Convenient Synthesis of 4-Methoxy-3-nitro-1,2-benzenediamine and its Conversion into 6-Methoxy-5-nitroquinoxalines

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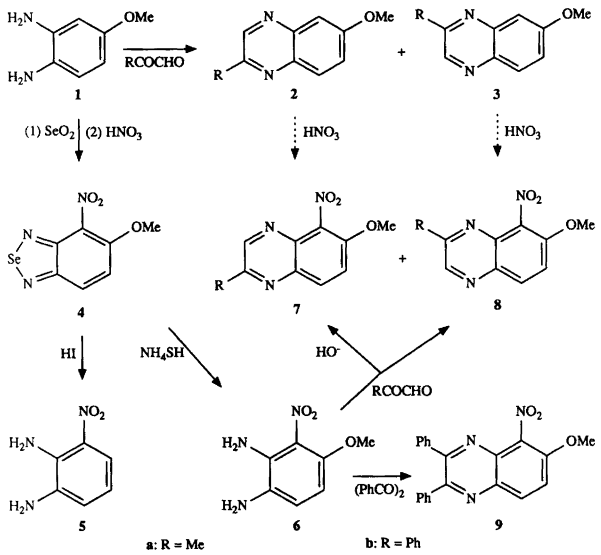
4-Methoxy-3-nitro-1,2-benzenediamine (**6**) has been prepared through nitration of 5-methoxy-2,1,3-benzoselenadiazole, followed by reductive removal of the selenium. Cyclocondensation of **6** with α-dicarbonyl compounds afforded the title quinoxalines, some of them novel and not easily obtainable by direct nitration. Methyl- or phenylglyoxal gave mixtures of quinoxalines in proportions strongly influenced by the acidity of the reaction medium.

The 2,1,3-benzoselenadiazole system has been successfully used in the synthesis of a number of elusive quinoxalines[1–5] and benzimidazoles[6] in this laboratory. Continuing our synthetic work with 2,1,3-benzoselenadiazoles and quinoxalines leading to food carcinogens, we report herein a simple route to 4-methoxy-3-nitro-1,2-benzenediamine (**6**, Scheme 1) and a convenient route to the title quinoxalines **7–11**. Some of these compounds are novel and not otherwise readily obtainable.

Unlike quinoxaline, which is inert towards nitration, quinoxalines substituted at the homocyclic ring with an electron-releasing group can be nitrated. For instance, 6-methoxyquinoxaline affords the 5-nitro derivative when treated with potassium nitrate and sulfuric acid at room temperature.[7,8] However, nitration of quinoxalines bearing an amino and/or an alkyl group can also lead to undesired by-products, as in the case of 2,6-dimethyl-7-methylamino- and 2,7-dimethyl-6-methylaminoquinoxaline.[9] Moreover, quinoxalines fused or attached to a nitration-susceptible ring system, are difficult, if not impossible, to nitrate exclusively *ortho* to the activating substituent. Indeed, with potassium nitrate in sulfuric acid at 0–20 °C, 9-methoxyacenaphtheno[1,2-*b*]quinoxaline[10] gave a mixture containing only a small amount of the 8-nitro derivative (**10**), as shown by the ^{1}H NMR spectrum of the crude product. Further, in the nitration of the randomly chosen 6-methoxy-2-phenylquinoxaline (**2b**, Scheme 1) under the same conditions, no 5-nitro derivative (**7b**) was formed, as indicated by the absence of the characteristic singlet at δ 9.36 due to the 3-H proton. Therefore, it is desirable to introduce the nitro substituent at some earlier stage of the synthetic sequence.[1] Thus, a convenient synthesis of 4-methoxy-3-nitro-1,2-benzenediamine (**6**) would facilitate or even render possible, the preparation of such quinoxalines and other heterocycles, circumventing the difficulties encountered on nitration.

Results and discussion

Diamine **6** has been synthesized previously from *p*-anisidine through 4-methoxy-2,3-dinitroaniline in five steps.[11] However, the catalytic reduction of commercial 4-methoxy-2-nitroaniline affords 4-methoxy-1,2-benzenediamine (**1**), an ideal starting material for the convenient synthesis of **6**, see Scheme 1. The efficient ring closure of **1** with selenium dioxide, followed by nitration at room temperature, afforded the unknown 5-methoxy-4-nitro-2,1,3-benzoselenadiazole (**4**) in high yield. Previously, 57 %



Scheme 1. Synthesis of 4-methoxy-3-nitro-1,2-benzenediamine (**6**) and its conversion into 6-methoxy-5-nitroquinoxalines (**7–9**).

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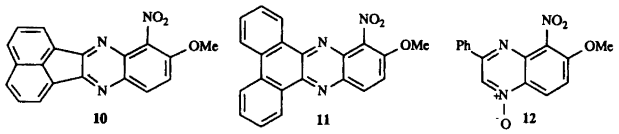

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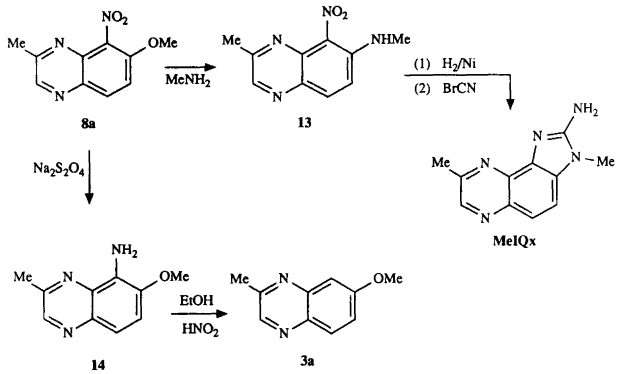
hydriodic acid or ammonium sulfide has been employed for the removal of selenium from 4-nitro-2,1,3-benzoselenadiazoles, without affecting the nitro group.[1-6,12] However, reductive ring opening of **4** with hydriodic acid afforded the unexpected product 3-nitro-1,2-benzenediamine (**5**) in good yield. Use of ammonium sulfide did not affect the methoxy group in any way and efficiently afforded the desired diamine **6** in 74 % isolated yield.

Reflux of diamine **6** in methanol, catalysed by acid, readily afforded **9**, **10** and **11** with benzil, 1,2-acenaphthenequinone and 9,10-phenanthrenequinone, respectively. Condensation of **6** with methyl- or phenyl-glyoxal in methanol gave a mixture of the corresponding novel quinoxalines **7** and **8**. In accordance with our recent results on the selective condensation of the 4-bromo or 4-chloro analogue of **6** with methylglyoxal,[3] isomer **7** was the major (80 %) product formed in the presence of base (KOH). Under acidic (HCl) or neutral conditions the major (90 %) regioisomer was **8**. This dramatic influence of the nitro substituent on the nucleophilicity of the two amino groups is also demonstrated by comparing the above results with those obtained from the condensation of **1** with methylglyoxal. The isomers **2a** and **3a** were formed in a 3:2 ratio under acidic conditions, and in a 1:3 ratio under neutral or basic conditions. Similarly, Loriga *et al.*[13] found that condensation of **1** with phenylglyoxal afforded **2b** and **3b** in an almost 1:1 ratio under acidic conditions, and in a ratio of 1:8 under neutral conditions.

In order to distinguish unambiguously between **7a** and **8a**, we heated the isomer believed to be **8a** with an excess of methylamine. Previous[14] experiments, which were performed in aqueous alcoholic solution, led to no reaction, but with 2-ethoxyethanol (b.p. 135 °C) as the solvent, the methoxy group was displaced readily. The product was the known[14] 2-methyl-7-methylamino-8-nitroquinoxaline (**13**, Scheme 2) rather than its 6-methylamino-5-nitro isomer.



Scheme 2. Reactions of 7-methoxy-2-methyl-8-nitroquinoxaline (**8a**) used for structure determination and for synthesis of the food mutagen MeIQx.

Isomers **2a** and **3a** were distinguished by the fact that **3a** was obtained exclusively from **8a** via the amine **14** (Scheme 2). Isomers **7b** and **8b** were distinguished on the basis of our previous results from the condensation of 3-nitro-1,2-benzenediamines under neutral or acidic conditions,[1-3] and by analogy with the structure assignment based on the chemical shift of the pyrazine singlet.[14] Confirmation was obtained by conversion of the isomer believed to be **8b** into its mono-*N*-oxide. The oxide function is known to shield an *ortho* proton and to deshield a *peri* proton.[15-17] Since its ^{1}H NMR spectrum clearly showed both these effects, the *N*-oxide must have the structure **12**. Hence, the oxidized isomer was, indeed, **8b**. Alternatively, isomeric quinoxalines can be distinguished by their proton-coupled ^{13}C NMR spectra.[3]

Owing to its smooth reaction with methylamine, **8a** is an alternative synthetic precursor of the food carcinogen 2-amino-3,8-dimethyl-1*H*-imidazo[4,5-*f*]quinoxaline (MeIQx,[18] Scheme 2), a compound found in cooked proteinaceous foods[19] and model reaction systems.[20] Similar displacements of the methoxy group in **7–11** could be used in the syntheses of other heterocyclic compounds.

In conclusion, an improved synthesis of the diamine **6**, from the commercially available 4-methoxy-2-nitroaniline through the novel benzoselenadiazole **4**, is reported. The quinoxalines **9–11**, which are difficult to obtain by nitration, were readily prepared by reaction of **6** with benzil, 1,2-acenaphthenequinone and 9,10-phenanthrenequinone, respectively. Regioselective condensation of **6** with methyl- and phenyl-glyoxal, under different pH conditions affords efficiently the novel isomeric quinoxalines **7** and **8**. Quinoxaline **8a** offers an alternative intermediate for the synthesis of the food carcinogen MeIQx.

Experimental

General. Melting points are corrected and were determined on a Mettler FP62 instrument. The ^{1}H NMR spectra were obtained on a Varian VXR-400 spectrometer at 20 °C and referenced to the solvent [δ($CHCl_3$) 7.26]. The mass spectra (70 eV, direct insertion) were obtained on a Finnigan 4021 instrument with electron impact ionization and an ion source temperature of 250 °C. Flash liquid chromatography (FC) was performed on silica gel (230–400 mesh ASTM, Merck). All reactions and purifications were monitored by TLC (UV detection) on aluminium sheets coated with silica gel 60 F_{254} (Merck).

Condensation of **1** *with methylglyoxal.* A mixture of commercial 4-methoxy-2-nitroaniline (1.68 g, 10 mmol), Raney nickel (one teaspoonful) and ethanol (50 ml) was hydrogenated under ambient conditions with vigorous stirring. The reaction was complete after ca. 1 h, TLC: CH_2Cl_2–EtOAc 1:1 v/v. The catalyst was filtered off, and the resulting solution of **1** was treated with methylglyoxal as described below for the preparation of **7a** and **8a** from **6**. One half of the solution was treated under acidic conditions and

the other half under basic conditions. The separation of **2a** from **3a** by FC was not successful. The ^{1}H NMR spectrum of the mixture was therefore compared with that of **3a**, obtained from **14**. In that way, the following spectrum of 6-methoxy-2-methylquinoxaline (**2a**) was deduced. ^{1}H NMR ($CDCl_3$): δ 2.73 (3 H, s), 3.96 (3 H, s), 7.35 (1 H, d, *J* 2.7 Hz), 7.39 (1 H, dd, *J* 2.7 and 9.1 Hz), 7.87 (1 H, d, *J* 9.2 Hz), 8.66 (1 H, s).

5-Methoxy-4-nitro-2,1,3-benzoselenadiazole (**4**). A mixture of 4-methoxy-2-nitroaniline (20 g, 119 mmol) and Raney nickel (2 teaspoonsful) in ethanol (300 ml) was hydrogenated under ambient conditions with vigorous stirring until the orange colour faded, TLC: CH_2Cl_2–EtOAc, 1:1 v/v. The catalyst was filtered off, and to the filtrate was added a 15% w/v aqueous solution (90 ml) of selenium dioxide (122 mmol) with stirring. The precipitated pale product (20 g) was combined with a further amount (2.3 g) obtained after concentration of the filtrate. Recrystallization (ethanol) gave pure 5-methoxy-2,1,3-benzoselenadiazole as white crystals (21 g, 82 %), m.p. 109–111 °C (lit.[21] 110–111 °C). This product (20 g, 93 mmol) was dissolved in conc. sulfuric acid (80 ml) and cooled in an ice–water bath. A cold mixture of fuming nitric acid (7 ml, 167 mmol) and conc. sulfuric acid (24 ml) was added dropwise to the solution. The reaction mixture was allowed to stand at room temperature for 1 h and was then poured onto ice, TLC: CH_2Cl_2–EtOAc, 1:1 v/v. The precipitated product was collected and recrystallized (acetic acid) to give pure **4** as pale yellow needles (21 g, 87 %), m.p. 239–241 °C. ^{1}H NMR ($CDCl_3$): δ 4.13 (3 H, s), 7.56 (1 H, d, *J* 9.8 Hz), 8.00 (1 H, d, *J* 9.9 Hz). MS, *m/z* (rel. int.): 259 (5, *M*), 229 (4), 212 (2), 201 (2), 121 (14), 80 (100). Anal. $C_7H_5N_3O_3Se$: C, H, N.

3-Nitro-1,2-benzenediamine (**5**). A mixture of **4** (100 mg, 0.39 mmol), 37 % hydrochloric acid (6 ml) and 57 % hydriodic acid (2 ml, 15 mmol) was stirred at room temperature for 2 h, TLC: CH_2Cl_2–EtOAc, 1:1 v/v. To the dark reaction mixture was added a 10 % sodium hydrogen sulfite solution (5 ml) and the mixture was warmed to 80 °C. This was filtered whilst hot and the filtrate was allowed to cool to 4 °C. The yellow needle-like hydrochloride was collected and washed with 1 M hydrochloric acid. Crystallization from ethanolic ammonia afforded the pure diamine (45 mg, 76 %), m.p. 158–159 °C, undepressed on admixture with a commercial sample.

4-Methoxy-3-nitro-1,2-benzenediamine (**6**). Compound **4** (15 g, 58 mmol) in methanol (250 ml) and a 40 % aq. ammonium sulfide solution (50 ml, 370 mmol) was refluxed for 2 h with efficient stirring, TLC: CH_2Cl_2–EtOAc, 1:1 v/v. The dark red mixture was filtered whilst hot and then diluted with water (50 ml). This was concentrated to ca. 80 ml under vacuum. On cooling, **6** was obtained as dark red crystals (7.7 g, 74 %), m.p. 117–119 °C (lit.[11] 116–117 °C). ^{1}H NMR ($CDCl_3$): δ 3.1 (2 H, br s), 3.83 (3 H, s), 4.9 (2 H, br s), 6.22 (1 H, d, *J* 8.6 Hz), 6.80 (1 H, d, *J* 8.6 Hz). MS, *m/z* (rel. int.): 183 (100, *M*), 167 (6), 166 (33), 165 (14), 150 (36), 135 (23), 134 (5), 120 (28).

Preparation of **7** *and* **8**. *Acidic conditions.* A mixture of **6** (400 mg, 2.2 mmol), phenylglyoxal or 40 % aq. methylglyoxal (2.2 mmol), and 5 M hydrochloric acid (1 ml) was refluxed in methanol (65 ml) for 10 min, TLC: CH_2Cl_2. The reaction mixture was poured into ice–water (50 ml) and the precipitate was filtered off. The filtrate was neutralized ($NaHCO_3$) and extracted with chloroform. The extract was evaporated. FC of the residue separated the isomeric quinoxalines: **7a**, R_f 0.62 and **8a**, R_f 0.56 (CH_2Cl_2–EtOAc, 8:1 v/v); **7b**, R_f 0.47 and **8b**, R_f 0.18 (light petroleum ether–EtOAc, 5:3 v/v). Each isomer was recrystallized from methanol to give pure **7a** (19 mg, 4 %), **8a** (294 mg, 61 %), **7b** (20 mg, 3 %) and **8b** (360 mg, 58 %).

Basic conditions. A hot solution of potassium hydroxide (125 mg, 2.2 mmol) in methanol (5 ml) was added to a hot solution of **6** (400 mg, 2.2 mmol) in methanol (50 ml). To the mixture, a solution of phenylglyoxal or 40 % aqueous methylglyoxal (2.2 mmol) in methanol (3 ml) was added immediately after the addition of the base and the mixture was refluxed for 5–10 min, TLC: CH_2Cl_2. The products were precipitated by addition of water (20 ml) and separated as described in the preceding paragraph: **7a** (271 mg, 56 %), **8a** (52 mg, 11 %), **7b** (365 mg, 59 %) and **8b** (74 mg, 12 %).

6-Methoxy-2-methyl-5-nitroquinoxaline (**7a**). M.p. 170.5–171.5 °C. ^{1}H NMR ($CDCl_3$): δ 2.78 (3 H, s), 4.09 (3 H, s), 7.60 (1 H, d, *J* 9.7 Hz), 8.14 (1 H, d, *J* 9.5 Hz), 8.77 (1 H, s). MS, *m/z* (rel. int.): 219 (95, *M*), 189 (28), 161 (39), 158 (23), 143 (47), 75 (100). Anal. $C_{10}H_9N_3O_3$: C, H, N.

7-Methoxy-2-methyl-8-nitroquinoxaline (**8a**). M.p. 191–192 °C. ^{1}H NMR ($CDCl_3$): δ 2.77 (3 H, s), 4.09 (3 H, s), 7.54 (1 H, d, *J* 9.5 Hz), 8.18 (1 H, d, *J* 9.4 Hz), 8.68 (1 H, s). MS, *m/z* (rel. int.): 219 (75, *M*), 189 (28), 161 (25), 158 (16), 143 (34), 43 (100). Anal. $C_{10}H_9N_3O_3$: C, H, N.

6-Methoxy-5-nitro-2-phenylquinoxaline (**7b**). M.p. 207–208 °C, ^{1}H NMR ($CDCl_3$): δ 4.13 (3 H, s), 7.5–7.6 (3 H, m), 7.65 (1 H, d, *J* 9.6 Hz), 8.1–8.2 (2 H, m), 8.28 (1 H, d, *J* 9.5 Hz), 9.36 (1 H, s). MS, *m/z* (rel. int.): 281 (34, *M*), 251 (4), 235 (1), 223 (12), 220 (4), 205 (15), 75 (100). Anal: $C_{15}H_{11}N_3O_3$: C, H, N.

7-Methoxy-8-nitro-2-phenylquinoxaline (**8b**). M.p. 191–192 °C, ^{1}H NMR ($CDCl_3$): δ 4.13 (3 H, s), 7.50–7.56 (3 H, m), 7.58 (1 H, d, *J* 9.4 Hz), 8.2–8.3 (2 H, m), 8.23 (1 H, d, *J* 9.3 Hz), 9.32 (1 H, s). MS, *m/z* (rel. int.): 281 (33, *M*), 251 (10), 235 (1), 223 (7), 220 (4), 205 (8), 77 (100). Anal: $C_{15}H_{11}N_3O_3$: C, H, N.

6-Methoxy-5-nitro-2,3-diphenylquinoxaline (**9**). A mixture of **6** (400 mg, 2.2 mmol), benzil (462 mg, 2.2 mmol) and

5 M hydrochloric acid (1 ml) in ethanol (50 ml) was refluxed for 40 min, TLC: CH_2Cl_2–EtOAc, 1:1 v/v. The mixture was poured into ice–water (50 ml) and the precipitate was collected and purified by FC ($CHCl_3$). Recrystallization (ethanol–toluene, 1:1 v/v) gave pure **9** as yellow crystals (660 mg, 84 %), m.p. 215–216 °C (lit.[11] 216–217 °C). ^{1}H NMR ($CDCl_3$): δ 4.13 (3 H, s), 7.27–7.56 (10 H, m), 7.61 (1 H, d, *J* 9.5 Hz), 8.27 (1 H, d, *J* 9.4 Hz). MS, *m/z* (rel. int.): 357 (17, *M*), 309 (6), 281 (5), 280 (3), 178 (9), 105 (100).

9-Methoxy-8-nitroacenaphtheno[1,2-b]quinoxaline (**10**) was prepared as for **9** but from **6** and 1,2-acenaphthenequinone. Yield 85 %, m.p. 275 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ 4.13 (3 H, s), 7.57 (1 H, d, *J* 9.4 Hz), 7.86 (2 H, dd, *J* 8.2 and 7.1 Hz), 8.14 (1 H, d, *J* 8.2 Hz), 8.16 (1 H, d, *J* 8.2 Hz), 8.31 (1 H, d, *J* 9.4 Hz), 8.39 (1 H, d, *J* 7.0 Hz), 8.44 (1 H, d, *J* 7.0 Hz). MS, *m/z* (rel. int.): 329 (100, *M*), 299 (10), 283 (4), 271 (21), 268 (10), 253 (71). Anal. $C_{19}H_{11}N_3O_3$: C, H, N.

11-Methoxy-10-nitrodibenzo[a,c]*phenazine* (**11**) was prepared as for **9** but from **6** and 9,10-phenanthrenequinone. Yield 74 %, m.p. 139–140 °C. ^{1}H NMR ($CDCl_3$): δ 4.19 (3 H, s), 7.7–7.8 (2 H, m), 7.73 (1 H, d, *J* 10.4 Hz), 7.8–7.9 (2 H, m), 8.43 (1 H, d, *J* 10.1 Hz), 8.55 (2 H, t, *J* 9.5 Hz), 9.30 (2 H, t, *J* 9.4 Hz). MS, *m/z* (rel. int.): 355 (100, *M*), 325 (6), 309 (3), 297 (11), 279 (64), 266 (11). Anal. $C_{21}H_{13}N_3O_3$: C, H, N.

6-Methoxy-5-nitro-3-phenylquinoxaline 1-oxide (**12**). To a hot solution of **8b** (71 mg, 0.25 mmol) in glacial acetic acid (2 ml) was added a 30 % hydrogen peroxide solution (1 ml). The mixture was kept at 80 °C for 3 h, TLC: CH_2Cl_2–EtOAc, 5:1 v/v. On cooling, the product precipitated as pale yellow crystals which were filtered and washed with cold water. Recrystallization (acetic acid) gave pure **12** (61 mg, 81 %), m.p. 264–265 °C. ^{1}H NMR ($CDCl_3$): δ 4.13 (3 H, s), 7.51 (1 H, d, *J* 9.7 Hz), 7.5–7.6 (3 H, m), 8.08 (2 H, m), 8.67 (1 H, d, *J* 9.7 Hz), 8.81 (1 H, s). MS, *m/z* (rel. int.): 297 (28, *M*), 281 (4), 267 (7), 251 (1), 239 (1), 105 (26), 77 (53), 44 (100). Anal. $C_{15}H_{11}N_3O_4$: C, H, N.

2-Methyl-7-methylamino-8-nitroquinoxaline (**13**). The compound was obtained by refluxing **8a** with an excess of 40 % aq. methylamine in 2-ethoxyethanol as described for 5-chloro-7-methyl-4-nitro-2,1,3-benzoselenadiazole.[2] Yield 81 %, m.p. 187–188 °C (lit.[14] 187.5–188.5 °C).

8-Amino-7-methoxy-2-methylquinoxaline (**14**). A mixture of **8a** (110 mg, 0.5 mmol) and sodium dithionite (400 mg, 2.5 mmol) in methanol (25 ml) and water (3 ml) was refluxed for 1 h, TLC: CH_2Cl_2–EtOAc, 5:1 v/v. The whole mixture was concentrated to ca. 3 ml. The yellow crystals were collected by filtration and washed with water. Pure **14** (88 mg, 93 %) was obtained by recrystallization (H_2O–MeOH, 8:1 v/v), m.p. 103–104 °C. ^{1}H NMR ($CDCl_3$): δ 2.72 (3 H, s), 4.00 (3 H, s), 7.38 (1 H, d, *J* 9.1 Hz), 7.43 (1 H, d, *J* 9.1 Hz), 8.58 (1 H, s). MS, *m/z* (rel. int.): 189 (59, *M*), 174 (100), 158 (1), 146 (64). Anal: $C_{10}H_{11}N_3O$: C, H, N.

7-Methoxy-2-methylquinoxaline (**3a**). To a solution of **14** (10 mg, 0.05 mmol) in ethanol (0.5 ml) and conc. sulfuric acid (0.2 ml) was added sodium nitrite (7 mg, 0.1 mmol) while the solution was kept cold in an ice bath. After the addition, the mixture was removed from the ice bath and warmed gently in a 60 °C water bath for about 10 min. On cooling, the mixture was neutralized with ammonia and extracted with chloroform. Purification by FC (CH_2Cl_2–EtOAc, 5:1 v/v) gave pure **3a** (6 mg, 67 %), m.p. 69–70 °C. ^{1}H NMR ($CDCl_3$): δ 2.74 (3 H, s), 3.96 (3 H, s), 7.31 (1 H, d, *J* 2.8 Hz), 7.34 (1 H, dd, *J* 2.7 and 9.0 Hz), 7.93 (1 H, d, *J* 9.2 Hz), 8.59 (1 H, s). MS, *m/z* (rel. int.): 174 (100, *M*), 159 (3), 143 (1), 131 (20), 117 (25), 106 (74). Anal: $C_{10}H_{10}N_2O$: C, H, N.

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