

Convenient Synthesis of 2,2-Dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines

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Abstract: A convenient general synthesis of 2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines is described using Wittig reaction. The *o*-nitrobenzaldehydes (**1a-d**) on reaction with phosphorane **2** provided (*E*)-ethyl- α -(2,2-dimethylprop-2-ene)-2-nitrocinnamates (**3a-d**) in high yields, which on PPA cyclisation followed by reductive cyclisation using Fe/HCl afforded dihydropyranoquinolines (**5a-d**). Alternatively, the pyranoquinolines **5a-d** were also synthesised from esters **3a-d** employing domino reductive cyclisation in a single step.

Key words: pyranoquinoline, Wittig reaction, lactones, domino reaction, reductive cyclisation

Quinoline and its annulated derivatives are important compounds for synthetic and biological chemists.^[1] These alkaloids are useful as antimalarial, antihypertensive, anti-inflammatory, antiasthmatic, antibacterial and tyrosine kinase inhibiting agents.^[2] Significant number of quinoline alkaloids have 2,2-dimethylpyran unit attached to quinoline ring. These pyranoquinoline alkaloids displays wide range of biological activities.^[3] *Balfourodendron riedelianum* (Rutaceae), a small Brazilian tree is a rich source of pyrano[2,3-*b*]quinolines and furo[2,3-*b*]quinolines.^[4] The extract of this plant is used in folk medicine for the treatment of gastrointestinal ailments.^[5] Flindersin (1), ribalinine (2), helietidine (3), dutadrupine (4) are some examples of quinoline alkaloids containing pyran unit (Figure I).

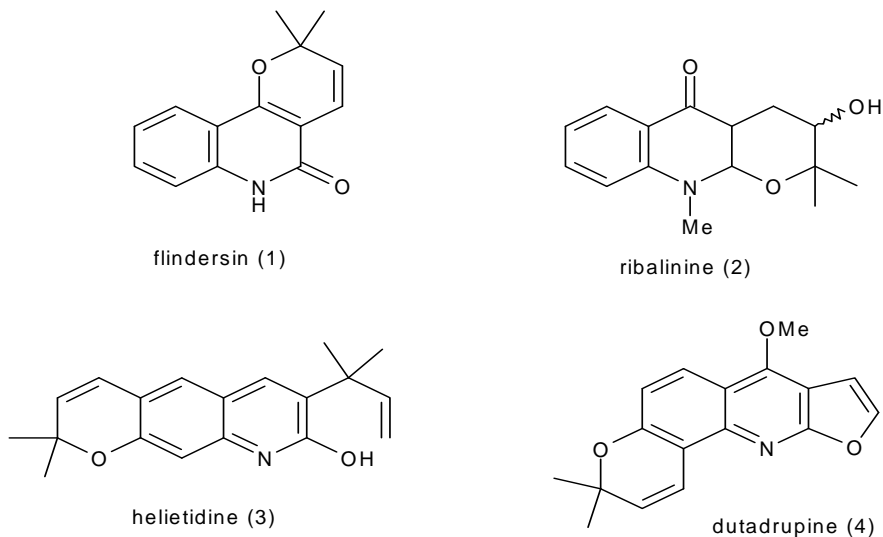
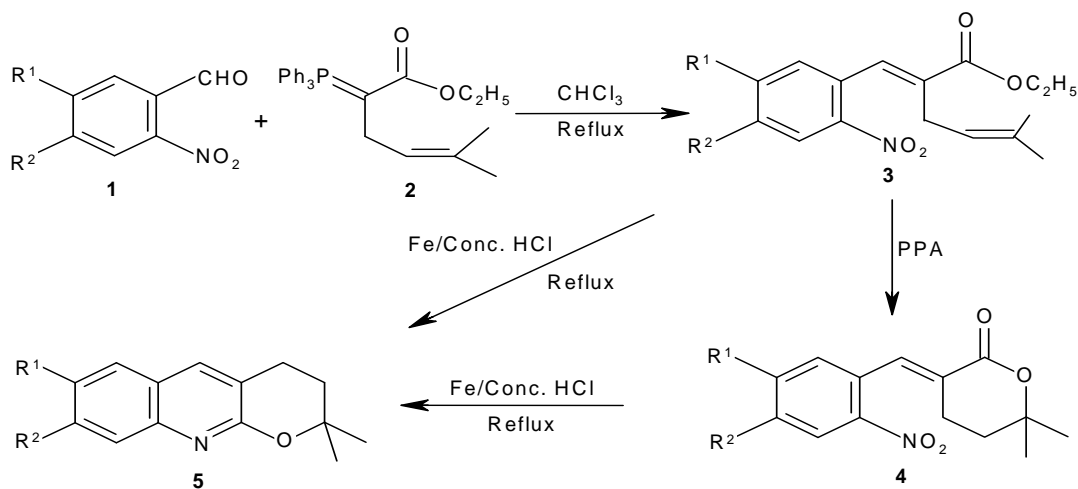


Figure I

Owing to their potent biological activities numerous methods have been developed for these alkaloids.^[6]

RESULTS AND DISCUSSION

In continuation with our studies exploiting phosphorous chemistry,^[7] we report herein a convenient general synthesis of 2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines (**5a-d**). Wittig reaction of the phosphorane^[8] (**2**) with *o*-nitrobenzaldehydes (**1a-d**) gave exclusively ethyl (*E*)-5-methyl-2[(2-nitrophenyl)methylidene]hex-4-enoates (**3a-d**). The unsaturated esters (**3a-d**) were further cyclised to δ -(*E*)-lactones (**4a-d**) using PPA. No isomerisation of the *E*-lactone to *Z*-lactone was observed during this acid mediated cyclisation.



Scheme I

Table I

Entry	R ¹	R ²	Yield (%)			
			3	4	5	5 from 3
a	H	H	90	85	54	19
b	OR	H	82 (R=COOEt)	95 (R=COOEt)	85 (R=OH)	36 (R=OH)
c	OCH ₃	OCH ₃	66	80	76	25
d	- OCH ₂ O -		68	82	83	33

The lactones (**4a-d**) were then subjected to reductive cyclisation^[9] using Fe and conc. HCl to furnish corresponding dihydropyranoquinolines (**5a-d**), where in reduction of nitro to amino, isomerisation of *E* to *Z*-lactone and cyclisation took place in one-pot in a domino fashion^[10] (**Scheme I**). Furthermore, in order to make our synthesis more concise, an alternate method was attempted, wherein Wittig product (**3a-d**) was directly subjected to reductive cyclisation employing Fe and conc. HCl to get the corresponding dihydropyranoquinolines (**5a-d**), without isolating the lactone intermediates (**4a-d**). However, the yield of isolated product (**5a-d**) during this one-pot concurrent lactonisation/isomerisation/reductive cyclisation was found to be somewhat lower than the overall yield from the two step strategy mentioned above. The results are summarized in **Table I**.

In conclusion, we have developed a new and effective methodology for the synthesis of 2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines using phosphorane chemistry. The noteworthy step is the one-pot reductive cyclisation to yield directly annulated tricyclic ring system.

EXPERIMENTAL

Thin layer chromatography was performed on silica gel G (13% CaSO₄ as binder). Column chromatography was performed on silica gel (60-120 mesh). IR spectra were recorded on Shimadzu FT-IR spectrophotometer (KBr pellet). ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) were recorded on a Bruker instrument. The multiplicities of carbon signals were obtained from Distortionless Enhancement by Polarization Transfer (DEPT) experiments. Chemical shift (ppm) are relative to the internal standard Me₄Si (0 ppm). HRMS were recorded on a MicroMass ES-QTOF.

General Procedure for the Preparation of Ethyl (2E)-5-methyl-2[(2-nitrophenyl)methylidene]hex-4-enoates (3a-d);

A solution of aldehyde (1 mmol) **1a-d** in chloroform (10 mL) was refluxed with phosphorane⁶ **2** (1 mmol) for 3 hr. The solvent was removed under reduced pressure to give a residue which was purified by column chromatography (silica gel, hexanes-EtOAc, 9:1) to give pure **3a-d** as viscous liquids.

Data

Ethyl (2E)-5-methyl-2[(2-nitrophenyl)methylidene]hex-4-enoate (3a)

Yield: 90%; thick viscous yellow liquid; IR (KBr): 1713 cm^{-1} (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.35 (t, J = 7.2 Hz, 3H), 1.42 (s, 3H), 1.64 (s, 3H), 2.98 (d, J = 6.3 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 5.03 (m, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.9 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.23 (CH₃), 17.64 (CH₃), 25.66 (CH₃), 27.06 (CH₂), 61.04 (OCH₂), 120.97 (CH), 124.72 (CH), 128.90 (CH), 131.18 (CH), 132.07 (C), 132.81 (C), 133.28 (CH), 133.91 (C), 135.59 (CH), 147.71 (C), 167.28 (C=O). GC/MS: m/z 289 [M⁺].

Ethyl (2E)-2-({5-[(ethoxycarbonyl)oxy]-2-nitrophenyl}methylidene)-5-methylhex-4-enoate (3b)

Yield: 82%; thick viscous yellow liquid; IR (KBr): 1722, 1770 cm^{-1} (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.26-1.43 (m, 6H), 1.64 (s, 6H), 2.93 (d, J = 6.6 Hz, 2H), 4.19-4.33 (m, 4H), 4.95 (br s, 1H), 7.15 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.29 (dd, J = 9.0, 2.4 Hz, 1H), 7.79 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.11 (CH₃), 14.20 (CH₃), 17.54 (CH₃), 25.61 (CH₃), 26.99 (CH₂), 61.11 (OCH₂), 65.56 (OCH₂), 120.65 (CH), 121.23 (CH), 123.52 (CH), 126.56 (CH), 133 (C), 134.11 (C), 134.40 (C), 134.72 (CH), 144.71 (C), 152.32 (C), 154.06 (C), 167.03 (C=O). GC/MS: m/z 377 [M⁺].

Ethyl (2E)-2-[(4,5-dimethoxy-2-nitrophenyl)methylidene]-5-methylhex-4-enoate (3c)

Yield: 66%; thick viscous yellow liquid. IR (KBr): 1709 cm^{-1} (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.37 (t, J = 7.2 Hz, 3H), 1.49 (s, 3H), 1.67 (s, 3H), 3.00 (d, J = 6.0 Hz, 2H), 3.92 (s, 3H), 4.00 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 5.1 (m, 1H), 6.77 (s, 1H), 7.75 (s, 1H), 7.94 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.24 (CH₃), 17.85 (CH₃), 25.62 (CH₃), 27.28 (CH₂), 56.33 (OCH₃), 56.40 (OCH₃), 60.99

(OCH₂), 107.70 (CH), 112.42 (CH), 121.77 (CH), 126.66 (C), 132.75 (C), 132.83 (C), 136.82 (CH), 140.15 (C), 148.55 (C), 152.97 (C), 167.41 (C=O). GC/MS: *m/z* 349 [M⁺].

Ethyl (2*E*)-5-methyl-2-[(6-nitro-1,3-benzodioxol-5-yl)methylidene]hex-4-enoate (3d)

Yield: 68%; thick viscous yellow liquid. IR (KBr): 1713 cm⁻¹ (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.35 (t, *J* = 7.2 Hz, 3H), 1.51 (s, 3H), 1.67 (s, 3H), 3.00 (d, *J* = 6.6 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 5.06 (m, 1H), 6.17 (s, 2H), 6.74 (s, 1H), 7.65 (s, 1H), 7.83 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.21 (CH₃), 17.68 (CH₃), 25.66 (CH₃), 27.15 (CH₂), 60.99 (OCH₂), 103.20 (CH₂), 105.50 (CH), 109.74 (CH), 121.02 (CH), 128.74 (C), 132.74 (C), 133.05 (C), 136.22 (CH), 141.87 (C), 147.78 (C), 151.77 (C), 167.30 (C=O). GC/MS: *m/z* 333 [M⁺].

General Procedure for the Preparation of (3*E*)-6,6-Dimethyl-3-[(2-nitrophenyl)methylidene]tetrahydro-2*H*-pyran-2-ones (4a-d);

Compound **3a-d** (1 mmol) were added to the stirred solution of polyphosphoric acid (2 mL). The reaction mixture was warmed on water bath for 5 min. Chilled water (15 mL) was added to the reaction mixture and it was subsequently extracted with diethyl ether (3 × 10 mL). The organic layer was washed with saturated NaHCO₃ solution (2 × 30 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes-EtOAc, 9:1) to give pure **4a-d**.

Data

(3*E*)-6,6-Dimethyl-3-[(2-nitrophenyl)methylidene]tetrahydro-2*H*-pyran-2-one (4a)

Yield: 85%; white solid; mp 96-98 °C. IR (KBr): 1692 cm⁻¹ (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.46 (s, 6H), 1.85 (t, *J* = 6.9 Hz, 2H), 2.56 (dt, *J* = 6.9, 2.4 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 8.11 (br s, 1H), 8.17 (d, *J* = 8.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 21.66 (CH₂), 27.96 (2 × CH₃), 33.13 (CH₂), 80.94 (C), 125 (CH), 127.04 (C), 129.41 (CH), 130.66 (CH), 131.21 (C), 133.43 (CH), 138.15 (CH), 147.72 (C), 165.79 (C=O). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₄H₁₅NNaO₄: 284.0899; found: 284.0893.

3-[(E)-(6,6-Dimethyl-2-oxodihydro-2H-pyran-3(4H)-ylidene)methyl]-4-nitrophenyl ethyl**carbonate (4b)**

Yield: 95%; white solid; mp 104-106 °C. IR (KBr): 1774, 1717 cm⁻¹ (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.34 (t, *J* = 7.2 Hz, 3H), 1.40 (s, 6H), 1.78 (t, *J* = 6.9 Hz, 2H), 2.53 (dt, *J* = 6.9, 2.4 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.03 (br s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.11 (CH₃), 21.60 (CH₂), 27.95 (2 × CH₃), 33.08 (CH₂), 65.68 (CH₂), 81.00 (C), 121.56 (CH), 123.08 (CH), 126.89 (CH), 127.63 (C), 133.22 (C), 137.22 (CH), 144.66 (C), 152.31 (C), 154.10 (C), 165.48 (C=O). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₇H₁₉NNaO₇: 372.1059; found: 372.1059.

(3E)-3-[(4,5-Dimethoxy-2-nitrophenyl)methylidene]-6,6-dimethyltetrahydro-2H-pyran-2-one (4c)

Yield: 80%; yellow solid; mp 181-182 °C. IR (KBr): 1692 cm⁻¹ (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.46 (s, 6H), 1.85 (t, *J* = 6.9 Hz, 2H), 2.55 (dt, *J* = 6.6, 2.1 Hz, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 6.73 (s, 1H), 7.76 (s, 1H), 8.11 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 21.75 (CH₂), 27.98 (2 × CH₃), 33.20 (CH₂), 56.47 (OCH₃), 56.62 (OCH₃), 80.83 (C), 107.97 (CH), 111.63 (CH), 125.75 (C), 126.16 (C), 139.17 (CH), 140.33 (C), 148.88 (C), 153.14 (C), 166.02 (C=O). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₆H₁₉NNaO₆: 344.1110; found 344.1113.

(3E)-6,6-Dimethyl-3-[(6-nitro-1,3-benzodioxol-5-yl)methylidene]tetrahydro-2H-pyran-2-one (4d)

Yield: 82%; yellow solid; mp 176-177 °C. IR (KBr): 1697 cm⁻¹ (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 1.45 (s, 6H), 1.85 (t, *J* = 6.9 Hz, 2H), 2.56 (dt, *J* = 6.9, 2.4 Hz, 2H), 6.18 (s, 2H), 6.73 (s, 1H), 7.67 (s, 1H), 8.04 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 21.65 (CH₂), 27.94 (2 × CH₃), 33.11 (CH₂), 80.83 (C), 103.38 (OCH₂O), 105.79 (CH), 109.00 (CH), 126.14 (C), 127.84 (C), 138.91 (CH), 142 (C), 148.13 (C), 151.94 (C), 165.9 (C=O). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₅H₁₅NNaO₆: 328.0797; found 328.0800.

General Procedure for the Preparation of 2,2-Dimethyl -3,4-dihydro-2H-pyrano[2,3-*b*]quinolines (5a-d);

To a magnetically stirred mixture of esters **3a-d** or **4a-d** (1 mmol) and Fe powder (15 mmol) was added conc. HCl (8 mL). The reaction mixture was allowed to stir for 15 minutes, and was subsequently refluxed on water bath. After completion of the reaction (the progress of the reaction was monitored by TLC), the reaction mixture was filtered and residue was washed with water (3 × 5 mL). This combined filtrate was washed with diethyl ether (2 × 10 mL) and was filtered on celite. The filtrate was basified with solid NaOH pellets (liquour ammonia was used to basify compound **3b** and **4b**) and the compound was subsequently extracted in diethyl ether (3 × 15 mL). The combined organic extracts were dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes-EtOAc, 8:2) to give pure **5a-d**.

Data

2,2-Dimethyl-3,4-dihydro-2H-pyrano[2,3-*b*]quinoline (5a)

Yield: 19% (from 3), 54% (from 4); white solid; mp 103-105 °C. IR (KBr): 1622, 1562, 1492, 1415 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.50 (s, 6H), 1.96 (t, *J* = 6.6 Hz, 2H), 3.04 (t, *J* = 6.3 Hz, 2H), 7.36 (t, *J* = 7.8, 7.2 Hz, 1H), 7.58 (t, *J* = 8.1, 7.2 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.88 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 22.62 (CH₂), 27.36 (2 × CH₃), 32.41 (CH₂), 77.08 (C), 117.66 (C), 123.88 (CH), 125.19 (C), 126.56 (CH), 127.22 (CH), 129.02 (CH), 137.51 (CH), 146.42 (C), 159.72 (C). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₄H₁₅NNaO: 236.1051; found: 236.1049.

2,2-Dimethyl-3,4-dihydro-2H-pyrano[2,3-*b*]quinolin-7-ol (5b)

Yield: 36% (from 3), 85% (from 4); white solid; mp 223-225 °C. IR (KBr): 3300 (OH), 1612, 1517, 1434, 1367 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.41 (s, 6H), 1.87 (t, *J* = 6.9 Hz, 2H), 2.93 (t, *J* = 6.9 Hz, 2H), 5.11 (br s, 1H), 6.96 (d, *J* = 2.7 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.67 (s, 1H), 7.69 (d, *J* = 9.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 22.59 (CH₂), 27.28 (2 × CH₃), 32.39 (CH₂), 70.19 (C), 108.46 (CH), 118.06 (CH), 120.69 (CH), 125.83 (CH), 128.52 (C), 136.16 (C), 141.62 (C), 152.02 (C), 158.20 (C). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₄H₁₅NNaO₂: 252.1; found: 252.0999.

7,8-Dimethoxy-2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline (5c)

Yield: 25% (from 3), 76% (from 4); white solid; mp 156-158 °C. IR (KBr): 1612, 1496, 1458, 1381 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.47 (s, 6H), 1.93 (t, *J* = 6.6 Hz, 2H), 2.97 (t, *J* = 6.6 Hz, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 6.95 (s, 1H), 7.2 (s, 1H), 7.7 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 22.43 (CH₂), 27.28 (2 × CH₃), 32.51 (CH₂), 55.87 (2 × CH₃), 76.53 (C), 104.69 (CH), 106.62 (CH), 114.85 (C), 119.92 (C), 136 (CH), 143.05 (C), 147.81 (C), 152.07 (C), 158.66 (C). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₆H₁₉NNaO₃: 296.1263; found: 296.1263.

7,8-Methylenedioxy-2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline (5d)

Yield: 33% (from 3), 83% (from 4); white solid; mp 177-179 °C. IR (KBr): 1620, 1480, 1465, 1388 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.44 (s, 6H), 1.89 (t, *J* = 6.6 Hz, 2H), 2.92 (t, *J* = 6.6 Hz, 2H), 6.02 (s, 2H), 6.91 (s, 1H), 7.15 (s, 1H), 7.65 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 22.32 (CH₂), 27.26 (2 × CH₃), 32.44 (CH₂), 76.65 (C), 101.26 (CH₂), 102.08 (CH), 104.40 (CH), 114.78 (C), 121.10 (C), 136.57 (CH), 144.24 (C), 145.83 (C), 150.21 (C), 158.60 (C). HRMS: *m/z* [M + Na]⁺ Calcd for C₁₅H₁₅NNaO₃: 280.0950; found: 280.0958.

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