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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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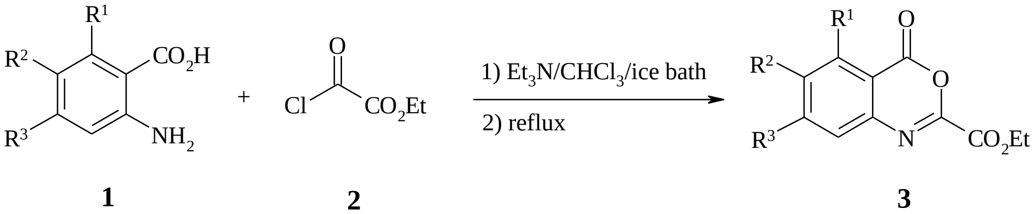
Abstract – Simple one-pot synthesis of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates is described by condensation reaction of anthranilic acid derivatives with ethyl 2-chloro-2-oxoacetate in $CHCl_3$. High yields of the products obtain in high purity with simple work-up.

4*H*-3,1-Benzoxazin-4-ones as an important class of fused heterocyclic compounds have considerable interest owing to their industrial[1] and wide biological[2] 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 quinazolinones[5] 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 codition.[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 $CHCl_3$, 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).



1 **2** **3**

Scheme 1

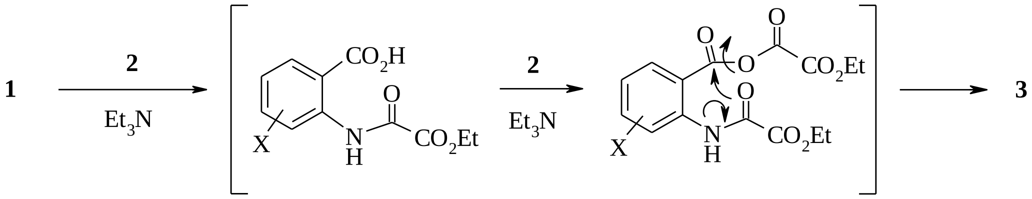
The reaction conditions are mild with very simple work-up of the reaction mixture. Results are summarized in Table 1.

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 Et_3N in $CHCl_3$

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

[a]In all cases, the products were identified and characterized by their physical and spectral data. [b]Reflux times in $CHCl_3$ for second step. [c]Isolated yields.

The proposed mechanism is shown in scheme 2.



4 **5**

Scheme 2

In the first step, condensation reaction of anthranilic acids **1** with ethyl 2-chloro-2-oxoacetate (**2**) in the presence of Et_3N produces the intermediates **4** and **5** respectively. Then, cyclization reaction of **5** under reflux condition of the mixture in $CHCl_3$ 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 ^{13}C NMR. In the case of ^{13}C 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 $CHCl_3$ 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 $CHCl_3$ at room temperature and then, 2.2 mmol of ethyl chloroformylformate (in the case of **1d**, 3 mmol of Et_3N and 3 mmol of **2**) was added dropwised 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. $NaHCO_3$ and then with H_2O 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 ºC [129-130 ºC[9a,9d]].

Ethyl 5-methyl-4-oxo-4H-benzo[d][1,3]oxazine-2-carboxylate (**3b**)
Mp 109-111 ºC. IR (KBr): ν = 1773, 1731 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.40 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 2.78 (s, 3H, CH_3), 4.44 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 7.39 (d, $^3J_{HH}$ = 7.2 Hz, 1H-Ar), 7.65 (m, 2H-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): 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 $C_{12}H_{11}NO_4$ (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 ºC. IR (KBr): ν = 1751, 1728 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.32 (t, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 3.91 and 3.94 (2s, 6H, OCH_3), 4.35 (q, $^3J_{HH}$ = 6.2 Hz, 2H, CH_2), 7.36 (s, 1H-Ar), 7.47 (s, 1H-Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): 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 $C_{13}H_{13}NO_6$ (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 ºC. IR (KBr): ν = 1786, 1769, 1743 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.34-1.26 (m, 6H, CH_3), 4.38-4.26 (m, 4H, CH_2), 7.69-7.36 (m, 3H- Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$): 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 $C_{15}H_{13}NO_8$ (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 ºC. IR (KBr): ν = 1758, 1735 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.45 (t, $^3J_{HH}$ = 6.2 Hz, 3H, CH_3), 4.51 (q, $^3J_{HH}$ = 6.2 Hz, 2H, CH_2), 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). ^{13}C NMR (62.9 MHz, $CDCl_3$): 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 $C_{11}H_8BrNO_4$ (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 ºC. IR (KBr): ν = 1767, 1739 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.42 (t, $^3J_{HH}$ = 6.5 Hz, 3H, CH_3), 4.46 (q, $^3J_{HH}$ = 6.5 Hz, 2H, CH_2), 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); ^{13}C NMR (62.9 MHz, $CDCl_3$): 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 $C_{11}H_8ClNO_4$ (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 ºC. IR (KBr): ν = 1759, 1738 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$): δ (ppm) = 1.44 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 4.49 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2), 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); ^{13}C NMR (62.9 MHz, $CDCl_3$): 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 $C_{11}H_8ClNO_4$ (253.64): C, 52.09; H, 3.18; N, 5.52. Found: C, 52.13; H, 3.16; N, 5.49.