Research Article

Ali Sharifi*, Maryam Moazami, Mohammad Saeed Abaee and Mojtaba Mirzaei

Ionic liquid-catalyzed synthesis of (1,4-benzoxazin-3-yl) malonate derivatives via cross-dehydrogenative-coupling reactions

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Abstract: A convenient $C(sp^3)$–$C(sp^3)$ oxidative dehydrogenative coupling reaction of 1,4-benzoxazin-2-ones with malonate esters was developed under mild conditions to obtain the respective ester malonates in high yields. Reactions take place in [omim]$FeCl_4$, acting as both the solvent and the catalyst. Under [omim]Cl/$FeCl_3$-DDQ conditions, derivatives of **1** coupled with malonate **2** to give the target molecules within 1–2 h time periods. The ionic liquid was recovered and reused in the next reactions without losing its efficiency.

Keywords: ionic liquids, benzoxazinones, CDC reactions, heterocycles

1 Introduction

Enforced by the increasing global demands to implement severe environmentally clean protocols [1], ionic liquids (ILs) have found a wide range of applications in recent decades, as benign surrogates for conventional solvents in research [2,3] and industry [4]. This is due to low vapor pressure, high thermal durability, good shelf storage, and an increased tendency to give homogenized mixtures with various reagents, catalysts, and reactants [5]. Particularly important from the synthetic viewpoint is the improved selectivity and reactivity [6] associated with many organic reactions conducted in ILs [7] through designing appropriate ILs with desired chemical and physical properties for certain transformations [8].

Carbon–carbon (C–C) bond construction is perhaps the most fundamental synthetic process in organic chemistry to access more complex molecules from simpler reactants [9]. The direct coupling of two C–H bonds, known as cross-dehydrogenative-coupling (CDC) reactions [10,11], is one of the most frequently practiced methods for the formation of new C–C moieties due to the wide availability of C–Hs in the structure of various organic reactants [12,13] and a high atom economy that the process inherits [14]. In this context, one-electron oxidative CDC reactions have become one of the fast-growing approaches in recent years [15].

An important group of heterocyclic molecules is 1,4-benzoxazinones [16]. This type of structure can be frequently found in biologically active molecules [17]. Furthermore, there are complex molecules that have 1,4-benzoxazinone skeleton in their structure and possess pharmaceutical [18], optical [19], or biological properties [20,21]. Some related illustrative examples are presented in Figure 1 [22–24]. Thus, developing new methodologies for an efficient synthesis and derivatization of benzoxazinones is in high demand in current organic synthesis. In this regard, the C–C coupling approach has been used in recent years by a few groups of researchers via peroxidation of benzoxazinones with *tert*-butyl hydroperoxide [25], amination of benzoxazinones with dialkyl azodicarboxylates [26], photocatalyzed oxidative coupling of benzoxazinones with a variety of nucleophiles such as indole derivatives [15,27] and other aromatic moieties [16], and coupling reaction of benzoxazinones with malonic esters or ketones [17].

In the framework of our studies to design the IL-mediated procedures in heterocyclic chemistry [28,29], we recently reported a CDC of benzoxazinones with indoles under $FeCl_3$ catalysis in [omim]Cl or by ball milling [30,31]. On this track, now we would like to report a convenient procedure for IL-mediated coupling of 1,4-benzoxazinones with malonate derivatives using [omim]Cl/$FeCl_3$ as the solvent/catalyst of the process, as shown in Scheme 1 for

* **Corresponding author: Ali Sharifi,** Organic Chemistry Department, Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran, e-mail: sharifi@ccerci.ac.ir
Maryam Moazami, Mohammad Saeed Abaee, Mojtaba Mirzaei: Organic Chemistry Department, Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran

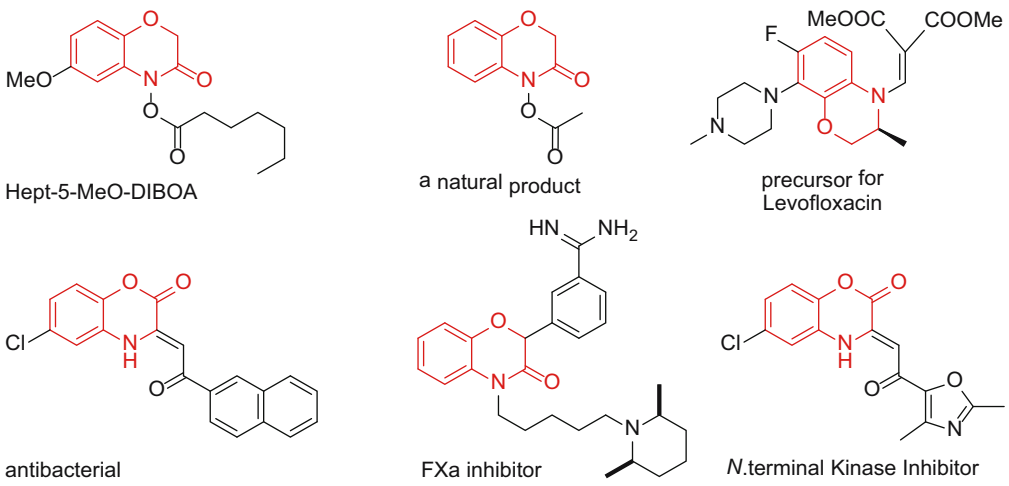
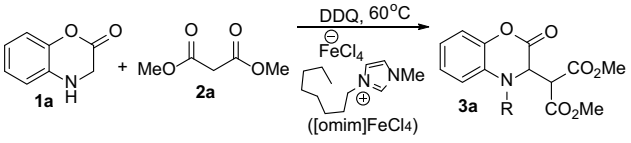


Figure 1: Examples of important 1,4-benzoxazinones structures.



Scheme 1: CDC coupling of **1a** with **2a** for the synthesis of **3a**.

the model reaction of **1a** with **2a** taking place in the presence of the oxidant DDQ.

2 Results and discussion

We first optimized the conditions for the synthesis of **3a** as the model reaction (Table 1). The best conditions were obtained when we treated a mixture of **1a** and **2a** in the presence of [omim]$FeCl_4$ and DDQ at 60°C (entry 1). Thus, **3a** was obtained in a 96% yield after 1 h. In the absence of the IL (entry 2) or by the substitution of the IL with an equivalent non-IL catalyst/solvent (entry 3), the yield diminished slightly or partially. Similarly, the reactions at temperatures lower (entry 4) or higher (entry 5) than 60°C did not improve the outcome. The yield of **3a** showed to be dependent of the type of the oxidant, with DDQ giving the best conversion (entries 6–13).

Further experiments were conducted for more optimization of the conditions. To compare the performance of other ILs with [omim]$FeCl_4$, the synthesis of **3a** was examined in other methylimidazolium-$FeCl_4$-based ILs. As shown in Figure 2a, by a growth in the size of the alkyl substitution of the imidazolium cation, the yield of **3a** is increased, perhaps due to the increase in hydrophobicity

Table 1: Optimization of the reaction conditions[a]

Entry	Catalyst	Oxidant	Temperature (°C)	Yield %[b]
1	[omim]$FeCl_4$	DDQ	60	96
2	—	DDQ	60	0
3	MeCN/$FeCl_3$	DDQ	60	70
4	[omim]$FeCl_4$	DDQ	40	55
5	[omim]$FeCl_4$	DDQ	80	73
6	[omim]$FeCl_4$	TBHP	60	0
7	[omim]$FeCl_4$	O_2	60	0
8	[omim]$FeCl_4$	$(NH_4)_2S_2O_8$	60	20
9	[omim]$FeCl_4$	$K_2S_2O_8$	60	27
10	[omim]$FeCl_4$	H_2O_2	60	33
11	[omim]$FeCl_4$	Tetrachloro-1,4-benzoquinone	60	75
12	[omim]$FeCl_4$	1,4-Benzoquinone	60	87
13	[omim]$FeCl_4$	Benzoyl peroxide	60	90

[a]DDQ (0.5 equiv), IL (1.0 equiv), 60°C, 1 h.
[b]Isolated yields.
TBHP: tert-butyl hydroperoxide.

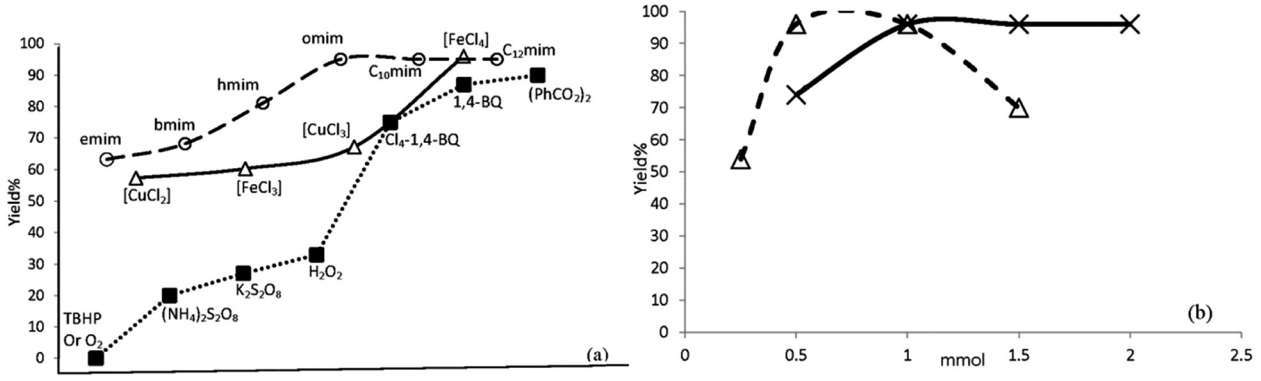


Figure 2: Dependency of the yield of **3a** to (a) the change in the type of the oxidant (dotted line) or the anion (solid line) and the cation (dashed line) of the IL and (b) the change in the amount of DDQ (dashed line) or [omim]$FeCl_4$ (solid line).

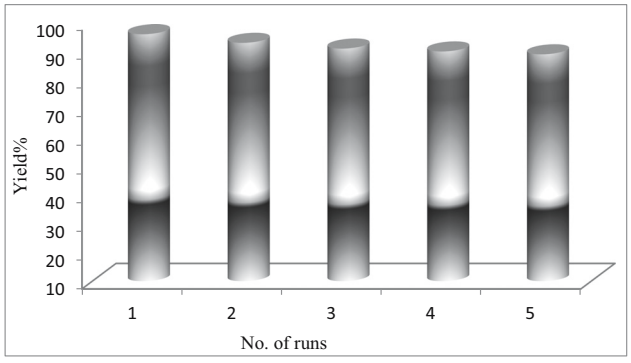


Figure 3: Successful reuse of the medium.

of the IL and better dissolving the organic reactants (dashed line). On the other hand, $FeCl_4$ served as the best counter ion for [omim] cation (solid line), while the replacement of DDQ with other oxidants (dotted line) did not lead to better results. Figure 2b also shows the results for altering the amount of the DDQ (dotted line) or [omim]$FeCl_4$ (broken line).

This is important from an environmental point of view to recover solvents, catalysts, or reagents after completion of the reactions and reuse them in subsequent runs. Therefore, after each workup, the product was extracted with ethyl acetate, the IL was recovered by removing the volatile portion under reduced pressure, the medium was remade to its required amounts, and it was recycled in the next reactions successfully. The concept is shown in Figure 3 for five consecutive reuses of the medium without significant loss of its performance.

To evaluate the generality of the method, we then repeated the reaction using other derivatives of **1** and **2** (Scheme 2). As a result, reactions of three standard *N*-benzyl-benzoxazin-2-one derivatives **1a**–**c** (with different electronic natures) with **2a**–**c** gave the respective products **3a**–**h** in 75–96% isolated yields. The reactions were completed under the optimized conditions, with more sluggish reactants getting slightly longer times.

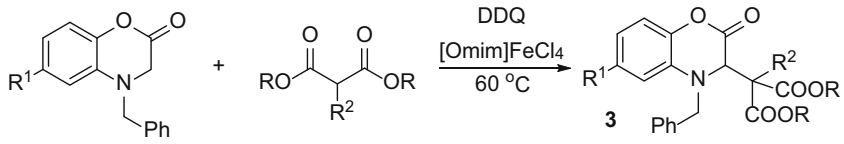
Based on these observations, a mechanism for the coupling can be suggested, as shown in Figure 4 for the reaction of **1a** with **2a**. The fact that the reaction is an oxidative process is well documented [32]. Thus, primarily **1a** is oxidized to its respective radical cation **A**, while the resulting Fe^{2+} ion reduces DDQ to DDQ^- to maintain the recovery cycle of iron. The loss of a hydrogen atom by **A** ends up with the formation of **B** and DDQH. Further reduction of DDQH to $DDQH_2$ by malonate ester **2a** provides anion **C**, which can couple with cation **B** to give the final product **3a**. Isolation of a side product from the reaction mixture, which by ^{1}H NMR (nuclear magnetic resonance) analysis corresponds to the structure **11** (dimer of **1a**), supports the proposed mechanism. The formation of this dimer suggests that a radical process is involved in this reaction.

3 Conclusion

In summary, we could develop a new procedure for the IL-mediated C(sp^3)–C(sp^3) oxidative dehydrogenative coupling of 1,4-benzoxazin-2-ones with malonate ester derivatives. The reactions are performed under mild conditions, and the medium, which acts as both the catalyst and the solvent, is successfully recycled several times. The application of the procedure in coupling other reactants is currently under investigation in our laboratory.

4 Experimental

All reagents and solvents were commercially available and used as received. The progress of the reactions was



1a: R^1 = H
1b: R^1 = Me
1c: R^1 = Cl

2a: R^2 = H, R = Me
2b: R^2 = Me, R = Et
2c: R^2 = Et, R = Et

Product	R^1	R^2	R	Time (h)	%Yield
3a	H	H	Me	1.0	96
3b	H	Me	Et	1.5	90
3c	H	Et	Et	2.0	75
3d	Me	H	Me	1.0	93
3e	Me	Me	Et	1.5	88
3f	Me	Et	Et	2.0	83
3g	Cl	H	Me	1.0	95
3h	Cl	Me	Et	1.5	90

Scheme 2: Synthesis of various derivatives of **3**.

monitored by thin layer chromatography (TLC) using silica gel-coated plates and ethyl acetate (EtOAc)/petroleum ether mixture as the eluent. Melting points are uncorrected and are obtained by Buchi Melting Point 530. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra are obtained on an fourier transform-nuclear magnetic resonance (FT-NMR) Bruker Ultra Shield^{TM} instrument as $CDCl_3$ solutions, and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. ILs were prepared using known procedures [33]. The identity of the known products was confirmed by comparing their melting points and their ^{1}H NMR data with those of authentic compounds available in the literature [17]. New products were characterized based on their spectral data.

4.1 Typical [omim]$FeCl_4$-catalyzed synthesis of 3

DDQ (110 mg, 0.5 mmol) was added to a mixture of dimethyl malonate (**2a**, 264 mg, 2.0 mmol), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1a**, 239 mg, 1.0 mmol) in [omim]$FeCl_4$

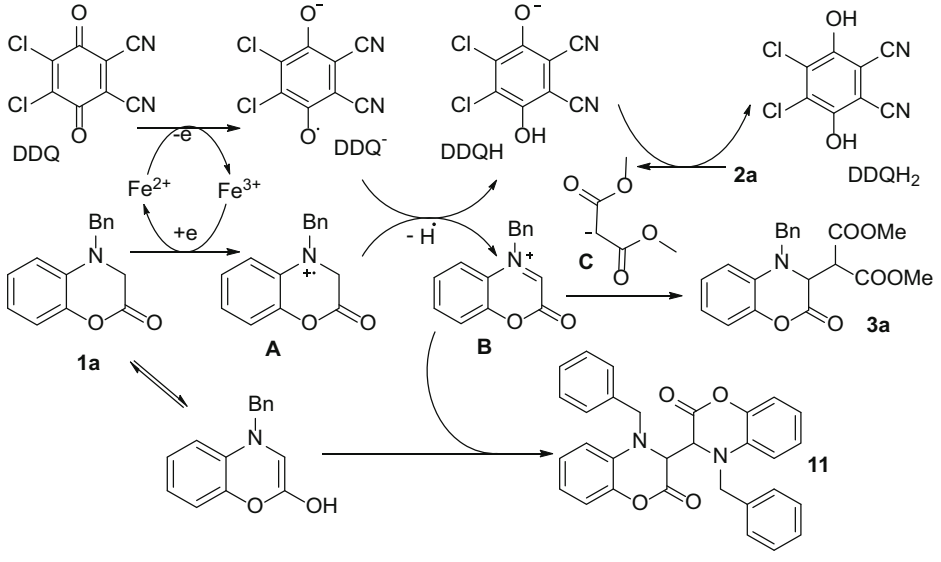


Figure 4: A plausible mechanism of the reaction.

(0.4 g, 1.0 mmol), and the mixture was stirred at 60°C for 1 h. The mixture was extracted with EtOAc (10 mL), and the extract was washed with H_2O (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was fractionated by column chromatography on silica gel using acetone/hexanes (1:10) as the eluent to afford **3a** (355 mg, 96%). The IL, which remains on the top of the column, is collected, diluted with EtOAc (5 mL), and filtered (to remove the silica gel particles). The volatile content is removed under reduced pressure, and the remaining IL is recycled into the next reaction.

5 Spectral data of new products

5.1 Diethyl 2-(4-benzyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-3-yl)-2-methylmalonate (3b)

White solid in 80% yield: Melting point (M.P.) 77–79°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.23 (m, 3H), 7.13 (d, J = 6.6 Hz, 2H), 7.02 (3, J = 7.6 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 5.0 (s, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.53 (d, J = 15.6 Hz, 1H), 4.11 (m, 1H), 4.08–3.99 (m, 3H), 1.45 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 169.2, 163.0, 143.4, 139.5, 132.0, 128.8, 127.9, 127.8, 125.1, 121.3, 118.5, 116.5, 63.9, 62.1, 62.0, 59.2, 58.3, 18.5, 13.8, 13.7; mass (MS) (70 eV) m/z (%) 411, 320, 239, 146, 90, 65; infrared (IR) (Potassium Bromide [KBr], cm^{-1}) 3,447, 2,984, 1,732, 1,504, 1,248, 1,104, 746. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.25; H, 6.20; N, 3.55.

5.2 Diethyl 2-(4-benzyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-3-yl)-2-ethylmalonate (3c)

White solid in 75% yield: M.P. 93–95°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 3H), 7.13 (d, J = 6.5 Hz, 2H), 7.0 (t, J = 7.7 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.86 (t, J = 7.7 Hz, 1H), 4.92 (s, 1H), 4.78 (d, J = 15.5 Hz, 1H), 4.56 (d, J = 15.5 Hz, 1H), 4.09–4.02 (m, 1H), 3.99–3.91 (m, 1H), 3.86–3.79 (m, 1H), 3.77–3.70 (m, 1H), 2.18–2.09 (m, 1H), 1.99–1.90 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 168.8, 162.6, 143.5, 136.6, 131.6, 128.7, 127.6, 127.5, 124.9, 121.4, 119.0, 116.4, 63.6, 62.3, 61.8, 61.6, 58.3, 26.9, 13.77, 13.74, 9.3; MS (70 eV) m/z (%) 425, 239, 209, 160, 119, 90, 65, 41; IR (KBr, cm^{-1}) 2,982, 1,730, 1,504, 1,233, 1,026, 748. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.66; H, 6.53; N, 3.41.

5.3 Diethyl 2-(4-benzyl-6-methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-3-yl)-2-methylmalonate (3e)

White solid in 88% yield: M.P. 58–60°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.23 (m, 3H), 7.13 (d, J = 6.7 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.69 (d, J = 8.2 Hz, 1H), 4.96 (s, 1H), 4.78 (d, J = 15.5 Hz, 1H), 4.50 (d, J = 15.5 Hz, 1H), 4.18–4.0 (m, 4H), 2.27 (s, 3H), 1.44 (s, 3H), 1.26–1.21 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 169.2, 163.1, 141.5, 136.7, 134.8, 131.7, 128.7, 127.8, 127.5, 122.1, 119.0, 116.2, 63.6, 62.1, 62.0, 59.2, 58.4, 21.1, 18.4, 13.8, 13.7; MS (70 eV) m/z (%) 425, 356, 302, 300, 91; IR (KBr, cm^{-1}) 2,979, 1,775, 1,726, 1,505, 1,446, 1,249, 1,107, 850, 736. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.34; H, 4.44; N, 3.39.

5.4 Diethyl 2-(4-benzyl-6-methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-3-yl)-2-ethylmalonate (3f)

White solid in 83% yield: M.P. 71–73°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (m, 3H), 7.14 (d, J = 6.8 Hz, 2H), 6.84 (d, J = 8.2 Hz, 1H), 6.75 (s, 1H), 6.67 (d, J = 8.2 Hz, 1H), 4.87 (s, 1H), 4.78 (d, J = 15.4 Hz, 1H), 4.52 (d, J = 15.4 Hz, 1H), 4.09–4.04 (m, 1H), 3.97–3.91 (m, 1H), 3.89–3.84 (m, 1H), 3.78–3.73 (m, 1H), 2.26 (s, 3H), 2.17–2.09 (m, 1H), 1.99–1.91 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 168.9, 162.8, 141.5, 136.7, 134.6, 131.3, 128.7, 127.8, 127.6, 122.1, 119.5, 116.0, 63.4, 62.3, 61.7, 61.6, 58.4, 26.9, 21.1, 13.75, 13.72, 9.2; MS (70 eV) m/z (%) 439, 348, 252, 174, 132, 91, 65, 43; IR (KBr, cm^{-1}) 2,983, 1,756, 1,721, 1,201, 1,028, 805, 731. Anal. Calcd for $C_{25}H_{29}O_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.40; H, 6.70; N, 3.32.

5.5 Diethyl 2-(4-benzyl-6-chloro-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-methylmalonate (3h)

White solid in 90% yield: M.P. 113–114°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (m, 3H), 7.12 (d, J = 7.2 Hz, 2H), 6.91

(d, J = 2.3 Hz, 1H), 6.89 (s, 1H), 6.82 (dd, J = 8.6, 2.2 Hz, 1H), 4.97 (s, 1H), 4.75 (d, J = 15.7 Hz, 1H), 4.55 (d, J = 15.7 Hz, 1H), 4.19–4.11 (m, 1H), 4.10–3.98 (m, 3H), (d, J = 15.9 Hz, 1H), 4.5 (d, J = 15.9 Hz, 1H), 4.25–4.17 (m, 1H), 4.17–4.07 (m, 3H), 1.46 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 169.1, 162.2, 141.8, 136.0, 133.2, 130.1, 128.9, 128.0, 127.3, 120.9, 117.9, 117.4, 63.4, 62.3, 62.2, 59.2, 57.8, 18.6, 13.8, 13.7; MS (70 eV) m/z (%) 445, 272, 149, 91; IR (KBr, cm^{-1}) 2,981, 1,775, 1,724, 1,502, 1,161, 846, 801. Anal. Calcd for $C_{23}H_{24}ClNO_6$: C, 61.95; H, 5.43; N, 3.14. Found: C, 62.11; H, 5.32; N, 3.02.

5.6 4,4′-Dibenzyl-3,3′,4,4′-tetrahydro-2*H*,2′*H*-[3,3′-bibenzo[*b*][1,4]oxazine]-2,2′-dione (11)[16]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.29 (m, 5H), 7.11 (d, J = 7.7 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 5.49 (s, 1H), 4.82 (d, J = 15.1 Hz, 1H), 4.61 (d, J = 15.1 Hz, 1H).

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Conflict of interest: Authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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