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PREPARATION OF 7-SUBSTITUTED 4,5-DIHYDRO-7*H*-PYRANO[3,4-*c*]-ISOXAZOLE DERIVATIVES [1]

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Abstract — An easy approach to 7-substituted 4,5-dihydro-7*H*-pyrano[3,4-*c*]-isoxazole derivatives (**3a**-**b** and **6a**-**d**) is described by the reaction of 2-aryl substituted 1-nitro-3-oxa-6-heptynes (**2**, **5a** and **5b**) with *n*-BuLi, followed by treatment with acetic anhydride.

In the previous communication,[2] we reported the preparation of 7-(1-methoxyindol-3-yl)-4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazole (**3a**) in 48% yield by treatment of 2-(1-methoxyindol-3-yl)-1-nitro-3-oxa-6-heptyne[3] (**2**) with *n*-BuLi (1 molar eq.) at –18 °C, followed by quenching with a proton source at the same reaction temperature. As a proton source, aq. AcOH should have been used based on the observations that the quenching of the above reaction either with H_2O or aq. NH_4Cl caused partly retro-Michael reaction of unreacted **2** to give nitro-vinyl compound (**1**).

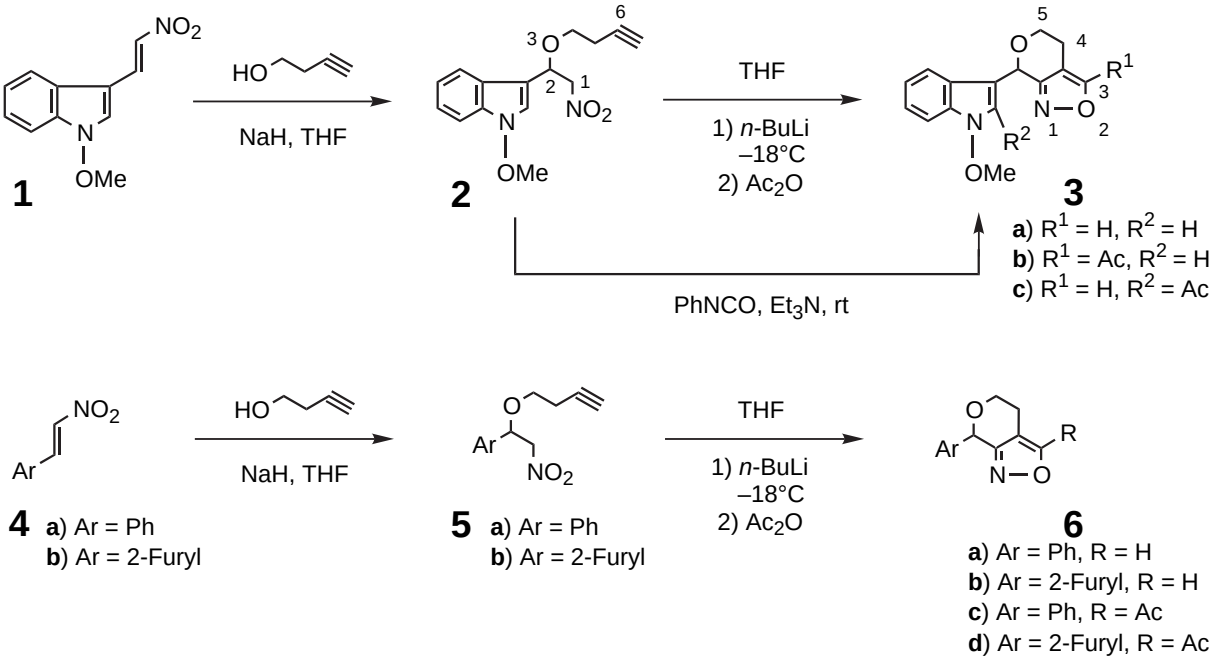
We attempted to extend the above reaction to 2-aryl substituted 1-nitro-3-oxa-6-heptynes (**5a** and **5b**), prepared by the Michael addition reaction of sodium 3-butyn-1-oxide to **4a** and **4b**, respectively. Soon, we found that the reactions of **5a** and **5b** with *n*-BuLi (1 molar eq.) at –18 °C, followed by treatment with aq. AcOH, provided neither **6a** nor **6b**. Therefore, we repeated many times the above reaction of **2** with *n*-BuLi, followed by quenching with aq. AcOH, *in vain*. The results were recovery of **2** and no formation of **3a** was observed. Finally, we were convinced of the mistake that, to our regret, Ac_2O had been used instead of AcOH.

By employing one molar eq. of *n*-BuLi and Ac_2O as a trapping reagent of the resultant lithiated species, the transformation of **2** to **3a** was reproduced in 37% yield, almost the same yield as the reported one (48%).[2] When 2 molar eq. of *n*-BuLi was used, new product (**3b**) was formed together with **3a** in 8 and 45% yields, respectively. In the case of using 3 molar eq. of *n*-BuLi, yield of **3b** increased to 21%, while the yield of **3a** decreased to 15% in addition to tar formation. Under similar reaction conditions using one molar eq. of *n*-BuLi, **5a** and **5b** produced **6a**[4] and **6b** in 40 and 46% yields, respectively. In these cases, the use of excess amount of *n*-BuLi provided **6c** or **6d** as a by-product together with **6a** or **6b**.

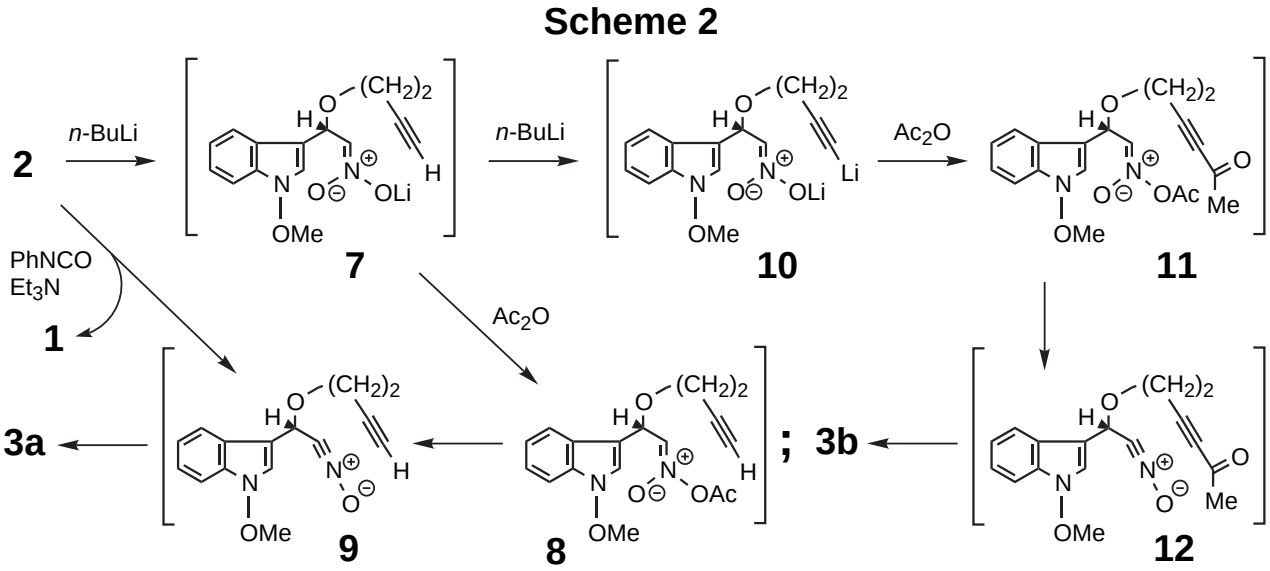
The structure of **3a** was confirmed by the direct comparison with the authentic product (**3a**), obtained in 62% yield by the reaction of **2** with phenyl isocyanate (2 mol eq.) in the presence of NEt_3 at room temperature for 3 days, which is a well known 1,3-dipolar cycloaddition reaction of nitrile oxide.[5] Under the reaction conditions, however, **2** is prone to undergo retro-Michael reaction. As a result, concomitant formations of 25% yield of **1** and products originated from phenyl isocyanate were observed and this was what made the purification of **3a** not simple. The possibility that **3b** has a structure of **3c**

was eliminated based on the disappearance of the C3-proton (1H, t, J=1.2 Hz) coupled with C4-methylene protons, which is observed in the ^{1}H-NMR spectrum of **3a**.

Scheme 1



Scheme 2



A trial to obtain **3b** by the treatment of **3a** with *n*-BuLi, followed by quenching with aq. Ac_2O, ended in failure resulting in the quantitative recovery of **3a**. These results suggest a reaction mechanism as shown in Scheme 2. The nitronate (**7**), formed by the action of *n*-BuLi, reacts with Ac_2O to generate **9** through **8**. Subsequent 1,3-dipolar cycloaddition reaction of nitrile oxide (**9**) provides **3a**. In the presence of excess *n*-BuLi, **7** would generate dianion (**10**), which would be trapped with Ac_2O to give **12** through **11**. 1,3-Dipolar cycloaddition of nitrile oxide to the resultant acetylated acetylene part would afford **3b**.

As for the yield of **3a**, phenyl isocyanate-Et_3N method is better than the present *n*-BuLi method. But the former requires longer reaction time at room temperature and separation of the product is not simple particularly when substrates are sensitive to mild base to undergo retro-Michael reaction. In contrast, the latter *n*-BuLi method proceeds rapidly at –18°C within 20 min and the purification of product is easy due to the lack of retro-Michael reaction. What is better, it has probability for becoming a suitable preparation method for the pharmacologically interesting 3-acylated 4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazole derivatives by employing appropriate acylating reagents. Studies along this line are in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.).

2-(1-Methoxyindol-3-yl)-1-nitro-3-oxa-6-heptyne (2) from 1 — 3-Butyn-1-ol (0.36 mL, 4.76 mmol) was added to a suspension of NaH (54.1 mg, 60% dispersion in oil, 1.35 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred for 10 min at 0 °C. To the resulting mixture, a solution of **1** (51.5 mg, 0.24 mmol) in anhydrous THF (1.5 mL) was added and the mixture was stirred for 10 min at 0 °C. After addition of AcOH (0.07 mL, 1.22 mmol), the whole was filtered through SiO_2, and the pad was rinsed with AcOEt. The filtrate was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:10, v/v) to give **2** (63.9 mg, 95%). **2**: pale yellow viscous oil. IR (film): 3292, 2119, 1558, 1379, 1362, 1103, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.93 (1H, t, *J*=2.7 Hz), 2.37—2.49 (2H, m), 3.52 (1H, ddd, *J*=9.3, 7.5, 6.4 Hz), 3.61 (1H, dt, *J*=9.3, 7.1 Hz), 4.11 (3H, s), 4.52 (1H, dd, *J*=12.9, 3.7 Hz), 4.88 (1H, dd, *J*=12.9, 10.0 Hz), 5.40 (1H, dd, *J*=10.0, 3.7 Hz), 7.17 (1H, dd, *J*=8.1, 7.1 Hz), 7.30 (1H, dd, *J*=8.1, 7.1 Hz), 7.35 (1H, s), 7.46 (1H, d, *J*=8.1 Hz), 7.71 (1H, d, *J*=8.1 Hz). HR-MS *m/z:* Calcd for $C_{15}H_{16}N_2O_4$: 288.1110. Found: 288.1110.

4,5-Dihydro-7-(1-methoxyindol-3-yl)-7*H*-pyrano[3,4-*c*]isoxazole (3a) from 2 —

1) ***n*-BuLi method** — *n*-BuLi (0.50 mL, 1.56 M solution in hexane, 0.78 mmol) was added to a solution of **2** (209.7 mg, 0.73 mmol) in anhydrous THF (10 mL) with stirring at –18 °C under nitrogen atmosphere. After stirring for 10 min at –18 °C, Ac_2O (0.08 mL, 0.85 mmol) was added and the mixture was stirred for an additional 10 min at –18 °C. After addition of brine, the whole was extracted with AcOEt. The extract was dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:5, v/v) to give unreacted **2** (78.0 mg, 37%) and **3a** (72.9 mg, 37%) in the order of elution. **3a**: pale yellow viscous oil. IR (film): 2937, 2861, 1612, 1452, 1439, 1097, 1054, 955, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 2.76—2.86 (2H, m), 3.84 (1H, ddd, *J*=11.7, 7.1, 5.1 Hz), 4.07 (3H, s), 4.04—4.09 (1H, m), 6.20 (1H, br s), 7.13 (1H, ddd,

J=8.1, 7.1, 1.0 Hz), 7.26 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.30 (1H, d, *J*=0.7 Hz), 7.42 (1H, dt, *J*=8.1, 1.0 Hz), 7.65 (1H, dt, *J*=8.1, 1.0 Hz), 8.28 (1H, t, *J*=1.2 Hz). HR-MS *m/z:* Calcd for $C_{15}H_{14}N_2O_3$: 270.1004. Found: 270.1003.

2) **Phenyl isocyanate method** — A mixture of **2** (202.9 mg, 0.71 mmol), Et_3N (0.20 mL, 1.44 mmol) and phenyl isocyanate (0.16 mL, 1.47 mmol) in anhydrous THF (10 mL) was stirred at rt for 3 days under nitrogen atmosphere. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed repeatedly on SiO_2 succesively with $CHCl_3$–hexane (1:2, v/v) and AcOEt–hexane (1:5, v/v) to give **1** (39.0 mg, 25%) and **3a** (117.4 mg, 62%) in the order of elution.

3-Acetyl-4,5-dihydro-7-(1-methoxyindol-3-yl)-7*H*-pyrano[3,4-*c*]isoxazole (3b) and 3a from 2 — *n*-BuLi (0.95 mL, 1.56 M solution in hexane, 1.48 mmol) was added to a solution of **2** (203.9 mg, 0.71 mmol) in anhydrous THF (10 mL) with stirring at –18°C under nitrogen atmosphere. After stirring for 10 min at –18°C, Ac_2O (0.14 mL, 1.48 mmol) was added and the mixture was stirred for an additional 10 min at –18°C. After addition of brine, the whole was extracted with AcOEt. The extract was dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:5, v/v) to give unreacted **2** (31.0 mg, 15%), **3b** (17.4 mg, 8%) and **3a** (85.6 mg, 45%) in the order of elution. **3b**: pale yellow viscous oil. IR (film): 2939, 1695, 1616, 1454, 1362, 1269 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.64 (3H, s), 3.02 (2H, t, *J*=5.9 Hz), 3.84 (1H, dt, *J*=11.7, 5.9 Hz), 4.06 (1H, dt, *J*=11.7, 5.9 Hz), 4.08 (3H, s), 6.19 (1H, br s), 7.13 (1H, ddd, *J*=8.3, 7.1, 1.0 Hz), 7.27 (1H, s), 7.27 (1H,ddd, *J*=8.3, 7.1, 1.0 Hz), 7.43 (1H, dt, *J*=8.3, 1.0 Hz), 7.63 (1H, dt, *J*=8.3, 1.0 Hz). HR-MS *m/z:* Calcd for $C_{17}H_{16}N_2O_4$: 312.1110. Found: 312.1106.

1-Nitro-3-oxa-2-phenyl-6-heptyne (5a) from 4a — In the same procedure as described for the preparation of **2**, 3-butyn-1-ol (1.6 mL, 21.2 mmol), NaH (208.6 mg, 60% dispersion in oil, 5.22 mmol) in anhydrous THF (5 mL), and a solution of **4a** (157.1 mg, 1.05 mmol) in anhydrous THF (5 mL) were used. After the same work-up using AcOH (0.3 mL, 5.25 mmol) and column-chromatography, **5a** (227.9 mg, 99%) was obtained. **5a**: colorless viscous oil. IR (film): 3294, 2922, 2879, 2121, 1558, 1381, 1109 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.95 (1H, t, *J*=2.7 Hz), 2.38—2.49 (2H, m), 3.48 (1H, ddd, *J*=9.0, 7.1, 6.4 Hz), 3.54 (1H, dt, *J*=9.0, 7.1 Hz), 4.39 (1H, dd, *J*=12.9, 3.4 Hz), 4.63 (1H, dd, *J*=12.9, 10.1 Hz), 5.11 (1H, dd, *J*=10.1, 3.4 Hz), 7.35—7.43 (5H, m). HR-MS *m/z:* Calcd for $C_{12}H_{13}NO_3$: 219.0896. Found: 219.0893.

2-(2-Furyl)-1-nitro-3-oxa-6-heptyne (5b) from 4b — In the same procedure as described for the preparation of **2**, 3-butyn-1-ol (0.7 mL, 9.27 mmol), NaH (277.5 mg, 60% dispersion in oil, 6.94 mmol) in anhydrous THF (5 mL), and a solution of **4b** (640.0 mg, 4.60 mmol) in anhydrous THF (5 mL) were used. After the same work-up using AcOH (0.51 mL, 9.18 mmol) and column-chromatography, **5b** (895.2 mg, 93%) was obtained. **5b**: pale yellow oil. IR (film): 3296, 2925, 2881, 2121, 1558,

1381, 1149, 1109, 1089 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 1.95 (1H, t, *J*=2.7 Hz), 2.35—2.47 (2H, m), 3.55 (1H, ddd, *J*=9.3, 7.6, 6.6 Hz), 3.60 (1H, ddd, *J*=9.3, 7.6, 6.6 Hz), 4.55 (1H, dd, *J*=13.2, 3.7 Hz), 4.83 (1H, dd, *J*=13.2, 9.8 Hz), 5.17 (1H, dd, *J*=9.8, 3.7 Hz), 6.39 (1H, dd, *J*=3.2, 2.0 Hz), 6.45 (1H, dd, *J*=3.2, 1.0 Hz), 7.44 (1H, dd, *J*=2.0, 1.0 Hz). HR-MS *m/z:* Calcd for $C_{10}H_{11}NO_4$: 209.0688. Found: 209.0680.

4,5-Dihydro-7-phenyl-7*H*-pyrano[3,4-*c*]isoxazole[4] (**6a**) **from 5a** — In the same procedure as described for the preparation of **3a**, *n*-BuLi (0.47 mL, 1.56 M solution in hexane, 0.73 mmol), a solution of **5a** (160.1 mg, 0.73 mmol) in anhydrous THF (10 mL), Ac_2O (0.08 mL, 0.85 mmol) were used. After the same work-up and column-chromatography with AcOEt–hexane (1:10, v/v), **5a** (61.0 mg, 38%) and **6a** (63.8 mg, 40%) were obtained in the order of elution. **6a**[4]: colorless viscous oil. IR (film): 3116, 2862, 1612, 1093, 1057, 739, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.76 (1H, dtd, *J* = 16.3, 4.5, 1.2 Hz), 2.85 (1H, dddd, *J* = 16.3, 8.6, 5.4, 1.2 Hz), 3.82 (1H, ddd, *J*=12.0, 8.6, 4.5 Hz), 4.11 (1H, ddd, *J*=12.0, 5.4, 4.5 Hz), 5.84 (1H, s), 7.33 (1H, tt, *J*=7.8, 1.2 Hz), 7.31—7.40 (2H, m), 7.45—7.48 (1H, m), 8.24 (1H, t, *J*=1.2 Hz). HR-MS *m/z:* Calcd for $C_{12}H_{11}NO_2$: 201.0790. Found: 201.0787.

2- Acetyl-4,5-dihydro-7-phenyl-7*H*-pyrano[3,4-*c*]isoxazole (6c) and 6a from 5a — In the same procedure as described for the preparations for **3a** and **3b**, *n*-BuLi (0.95 mL, 1.56 M solution in hexane, 1.48 mmol), a solution of **5b** (162.3 mg, 0.74 mmol) in anhydrous THF (10 mL), and Ac_2O (0.15 mL, 1.59 mmol) were used. After the same work-up and column-chromatography with AcOEt–hexane (1:3, v/v), **6c** (11.7 mg, 6%) and **6a** (54.3 mg, 36%) were obtained in the order of elution. **6c**: colorless oil. IR (film): 1697, 1616, 1363, 748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.62 (3H, s), 3.02 (2H, dd, *J*=6.5, 5.1 Hz), 3.82 (1H, dt, *J*=11.8, 6.5 Hz), 4.12 (1H, dt, *J*=11.8, 5.1 Hz), 5.84 (1H, s), 7.33—7.42 (3H, m), 7.43—7.47 (2H, m). High Resolution MS *m/z*: Calcd for $C_{14}H_{13}NO_3$: 243.0895. Found: 243.0901.

7-(2-Furyl)-4,5-Dihydro-7*H*-pyrano[3,4-*c*]isoxazole (6b) from 5b — In the same procedure as described for the preparation of **3a**, *n*-BuLi (0.47 mL, 1.56 M solution in hexane, 0.73 mmol), a solution of **5b** (151.1 mg, 0.72 mmol) in anhydrous THF (10 mL), and Ac_2O (0.08 mL, 0.85 mmol) were used. After the same work-up and column-chromatography with AcOEt–hexane (1:4, v/v), **5b** (56.8 mg, 38%) and **6b** (63.6 mg, 46%) were obtained in the order of elution. **6b**: colorless viscous oil. IR (film): 3122, 2927, 2866, 1612, 1439, 1051, 746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.73—2.83 (2H, m), 3.85 (1H, ddd, *J*=11.7, 6.6, 5.1 Hz), 4.02 (1H, ddd, *J*=11.7, 5.9, 5.1 Hz), 5.96 (1H, s), 6.37 (1H, dd, *J*=3.2, 2.0 Hz), 6.38 (1H, dt, *J*=3.2, 1.0 Hz), 7.46 (1H, dd, *J*=2.0, 1.0 Hz), 8.27 (1H, t, *J*=1.2 Hz). HR-MS *m/z:* Calcd for $C_{10}H_9NO_3$: 191.0582. Found: 191.0595.

3- Acetyl-7-(2-furyl)-4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazole (6d) and 6b from 5b — In the same procedure as described for the preparations for **3a** and **3b**, *n*-BuLi (0.93 mL, 1.56 M solution

in hexane, 1.45 mmol), a solution of **5b** (151.3 mg, 0.72 mmol) in anhydrous THF (10 mL), and Ac_2O (0.15 mL, 1.59 mmol) were used. After the same work-up and column-chromatography with AcOEt–hexane (1:4, v/v), unreacted **5b** (20.0 mg, 13%), **6d** (24.0 mg, 14%) and **6b** (35.0 mg, 25%) were obtained in the order of elution. **6d**: colorless viscous oil. IR (film): 2925, 2870, 1695, 1617, 1274, 1163, 748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 2.64 (3H, s), 3.00 (2H, dt, *J*=1.2, 5.9 Hz), 3.86 (1H, dt, *J*=11.8, 5.9 Hz), 4.01 (1H, dt, *J*=11.8, 5.9 Hz), 5.96 (1H, s), 6.39 (2H, d, *J*=1.3 Hz), 7.47 (1H, t, *J*=1.3 Hz). HR-MS *m/z:* Calcd for $C_{12}H_{11}NO_4$: 233.0688. Found: 233.0690.

REFERENCES AND NOTES

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