A Platinum Open Access Journal for Organic Chemistry

Paper

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Arkivoc **2021**, part x, 0-0

to be inserted by editorial office

Synthesis of (1,4-benzoxazinones-3-yl)malonate derivatives via cross-dehydrogenative-coupling reactions under ball-milling conditions

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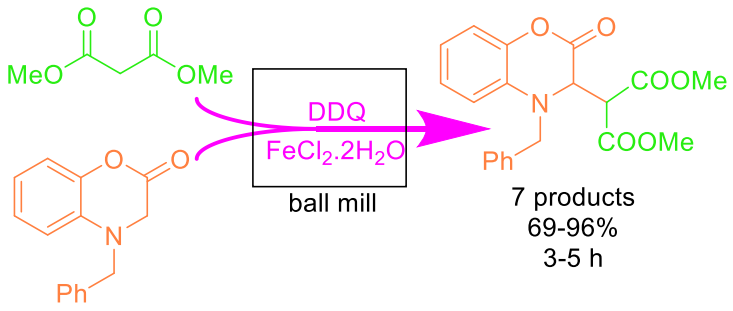
Received mm-dd-yyyy **Accepted Manuscript** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

A new method was developed for C(sp^3)–C(sp^3) oxidative dehydrogenative coupling of 1,4-benzoxazin-2-ones with malonate derivatives under ball milling to obtain the respective malonate esters. Reactions take place under solvent-free conditions using $FeCl_2.2H_2O$ and DDQ as the catalyst and the oxidant. Conditions are relatively mild and the target products are obtained in high yields within 3-5 h time period.



Keywords: CDC coupling, 1,4-benzoxazinones, heterocycles, $FeCl_2$ catalyst, ball milling

Introduction

The formation of new carbon-carbon (C-C) bonds is a fundamental transformation in synthetic organic chemistry for assembly of structures of choice from smaller molecules.[1] A rapidly growing approach for this goal in recent years has been the cross-dehydrogenative-coupling (CDC) reactions,[2] consisting of direct coupling of two C-H bonds being available in the organic reactants. In addition, the method acts selectively in many occasions[3] and is atom economic as well.[4]

The global movement for severe environmental protection has had a great impact on the design and implementation of benign methods for various chemical reactions in recent decades.[5] One particular advantage in this regard has been the use of nonconventional sources of energy[6] and non-toxic reagents.[7] Within the framework of sustainable chemistry, an outstanding development is observed in recent decades by designing new environmentally clean procedures for various synthetic organic transformations using safer sources of energy such as ball milling,[8] a technique that activates solid reactants by mechanical forces to undergo various functional group transformations and synthetic reactions.[9]

1,4-Benzoxazinones are a class of important heterocycles, due their presence in the structure of molecules with attractive chemical, medicinal, or biological activities.[10] Some of these compounds also exhibit photoactive properties.[11] In addition, benzoxazinones serve as synthetic precursors or are present in a variety of natural products.[12] A few related important molecules, exemplifying various applications, are depicted in Figure 1.[13-16] Therefore, the development of new methods for the synthesis and derivatization of 1,4-benzoxazinones is of continuous interest.[17-20] Iron is one of the most abundant elements on Earth and iron salts act as catalyst for several chemical transformations,[21] while they are inexpensive and nonharmful to humans and the environment.[22,23] These features make various types of iron catalysts very popular in organic synthesis and have resulted in many applications in recent decades.[24]

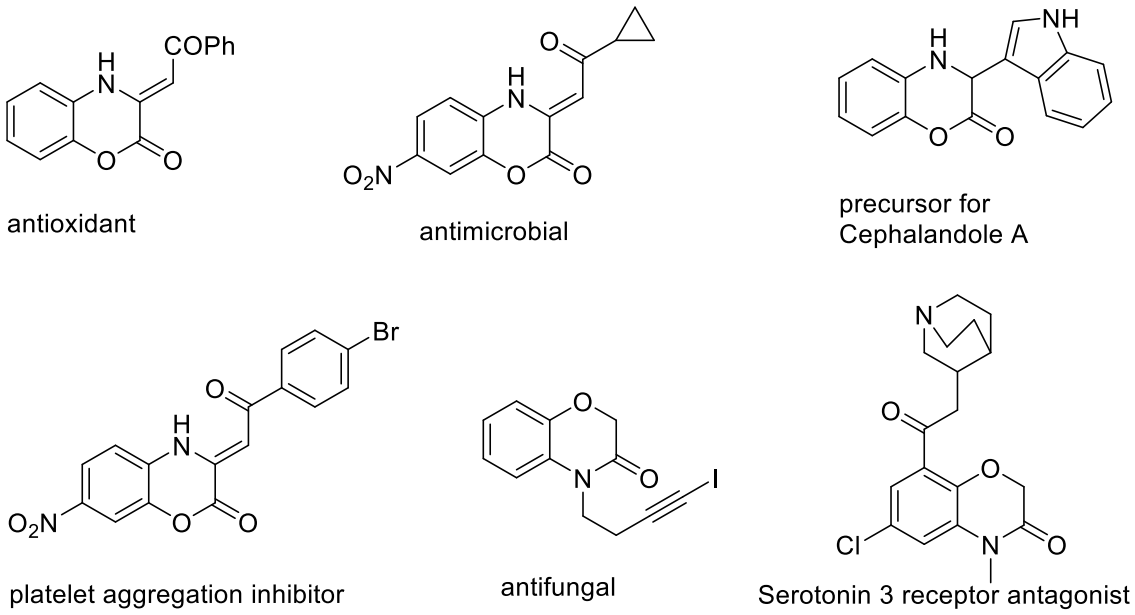
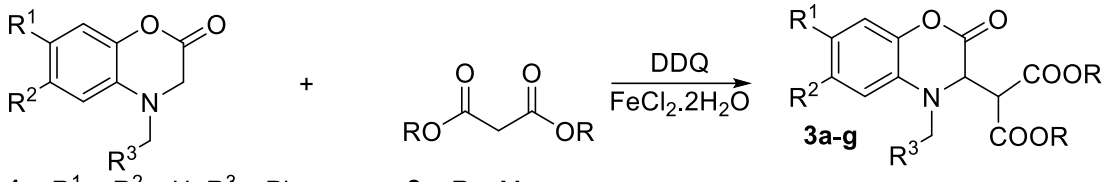


Figure 1. Selected 1,4-benzoxazinones with interesting properties.

In continuation of our investigations in heterocyclic chemistry,[25,26] we recently reported a ball-milled/Fe(II)-catalyzed CDC of 1,4-benzoxazinones with indoles.[27] Now, we would like to report a convenient

method for ball milling coupling of 1,4-benzoxazinones with malonate esters using $FeCl_2.2H_2O$ as the catalyst of the process, as shown in Scheme 1 for the coupling of derivatives of **1** with **2** using the oxidant, DDQ. As far as we know, there is one single report in the literature for the synthesis of malonate derivatives of 1,4-benzoxazinones-3-yl, where the process is carried out in the presence of a $Fe(OTf)_3$, DDQ, and MeCN at 60 ^oC.[28]



1a: $R^1 = R^2 = H$, $R^3 = Ph$ **2a**: R = Me
1b: $R^1 = H$, $R^2 = Me$, $R^3 = Ph$ **2b**: R = Et
1c: $R^1 = H$, $R^2 = Cl$, $R^3 = Ph$
1d: $R^1 = Me$, $R^2 = H$, $R^3 = CO_2Et$

Scheme 1

Results and Discussion

We initially optimized the conditions for the model reaction leading to **3a** (Table 1). The best conditions were obtained when a mixture of **1a** and **2a** was shaken at 20 Hz in an oscillatory ball mill apparatus in the presence of $FeCl_2.2H_2O$ and DDQ at room temperature giving 95% of **3a** after 3 h (entry 1). In the absence of either the catalyst (entry 2) or the oxidant (entry 3), the yield dropped to 0 %. With $FeCl_3$ (entry 4), various copper salts (entries 5-10) or $CoCl_2.6H_2O$ (entry 11) the yield dropped partially. Similarly, no improvement was observed by replacing DDQ with other oxidants (entries 12-19).

Table 1. Optimization of ball-milled synthesis of **3a**

Entry	Catalyst (5 mol%)	Oxidant (1.00 mmol)	Yield (%)[a,b]
1	$FeCl_2.2H_2O$	DDQ	95
2	-	DDQ	0
3	$FeCl_2.2H_2O$	-	0
4	$FeCl_3$	DDQ	87
5	CuBr	DDQ	85
6	$CuBr_2$	DDQ	83
7	CuCl	DDQ	82
8	$CuCl_2$	DDQ	80
9	$Cu(NO_3)_2.3H_2O$	DDQ	80
10	$Cu(OAc)_2.H_2O$	DDQ	82
11	$CoCl_2.6H_2O$	DDQ	78
12	$FeCl_2.2H_2O$	TBHP	0
13	$FeCl_2.2H_2O$	O_2	0
14	$FeCl_2.2H_2O$	H_2O_2	53
15	$FeCl_2.2H_2O$	$(NH_4)_2S_2O_8$	10

16	$FeCl_2.2H_2O$	$K_2S_2O_8$	15
17	$FeCl_2.2H_2O$	1,4-benzoquinone	20
18	$FeCl_2.2H_2O$	benzoyl peroxide	35
19	$FeCl_2.2H_2O$	tetrachloro-1,4-benzoquinone	45

[a] Isolated yields.

[b] 3 h reaction time.

We further optimized the conditions by altering the amounts of the catalyst and the oxidant (Table 2). Therefore, conducting six experiments using 1-15 mol% of $FeCl_2.2H_2O$ showed that 5 mol% of the salt is enough for the reaction to proceed (entries 1-6), while DDQ required the use of stoichiometric amounts. (entries 7-11).

Table 2. Optimization of the amounts of the catalyst and the oxidant for the synthesis of **3a**

Entry	$FeCl_2.2H_2O$ (mol%)	DDQ (mmol)	Yield (%)[a]
1	1	1.00	40
2	3	1.00	53
3	5	1.00	95
4	7	1.00	95
5	10	1.00	95
6	15	1.00	95
7	5	0.25	43
8	5	050	60
9	5	1.00	95
10	5	1.50	95
11	5	2.00	80

[a] Isolated yields.

To examine the generality of the procedure, the reaction was carried out using other derivatives of **1** and **2** (Table 3). Therefore, reactions of three different *N*-benzyl-benzoxazin-2-one derivatives **1a**-**c** (with different electronic natures) and a *N*-CH_2CO_2Et derivative **1d** with **2a**-**b** gave the corresponding products **3a**-**g** in 69-95% yield. The reactions completed under the optimized conditions within 3 h, except in the case of **1d** which took 5 h and gave a moderate yield.

The structure of the products was characterized based on their NMR studies. In the ^1H NMR spectra, presence of two doublets around 4.5 ppm with large coupling constants of about 15 Hz was the indication for the presence of the benzylic fragment in the structure of the products, while the two doublets at about 4.9 and 3.7 ppm were in accordance with the substitution of the malonate moieties at the 3 position of the benzoxazine rings. In addition, the ^{13}C NMR spectra showed exactly the expected numbers of the signals for each structure.

Based on the results, we propose a mechanism for the conversion, as shown in Figure 2 for the synthesis of **3a**. Previous observations have documented that the reaction goes through an oxidation pathway.[21] As a result, DDQ could be reduced at the first stage by Fe^{2+} to a radical. The resulting Fe^{3+} ion oxidizes **1a** to the radical cation **I**. Then, a hydrogen atom is abstracted from **I** to form **II**. On the other hand, Lewis basic functions present in the medium (such as the oxygen atoms of DDQ moieties or H_2O) can deprotonate malonate ester **2a** to its respective anion, which in the final stage couples with cation **II** to produce **3a**.

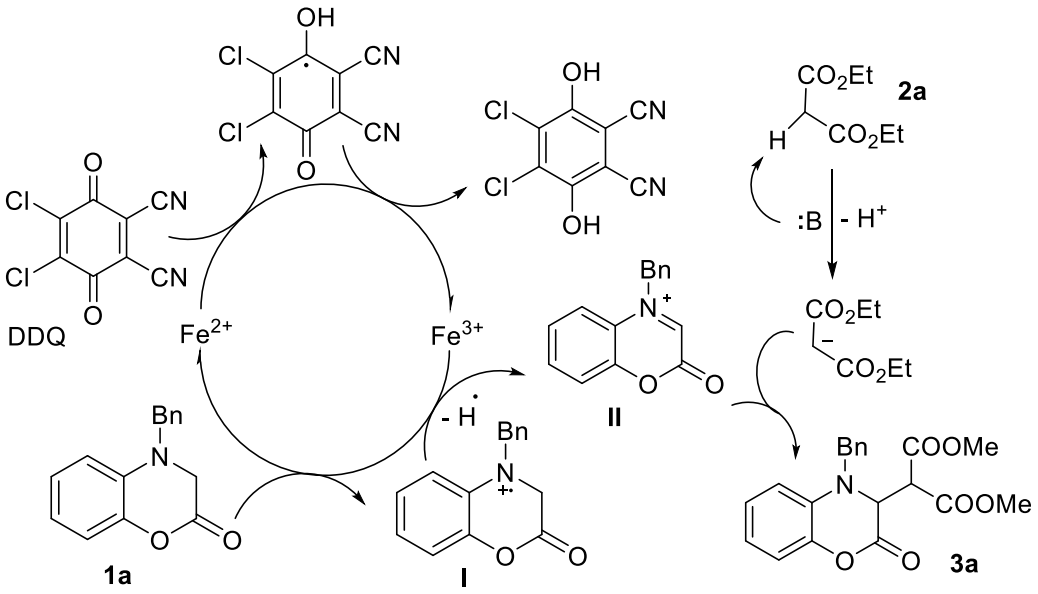
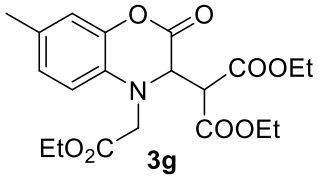


Figure 2. A proposed mechanism for the reaction.

Table 3. Synthesis of various derivatives of **3**

Entry	Reactants	Product	Time (h)	Yield (%)[a]
1	**1a** + **2a**	**3a**	3	95
2	**1a** + **2b**	**3b**	3	95
3	**1b** + **2a**	**3c**	3	93
4	**1b** + **2b**	**3d**	3	90
5	**1c** + **2a**	**3e**	3	95
6	**1c** + **2b**	**3f**	3	93

7	**1d** + **2b**	 **3g**	5	69

[a] Isolated yields.

Conclusions

In summary, we could develop a new method at ambient temperature for C(sp^3)–C(sp^3) oxidative dehydrogenative coupling of 1,4-benzoxazin-2-ones with malonate derivatives. Reaction takes place under solvent-free conditions in a ball mill apparatus and Fe(II) catalysis, which is an inexpensive reagent and is used in stoichiometric quantities. Compared to the single previous report on the synthesis of the title compounds,[28] this is a procedure carried out using a less expensive catalyst at ambient temperature.

Experimental Section

General. Reactions were monitored by TLC using silica gel coated plates and hexanes/acetone solutions as the eluent. Melting points are uncorrected. FT-IR spectra are recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers (cm^{-1}). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra are obtained on a FT-NMR Bruker Ultra Shield^{TM} instrument as $CDCl_3$ solutions and the chemical shifts are expressed as □ units using Me_4Si as the internal standard. Mass spectra are obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analyses are performed using a Thermo Finnigan Flash EA 1112 instrument. For ball milling conditions, reactions were carried out in a Retsch® Mixer Mills MM 200. All reagents and starting materials are purchased from commercial sources and are freshly used after being purified by standard procedures.

Typical ball-milled $FeCl_2.2H_2O$ catalyzed synthesis of 3a. DDQ (110 mg, 0.5 mmol) was added to a 5.0 mL stainless steel vial which was charged with 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), $FeCl_2.2H_2O$ (8.5 mg, 5 mol%) and a 10 mm stainless steel ball. The mixture was capped and shaken at 20 Hz in an oscillatory ball mill apparatus for 3h at room temperature. 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** (351 mg, 95%).

Spectral data of new products

Diethyl 2-(4-benzyl-6-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)malonate (3d). White solid in 90% yield: mp 88–90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H, Ar), 7.31 – 7.28 (m, 1H, Ar), 7.23 (d, *J* 6.7 Hz, 2H, Ar), 6.97 (d, *J* 8.1 Hz, 1H, Ar), 6.71 (d, *J* 7.21 Hz, 1H, Ar), 6.63 (s, 1H, Ar), 4.86 (d, *J* 6.7 Hz, 1H, CH), 4.62 (d, *J* 15.6 Hz, 1H, $PhCH_2$), 4.46 (d, *J* 15.6 Hz, 1H, $PhCH_2$), 4.23 – 4.08 (m, 4H, 2XCH2Me), 3.67 (d, *J* 6.6 Hz, 1H, CH), 2.27 (s, 3H, CH_3), 1.27– 1.18 (m, 6H, 2XCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 166.1, 163.2, 140.0, 136.3, 135.0, 131.0, 128.8, 127.8, 127.4, 121.4, 116.5, 116.4, 62.2, 62.1, 59.7, 54.5, 53.1, 21.2, 13.8, 13.7; MS

(70 eV) m/z (%) 411, 320, 274, 252, 224, 146, 91, 65; IR (KBr, cm^{-1}) 3422, 2919, 1734, 1508, 1213, 1028, 801. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.22; H, 6.23; N, 3.54.

Diethyl 2-(4-benzyl-6-chloro-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)malonate (3f). White solid in 93% yield: mp 110–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 3H, Ar), 7.23 (d, *J* 7.6 Hz, 2H, Ar), 7.01 (d, *J* 8.5 Hz, 1H, Ar), 6.85 (dd, *J* 8.5, 2.1 Hz, 1H, Ar), 6.78 (d, *J* 2.1 Hz, 1H, Ar), 4.9 (d, *J* 5.9 Hz, 1H, CH), 4.6 (d, *J* 15.9 Hz, 1H, $PhCH_2$), 4.5 (d, *J* 15.9 Hz, 1H, $PhCH_2$), 4.25 – 4.10 (m, 4H, $2XCH_2Me$), 3.68 (d, *J* 5.9 Hz, 1H, CH), 1.25 (t, *J* 7.1 Hz, 3H, CH_3), 1.22 (t, *J* 7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.8, 162.5, 140.1, 135.5, 132.5, 130.3, 129.0, 128.1, 127.2, 120.2, 117.6, 115.0, 62.4, 62.3, 59.3, 54.1, 53.3, 13.8, 13.7; MS (70 eV) m/z (%) 432, 431, 340, 294, 272, 149, 91, 65; IR (KBr, cm^{-1}) 2983, 1734, 1609, 1503, 1214, 1028, 836. Anal. Calcd for $C_{22}H_{22}ClNO_6$: C, 61.19; H, 5.13; N, 3.24. Found: C, 61.30; H, 5.05; N, 3.11.

Diethyl 2-(4-(2-ethoxy-2-oxoethyl)-7-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)malonate (3g). Colorless liquid in 69% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H, Ar), 6.87 (d, *J* 8.2 Hz, 1H, Ar), 6.72 (d, *J* 8.1 Hz, 1H, Ar), 4.73 (d, *J* 8.1 Hz, 1H, CH), 4.30 – 4.05 (m, 8H, $4XCH_2$), 3.67 (d, *J* 8.1 Hz, 1H, CH), 2.3 (s, 3H, CH_3), 1.31 – 1.2 (m, 9H, $3XCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 166.3, 165.9, 162.7, 142.8, 132.4, 127.3, 125.8, 118.3, 117.4, 62.3, 62.0, 61.5, 60.8, 55.5, 54.2, 20.6, 14.0, 13.87, 13.84; MS (70 eV) m/z (%) 407, 315, 248, 220, 192, 134, 84; IR (KBr, cm^{-1}) 2984, 1739, 1516, 1342, 1249, 1206, 1028, 810. Anal. Calcd for $C_{20}H_{25}NO_8$: C, 58.96; H, 6.19; N, 3.44. Found: C, 58.78; H, 5.99; N, 3.52.

Acknowledgements

The Grant Council at CCERCI (# 96-111) is gratefully acknowledged for financial support of this work.

Supplementary Material

Supplemental data for this article can be accessed on the publisher's website.

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