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AN EFFICIENT APPROACH FOR THE ONE-POT SYNTHESIS OF ETHYL 4-OXO-4*H*-BENZO[*d*][1,3]OXAZINE-2-CARBOXYLATES

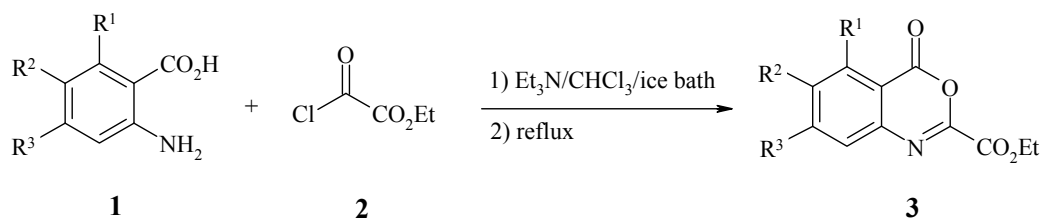
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Abstract – Simple one-pot synthesis of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates is described by condensation reaction of anthranilic acid derivatives with ethyl 2-chloro-2-oxoacetate in CHCl₃. High yields of the products obtain in high purity with simple work-up.

4*H*-3,1-Benzoxazin-4-ones as an important class of fused heterocyclic compounds have considerable interest owing to their industrial¹ and wide biological² applications. They are found in nature^{3,4} and have been used as key intermediates in the synthesis of a wide variety of biologically important heterocyclics such as quinazolinones⁵ and quinolines.⁶ The reactivity and chemical behavior of 4*H*-3,1-benzoxazin-4-ones are due to the susceptibility of the C-4 carbonyl to nucleophilic attack.⁷ The chemistry of 2-alkyl, 2-aryl and 2-hetero substituted 4*H*-3,1-benzoxazin-4-ones has been reviewed by Coppola.⁸

Contrary to the parent compounds 2-alkyl and 2-aryl 4*H*-3,1-benzoxazin-4-ones, very few synthetic routes have ever been published for 2-functionalized substitutions such as 2-carboxylate groups.⁹ The most accessible method for the synthesis of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylate has proven to be the one based on the reaction of anthranilic acid with diethyl oxalate in high temperature and then cyclization reaction of the separated ethyl (2-carboxyphenyl)oxamate with acetic anhydride under reflux condition.^{9a} Since the effective methods to modify the preparation of such highly important compounds are still a worthwhile effort in heterocycles synthesis, herein, we wish to report a simple and efficient protocol for the one-pot synthesis of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates using condensation and cyclization reaction of anthranilic acid derivatives with ethyl 2-chloro-2-oxoacetate in the presence of triethylamine under mild reaction conditions. We observed when the anthranilic acid derivatives **1** react with two equimolar amounts of ethyl 2-chloro-2-oxoacetate in the presence of triethylamine in CHCl₃, ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates **3** are obtained in high yields without need to separation and purification of the intermediates ethyl (2-carboxyphenyl)oxamates, and also without need to use of any catalysts (Scheme 1).



Scheme 1

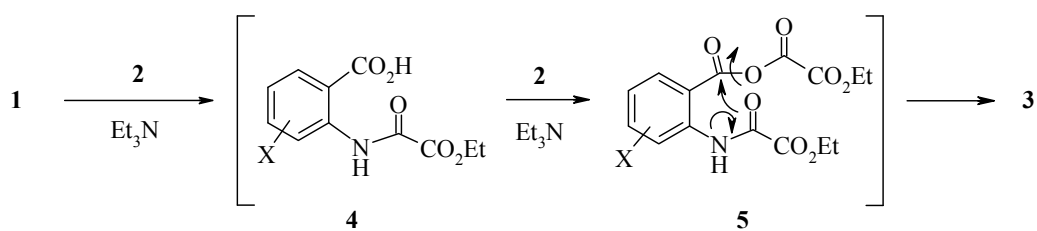
The reaction conditions are mild with very simple work-up of the reaction mixture. Results are summarized in Table 1.

Table 1. Synthesis of compounds **3**^a from the cyclization reaction of anthranilic acid derivatives **1** with ethyl 2-chloro-2-oxoacetate **2** in the presence of Et₃N in CHCl₃

1	3			Time (min) ^b	Yield 3 (%) ^c
	R ¹	R ²	R ³		
a	H	H	H	30	95
b	Me	H	H	40	95
c	H	MeO	MeO	90	93
d	H	EtO-CO-COO	H	120	83
e	H	Br	H	80	80
f	H	Cl	H	90	85
g	H	H	Cl	60	90

^aIn all cases, the products were identified and characterized by their physical and spectral data. ^bReflux times in CHCl₃ for second step. ^cIsolated yields.

The proposed mechanism is shown in scheme 2.



Scheme 2

In the first step, condensation reaction of anthranilic acids **1** with ethyl 2-chloro-2-oxoacetate (**2**) in the presence of Et₃N produces the intermediates **4** and **5** respectively. Then, cyclization reaction of **5** under reflux condition of the mixture in CHCl₃ leads to the desired benzoxazine-4-ones **3**.

The identification and characterization of the products were carried out by means of their physical and spectroscopic data. In IR spectra of compounds **3**, lactone and ester CO-stretching bands observe in about 1770-1755 cm⁻¹ and 1740-1725 cm⁻¹ respectively. Also, these two carbonyl groups appear in about 158-160 ppm in ¹³C NMR. In the case of ¹³C NMR of **3d**, two additional carbonyl groups related to the reaction of OH substitution with **2** are appeared at about 159 and 170 ppm. In all cases molecular ion peaks with good abundances appear in Mass-spectral.

In conclusion, a simple and convenient procedure is described for the one-pot synthesis of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates **3** by first, condensation reaction of anthranilic acid derivatives with ethyl 2-chloro-2-oxoacetate and then, cyclization reaction of the mixture in CHCl₃ under reflux condition. The reactions were carried out under mild conditions in the absence of any catalyst. High yields of the products obtained in high purity with simple work-up.

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10. *General reaction procedure*: In a 25 mL round flask a mixture of 1 mmol of an anthranilic acid derivative **1** and 2.2 mmol of triethylamine was stirred in CHCl₃ at room temperature and then, 2.2 mmol of ethyl chloroformylformate (in the case of **1d**, 3 mmol of Et₃N and 3 mmol of **2**) was added dropwise to this solution and the mixture was stirred in an ice bath for about 30 min. Then, the

reaction mixture was refluxed for the times as indicated in Table 1. The solvent was removed under reduced pressure and the precipitate was washed with 2 mL of *n*-hexane (three times) and filtered to remove the trace residual of ethyl chloroformylformate. The products were washed with 10% aq. NaHCO₃ and then with H₂O and dried in air. They may be recrystallized from *n*-Hexane/EtOAc, if needed.

Ethyl 4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (3a)

Mp 129-131 °C [129-130 °C^{9a, 9d}].

Ethyl 5-methyl-4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (3b)

Mp 109-111 °C. IR (KBr): $\nu = 1773, 1731 \text{ cm}^{-1}$; ¹H NMR (250.1 MHz, CDCl₃): δ (ppm) = 1.40 (t, ³J_{HH} = 7.0 Hz, 3H, CH₃), 2.78 (s, 3H, CH₃), 4.44 (q, ³J_{HH} = 7.0 Hz, 2H, CH₂), 7.39 (d, ³J_{HH} = 7.2 Hz, 1H-Ar), 7.65 (m, 2H-Ar); ¹³C NMR (62.9 MHz, CDCl₃): δ (ppm) = 14.1, 22.4, 63.6, 116.5, 126.6, 133.2, 135.9, 143.4, 146.2, 147.6, 157.0, 157.9; EI-MS (70 eV): m/z (%) = 233 (M⁺, 25); Anal. Calcd for C₁₂H₁₁NO₄ (233.22): C, 61.80; H, 4.75; N, 6.01. Found: C, 61.77; H, 4.79; N, 6.06.

Ethyl 6,7-dimethoxy-4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (3c)

Mp 204-206 °C. IR (KBr): $\nu = 1751, 1728 \text{ cm}^{-1}$; ¹H NMR (250.1 MHz, CDCl₃): δ (ppm) = 1.32 (t, ³J_{HH} = 6.2 Hz, 3H, CH₃), 3.91 and 3.94 (2s, 6H, OCH₃), 4.35 (q, ³J_{HH} = 6.2 Hz, 2H, CH₂), 7.36 (s, 1H-Ar), 7.47 (s, 1H-Ar); ¹³C NMR (62.9 MHz, CDCl₃): δ (ppm) = 14.4, 56.6, 57.0, 63.1, 107.9, 109.9, 111.2, 141.1, 146.7, 151.4, 156.6, 158.0, 158.1; EI-MS (70 eV): m/z (%) = 279 (M⁺, 59); Anal. Calcd for C₁₃H₁₃NO₆ (279.24): C, 55.92; H, 4.69; N, 5.02. Found: C, 55.97; H, 4.65; N, 4.98.

Ethyl 6-(ethyl oxalato)-4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (3d)

Mp 139-141 °C. IR (KBr): $\nu = 1786, 1769, 1743 \text{ cm}^{-1}$; ¹H NMR (250.1 MHz, CDCl₃): δ (ppm) = 1.34-1.26 (m, 6H, CH₃), 4.38-4.26 (m, 4H, CH₂), 7.69-7.36 (m, 3H-Ar); ¹³C NMR (62.9 MHz, CDCl₃): δ (ppm) = 14.2, 14.4, 62.4, 63.1, 112.2, 119.9, 125.7, 137.5, 144.8, 147.5, 154.1, 158.2, 158.6, 159.8, 169.5; EI-MS (70 eV): m/z (%) = 335 (M⁺, 5); Anal. Calcd for C₁₅H₁₃NO₈ (335.26): C, 53.74; H, 3.91; N, 4.18. Found: C, 53.71; H, 3.93; N, 4.15.

Ethyl 6-bromo-4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (3e)

Mp 165-167 °C. IR (KBr): $\nu = 1758, 1735 \text{ cm}^{-1}$; ¹H NMR (250.1 MHz, CDCl₃): δ (ppm) = 1.45 (t, ³J_{HH} = 6.2 Hz, 3H, CH₃), 4.51 (q, ³J_{HH} = 6.2 Hz, 2H, CH₂), 7.32 (s, ³J_{HH} = 8.2 Hz, 1H-Ar), 8.11 (s, 1H-Ar), 8.52 (d, ³J_{HH} = 8.2 Hz, 1H-Ar). ¹³C NMR (62.9 MHz, CDCl₃): δ (ppm) = 14.6, 64.1, 117.1, 119.3, 122.4, 134.8, 137.5, 139.3, 155.3, 160.7, 169.3. EI-MS (70 eV): m/z (%) = 299 [(M⁺ + 2), 10], 297 (M⁺, 9); Anal. Calcd for C₁₁H₈BrNO₄ (298.09): C, 44.32; H, 2.70; N, 4.70. Found: C, 44.35; H, 2.68; N, 4.71.

Ethyl 6-chloro-4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (3f)

Mp 169-171 °C. IR (KBr): $\nu = 1767, 1739 \text{ cm}^{-1}$; ¹H NMR (250.1 MHz, CDCl₃): δ (ppm) = 1.42 (t, ³J_{HH} = 6.5 Hz, 3H, CH₃), 4.46 (q, ³J_{HH} = 6.5 Hz, 2H, CH₂), 7.69 (d, ³J_{HH} = 8.2 Hz, 1H-Ar), 7.96 (dd, ³J_{HH} = 8.2 Hz, ⁴J_{HH} = 1.5 Hz, 1H-Ar), 8.35 (d, ³J_{HH} = 1.5 Hz, 1H-Ar); ¹³C NMR (62.9 MHz, CDCl₃): δ (ppm) = 14.0, 63.9, 119.5, 124.6, 130.2, 131.4, 140.2, 143.7, 147.8, 156.4, 157.5; EI-MS (70 eV): m/z (%) = 255 [(M⁺ + 2), 6], 253 (M⁺, 18); Anal. Calcd for C₁₁H₈ClNO₄ (253.64): C, 52.09; H, 3.18; N, 5.52. Found: C, 52.12; H, 3.20; N, 5.49.

Ethyl 7-chloro-4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (3g)

Mp 107-109 °C. IR (KBr): $\nu = 1759, 1738 \text{ cm}^{-1}$; ¹H NMR (250.1 MHz, CDCl₃): δ (ppm) = 1.44 (t, ³J_{HH} = 7.2 Hz, 3H, CH₃), 4.49 (q, ³J_{HH} = 7.2 Hz, 2H, CH₂), 7.61 (d, ³J_{HH} = 8.2 Hz, 1H-Ar), 7.82 (s, 1H-Ar), 8.18 (d, ³J_{HH} = 8.2 Hz, 1H-Ar); ¹³C NMR (62.9 MHz, CDCl₃): δ (ppm) = 14.0, 63.8, 116.5, 128.4, 130.2, 131.2, 143.5, 145.9, 148.8, 156.9, 157.5; EI-MS (70 eV): m/z (%) = 255 [(M⁺ + 2), 4], 253 (M⁺, 11); Anal. Calcd for C₁₁H₈ClNO₄ (253.64): C, 52.09; H, 3.18; N, 5.52. Found: C, 52.13; H, 3.16; N, 5.49.