Synthesis of 2- and 4-hydroxymethyl Loratadine, usual impurities in Loratadine syrup formulations

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Dedicated to Prof. José Elguero

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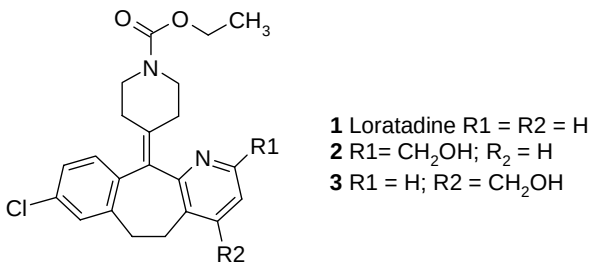
Abstract

The synthesis of two contaminants of Loratadine, generated when the product is formulated as a syrup, is described. The products, identified as 2- and 4-hydroxymethyl derivatives of the starting compounds, are obtained by the corresponding substitution of the pyridine moiety of Loratadine.

Keywords: Fused pyridines, pharmaceuticals, Loratadine, synthesis, contaminants

Introduction

Loratadine, **1,** is [4-(8-chloro-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidine -1-carboxylic acid ethyl ester]. It is a non-sedating anthistamine,[1] marketed, *inter alia*, as a syrup. The formation of the 2- and 4-hydroxymethyl derivatives **2**,**3** (Figure 1) on the pyridine ring has been described, which result from a redox process of the drug with other formulation components.[2,3] Accelerated degradation experiments showed the formation of 0.5% of both contaminants in the syrup, dependent on the presence of air, and eventually related to the *in situ* generation of formaldehyde. [3] The preparation of both contaminants has been necessary to prepare references for quality control of drug formulations, and a scheme has been developed starting from the parent Loratadine **1**.

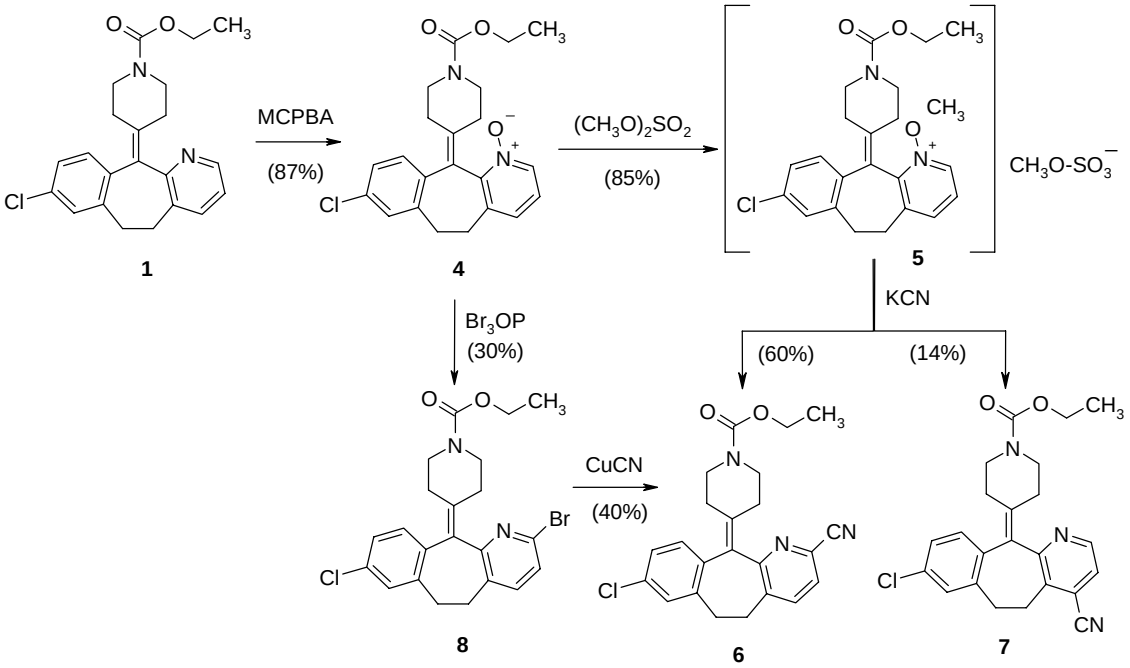


1 Loratadine R1 = R2 = H
2 R1= CH_2OH; R_2 = H
3 R1 = H; R2 = CH_2OH

Figure 1

Results and Discussion

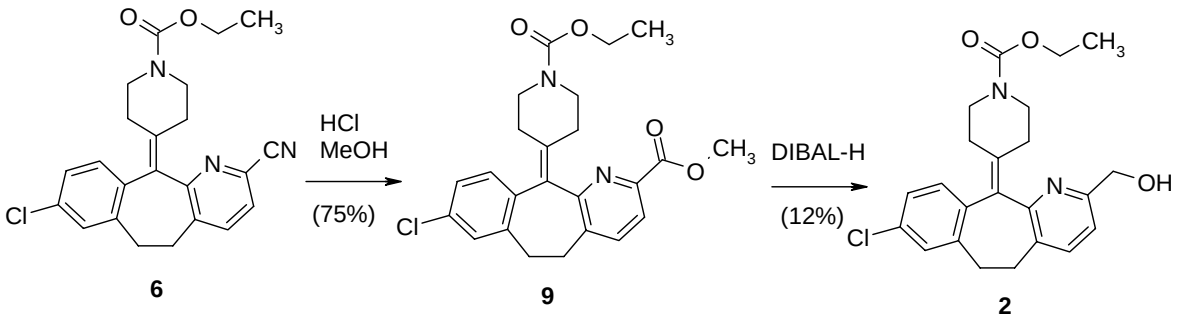
The substitution of the pyridine moiety has been performed using the strategy of Okamota and Tani,[4] and Feely and Beavers-Tani,[5] as a crucial step (Scheme 1), by cyanide nucleophilic substitution of the corresponding 1-methoxypyridinium salts. The starting Loratadine **1** was converted into the N-oxide **4**, and then into the N-methoxypyridinium salt **5**. The attack of cyanide ion produced a mixture of the corresponding nitriles **6** and **7**, in which the 2-isomer predominated (4:1). Both products were separated by chromatography, and used to prepare the final compounds.



Scheme 1

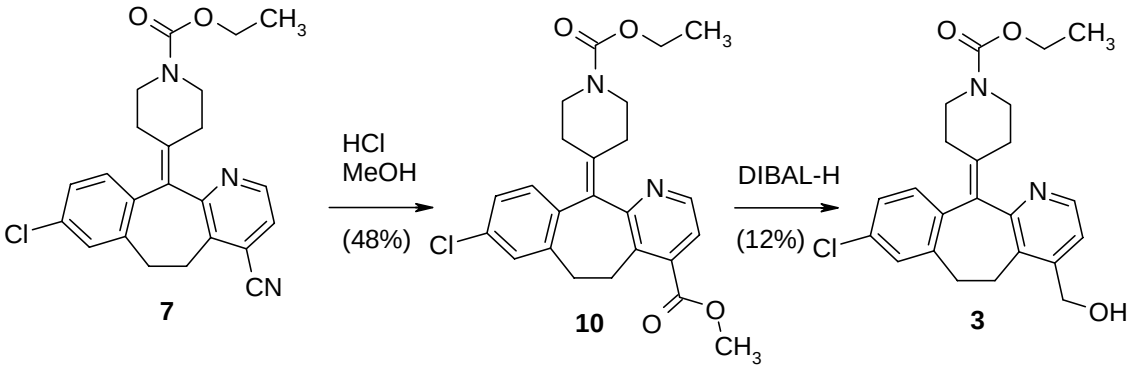
A more selective approach to **6** was performed by bromination of the N-oxide **4**, in the presence of Br_3PO, by adapting the process described by Jung *et al.*,[6] which allowed the preparation of **8**. An alternative chlorination with Cl_3PO, always produced smaller yields. Then, treatment of **8** with CuCN produced **6**. Extensive deacylation of the piperidine nitrogen was produced in both steps, and was the cause of the observed reduction of yields.

The process for obtaining **2** is indicated in Scheme 2, in which a classical Pinner process converted **6** into the ester **9**. Finally, the best results in the reduction step were obtained with DIBAL-H, which produced the hydroxymethyl derivative **2** in small yield.



Scheme 2

A similar approach was applied to **7**, going to the ester **10**, which, on reduction, produced the hydroxymethyl derivative 3 (Scheme 3) also, in small yield.



Scheme 3

Identification of the products in the reduction steps **9**–**2** and **10**–**3**, was performed by HPLC-MS of the crude mixture obtained in the process. The acid **11** was detected in the mixture used to obtain **2**, with a yield of 43 %, while **12** was detected in the mixture used to obtain **3**, with a yield of 48 % (Figure 2).[7]

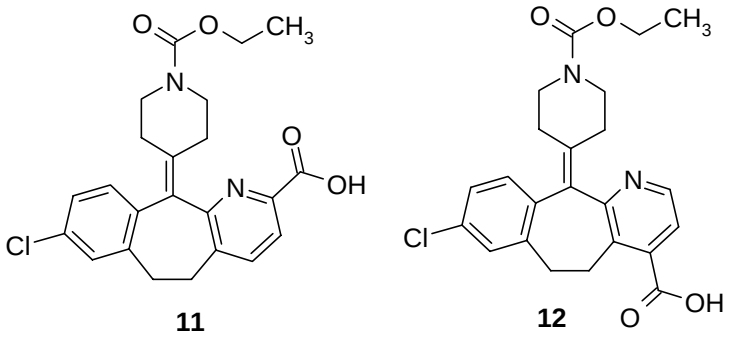


Figure 2

Experimental Section

General Procedures. All melting points were measured in capillary tubes and are uncorrected. IR spectra were determined on KBr disks using a Nicolet Impact 410 spectrophotometer. ^{1}H NMR spectra were obtained at 200 or 300 MHz on VARIAN GEMINI or UNITY apparatus. Chemical shifts (δ) were determined using TMS as internal standard, and multiplicity (s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; m, multiplet) is indicated for every signal. HPLC-MS analyses were performed on an Agilent 1100 apparatus. A chromatographic column Luna C18 (150 × 4.6 mm) 5 μm Phenomenex, was used, with a mobile phase formed by a triple gradient of 4% aq. formic acid (A), water (B), and acetonitrile (C). The gradient started as A (2.5%), B (93%) and C (4.5%), and in 30 min. reached A (2.5%), B (4.5%) and C (93%). In the Mass detector, the fragmenter operated at 70 eV. HRMS was performed on an Applied Biosystems 4700 spectrometer. Elemental analysis was performed on a LECO CHNS-932 instrument. All reactions were carried under Ar using solvents dried by routine procedures. Column chromatography was performed using silica gel (60 F_{254}, 70–200 μm) as the stationary phase. RT means room temperature.

4-(8-Chloro-1-oxy-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylic acid ethyl ester (4). In a 25 mL round-bottomed flask adapted with a condenser, 1g (2.61 mmol) of Loratadine was loaded and dissolved in CH_2Cl_2 (8 mL). Then 0.61g (2.72 mmol) of MCPBA was added in one portion and the mixture was stirred at 60 ºC for 25 h. The (reaction was monitored by TLC (hexane/AcOEt/MeOH 1:1:0.1). When the reaction was finished, the mixture was cooled to RT and the solvent evaporated to dryness to give a viscous crude material. This was purified by flash chromatography (SiO_2, hexane/AcOEt/MeOH 1:1:0.1) to give compound **4** as a white solid (0.9g, 87%). Mp 139–141 ºC. IR (KBr, cm^{-1}): 3437, 2924, 2855, 1695, 1478, 1428, 1385, 1240, 1220, 1116, 995, 795. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.08 (t, 1H, J = 3.8 Hz); 7.26–7.20 (m, 1H); 7.14–7.06 (m, 4H); 4.11 (q, 2H, J = 7.1 Hz); 3.84–3.64 (m, 2H); 3.47–3.30 (m, 4H); 2.96–2.75 (m, 2H); 2.59-2.46 (m, 1H); 2.38–2.25 (m, 2H); 2.14–1.90 (m, 1H); 1.25 (t, 3H, J = 7.1 Hz) ppm. MS (ESI^+): *m/z*: 399 (M+1). Anal. Calcd. for $C_{22}H_{23}ClN_2O_3$: C, 66.24; H, 5.81; N, 7.02. Found: C, 66.49; H, 5.70; N, 6.88%.

4-(8-Chloro-2-cyano-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylic acid ethyl ester (**6**) and **4-(8-Chloro-4-cyano-5,6-dihydrobenzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylic acid ethyl ester (7).** Compound **4** (17g, 42.7 mmol) dissolved in acetone (500 mL), stirring at 60 ºC had dimethyl sulfate (4.05 mL, 42.7 mmol) added dropwise. The reaction mixture was stirred at the same temperature for 6 hours further. The solvent was evaporated to give 19.86g of the pyridinium salt **5** as a brown oil. This was used in the next step without further purification. Then, KCN (8.2g, 0.13 mol) was dissolved in water (100 mL) and **5** (19.86g, 0.15 mol) dissolved in water (200 mL) was added slowly. The reaction mixture was stirred at RT for 10 min, then was extracted with diethyl ether (3x100 mL). The organic layer was separated and a solid formed. This solid

was filtered and characterized as compound **6**. The filtrate was washed with HCl 10% (2x50 mL), the aqueous layer neutralized with saturated aq. Na_2CO_3 and extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered, concentrated to dryness, and the crude mixture purified by flash chromatography (SiO_2, Hexane/AcOEt 1:1) to give compounds **6** (11.76g, 60%, yellow solid) and **7** (2.38g, 14%, yellow solid).

6: Mp 193–195 ºC. IR (KBr, cm^{-1}): 3439, 2922, 2853, 2229, 1690, 1485, 1465, 1438, 1231, 1119, 1091. 985. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.59–7.47 (m, 2H); 7.20–7.09 (m, 3H); 4.15 (q, 2H, J = 7.1 Hz); 3.78–3.72 (m, 2H); 3.47–3.36 (m, 2H); 3.29–3.16 (m, 2H); 2.98–2.77 (m, 2H); 2.55–2.19 (m, 4H); 1.26 (t, 3H, J = 7.1 Hz) ppm. MS (ESI^+): *m/z*: 408 (M+1). Anal. Calcd. for $C_{23}H_{22}ClN_3O_2$: C, 67.73; H, 5.44; N, 10.30. Found: C, 67.49; H, 5.60; N, 10.18%.

7: mp 99–100 ºC. IR (KBr, cm^{-1}): 3427, 2923, 2852, 2360, 1697, 1472, 1436, 1278, 1223, 1115, 1086, 986. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.57 (d, 1H, J = 4.8 Hz); 7.39 (d, 1H, J = 4.8 Hz); 7.16–7.12 (m, 3H); 4.17 (q, 2H, J = 6.9 Hz); 3.90–3.72 (m, 2H); 3.51–3.38 (m, 2H); 3.34–3.82 (m, 4H); 2.34–2.37 (m, 4H); 1.25 (t, 3H, J = 6.9 Hz) ppm. MS (ESI^+): *m/z*: 408 (M+1). Anal. Calcd. for $C_{23}H_{22}ClN_3O_2$: C, 67.73; H, 5.44; N, 10.30. Found: C, 67.89; H, 5.60; N, 10.07%.

4-(2-Bromo-8-chloro-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylic acid ethyl ester (8). The procedure of Jung *et al*.[6] was adapted. Compound **4** (10g, 25 mmol) and Et_3N (4.1 mL, 30 mmol) were dissolved in CH_2Cl_2 (60 mL). Then, the mixture was cooled at 0 ºC and a solution of Br_3OP (8.6g, 30 mmol) dissolved in CH_2Cl_2 (30 mL) was added dropwise. The reaction was stirred at 0 ºC for 30 min. and then heated to 60 ºC for 10 h. After cooling at RT and washing with water (2x50 mL) the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash chromatography (SiO_2, Hexane/AcOEt 5:1) to give **10** as a white solid (3.5g, 30%). Mp 164–166 ºC. IR (KBr, cm^{-1}): 3398, 1699, 1622, 1417, 1384, 1340, 1276, 1230, 1112, 1066, 723, 612. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.38 (d, 1H, J = 7.9 Hz); 7.26–7.10 (m, 4H); 4.14 (q, 2H, J = 7.1 Hz); 3.91–3.36 (m, 2H); 3.31–3.20 (m, 2H); 3.17–3.04 (m, 2H); 2.90–2.76 (m, 2H); 2.54–2.28 (m, 4H); 1.25 (t, 3H, J = 7.1 Hz) ppm. MS (ESI^+): *m/z*: 463 (M+1). Anal. Calcd. for $C_{22}H_{22}BrClN_2O_2$: C, 57.22; H, 4.80; N, 6.07. Found: C, 57.49; H, 4.60; N, 6.18%.

4-(8-Chloro-2-cyano-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylic acid ethyl ester (6). Compound **8** (0.2g, 0.43 mmol) was suspended in DMF (3 mL) and pyridine (3 drops) and CuCN (0.039 g, 0.43 mmol) were added at RT. The mixture was then heated for 5 h at 180 ºC, then cooled and poured into ammonium hydroxide solution (3.8 mL NH_3 and 3.8 g of crushed ice). The suspension formed was extracted with CH_2Cl_2 (3x5 mL). The organic layer was washed with 5% HCl (2x5 mL), then water (2x5 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography (SiO_2, Hexane/AcOEt 3:1) yielding 0.04g (40%) of compound **6** as a yellow solid. Anal. Calcd. for $C_{23}H_{22}ClN_3O_2$: C, 67.73; H, 5.44; N, 10.30. Found: C, 67.49; H, 5.60; N, 10.18%.

8-Chloro-11-(1-ethoxycarbonylpiperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclo-hepta-[1,2-b]pyridine-2-carboxylic acid methyl ester (9). Compound **6** (0.33g, 0.8 mmol) was

dissolved in CH_2Cl_2 (7 mL) and methanol (7 mL). The mixture was cooled at 0 ºC and HCl gas bubbled through it for 5 hours, then it was stirred at RT for 15h. The solvent was evaporated to dryness and the residue washed with water (50 mL), and extracted with CH_2Cl_2 (3x50 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (SiO_2, hexane/AcOEt 2:1) to give **9** (0.32g, 75%) as a yellow solid. Mp 145–148 ºC. IR (KBr, cm^{-1}): 3455, 2923, 2853, 1697, 1433, 1319, 1279, 1228, 1138, 1114, 1025, 991. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.91 (d, 1H, J = 7.8 Hz); 7.57 (d, 1H, J = 7.8 Hz); 7.21–7.12 (m, 3H); 4.13 (q, 2H, J = 7.1 Hz); 3.95 (s, 3H); 3.88–3.75 (m, 2H); 3.44–3.35 (m, 2H); 3.15–3.08 (m, 2H); 2.96–2.77 (m, 2H); 2.53–2.28 (m, 4H); 1.25 (t, 3H, J = 7.1 Hz) ppm. MS (ESI^+): *m/z*: 441 (M+1). Anal. Calcd. for $C_{24}H_{25}ClN_2O_4$: C, 65.38; H, 5.72; N, 6.35. Found: C, 65.59; H, 5.60; N, 6.14%.

4-(8-Chloro-2-hydroxymethyl-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidine-1-carboxylic acid ethyl ester (2). Compound **9** (0.31g, 0.7 mmol) was dissolved in CH_2Cl_2 and cooled at 0 ºC under N_2 . Then, DIBAL-H (0.5 mL, 3.5 mmol) was added in three portions. After each addition, the reaction mixture was heated at reflux for 16 h. When the reaction was finished (monitored by LC–MS), the mixture was cooled at RT and washed with sat. aq. sodium tartrate. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (SiO_2, hexane/AcOEt 2:1) yielding 0.049g (12%) of **2** as a white solid. Mp 88–90 ºC. IR (KBr, cm^{-1}): 3452, 2922, 2853, 1698, 1683, 1651, 1557, 1455, 1385, 1232, 1081, 667. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.44 (d, 1H, J = 7.8 Hz); 7.19–7.04 (m, 4H); 4.70 (s, 2H); 4.15 (q, 2H, J = 7.1 Hz); 3.79–3.70 (m, 2H); 3.41–3.31 (m, 2H); 3.25–3.16 (m, 2H); 2.91–2.77 (m, 2H); 2.50–2.45 (m, 1H); 2.38–2.28 (m, 3H); 1.25 (t, 3H, J = 7.1 Hz) ppm. MS (ESI^+): *m/z*: 413 (M+1). Anal. Calcd. for $C_{23}H_{25}ClN_2O_3$: C, 66.90; H, 6.10; N, 6.78. Found: C, 67.08; H, 5.91; N, 6.63%.

8-Chloro-11-(1-ethoxycarbonylpiperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclo-hepta[1,2-b]-pyridine-4-carboxylic acid methyl ester (10). Compound **7** (1.26g, 3.1 mmol) was dissolved in CH_2Cl_2 (40 mL) and methanol (40 mL). The mixture was cooled at 0 ºC and HCl gas bubbled through it for 5 h and then it was stirred at RT for 15 h. The solvent was evaporated to dryness and the residue washed with water (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (SiO_2, hexane/AcOEt 2:1) to give **10** (0.67g, 48%) as a yellow solid. Mp 150–153 ºC. IR (KBr, cm^{-1}): 3434, 2925, 2851, 1731, 1698, 1470, 1434, 1279, 1224, 1111, 990, 776. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.48 (d, 1H, J = 4.94 Hz); 7.48 (d, 1H, J = 5.1 Hz); 7.09 (m, 3H); 4.13 (q, 2H, J = 7.1 Hz); 3.93 (s, 3H); 3.78–3.50 (m, 2H); 3.47–3.34 (m, 2H); 3.21–3.11 (m, 2H); 3.03–2.97 (m, 2H); 2.45–2.34 (m, 4H); 1.24 (t, 3H, J = 7.1 Hz) ppm. MS (ESI^+): *m/z*: 441 (M+1). Anal. Calcd. for $C_{24}H_{25}ClN_2O_4$: C, 65.38; H, 5.72; N, 6.35. Found: C, 65.53; H, 5.81; N, 6.44%.

4-(8-Chloro-4-hydroxymethyl-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridino-11-ylidene)-piperidine-1-carboxylic acid ethyl ester (3). Compound **10** (0.3g, 0.68 mmol) was dissolved in CH_2Cl_2 (12 mL) and cooled at 0 ºC under nitrogen. Then, DIBAL-H (0.48 mL, 3.4 mmol) was

added in three portions. After each addition the reaction mixture was refluxed for 16 hours. When the process was finished (monitored by LC–MS), the mixture was cooled at RT, washed with sat. aq. sodium tartrate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash chromatography (SiO_2, hexane/AcOEt 2:1) yielding 0.034g (12%) of **3** as a white solid. Mp 83–85 ºC. IR (KBr, cm^{-1}): 3432, 2923, 2852, 1698, 1651, 1435, 1260, 1225, 1115, 1083, 843, 807. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.43 (d, 1H, J = 4.6 Hz); 7.28–7.22 (m, 1H); 7.13 (m, 3H); 4.70 (s, 2H); 4.15 (q, 2H, J = 7.1 Hz); 3.91–3.70 (m, 2H); 3.49–3.31 (m, 2H); 3.28–3.02 (m, 2H); 2.90–2.78 (m, 2H); 2.5–2.28 (m, 4H); 1.31 (t, 3H, J = 7.1 Hz) ppm. MS (ESI^+): *m/z*: 413 (M+1). Anal. Calcd. for $C_{23}H_{25}ClN_2O_3$: C, 66.90; H, 6.10; N, 6.78. Found: C, 66.76; H, 5.89; N, 6.63%.

Acknowledgements

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References and Notes

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7. Both compounds were identified by HRMS. Calculated exact mass for $C_{23}H_{23}ClN_2O_4$ of 426.1346. Found for **11**: 426.1343. Found for **12**: 426.1348.