 4'-H), 6.88-6.92 (2H, m, 3",5"-H), 7.18-7.21 (2H, m, 2",6"-H), 7.42 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.60 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.81-7.86 (2H, m, 5',6-H), 8.06 (1H, s, 2-H), 8.42 (1H, d, *J* = 9.6 Hz, 8-H), 9.68 (1H, d, *J* = 9.6 Hz, 4-H); MS: *m/z* 346 (M^+). *Anal.* Calcd for $C_{21}H_{15}FN_2O_2$: C, 72.82; H, 4.37; N, 8.09. Found: C, 72.69; H, 4.23; N, 7.83.

Methyl 1-[1-(4-Nitrophenyl)pyrazol-3-yl]azulene-3-carboxylate (5f): Bluish green crystals (from benzene), yield 38%, mp 150-151 ºC; IR (KBr): ν 1691 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 3.96 (3H, s, CO_2CH_3), 6.66 (1H, d, *J* = 1.7 Hz, 4'-H), 7.38 (2H, d, *J* = 8.6 Hz, 2",6"-H), 7.41 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 7.67-7.75 (2H, m, 6-H + 5- or 7-H), 7.92 (1H, d, *J* = 1.7 Hz, 5'-H), 8.07 (2H, d, *J* = 8.6 Hz, 3",5"-H), 8.55 (1H, s, 2-H), 8.42 (1H, d, *J* = 9.6 Hz, 8-H), 9.74 (1H, d, *J* = 9.6 Hz, 4-H); MS: *m/z* 373 (M^+). *Anal.* Calcd for $C_{21}H_{15}N_3O_4$: C, 67.56; H, 4.05; N, 11.25. Found: C, 67.69; H, 4.23; N, 11.43.

Methyl 1-Acetylazulene-3-carboxylate Phenylhydrazone (6).

A mixed solution of methyl 1-acetylazulene-3-carboxylate (**1**) (57 mg, 0.25 mmol) and phenylhydrazine hydrochloride (72 mg, 0.50 mmol) in ethanol (20 mL) was refluxed for 4 h. After removal of the solvent, the residue was chromatographed on a silica gel column with benzene to afford methyl 1-acetylazulene-3-carboxylate phenylhydrazone (**6**) as bluish green crystals (from benzene); yield 60 mg (76%), mp 114-116 ºC; IR (KBr): ν 3415 (NH), 1693 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.73 (3H, s, CH_3),

3.97 (3H, s, CO_2CH_3), 7.41-7.46 (5H, m, Ar-H), 7.79-7.85, m, 6-H + 5- or 7-H), 8.02 (1H, dd, *J* = 9.6, 9.6 Hz, 5- or 7-H), 8.80 (1H, s, 2-H), 9.82 (1H, d, *J* = 9.6 Hz, 8-H), 10.04 (1H, d, *J* = 9.6 Hz, 4-H); MS: *m/z* 318 (M^+). *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.39; H, 5.63; N, 8.71.

Reaction of the Phenylhydrazone (6) with DMFDMA.

A mixture of the phenylhydrazone (**6**) (63 mg, 0.20 mmol) and DMFDMA (39 mg, 0.30 mmol) in DMF (20 mL) was heated under refluxing for 4 h. The removal of the solvent under reduced pressure and the residue was chromatographed on a silica gel column with benzene to afford the product (**5b**), yield 51 mg (78%), mp 120-121 ºC.

REFERENCES

1. F. Al-Omran, M. M. Abdel Khalik, A. Abou-Khair, and M. H. Elnagdi, *Synthesis*, 1997, 91.
2. K. M. Al-Zaydi and E. A. Hafez, *J. Chem. Res. (S),* 1999, 360; *J. Chem. Res. (M),* 1999, 1621.
3. A. A. Al-Naggar, M. M. Abdel Khalik, and M. H. Elnagdi, *J. Chem. Res. (S),* 1999, 648; *J. Chem. Res. (M),* 1999, 2801.
4. B. Al-Saleh, N. A. Al-Awedi, H. Al-Kandari, M. M. Abdel Khalik, and M. H. Elnagdi, *J. Chem. Res. (S),* 2000, 16; *J. Chem. Res. (M),* 2000, 201.
5. a) T. Yanagisawa, S. Wakabayashi, T. Tomiyama, M. Yasunami, and K. Takase, *Chem. Pharm. Bull.,* 1988, **36**, 641. b) T. Yanagisawa, K. Kosakai, T. Tomiyama, and M. Yasunami, *Chem. Pharm. Bull.*, 1990, **38**, 3355. c) T. Yanagisawa, K. Kosakai, C. Izawa, T. Tomiyama, and M. Yasunami, *Chem. Pharm. Bull.*, 1991, **39**, 2429.
6. D.-L. Wang and K. Imafuku, *J. Heterocycl. Chem.*, 2002, **37**, 1019.
7. T. Mori, K. Imafuku, M.-Z. Piao, and K. Fujimori, *J. Heterrocycl. Chem.*, 1996, **33**, 841.
8. S. Yamashiro and K. Imafuku, *J. Heterocycl. Chem.*, 2002, **39**, 359.
9. Y. Miyashita, S. Kikuchi, and K. Imafuku, *Heterocycles*, 2003, **59**, 359.
10. H. Takao, D.-L. Wang, S. Kikuchi, and K. Imafuku, *J. Heterocycl. Chem.*, 2004, **41**, 723.
11. T. Amemiya, M. Yasunami, and K. Takase, *Chem. Lett.*, 1977, 587.