An Efficient Synthesis of Polysubstituted 3-Halo-2(1*H*)-Pyridinones

Claude Agami, Luc Dechoux,* Séverine Hebbe, Julien Moulinas

Laboratoire de Synthèse Asymétrique associé au CNRS, Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France
Fax +(33)0144272620; E-mail: dechoux@ccr.jussieu.fr

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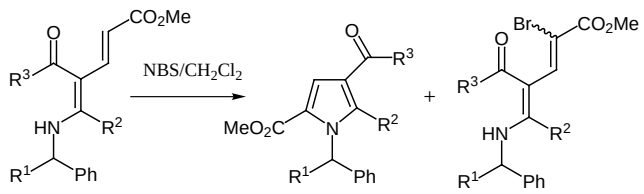
Abstract: A series of 3-halo-2(1*H*)-pyridinones **4** have been synthesized by treatment of δ-dienaminoesters **1** with *N*-halosuccinimide in basic medium. The chemoselectivity of the reaction is discussed.

Key words: pyridinones, pyrroles, δ-dienaminoesters

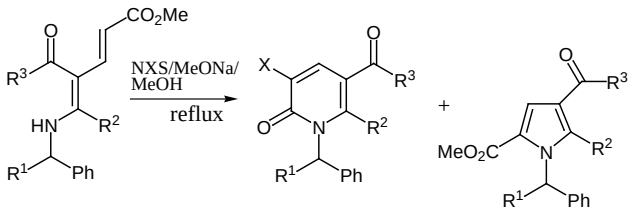
The 2(1*H*)-pyridinone system is a common intermediate for the synthesis of a wide variety of nitrogen heterocycles such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[1] Compounds containing the 2(1*H*)-pyridinone moiety are crucial structural components of numerous biologically active natural products. In particular, they constitute the skeleton of elfamycin antibiotics[2] and the antifungal compound ilicolicin.[3] Simple 2(1*H*)-pyridinones find applications in pharmacology due to their antimicrobial activity.[4] Although many methods for synthesizing 2(1*H*)-pyridinones have been reported,[5] halogenated 2(1*H*)-pyridinones starting from acyclic substrates to our knowledge, have not been described. Moreover, halogenated 2(1*H*)-pyridinones are essential since they allow a means of introducing an alkyl substituent through transition metal catalysis[6] or halogen-metal exchange.[7] It has been found that δ-dienaminoesters **1** can readily be cyclized to 3-halo-2(1*H*)-pyridinones **4** when the reagent, *N*-halosuccinimide is used. This paper reports a complete description of this reaction. In the course of studying the reactivity of δ-dienaminoesters with halogenating reagent, we have recently found that when δ-dienaminoesters **1** are treated with 1.2 equiv of NBS in dichloromethane, pyrroles **2** are formed in good yields (Scheme 1).[8]



1 **2** **3**

Scheme 1

In this reaction, the bromo-δ-dienaminoesters **3**, were formed as by-products in moderate yields. In order to study scope and limitations we checked the reaction under different experimental conditions. We found that adding 1.2 equivalents of NBS to a solution of substrates **1** in methanol containing 1 equivalent of sodium methoxide led to an inversion of the chemoselectivity. The bromo-δ-dienaminoesters **3** were formed within 5 minutes and cyclized[9] to give the substituted 3-bromo-2(1*H*)-pyridinones **4** in good yields after being refluxed 1–6 hours (Scheme 2, Table).



1 **4** **2**

Scheme 2

Examination of the results in the Table shows that this method gives satisfactory results when R^2 is hydrogen (Table, entries 1–3).[10] The 3-bromo-2-(1*H*)-pyridinones **4a**–**c** were formed in good yields. In these cases, the substituent R^1 does not influence the selectivity but only the rate of the reaction. Indeed substitution α to the phenyl group decreases the rate of cyclization (1 hour when R^1 = H and 6 hours when R^1 = Me). The moderate yield obtained with substrate **1c** (Table, entry 3) is due to problems in purification.

In contrast, when R^2 is a methyl group (Table, entries 4, 5), the yields decreased due to the concurrent formation of pyrroles **2d**,**e**. Nevertheless, the ratio of **4**:**2** is still in favor of the expected 3-bromo-2(1*H*)-pyridinones **4d**,**e**. Although the origin of the decrease of selectivity is not clear, it seems that the methyl group stabilizes a carbocation intermediate and facilitates the formation of pyrroles **2**. It should also be noted that a cisoid conformation for the cyclization of compounds **5** into pyrroles **2** is necessary. It is likely that this conformation is more favorable when R^2 = Me (Scheme 3). The β-enaminoketone **1d** (Table, entry 4) showed similar reactivity. The method was extended to the synthesis of 3-iodo- and 3-chloro-2(1*H*)-pyridinones **4f**,**g** (Table, entries 6,7). It is noteworthy that 3 equivalents of NCS and a large excess of sodium methoxide were necessary to complete the reaction.

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Table Synthesis of 3-Halo-2-(1*H*)-pyridinones **4**

Entry	Substrate	R^1	R^2	R^3	X	Product	Ratio **4:2**	Yield (%)
1	**1a**	H	H	OCH_3	Br	**4a**	>95:5	82
2	**1b**	CH_3	H	OCH_3	Br	**4b**	>95:5	83
3	**1c**	CH_2OH	H	OCH_3	Br	**4c**	>95:5	41
4	**1d**	H	CH_3	CH_3	Br	**4d**	63:37	47
5	**1e**	H	CH_3	OCH_3	Br	**4e**	84:16	64
6	**1a**	H	H	OCH_3	I	**4f**	>95:5	84
7	**1a**	H	H	OCH_3	Cl	**4g**	>95:5	37

The selectivity of the reaction (formation of pyridinones **4** versus pyrroles **2**) is dependent not only on the nature of the radical R^2 but also on the basicity of the reaction medium. Under neutral conditions, formation of pyrroles **2** is favoured. In contrast, in basic medium 3-halo-2-(1*H*)-pyridinones **4** are synthesized in good yields. The mechanistic pathway for these transformations involves imines **5** as intermediates (Scheme 3). The reactive intermediates may evolve by processes A (intramolecular displacement of halogen) or B (deprotonation with sodium methoxide) to form pyrroles **2** and halo-δ-dienaminoesters **3** respectively which afford finally the 3-halo-2-(1*H*)-pyridinones **4**.

In conclusion, it appears that this synthetic two or three-step sequence starting from commercially available primary amines is straightforward for the preparation of 3-halo-2(1*H*)-pyridinones **4**. This procedure does not require harsh reaction conditions or sensitive reagents and gives high yields. We are currently investigating the use of 3-bromo-2-(1*H*)-pyridinones **4b**,**c** in asymmetric synthesis in order to prepare polysubstituted enantiopure piperidines.

^{1}H and ^{13}C spectra ($CDCl_3$) were recorded on a Bruker ARX 250 spectrometer at 250 MHz and 63 MHz, respectively. Chemical shifts are reported in ppm from TMS. Optical rotations were reassured with a Perkin-Elmer 141 instrument. Column chromatography was performed on silica gel, 230-400 Mesch (Merck). Melting points were uncorrected and determined with a IA9100 Electrothermal instrument. IR spectra were determined with a Nicolet Avatar 320 FT instrument. Elemental analysis were carried out at the "Service des microanalyse de l'Université Paris VI" at Paris.

δ-Dienaminoesters 1a–c; Typical procedure

To a solution of benzylamine (2 mL, 18.7 mmol) in MeOH (62 mL) was added of methyl propiolate (6.6 mL, 74 mmol). The reaction mixture was refluxed for 2 d and then the solvent evaporated under vacuum. The residue was recrystallized in MeOH to furnish compound **1a** as a white solid (3.08 g; 60%).

δ-Dienaminoester 1a

Mp: 107 °C.

IR (cm^{-1}): 1708, 1666.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.63 (s, 3 H, CO_2CH_3), 3.69 (s, 3 H, CO_2CH_3), 4.39 (s, 2 H, CH_2), 5.97 (d, 1 H, *J* = 15.7 Hz, CH), 7.14−7.33 (m, 7 H, Ar, 2 × CH), 9.10 (m, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 50.9, 51.0 (CO_2CH_3), 52.9 (CH_2), 95.2 (C_q), 108.0 (CH); 127.2 (Ar), 128.1 (Ar), 128,9 (Ar), 136.7 (Ar_q), 143.2 (CH), 157.0 (CH), 169.1 (CO), 169.4 (CO).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.45; H, 6.38; N, 4.99.

δ-Dienaminoester 1b

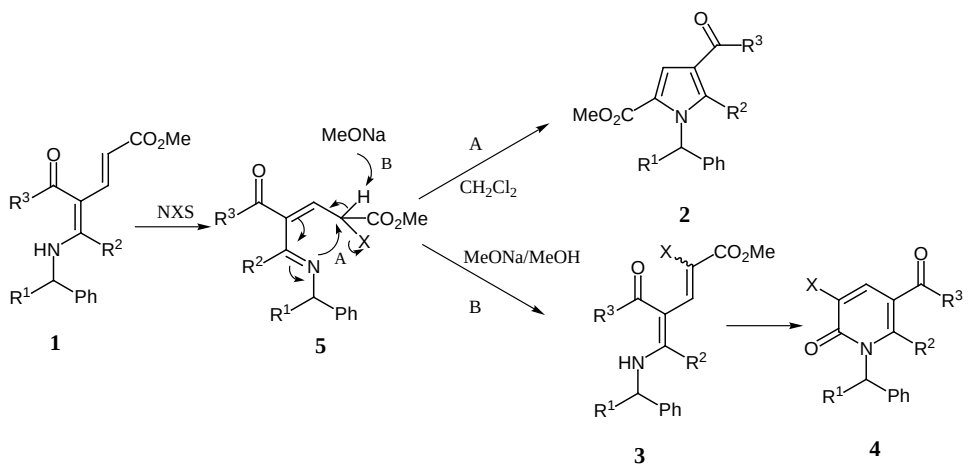
(56%), mp: 63 °C.

$[\alpha]_D^{20}$ +17 (*c* 0.65, $CHCl_3$).

IR (cm^{-1}): 1703, 1666, 1599.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.55 (d, 3 H, *J* = 7 Hz, CH_3), 3.64 (s, 3 H, CO_2CH_3), 3.73 (s, 3 H, CO_2CH_3), 4.48 (quint, 1 H, *J* = 7 Hz, CH), 5.94 (d, 1 H, *J* = 15.5 Hz, CH), 7.12−7.35 (m, 7 H, Ar, 2 × CH), 9.17 (m, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.2 (CH_3), 50.8, 51.0 (CO_2CH_3), 57.9 (CH), 95.0 (CH), 107.8 (C_q), 126.0 (Ar), 127.9 (Ar), 128.9 (Ar), 142.1 (Ar_q), 143.2 (CH), 155.7 (CH), 169.1 (CO), 169.4 (CO).



Scheme 3

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.36; H, 6.64; N, 4.79.

δ-Dienaminoester 1c
(49%), mp: 126 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.20 (s, 1 H, OH), 3.63 (s, 3 H, CO_2CH_3), 3.73 (s, 3 H, CO_2CH_3), 3.79 (dd, 1 H, *J* = 11.5, 7.5 Hz, CH_2), 3.88 (dd, 1 H, *J* = 11.5, 4.5 Hz, CH_2), 4.45 (ddd, 1 H, *J* = 4.5, 7.5, 6.5 Hz, CH), 5.99 (d, 1 H, *J* = 15.5 Hz, CH), 7.23−7.41 (m, 7 H, Ar, 2 × CH), 9.47 (m, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 50.9, 51.1 (CO_2CH_3), 64.5 (CH), 66.2 (CH_2), 95.4 (C_q), 107.1 (CH), 126.8 (Ar), 128.4 (Ar), 129.0 (Ar), 137.5 (C_q), 143.5 (CH), 156.7 (CH), 169.4 (CO), 169.5 (CO).

$[\alpha]_D^{20}$ +20 (*c* 0.15, $CHCl_3$).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94, H, 6.27, N, 4.59. Found: C, 63.23, H, 6.73, N, 4.22.

δ-Dienaminoester 1d
To a solution of benzylamine (1.06 mL, 10 mmol) in MeOH (50 mL) was added of 2,4-pentanedione (1.53 mL, 15 mmol). The reaction mixture was refluxed for 2 h and methyl propiolate (2.5 mL, 28 mmol) was added at r.t. After refluxing for 2 d, the solvent was evaporated under vacuum. The residual oil was chromatographed on silica gel (hexane–EtOAc, 80:20) to furnish **1d** (2.02 g, 74%) as a white solid.

Mp: 60 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.21 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 3.74 (s, 3 H, CO_2CH_3), 4.56 (d, 2 H, *J* = 5.7 Hz, CH_2), 5.59 (d, 1 H, *J* = 15.7 Hz, CH), 7.80 (d, 1 H, *J* = 15.7 Hz, CH), 7.24−7.36 (m, 5 H, Ar), 11.20 (m, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.9 (CH_3), 29.4 ($COCH_3$), 47.6 (CO_2CH_3), 51.3 (CH_2), 95.9 (C_q), 104.9 (C_q), 113.5 (CH), 126.9 (Ar), 127.8 (Ar), 129.0 (Ar), 136.6 (Ar_q), 143.6 (CH), 166.4 (CO), 196.3 (CO).

δ-Dienaminoester 1e
To a solution of benzylamine (2 mL, 18.7 mmol) in MeOH (62 mL) was added methyl acetoacetate (2.4 mL, 22.4 mmol). The reaction mixture was refluxed for 2 h and then methyl propiolate (2.5 mL, 28 mmol) was added at r.t. After 2 d at reflux, the solvent was evaporated under vacuum. The residue was recrystallized in MeOH to furnish compound **1e** as a white solid (4.10 g, 76%). Mp:106 °C.

IR (cm^{-1}): 1693, 1646, 1572.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.75 (s, 3 H, CO_2CH_3), 3.79 (s, 3 H, CO_2CH_3), 4.58 (d, 2 H, *J* = 5.7 Hz, CH_2), 6.12 (d, 1 H, *J* = 15.2 Hz, CH), 7.26−7.42 (m, 5 H, Ar), 7.78 (d, 1 H, *J* = 15.2 Hz, CH), 11.02 (m, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.0 (CH_3), 47.7 (CH_2), 50.8 (CO_2CH_3), 51.0 (CO_2CH_3), 93.8 (C_{IV}), 110.1 (CH), 126.8 (Ar), 127.8 (Ar), 129,0 (Ar), 136.9 (Ar_{CIV}), 140.6 (CH), 166.6 (C_{IV}), 169.8 (CO), 170.8 (CO).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42, H, 6.62, N, 4.84. Found: C, 65.89, H, 6.63, N, 4.84.

3-Bromo-2(1*H*)-pyridinones 4a−e; Typical Procedure
To a solution of NaOMe (21.5 mg, 0.40 mmol) and δ-dienaminoester **1a** (110 mg, 0.40 mmol) in MeOH (4 mL) at r.t. was added NBS (85 mg, 0.48 mmol) in small quantities. The reaction was refluxed for 1 h and solvent evaporated under vacuum. The residue was quenched with an aq solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residual solid was chromatographed on silica gel (hexane–EtOAc, 80:20) to furnish **4a** (128 mg, 82%) as a white solid.

3-Bromo-2(1*H*)-pyridinone 4a
Mp: 139 °C.

IR (cm^{-1}): 1725, 1664.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CO_2CH_3), 5.20 (s, 2 H, CH_2), 7.35 (s, 5 H, H_{Ar}), 8.18 (d, 1 H, *J* = 2.5 Hz, CH), 8.24 (d, 1 H, *J* = 2.5 Hz, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.3 (CO_2CH_3), 54.3 (CH_2), 110.1 (C_q), 115.9 (C_q), 128.5 (Ar, 2 × C), 128.7 (Ar), 129.1 (Ar, 2 × C), 134.8 (Ar), 140.3 (CH), 141.5 (CH), 159.3 (CO), 163.6 (CO).

Anal. Calcd for $C_{14}H_{12}BrNO_3$: C, 52.20, H, 3.75, N, 4.35. Found: C, 51.40, H, 3.92, N, 4.17.

3-Bromo-2(1*H*)-pyridinone 4b
IR (cm^{-1}): 1725, 1666.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.78 (d, 3 H, *J* = 7 Hz, CH_3), 3.81 (s, 3 H, CO_2CH_3), 6.41 (q, 1 H, *J* = 7 Hz, CHAr), 7.27−7.43 (m, 5 H, Ar), 8.04 (d, 1 H, *J* = 2.5 Hz, CH), 8.22 (d, 1 H, *J* = 2.5 Hz, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.2 (CH_3), 52.2 (CO_2CH_3), 55.4 (CH), 110.2 (C_q), 115.5 (C_q), 127.3 (Ar, 2 × C), 128.6 (Ar, C), 129.1 (Ar, 2 × C), 138.7 (CH and Ar), 139.7 (CH), 158.7 (CO), 163.6 (CO).

3-Bromo-2(1*H*)-pyridinone 4c
IR (cm^{-1}): 3445, 1737, 1665.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.70 (s, 1 H, OH), 3.81 (s, 3 H, CO_2CH_3), 4.31 (d, 2 H, *J* = 6 Hz, CH_2), 6.31 (t, 1 H, *J* = 6 Hz, CHAr), 7.34−7.39 (m, 5 H, Ar), 8.24 (s, 2 H, 2 × CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.8 (CO_2CH_3), 61.7 (CH), 62.6 (CH_2), 110.2 (C_q), 115.3 (C_q), 128.0 (Ar, 2 × C), 128.9 (Ar, C), 129.2 (Ar, 2 × C), 135.5 (C_{Ar}), 140.1 (CH), 140.3 (CH), 159.6 (CO), 163.8 (CO).

3-Bromo-2(1*H*)-pyridinone 4d
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 2.61 (s, 3 H, $COCH_3$), 5.49 (s, 2 H, CH_2), 7.13−7.16 (m, 2 H, Ar), 7.24−7.36 (m, 3 H, Ar), 8.15 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.9 (CH_3), 29.5 ($COCH_3$), 49.2 (CH_2), 111.8 (C_q), 118.0 (C_q), 126.4 (Ar, 2 × C), 127.8 (Ar), 128.9 (Ar), 134.9 (Ar), 141.1 (CH), 152.4 (C_q), 159.3 (CO), 196.0 (CO).

3-Bromo-2(1*H*)-pyridinone 4e
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.71 (s, 3 H, CH_3), 3.85 (s, 3 H, CO_2CH_3), 5.49 (s, 2 H, CH_2), 7.13−7.33 (m, 5 H, Ar), 8.35 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.6 (CH_3), 49.1 (CH_2), 52.2 (CO_2CH_3), 109.6 (C_q), 112.0 (C_q), 126.4 (Ar, 2 × C), 127.7 (Ar, C), 128.9 (Ar, 2 × C), 135.0 (Ar), 141.7 (CH), 153.4 (C_{IV}), 159.6 (CO), 164.9 (CO).

3-Iodo-2(1*H*)-pyridinone 4f
To a solution of NaOMe (20.5 mg, 0.38 mmol) and δ-dienaminoester **1a** (105 mg, 0.38 mmol) in MeOH (3.8 mL) at r.t. was added NIS (104 mg, 0.46 mmol) in portions. The reaction was then refluxed for 4 h and then the solvent was evaporated under vacuum. The residue was quenched with an aq solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and chromatographed on silica gel (hexane–EtOAc, 80:20) to yield **4f** (99 mg, 84%) as a colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, CO_2CH_3), 5.12 (s, 2 H, CH_2), 7.19−7.37 (m, 5 H, Ar), 8.13 (d, 1 H, *J* = 2 Hz, CH), 8.40 (d, 1 H, *J* = 2 Hz, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.3 (CO_2CH_3), 54.7 (CH_2), 91.5 (C_q), 111.2 (C_q), 128.5 (Ar, 2 × C), 128.6 (Ar), 129.1 (Ar, 2 × C), 134.9 (Ar), 142.6 (CH), 147.4 (CH), 159.6 (CO), 163.4 (CO).

3-Chloro-2(1*H*)-pyridinone 4g

To a solution of NaOMe (21.5 mg, 0,40 mmol) and δ-dienaminoester **1a** (110 mg, 0.40 mmol) in MeOH (3.8 mL) at r.t. was added NCS (163 mg, 1.20 mmol) in portions. After 1 h, NaOMe (100 mg, 1.85 mmol) was added and the reaction mixture was then refluxed for 4 h and the solvent was evaporated under vacuum. The residue was quenched with an aq solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and chromatographed on silica gel (hexane–EtOAc, 80:20) to yield **4g** (42 mg, 37%) as a colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, CO_2CH_3), 5.14 (s, 2 H, CH_2), 7.20−7.33 (m, 5 H, Ar), 7.96 (d, 1 H, *J* = 2.3 Hz, CH), 8.07 (d, 1 H, *J* = 2.3 Hz, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 51.6 (CO_2CH_3), 51.9 (CH_2), 105.9 (C_q), 109.3 (C_q), 128.3 (Ar, 2 × C), 128.5 (Ar), 128.9 (Ar, 2 × C), 136.2 (Ar), 139.5 (CH), 140.6 (CH), 158.6 (CO), 163.6 (CO).

Bromo-δ-dienaminoester 3a

To a solution of δ-dienaminoester **1a** (276 mg, 1 mmol) in THF at r.t. was added NBS (214 mg, 1.20 mmol) in portions. After 10 min the reaction was quenched with an aq solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), evaporated under vacuum and chromatographed on silica gel (hexane–EtOAc, 70:30) to yield **3a** (267 mg, 75%) as a colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 4.52 (d, 2 H, *J* = 6 Hz, CH_2), 7.27−7.45 (m, 5 H, Ar), 8.30 (s, 1 H, CH), 8.61 (d, 1 H, *J* = 13.5 Hz, CH), 9.53 (t, 1 H, *J* = 6 Hz, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 51.2 (CO_2CH_3), 53.0 (CO_2CH_3), 53.4 (CH_2), 92.6 (C_q), 100.7 (C_q), 127.5 (Ar, 2 × C), 128.2 (Ar), 129.0 (Ar, 2 × C), 136.4 (Ar), 137.4 (CH), 155.6 (CH), 164.5 (CO), 169.2 (CO).

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