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A simple and expedient method for the stepwise synthesis of 2-ethoxy-(4*H*)-3,1-benzoxazine-4-ones

Asrin Bahmani, Mahnaz Sharafi-Kolkeshvandi, Farzad Nikpour *

Department of Chemistry, Faculty of Sciences, University of Kurdistan, P.O. Box 66315-416, Sanandaj, Iran

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Abstract

A simple and practical route is described for the synthesis of 2-ethoxy-(4*H*)-3,1-benzoxazine-4-ones using the coupling reaction of anthranilic acid derivatives with diethyl dicarbonate following with fast cyclization of the carbamate adduct with a dehydrocyclization agent such as cyanuric chloride and *N*,*N*′-dicyclohexylcarbodiimide in PEG at room temperature. High yields of the products obtained under mild reaction conditions with simple work-up of the reaction mixture.
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Keywords: 2-Ethoxy-(4*H*)-3,1-benzoxazine-4-ones; Diethyl dicarbonate; Cyanuric chloride; *N*,*N*′-Dicyclohexylcarbodiimide; Dehydrocyclization reagent

2-Substituted 4*H*-3,1-benzoxazin-4-one and its derivatives are used directly or indirectly in many clinical applications [1]. Because of the electronically unsaturated character of 4*H*-3,1-benzoxazinones, they are not satisfactorily stable rings. Thus, one of the most important features in 4*H*-3,1-benzoxazinones chemistry is their use as key starting materials for further transformations in design and synthesis of biologically active compound [2,3]. The chemistry of 2-substituted (4*H*)-3,1-benzoxazin-4-ones has been reviewed by Coppola [4].

Although there are many methods for the synthesis of 2-amino- and 2-alkylthio-(4*H*)-3,1-benzoxazine-4-ones [4a], however, few synthetic routes have ever been reported for 2-alkoxy substituents such as 2-ethoxy-(4*H*)-3,1-benzoxazin-4-ones with most being, limited in substrate scope [5,6]. The most accessible method for the synthesis of 2-alkoxy-(4*H*)-3,1-benzoxazine-4-ones has been proved to be the one based on the coupling reaction of anthranilic acid with alkyl chloroformate [7,9]. A dehydrative cyclization agent such as alkyl chloroformates, acetic anhydride, concentrated sulfuric acid, thionyl chloride and phosphorus oxychloride has been used to effect the cyclization of the produced carbamates [4a]. However, many of these methods have drawbacks or limitations such as the use of expensive and very toxic reagents, harsh reaction conditions, unsuitable for sensitive substituents on aromatic ring and produce of low to moderate yields of 2-ethoxybenzoxazin-4-ones. Herein, a practical, fast and convenient protocol for the synthesis of the title compounds is described. For the first step, we used diethyl dicarbonate in place of ethyl chloroformate. It is readily available, more stable than ethyl chloroformate and in reaction with a nucleophile such as anthranilic acid derivatives eliminates a molecule of CO_2 and EtOH which are green compounds. In the second step,

* Corresponding author.
E-mail address: fnikpour@uok.ac.ir (F. Nikpour).

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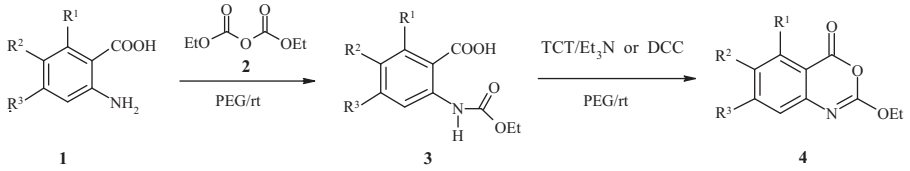


Scheme 1.

N,*N*′-dicyclohexylcarbodiimide (DCC) and 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, TCT) [10] were used as dehydrocyclization agent in PEG. They are significantly easier to handle and simple to use in organic synthesis in comparison with the mentioned dehydrocyclization agents. They have been used in benzoxazin-4-ones synthesis previously; however, the reaction conditions or the results are not satisfactory. For example, TCT was used under reflux conditions in toluene during very long reaction times [11] and low to moderate yields obtained using DCC in pyridine [5]. All of the reaction processes were carried out at room temperature and in PEG as an excellent green solvent (Scheme 1).

The results show that anthranilic acid derivatives react readily with diethyl dicarbonate and the produced carbamates cyclize clicky [12] with DCC or TCT in PEG. The reaction conditions are mild without need to use of any catalyst and with simple work-up of the reaction mixture. Also, this method could be utilized for the synthesis of a variety of substituents on aromatic ring. Results are summarized in Table 1.

As it is observed in Table 1, electron-donating groups increase the coupling reaction rate probably because they increase the nucleophile strength; however, electron-withdrawing substituents decrease the rate of carbamate formation. In the case of **1g**, the 5-OH substituent reacts with diethyl dicarbonate in the same reaction conditions employed. Thus, the produced EtO-CO-O group decreases the rate of carbamate formation. We observed no substituent effects on the rate of dehydrocyclization. Besides, Table 1 shows that TCT gives higher yields of the desired benzoxazine-4-ones **4** in comparison with DCC probably because of easier work-up of **4** from the reaction mixture when TCT is used. The plausible mechanism is proposed in Scheme 2.

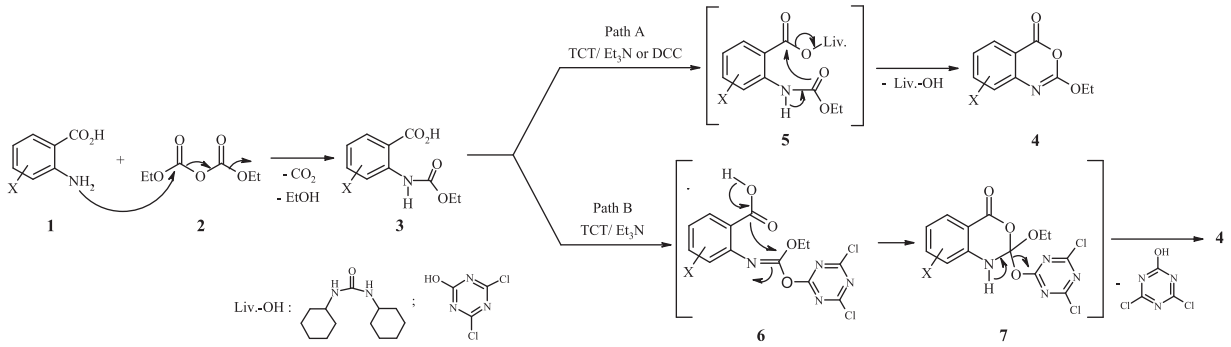
It is reasonable to assume that carbamates of **3** are produced by nucleophilic attack of anthranilic acids **1** to diethyl dicarbonate. In the second step, the reaction seems to proceed through the nucleophilic attack of the carboxyl oxygen **3** to the cyclization reagent and formation of the intermediates **5** (Path A) or through the carbamate carbonyl oxygen to TCT and formation of the intermediates **6** and **7** (Path B) which undergo a fast cyclization reaction to produce the desired benzoxazine-4-one **4** with the elimination of living group. Since the conversion of the carboxyl OH to a good living group is more common way, the pathway A is the more liable route for carrying out and progression of the reaction.

The identification and characterization of the products were carried out by their physical and spectroscopic data [13] and comparison of them with those of authentic samples. In IR spectra, C=O and C=N stretching bands were observed in about 1780–1745 cm^{-1} and 1650–1630 cm^{-1}, respectively. In the case of **4g** the carbonate C=O stretching

Table 1
Synthesis of **4** from the reaction of anthranilic acids **1a–g** with diethyl dicarbonate and dehydrocyclization reaction of carbamates **3** with DCC or TCT in PEG-400 at room temperature.

1	R^1	R^2	R^3	Time (h)[a]	Yield **3** (%)[b]	Yield **4** (%)[c]	Yield **4** (%)[d]
a	H	H	H	1.5	85	81	90
b	H	OMe	OMe	0.5	90	85	90
c	Me	H	H	0.5	90	85	85
d	H	Cl	H	4	85	77	80
e	H	Br	H	4	80	70	90
f	H	H	Cl	4	80	70	82
g	H	OH	H	3	85[e]	84[e]	80[e]

[a] For preparation of **3**.
[b] Isolated yields.
[c] Isolated yields with DCC.
[d] Isolated yields with TCT.
[e] R^2: EtO-CO-O.



Scheme 2.

band was observed in about 1730 cm^{-1}. The appearance of C4-carbon peak in about 158–156 ppm in ^{13}C NMR is a good reason for the formation of benzoxazine-4-one ring. In all cases molecular ion peaks with good to high abundances appear in mass-spectral.

In conclusion, we have reported an expedient and highly efficient method for the synthesis of various substituents of 2-ethoxy-(4*H*)-benzoxazin-4-ones under mild reaction conditions. The coupling reaction of anthranilic acid derivatives with diethyl dicarbonate following with dehydrocyclization of the produced carbamates with TCT or DCC in PEG, leads to the desired benzoxazin-4-ones. This protocol, especially when TCT is used as cyclodehyrating reagent, provides a practical alternative to the existing available methods for the synthesis of 2-ethoxy-(4*H*)-benzoxazin-4-ones as an important class of pharmacological active compounds. Some notable advantages of this procedure are the use of PEG as green solvent, the use of simple and available reagents, mild reaction conditions, click dehydrocyclization reaction process without need to use of any catalyst and simplicity of all of the reaction steps which produces high yields of the products with simple work-up of the reaction mixture.

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[13] Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-250 AVANCE instrument (250.1 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts are given in ppm (δ) relative to internal *TMS*, and coupling constants *J* are reported in Hz. Mass spectra were recorded with a Agilent-5975C mass spectrometer operating at an ionization potential of 70 eV. PEG with molecular weight 400 was used in all reactions. *General reaction procedure*: *Step 1:* In a 25 mL round flask, an anthranilic acid derivative **1** (3 mmol) was dissolved in PEG-400 (1.5 mL) and then diethyl dicarbonate (4.5 mmol) was added dropwise (in the case of **1g**, 7 mmol diethyl dicarbonate was used). The reaction mixture was stirred at room temperature for the times as indicated in Table 1. After of completion of the reaction, the residual of diethyl dicarbonate was removed under

reduced pressure. The carbamates **3** were washed with cold water and dried in air. *Step 2: TCT as dehydrocyclization reagent:* In a 25 mL round flask, a mixture of a carbamate derivative **3** (1 mmol), TCT (1 mmol), triethylamine (1 mmol) and PEG-400 (0.5 mL) was stirred at room temperature. The reaction was completed immediately. The mixture was washed with cold water (three times) and dried in air. The benzoxazine-4-ones **4** may be recrystallized from *n*-hexane/THF, if needed. *Step 2: DCC as dehydrocyclization reagent:* In a 25 mL round flask, a mixture of a carbamate derivative **3** (1 mmol), DCC (1 mmol), triethylamine (1 mmol) and PEG-400 (0.5 mL) was stirred at room temperature. The reaction was completed immediately. The mixture was poured onto cold water and extracted with $CHCl_3$. The organic layer was separated, dried over $MgSO_4$, and then, the solvent was removed under reduced pressure. The benzoxazine-4-ones **4** may be recrystallized from *n*-hexane/THF, if needed. *2-Ethoxy-(4H)-3,1-benzoxazine-4-one* (**4a**): White solid, mp: 87–89 °C (Lit. 88–90 °C) [6,8]. *2-Ethoxy-6,7-dimethoxy-(4H)-3,1-benzoxazine-4-one* (**4b**): White solid, mp: 164–166 °C (Lit. 155–156 °C) [5,8a]. IR (KBr): υ (cm^{-1}) = 1747 (C═O), 1630 (C═N). ^{1}H NMR (250 MHz in $CDCl_3$): δ 7.37 (s, 1H–Ar), 6.80 (s, 1H–Ar), 4.43 (q, 2H, $^3J_{HH}$ = 6.7 Hz, CH_2), 3.95 and 3.90 (2s, 6H, OCH_3), 1.41 (t, 3H, $^3J_{HH}$ = 6.7, CH_3). ^{13}C NMR (62.5 MHz in $CDCl_3$): δ 159.3, 156.7, 154.5, 147.7, 144.8, 107.8, 106.4, 106.3, 65.7, 56.4, 56.2, 14.0. EI-MS (70 eV): *m/z* (%) 251 ($M^{+\bullet}$, 100). *2-Ethoxy-5-methyl-(4H)-3,1-benzoxazine-4-one* (**4c**): White solid, mp: 102–104 °C (Lit. 104–105 °C) [5,8a]. *6-Chloro-2-ethoxy-(4H)-3,1-benzoxazine-4-one* (**4d**): white solid, mp: 83–85 °C. IR (KBr): υ (cm^{-1}) = 1778 (C═O), 1638 (C═N). ^{1}H NMR (250 MHz in $CDCl_3$): δ 7.98 (s, 1H–Ar), 7.60 (d, $^3J_{HH}$ = 8.5 Hz, 1H–Ar), 7.31 (d, $^3J_{HH}$ = 8.5 Hz, 1H–Ar), 4.48 (q, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 1.43 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3). ^{13}C NMR (62.5 MHz in $CDCl_3$): δ 158.4, 154.6, 146.8, 136.9, 131.1, 128.0, 126.8, 115.4, 66.3, 14.0. EI-MS (70 eV): *m/z* (%) 225 ($M^{+\bullet}$, 56), 227 [($M^{+\bullet}$ + 2), 18]. *6-Bromo-2-ethoxy-(4H)-3,1-benzoxazine-4-one* (**4e**): White solid, mp: 85–87 °C (Lit. 87–89 °C) [5]. *7-Chloro-2-ethoxy-(4H)-3,1-benzoxazine-4-one* (**4f**): White solid, mp: 80–82 °C. IR (KBr): υ (cm^{-1}) = 1780 (C═O), 1622 (C═N). ^{1}H NMR (250 MHz in $CDCl_3$): δ 7.99 (d, $^3J_{HH}$ = 8.5 Hz, 1H–Ar), 7.37 (d, $^4J_{HH}$ = 1.5 Hz, 1H–Ar), 7.26 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.5 Hz, 1H–Ar), 4.49 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2), 1.43 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3). ^{13}C NMR (62.5 MHz in $CDCl_3$): δ 158.7, 155.3, 149.4, 143.1, 130.1, 126.4, 125.1, 112.7, 66.4, 14.0. EI-MS (70 eV): *m/z* (%) 225 ($M^{+\bullet}$, 38), 227 [($M^{+\bullet}$ + 2), 13]. *2-Ethoxy-6-(ethyl carbonato)-(4H)-3,1-benzoxazine-4-one* (**4g**): White solid, mp: 69–71 °C. IR (KBr): υ (cm^{-1}) = 1772 (C═O), 1732 (C═O), 1633 (C═N). ^{1}H NMR (250 MHz in $CDCl_3$): δ 8.43 (s, 1H–Ar), 7.72 (d, $^3J_{HH}$ = 7.5 Hz, 1H–Ar), 7.44 (d, $^3J_{HH}$ = 7.5 Hz, 1H–Ar), 4.33-4.22 (m, 4H, $2CH_2$), 1.45–1.32 (m, 6H, $2CH_3$). ^{13}C NMR (62.5 MHz in $CDCl_3$): δ 158.6, 154.6, 154.5, 140.2, 139.8, 132.5, 126.0 (2C), 118.2, 63.7, 63.5, 14.6, 14.0. EI-MS (70 eV): *m/z* (%) 279 ($M^{+\bullet}$, 16).