Guanidinum Chloride as Dehydrocyclization Agent in the Synthesis of 2-Fuctionalized (4*H*)-3,1-Benzoxazine-4-ones

Farzad Nikpour,* Asrin Bahmani, Forugh Havasi, and Mahnaz Sharafi-Kolkeshvandi

Department of Chemistry, Faculty of Sciences, University of Kurdistan, Pasdaran Blvd., P.O. Box: 66135-416, Sanandaj, Iran
*E-mail: fnikpour@uok.ac.ir; farzad_nikpour@yahoo.com

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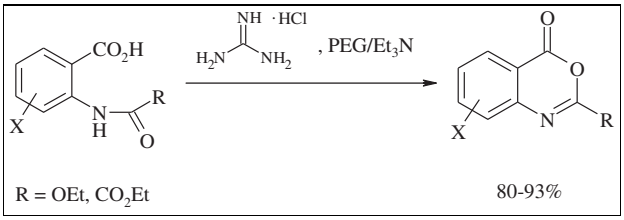

A facile and expedient route for the synthesis of 2-ethoxy- and 2-(ethylcarboxylate)-(4*H*)-3,1-benzoxazine-4-ones is described using guanidinium chloride as a safe and convenient dehydrocyclization agent. High yields of the products obtain under mild reaction conditions without need to use of any catalyst and with easy work-up of the reaction mixture.

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INTRODUCTION

2-Functionalized (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 due to the susceptibility of the C-4 carbonyl to nucleophilic attack, they are not satisfactorily stable rings. Especially, hetero substituents and chemically active functional groups on C-2 position affect the reactivity and the reaction rate of them. 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].

In general, 2-carbon-containing substituents and 2-alkoxy (4*H*)-3,1-benzoxazine-4-ones are formed from the coupling reaction of anthranilic acid derivatives with an acyl chloride or alkyl chloroformate, and then, a dehydrative cyclization agent such as ethyl chloroformate [5], acetic anhydride [6], concentrated sulfuric acid [7], thionyl chloride [8], phosphorus oxychloride [9], dicyclohexylcarbodiimide (DCC) [9], and cyanuric chloride [10] has been used to effect the cyclization of the produced amides or carbamates. Although some of these methods are useful, many of them have drawbacks or limitations such as the use of expensive and very toxic reagents, harsh reaction conditions, unsuitable for unstable substituents on aromatic ring and produce of low to moderate yields of the product. Thus, there is further scope to explore a mild and efficient method for the synthesis of the title compounds. No doubt, general effective methods to synthesize or to modify the preparation of biologically active compounds using nontoxic and simple molecules with different functionalities are worthwhile effort in organic syntheses.

RESULTS AND DISCUSSION

With the aim of extending synthetic methods and in continuation of our recent work on the synthesis of 2-(ethylcarboxylate)-(4*H*)-3,1-benzoxazine-4-ones [11], we now focused our attention on the simple and safe methods for dehydrocyclization reactions. Herein, a practical and green protocol for the synthesis of some benzoxazine-4-ones is described using guanidinium chloride [12] for the first time as dehydrocyclization agent. It is significantly easier to handle and safe to use in organic synthesis in comparison with the mentioned ones. The results of synthesis of 2-ethoxy-(4*H*)-3,1-benzoxazin-4-ones show that carbamates **3** [13] dehydrocyclized clickly [14] in the presence of guanidinium chloride without need to use of any catalyst (Scheme 1). All of the reaction processes were carried out in PEG as an excellent green solvent with easy work-up of the reaction mixture. Also, this method could be utilized for the synthesis of a variety of substituents on aromatic rings. Results are summarized in Table 1.

As it is observed in Table 1, electron-donating groups increase the formation rate of carbamate **3** probably because they increase the nucleophile strength; however, electron-withdrawing substituents decrease the coupling reaction rate. We observed no substituent effects on the rate of dehydrocyclization.

To emphasized the ability of guanidinium chloride as a general dehydrative cyclization agent in organic syntheses, we examined the preparation of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates **7** [11] from the amides **6**. The experiments showed that high yields of **7** obtained under mild reaction conditions with easy work-up the reaction mixture (Scheme 2). However, the reaction rates are not click here and need 0.5–3 h for cyclization probably

Scheme 1

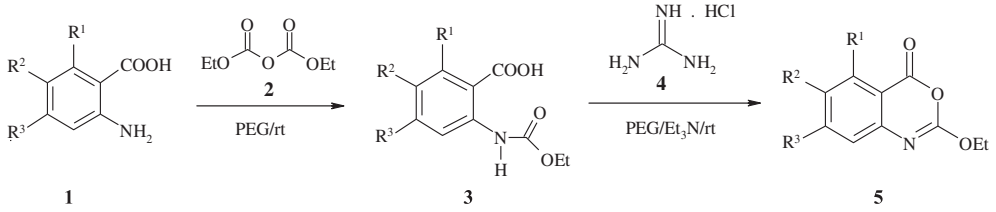


Table 1

Synthesis of benzoxazin-4-ones **5** from the reaction of anthranilic acids **1a–g** with diethyl dicarbonate and dehydrocyclization reaction of carbamates **3** with guanidinium chloride in PEG-400 at room temperature.

1	R^1	R^2	R^3	Time (h)[a]	Yield **3** (%)[b]	Yield **5** (%)[b]
a	H	H	H	1.5	85	85
b	H	OMe	OMe	0.5	90	93
c	Me	H	H	0.5	90	90
d	H	Cl	H	4	85	86
e	H	Br	H	4	80	88
f	H	H	Cl	4	80	90
g	H	OH	H	3	85[c]	92[c]

[a]For preparation of **3**.
[b]Isolated yields.
[c]R^2: EtO–CO–O.

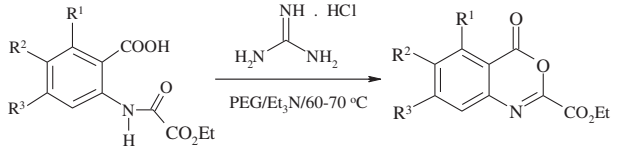
because of more electron-withdrawing effect of the 2-ethyl carcoxylate group that causes to reduce the nucleophilic strength of carbonyl oxygen of the amide in cyclization process (Scheme 3).

According to the obtained results and also based on the severe inclination of guanidine to convert to urea by absorption of water, the plausible mechanisms are proposed for cyclization step in Scheme 3.

Although we made no attempts to characterize the produced intermediates, it is reasonable to assume that the reaction proceeds through the nucleophilic attack of the carboxyl oxygen of carbamates **3** or amides **6** to guanidine and formation of the intermediate **8** (path A) or through the path B by nucleophilic attack of the carbamate oxygen **3** or carbonyl oxygen of the amides **6** to guanidine and formation of the intermediates **9**, which undergo a fast cyclization reaction to produce the desired benzoxazine-4-one **5** or **7** with the elimination of a molecule of urea. Because the conversion of the carboxyl OH to a good living group is fast and more common in organic synthesis, pathway A is the more liable route for carrying out and progression of the reaction.

The identification and characterization of products **5** and **7** were deduced from their physical and spectroscopic data and comparison of them with those of authentic samples. In IR spectra of **5**, 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 **5g**, an additional C═O stretching was observed in about 1730 cm^{-1} because of the carbonate formation. The appearance of C4-carbon peak in about 156–158 ppm in ^{13}C NMR is a good reason for the formation of benzoxazine ring. In IR spectra of **7**, lactone and ester CO-stretching bands were observed 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 **7g**, two additional carbonyl groups related to 6-substitution appeared at about 159 and 170 ppm. In all cases, molecular ion peaks with good to high abundances appear in mass spectral.

Scheme 2

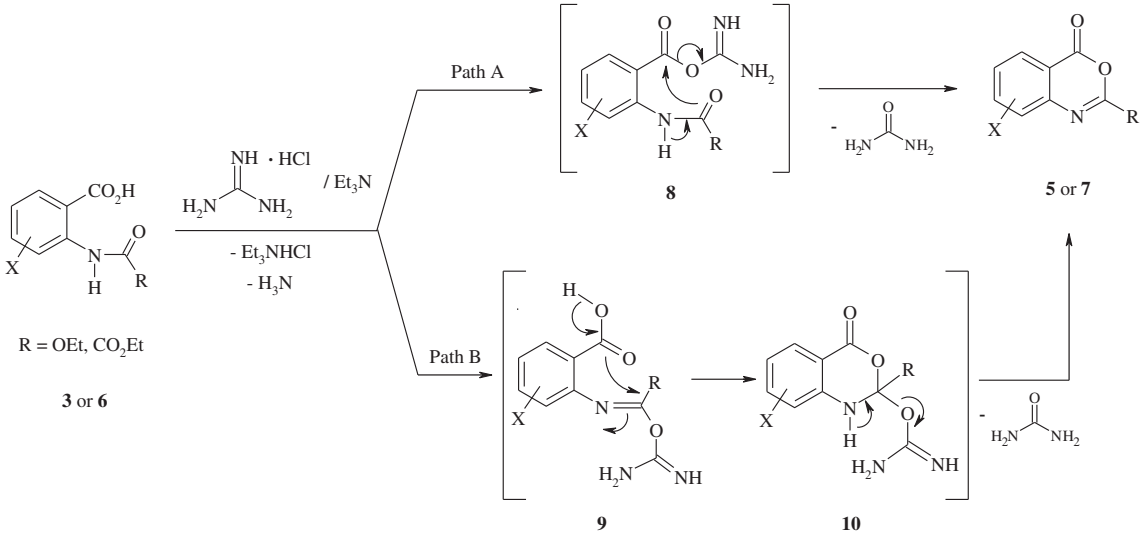


	R^1	R^2	R^3	Time (h)	Isolated yields **7** (%)
a	H	H	H	1.5	85
b	H	OMe	OMe	1.5	90
c	Me	H	H	0.5	92
d	H	Cl	H	2.5	85
e	H	Br	H	2.5	80
f	H	H	Cl	2	82
g	H	EtO_2C-COO	H	3	83

CONCLUSIONS

This protocol provides a practical alternative to the existing available methods for the synthesis of some 2-functionalized (4*H*)-benzoxazin-4-ones as an important class of clinical active compounds. The coupling reaction of anthranilic acid derivatives with suitable reagents following with dehydrocyclization of the produced carbamates or amides with guanidinium chloride leads to the desired benzoxazin-4-ones. The notable advantages of this procedure are the use of readily available and nontoxic reagents and solvent especially the use of guanidinium chloride for the first time as dehydrative cyclization agent that causes cyclization reaction without need to use of any catalyst. Also, mild reaction conditions and simplicity of all

Scheme 3



of the reaction steps cause to produce high yields of the products with easy work-up of the reaction mixture. Guanidinium chloride can be a general and suitable reagent for many dehydrocyclization reactions in organic synthesis.

EXPERIMENTAL

Melting points were measured with an Electrothermal 9100 apparatus (Rochford, UK). IR spectra were measured with a Shimadzu IR-460 spectrometer (Kyoto, Japan). NMR spectra were recorded with a Bruker DRX-250 AVANCE (Rheinstetten, Germany) 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 an Agilent-5975C inert XL MSD mass spectrometer (USA) operating at an ionization potential of 70 ev. Elemental analyses of C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer (Hanau, Germany). PEG with molecular weight 400 was used in all reactions.

General reaction procedure.

Synthesis of the carbamates 3. In a 25 mL round flask, 3 mmol of an anthranilic acid derivative **1a–g** was dissolved in 1.5 mL PEG, and then, 4.5 mmol of diethyl dicarbonate was added dropwise (in the case of **1g**, 7 mmol of diethyl dicarbonate was used). The reaction mixture was stirred at room temperature for the times as indicated in Table 1. After completion of the reaction, the residual of diethyl dicarbonate was removed under reduced pressure. The carbamates **3a–g** were washed with cold water and dried in air.

Synthesis of the benzoxazine-4-ones 5. In a 25 mL round flask, a mixture of 1 mmol of the carbamates **3**, 1.1 mmol of guanidinium chloride, 1.1 mmol of triethylamine, and 0.5 mL PEG was stirred at room temperature. The reaction was completed immediately. The mixture was washed first with cold water (three times) to remove the solvent, Et_3NHCl salt, and the residual of guanidinium chloride. The raw products were washed with 5% aqueous $NaHCO_3$ and then with H_2O and dried in air. The benzoxazine-4-ones **5** may be recrystallized from *n*-hexane/THF, if needed.

Synthesis of the amides 6. In a 25 mL round flask, a mixture of 3 mmol of an anthranilic acid derivative **1a–g** and 3.3 mmol of triethylamine was stirred in $CHCl_3$ at room temperature, and then, 3.3 mmol of ethyl chloroformylformate (in the case of **1g**, 6.5 mmol of Et_3N and 6.5 mmol ethyl chloroformylformate) was added dropwise to this solution, and the mixture was stirred in an ice bath for about 30 min. The solvent was removed under reduced pressure, and the precipitate was washed first with 3 mL of *n*-hexane (three times) and filtered to remove the residual of ethyl chloroformylformate and then with cold water (three times) to remove the Et_3NHCl salt and dried in air.

Synthesis of the benzoxazine-4-ones 7. In a 25 mL round flask, a mixture of 1 mmol of the amides **6**, 1.1 mmol of guanidinium chloride, 1.1 mmol of triethylamine, and 0.5 mL PEG was stirred at 60–70°C for the times as indicated in Scheme 2. After completion of the reaction, the mixture was washed first with cold water (three times) to remove the solvent, Et_3NHCl salt, and the residual of guanidinium chloride. The raw products were washed with 5% aqueous $NaHCO_3$ and then with H_2O and dried in air. They may be recrystallized from *n*-hexane/EtOAc, if needed [11].

2-Ethoxy-(4*H*)-3,1-benzoxazine-4-one (5a). White solid, mp: 87–89°C [7,9].

2-Ethoxy-6,7-dimethoxy-(4*H*)-3,1-benzoxazine-4-one (5b). White solid, mp: 164–166°C. IR (KBr): υ (cm^{-1}): = 1747 (C=O), 1630 (C=N). ^{1}H NMR (250.1 MHz in $CDCl_3$): δ (ppm) = 7.37 (s, 1H-Ar), 6.80 (s, 1H-Ar), 4.43 (q, $^3J_{HH}$ = 6.7Hz, 2H, CH_2), 3.95 and 3.90 (2s, 6H, OCH_3), 1.41 (t, $^3J_{HH}$ = 6.7, 3H, CH_3). ^{13}C NMR (62.9 MHz in $CDCl_3$): δ (ppm) = 159.3, 156.7, 154.5, 147.7, 144.8, 107.8, 106.4, 106.3, 65.7, 56.4, 56.2, 14.0. EIMS (70 eV): *m/z* (%) = 251 ($M^{+\cdot}$, 100). *Anal*. Calcd for $C_{12}H_{13}NO_5$ (251.24): C, 57.37; H, 5.21; N, 5.57. Found: C, 57.40; H, 5.24; N, 5.59.

2-Ethoxy-5-methyl-(4*H*)-3,1-benzoxazine-4-one (5c). White solid, mp: 102–104°C [15].

6-Chloro-2-ethoxy-(4*H*)-3,1-benzoxazine-4-one (5d). White solid, mp: 83–85°C. IR (KBr): υ (cm^{-1}) = 1778 (C=O), 1638 (C=N). ^{1}H NMR (250.1 MHz in $CDCl_3$): δ (ppm) = 7.98 (s, 1H-Ar), 7.60 (d, $^3J_{HH}$ = 8.5Hz, 1H-Ar), 7.31 (d, $^3J_{HH}$ = 8.5Hz, 1H-Ar), 4.48

(q, $^3J_{HH}$ = 7.0Hz, 2H, CH_2), 1.43 (t, $^3J_{HH}$ = 7.0Hz, 3H, CH_3). ^{13}C NMR (62.9 MHz in $CDCl_3$): δ (ppm) = 158.4, 154.6, 146.8, 136.9, 131.1, 128.0, 126.8, 115.4, 66.3, 14.0. EIMS (70 eV): *m/z* (%) = 225 ($M^{+\cdot}$, 56), 227 [(M^+ + 2), 18]. *Anal*. Calcd for $C_{10}H_8ClNO_3$ (225.63): C, 53.23; H, 3.57; N, 6.21. Found: C, 53.26; H, 3.56; N, 6.20.

6-Bromo-2-ethoxy-(4*H*)-3,1-benzoxazine-4-one (5e). White solid, mp: 85–87°C. IR (KBr): υ (cm^{-1}) = 1766 (C═O), 1635 (C═N). ^{1}H NMR (250.1 MHz in $CDCl_3$): δ (ppm) = 8.21 (d, $^4J_{HH}$ = 2.0 Hz, 1H-Ar), 7.78 (dd, $^3J_{HH}$ = 8.5Hz, $^4J_{HH}$ = 2.0 Hz, 1H-Ar), 7.29 (d, $^3J_{HH}$ = 8.5Hz, 1-Ar), 4.51 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 1.45 (t, $^3J_{HH}$ = 7.0Hz, 3H, CH_3). ^{13}C NMR (62.9 MHz in $CDCl_3$): δ (ppm) = 158.3, 155.0, 147.2, 139.8, 131.2, 127.0, 118.5, 115.9, 66.3, 14.0. EIMS (70 eV): *m/z* (%) = 269 ($M^{+\cdot}$, 72), 271 [(M^+ + 2), 71]. *Anal*. Calcd for $C_{10}H_8BrNO_3$ (270.08): C, 44.47; H, 2.98; N, 5.18. Found: C, 44.44; H, 2.97; N, 5.20.

7-Chloro-2-ethoxy-(4*H*)-3,1-benzoxazine-4-one (5f). White solid, mp: 80–82°C. IR (KBr): υ (cm^{-1}) = 1780 (C═O), 1622 (C═N). ^{1}H NMR (250.1 MHz in $CDCl_3$): δ (ppm) = 7.99 (d, $^3J_{HH}$ = 8.5Hz, 1H-Ar), 7.37 (d, $^4J_{HH}$ = 1.5Hz, 1H-Ar), 7.26 (dd, $^3J_{HH}$ = 8.5Hz, $^4J_{HH}$ = 1.5Hz, 1H-Ar), 4.49 (q, $^3J_{HH}$ = 7.2Hz, 2H, CH_2), 1.43 (t, $^3J_{HH}$ = 7.2Hz, 3H, CH_3). ^{13}C NMR (62.9 MHz in $CDCl_3$): δ (ppm) = 158.7, 155.3, 149.4, 143.1, 130.1, 126.4, 125.1, 112.7, 66.4, 14.0. EIMS (70 eV): *m/z* (%) = 225 (M^+, 38), 227 [($M^{+\cdot}$ + 2), 13]. *Anal*. Calcd for $C_{10}H_8ClNO_3$ (225.63): C, 53.23; H, 3.57; N, 6.21. Found: C, 53.27; H, 3.58; N, 6.20.

2-Ethoxy-6-(ethylcarbonato)-(4*H*)-3,1-benzoxazine-4-one (5g). White solid, mp: 69–71°C. IR (KBr): υ (cm^{-1}) = 1772 (C═O), 1732 (C═O), 1633 (C═N). ^{1}H NMR (250.1 MHz in $CDCl_3$): δ (ppm) = 8.43 (s, 1H-Ar), 7.72 (d, $^3J_{HH}$ = 7.5Hz, 1H-Ar), 7.44 (d, $^3J_{HH}$ = 7.5Hz, 1H-Ar), 4.33–4.22 (m, 4H, $2CH_2$), 1.45–1.32 (m, 6H, $2CH_3$). ^{13}C NMR (62.9MHz in $CDCl_3$): δ (ppm) = 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. EIMS (70 eV): *m/z* (%) = 279 ($M^{+\cdot}$, 16). *Anal*. Calcd for $C_{13}H_{13}NO_6$ (279.25): C, 55.91; H, 4.69; N, 5.02. Found: C, 55.96; H, 4.70; N, 5.00.

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