The First Efficient and General Copper-Catalyzed [2,3]-Sigmatropic Rearrangement of Tetrahydropyridininium Ylids.

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Supplementary Material

Note

^{13}C nmr data are assigned by inference from correlated spectra.

General Experimental Procedures

Dry organic solvents were obtained from Fluka Sure-Seal® Anhydrous High Purity solvents or freshly distilled under an atmosphere of N_2 prior to use. Where appropriate, commercial reagents were purified by standard procedures. Light petroleum refers to the fraction with the boiling range 40˚C to 60˚C. Toluene was distilled from sodium. *N*-methyl-3,4-didehydropiperidine derivatives were distilled prior use.

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 or a Perkin Elmer 1720-X spectrophotometers. Mass spectra were recorded on a Fisons VG Autospec machine. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker WM250, or a Jeol EX-400 spectrometers. Unless otherwise stated, deuterochloroform was used as solvent and tetramethylsilane was used as the internal standard. Chemical shifts in ^{1}H nmr spectra are expressed as ppm downfield from tetramethylsilane, and in ^{13}C nmr, relative to the internal solvent standard. Coupling constants (*J*) are quoted in Hz.

Reactions involving chemicals or intermediates sensitive to air and/or moisture were performed under an argon atmosphere in flame- or oven-dried apparatus. Flash column chromatography was performed using Merck Kieselgel 60 or Fluka Kieselgel 60 silica. Analytical thin layer chromatography (tlc) was performed on precoated Merck Kieselgel 60 F_{254} aluminium or glass backed plates and were visualised under U.V. conditions at 254 nm, and by staining basic permanganate or acidic ammonium molybdate.

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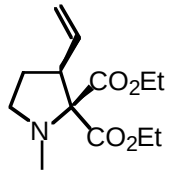
Preparation of 1-methyl-3-vinyl-pyrrolidine-2,2-dicarboxylic diethyl ester (2b).



A solution of *N*-methyl-3,4-didehydropiperidine hydrochloride (5.0 g, 37.4 mmol) in 2M aqueous sodium hydroxide (56.1 ml, 112.2 mmol, 3 eq) was extracted with pentane (4 x 25 ml). The combined extracts were dried ($MgSO_4$) and removal of solvent *in vacuo* gave *N*-methyl-3,4-didehydropiperidine as a colourless liquid (2.98 g, 82 %) which was used without further purification.

Catalyst (5 mol%) was added to a stirred solution of *N*-methyl-3,4-didehydropiperidine in toluene (25-38 ml), under nitrogen. The reaction mixture was heated to reflux, at which point diethyldiazomalonate was added, either dropwise as a toluene solution or at once, neat. The reaction mixture was heated at reflux for a further 12 hours upon which it was cooled, diethyl ether (15 ml) added and filtered through a glass sinter to remove any catalyst. The solvent was then removed *in vacuo* leaving a crude mixture, which was purified by column chromatography on silica gel, eluting with (1:1) diethyl ether/light petroleum to give the desired product as a yellow oil; ν_{max} (neat)/cm^{-1} 2981, 1757, 1728, 1450, 1274, 1218, 1076; d_H (250 MHz, $CDCl_3$) 1.14-1.25 (6H, m), 1.75 (1H, m), 2.14 (1H, m), 2.40 (3H, s), 2.75 (1H, ddd, *J* 6.5, 9.0, 9.0), 2.99 (1H, ddd, *J* 4.0, 9.2, 9.2), 3.20 (1H, ddd, *J* 6.3, 8.9, 8.9), 4.16 (4H, m), 4.95 (2H, m), 5.75 (1H, ddd, *J* 9.1, 10.0, 17.1); d_C (62.5 MHz, $CDCl_3$) 14.6, 14.7, 29.0, 37.5, 50.5, 53.8, 61.2, 61.4, 116.7, 138.3, 168.8, 169.1; *m/z* (CI) calcd for $C_{13}H_{21}NO_4$ $[M+H^+]$ 256.1549, found 256,1550.

Reaction with copper(II) acetylacetonate

Copper(II) acetylacetonate (13 mg, 5 mol%) was added to a solution of *N*-methyl-3,4-didehydropiperidine (97 mg, 1.0 mmol) in toluene (25 ml) as above. After addition of diethyldiazomalonate (186 mg, 1.0 mmol) in toluene (13 ml), at a rate of 150 ml/hr, the desired product (204 mg, 80 %) was isolated as a yellow oil.

Reaction with rhodium(II) acetate dimer

Rhodium(II) acetate dimer (22 mg, 5 mol%) was added to a solution of *N*-methyl-3,4-didehydropiperidine (97 mg, 1.0 mmol) in toluene (25 ml) as above. After addition of diethyldiazomalonate (186 mg, 1.0 mmol) in toluene (13 ml), at a rate of 150 ml/hr, the desired product (63 mg, 25 %) was isolated as a yellow oil.

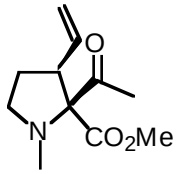
Reaction with copper(II) acetylacetonate

Copper(II) acetylacetonate (13 mg, 5 mol%), was added to a solution of *N*-methyl-3,4-didehydropiperidine (97 mg, 1.0 mmol) in toluene (38 ml) as above. After addition of neat diethyldiazomalonate (186 mg, 1.0 mmol), the desired product (916 mg, 90 %) was isolated as a yellow oil.

General procedure for reactions in table 2:

Copper(II) acetylacetonate (13 mg, 5 mol%) was added to a stirred solution of *N*-methyl-3,4-didehydropiperidine derivative (1.0 mmol) in toluene (40 ml), under argon. The reaction mixture was heated to reflux, at which point the diazocompound was added at once, neat. After 16 hrs the reaction was cooled, diethyl ether (15 mL) added, the mixture filtered through a glass sinter to remove any catalyst. The solvent was then removed *in vacuo* leaving a crude mixture, which was purified by column chromatography on silica gel to give the desired product.

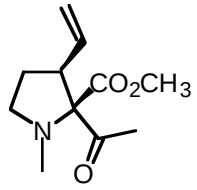
Preparation of *trans*-2-acetyl-1-methyl-3-vinyl-pyrrolidine-2-carboxylic acid methyl ester (15).



After purification by column chromatography on silica gel, eluting with (3:7) diethyl ether/light petroleum, the desired product was isolated (39 mg, 18 %) as a yellow oil; n_{max} (neat)/cm^{-1} 3081, 1682, 1633, 2985, 1723, 1718, 1399, 1282; d_H (250MHz, $CDCl_3$) 1.65 (1H, m), 2.00 (3H, s), 2.22 (1H,

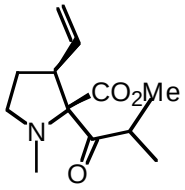
m), 2.29 (3H, s), 2.52 (1H, dt, *J* 7.6, 8.9), 3.12 (1H, dt, *J* 3.0, 8.9), 3.28 (1H, dt, *J* 4.9, 9.1), 3.71 (3H, s), 4.92 (1H *cis*, dd, *J* 1.5, 9.9), 4.99 (1H *trans*, dd, *J* 1.5, 17.0), 5.57 (1H, dt, *J* 9.9, 17.0); d_c (62.5MHz, $CDCl_3$) 29.1, 30.0, 37.5, 50.1, 51.9, 53.9, 84.1, 116.7, 138.7, 169.9, 204.1; *m/z* (CI) calcd for $C_{11}H_{17}NO_3$ [$M+H^+$] 212.1287, found 212.1282.

Preparation of *cis*-2-acetyl-1-methyl-3-vinyl-pyrrolidine-2-carboxylic acid methyl ester (15).



After purification by column chromatography on silica gel, eluting with (5:5) diethyl ether/light petroleum, the desired product was isolated (81 mg, 38 %) as a yellow oil; n_{max} (neat)/cm^{-1} 2982, 1725, 1719, 1395; d_H (250MHz, $CDCl_3$) 1.85 (1H, m), 2.05 (1H, m), 2.12 (3H, s), 2.30 (3H, s), 2.72 (1H, dt, *J* 5.1, 9.7), 2.83 (1H, dt, *J* 8.7, 9.8), 3.06 (1H, dt, *J* 5.3, 8.9), 3.67 (3H, s), 4.99 (1H, d, *J* 17.4), 5.01 (1H, d, *J* 8.3), 5.85 (1H, m); d_c (62.5MHz, $CDCl_3$) 28.2, 29.6, 37.5, 51.4, 51.6, 53.6, 83.5, 118.1, 137.5, 169.1, 204.8; *m/z* (CI) calcd for $C_{11}H_{17}NO_3$ [$M+H^+$] 212.1287, found 212.1286.

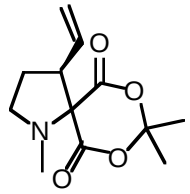
Preparation of 2-isobutyryl-1-methyl-3-vinyl-pyrrolidine-2-carboxylic acid methyl ester (16).



After purification by column chromatography on silica gel, eluting with (3:7) diethyl ether/light petroleum, the mixture of desired diastereoisomers was isolated (134 mg, 56 %) (*cis*:*trans*/75:25) as a yellow oil; [*refers to the minor *trans* isomer] n_{max} (neat)/cm^{-1} 2974, 1732, 1717, 1451, 1381, 1213; d_H (250MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.7), 1.07 (3H, d, *J* 6.7), 1.08 (3H, d, *J* 6.6)*, 1.13 (3H, d, *J* 6.6)* 1.79 (1H, m), 1.98 (1H, m)*, 2.12 (1H+1H*, m), 2.40 (3H, s)*, 2.44 (3H, s), 2.70 (1H+1H*, m), 2.90 (1H, m)*, 3.13 (1H, dt, *J* 3.4, 8.9), 3.43 (1H, br q, *J* 7.0), 3.76 (3H, s)*, 3.77 (1H, m)*, 3.78 (3H, s), 5.05 (2H+2H*, m), 5.71 (1H, dt, *J* 8.9, 17.2), 5.96 (1H, dt, *J* 8.7, 15.9)*; d_c (62.5MHz, $CDCl_3$) 19.6, 19.8, 20.5*, 20.6*, 29.9, 29.9*, 37.0*, 37.7*, 37.9, 38.3, 50.8*, 50.9. 51.4*, 52.0, 53.6*, 53.9, 83.7*,

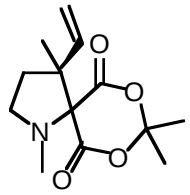
83.9, 116.5, 117.4*, 137.3*, 138.6, 169.2*, 170.9, 211.6, 211.8*; *m/z* (CI) calcd for $C_{13}H_{21}NO_3$ $[M+H^+]$ 240.1600, found 240.1606.

Preparation of 1,8,8-trimethyl-4-vinyl-7,9-dioxa-1-aza-spiro[4.5]decane-6,10-dione (5).



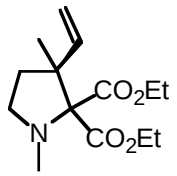
After purification by column chromatography on silica gel, eluting with (3:7) diethyl ether/light petroleum, the desired product was isolated (116 mg, 49%) as a pale yellow solid; m.p. 45-48 ºC (dec); n_{max} ($CHCl_3$)/cm^{-1} 2871, 2170, 1775, 1727, 1394, 1382, 1337; d_H (250MHz, $CDCl_3$) 1.73 (6H, s, 2 x C<u>H</u>$_3$-), 2.08 (1H, m), 2.25 (1H, m), 2.41 (3H, s), 3.15 (1H, dt, *J* 3.9, 9.2), 3.39 (2H, m), 5.21 (1H *cis*, d, *J* 9.7), 5.23 (1H *trans*, d, *J* 17.1), 5.74 (1H, dt, *J* 9.7, 17.1); d_c (62.5MHz, $CDCl_3$) 30.0, 30.4, 30.9, 36.4, 54.3, 56.7, 75.9, 105.9, 120.1, 135.6, 166.4, 169.5; *m/z* (CI) calcd for $C_{12}H_{17}NO_4$ $[M+H^+]$ 240.1236, found 240.1245.

Preparation of 1,4,8,8-tetramethyl-4-vinyl-7,9-dioxa-1-aza-spiro[4.5]decane-6,10-dione (13).



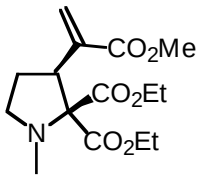
After purification by column chromatography on silica gel, eluting with (3:7) diethyl ether/light petroleum, the desired product was isolated (152 mg, 60%) as a white solid; m.p. 55-57 ºC (dec); n_{max} ($CHCl_3$)/cm^{-1} 2982, 2870, 1781, 1741, 1392, 1382, 1288; d_H (250MHz, $CDCl_3$) 1.21 (3H, s), 1.59 (3H, s), 1.63 (3H, s), 1.81 (1H, m), 2.20 (1H, m), 2.35 (3H, s), 3.22 (2H, m), 5.10 (1H, d, *J* 10.3), 5.12 (1H, d, *J* 16.8), 5.86 (1H, dd, *J* 10.3, 16.8). d_c (62.5MHz, $CDCl_3$) 22.6, 28.0, 31.7, 36.4, 36.7, 52.3, 55.4, 82.2, 105.7, 115.8, 140.8, 167.3, 167.6; *m/z* (CI) calcd for $C_{13}H_{19}NO_4$ $[M+H^+]$ 254.1392, found 254.1386.

Preparation of 1,3-dimethyl-3-vinyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (8).



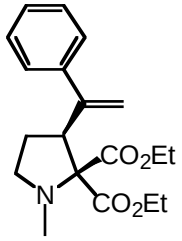
After purification by column chromatography on silica gel, eluting with (15:85) diethyl ether/light petroleum, the desired product was isolated (263 mg, 98%) as a colourless oil; ν_{max} (neat)/cm^{-1} 2982, 2850, 1724, 1450, 1075, 1038; δ_H (250MHz, $CDCl_3$) 1.20 (9H, m), 1.90 (1H, m), 2.10 (1H, s), 2.34 (3H, s), 2.96 (2H, t, *J* 7.6), 4.14 (4H, m), 4.96 (1H *cis*, d, *J* 10.8), 4.99 (1H *trans*, d, *J* 17.5), 6.07 (1H, dd, *J* 10.8, 17.5); δ_c (62.5MHz, $CDCl_3$) 14.6, 14.7, 22.5, 36.2, 37.9, 51.4, 52.8, 61.0 (x 2), 82.3, 113.5, 143.1, 168.8, 168.9; *m/z* (CI) calcd for $C_{14}H_{23}NO_4$ [M+H$^+$] 270.1705, found 270.1707.

Preparation of 3-(1-methoxycarbonyl-vinyl)-1-methyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (11).



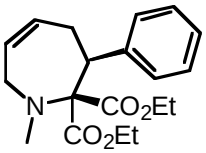
After purification by column chromatography on silica gel, eluting with (1:1) diethyl ether/light petroleum, the desired product was isolated (233 mg, 83%) as a pale yellow oil; ν_{max} (neat)/cm^{-1} 2982, 2971, 1726, 1274; δ_H (250MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.1), 1.20 (3H, t, *J* 7.2), 1.80 (1H, m), 2.20 (1H, m), 2.40 (3H, s), 2.67 (1H, dt, *J* 8.7, 8.8), 3.10 (1H, dt, *J* 2.8, 8.7), 3.67 (3H, s), 3.95 (1H, m), 4.02 (1H, m), 4.05 (1H, m), 4.15 (2H, q, *J* 7.2), 5.78 (1H, s), 6.23 (1H, s); δ_c (62.5MHz, $CDCl_3$) 14.2, 14.7, 31.1, 37.5, 45.1, 52.3, 53.9, 61.2, 61.4, 79.4, 126.8, 142.3, 167.8, 168.9, 169.3; *m/z* (CI) calcd for $C_{15}H_{23}NO_6$ [M+H$^+$] 314.1604, found 314.1606.

Preparation of 3-(1-phenyl-vinyl)-1-methyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (12).



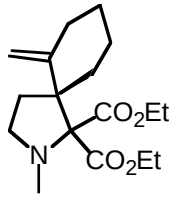
After purification by column chromatography on silica gel, eluting with (2:8) diethyl ether/light petroleum, the desired product was isolated (281 mg, 85%) as a colorless oil; n_{max} (neat)/cm^{-1} 2981, 2904, 1759, 1727, 1264, 1209, 1099, 1080, 1033; d_H (400MHz, $CDCl_3$) 0.94 (3H, dd, *J, J'* 7.1), 1.24 (3H, t, *J* 7.1), 1.97 (1H, m), 2.49 (1H, m, *J* 3.6, 9.1), 2.52 (3H, s), 2.66 (1H, dt, *J* 7.0, 9.1), 3.30 (1H, dt, *J* 3.6, 8.9), 3.67 (1H, dq, *J* 7.1, 10.7), 3.94 (1H, dd, *J* 4.6, 9.1), 4.03 (1H, dq, *J* 7.1, 10.7), 4.19 (2H, m), 5.39 (1H, s), 5.40 (1H, s), 7.21-7.32 (3H, m), 7.35-7.39 (2H, m); d_c (62.5MHz, $CDCl_3$) 14.0, 14.7, 32.4, 37.7, 49.1, 54.0, 61.0, 61.2, 80.1, 115.7, 126.8, 127.6, 128.5, 143.3, 151.5, 168.9, 169.3; *m/z* (CI) calcd for $C_{19}H_{25}NO_4$ [$M+H^+$] 332.1862, found 332.1850.

Preparation of 1-methyl-3-phenyl-1,3,4,7-tetrahydro-azepine-2,2-dicarboxylic acid diethyl ester (14).



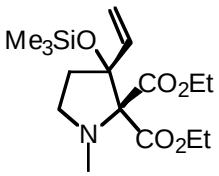
After purification by column chromatography on silica gel, eluting with (2:8) diethyl ether/light petroleum, the desired product was isolated (169 mg, 51%) as a colorless oil; n_{max} (neat)/cm^{-1} 3021, 2983, 2817, 1737, 1712, 1248, 1216; d_H (400MHz, $CDCl_3$) 0.88 (3H, dd, *J, J'* 7.1), 1.25 (3H, t, *J, J'* 7.1), 2.17 (1H, dd, *J* 8.0, 17.0), 2.48 (3H, s), 3.04 (1H, dd, *J* 6.4, 18.4), 3.45 (1H, br t), 3.60 (1H, dq, *J* 7.1, 10.7), 3.68 (1H, br m), 4.03 (1H, m), 4.05 (1H, dq, *J* 7.1, 10.7), 4.25 (2H, m), 5.58 (1H, br m), 5.78 (1H, br m), 7.15 (5H, m); d_c (62.5MHz, $CDCl_3$) 13.8, 14.9, 31.7, 44.0, 49.5, 52.8, 61.0, 61.2, 80.3, 127.0, 128.0, 128.9, 129.3, 131.1, 142.8, 167.5, 169.0; *m/z* (CI) calcd for $C_{19}H_{25}NO_4$ [$M+H^+$] 332.1862, found 332.1856.

Preparation of 2-methyl-6-methylene-2-aza-spiro[4.5]decane-1,1-dicarboxylic acid diethyl ester (10).



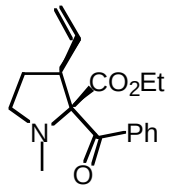
After purification by column chromatography on silica gel, eluting with (2:8) diethyl ether/light petroleum, the desired product was isolated (279 mg, 90%) as a colorless oil; n_{max} (neat)/cm^{-1} 2981, 2936, 2855, 2782, 1746, 1725, 1448, 1300, 1269, 1077, 1035; d_H (400MHz, $CDCl_3$) 1.25 (6H, m), 1.38 (1H, m), 1.50 (1H, m), 1.68 (3H,m), 1.76 (1H, m), 2.04 (1H, m), 2.15 (2H, m), 2.24 (1H, m), 2.42 (3H, s), 2.98 (1H, m), 4.21 (4H, m), 4.77 (1H, s), 4.97 (1H, s); d_c (62.5MHz, $CDCl_3$) 14.5, 14.6, 22.6, 27.1, 34.3, 35.2, 34.4, 38.0, 52.6, 56.1, 60.8, 61.2, 82.7, 109.6, 149.9, 169.4, 169.6; *m/z* (CI) calcd for $C_{17}H_{27}NO_4$ [$M+H^+$] 310.2018, found 310.2018.

Preparation of 1-methyl-3-(trimethyl-siloxy)-3-vinyl-pyrrolidine-2,2-dicarboxylic acid diethyl ester (9).



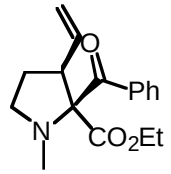
After purification by column chromatography on silica gel, eluting with (15:85) diethyl ether/light petroleum, the desired product was isolated (306 mg, 89%) as a colorless oil; n_{max} (neat)/cm^{-1} 2959, 2902, 2845, 2787, 1756, 1728, 1446, 1251, 1218, 1114, 1076, 1055; d_H (250MHz, $CDCl_3$) 0.00 (9H, s), 1.14 (3H, t, *J* 7.2), 1.20 (2H, t, *J* 7.1), 2.05 (1H, m), 2.32 (3H, s), 2.43 (1H, m), 2.77 (1H, dt, *J* 5.5, 9.0), 3.20 (1H, m), 4.00-4.18 (4H, m), 5.08 (1H *cis*, dd, *J* 1.3, 10.8), 5.19 (1H *trans*, dd , *J* 1.3, 17.4), 6.13 (1H, dd, *J* 10.8, 17.4); d_c (62.5MHz, $CDCl_3$) 0.00, 12.1, 12.2, 33.0, 35.7, 50.4, 58.4, 58.6, 82.4, 84.7, 113.5, 137.7, 165.6, 165.7; *m/z* (CI) calcd for $C_{16}H_{29}SiNO_5$ [$M+H^+$] 344.1893, found 344.1900.

Preparation of *trans*-2-benzoyl-1-methyl-3-vinyl-pyrrolidine-2-carboxylic acid ethyl ester (17).



After purification by column chromatography on silica gel, eluting with (15:85) diethyl ether/light petroleum, the desired product was isolated (94 mg, 33 %) as a yellow oil; n_{max} (neat)/cm^{-1} 3020, 2400, 2170, 1725, 1338, 1216; d_H (250MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.2), 1.70 (1H, m), 2.36 (3H, s), 2.37 (1H, q, *J* 7.8), 2.49 (1H, m), 3.22 (1H, dt, *J* 2.3, 8.6), 3.58 (1H, dt, *J* 3.9, 9.8), 4.02 (2H, q, *J* 7.2), 4.63 (1H, *cis*, dd, *J* 1.6, 10.0), 4.68 (1H *trans*, dd, *J* 1.6, 16.6), 5.49 (1H, dt, *J* 10.0, 16.6), 7.32 (2H, m), 7.41 (1H, m), 7.75 (2H, d, *J* 7.1); d_c (62.5MHz, $CDCl_3$) 14.4, 30.9, 37.8, 50.7, 53.3, 61.1, 82.4, 116.6, 128.6, 128.7, 132.9, 138.7, 138.9, 168.7, 196.8; *m/z* (CI) calcd for $C_{17}H_{21}NO_4$ $[M+H^+]$ 288.1600, found 288.1597.

Preparation of *cis*-2-benzoyl-1-methyl-3-vinyl-pyrrolidine-2-carboxylic acid ethyl ester (17).



After purification by column chromatography on silica gel, eluting with (15:85) diethyl ether/light petroleum, the desired product was isolated (102 mg, 35 %) as a pale yellow solid; m.p. 51-52 ^oC; n_{max} ($CHCl_3$)/cm^{-1} 2928, 2854, 1722, 1689; d_H (250MHz, $CDCl_3$) 1.13 (3H, dd, *J, J'* 7.1), 1.96 (1H, br m), 2.21 (1H, m), 2.39 (3H, s), 2.95-3.15 (2H, m), 3.27 (1H, q, *J* 8.4), 4.15 (2H, dq, *J* 0.7, 7.1), 4.90 (1H *trans*, dd, *J* 1.8, 14.3), 4.99 (1H *cis*, dd, *J* 1.8, 10.2), 5.99 (1H, m), 7.40 (2H, m), 7.49 (1H, m), 7.96 (2H, d, *J* 7.1); d_c (62.5MHz, $CDCl_3$) 14.5, 39.4, 38.1, 52.0, 53.8, 61.0, 82.5, 117.3, 128.5, 129.5, 132.9, 137.4, 137.7, 169.1, 196.8; *m/z* (CI) calcd for $C_{17}H_{21}NO_3$ $[M+H^+]$ 288.1600, found 288.1605.