Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-020-01941-y

ORIGINAL PAPER

[Omim]Cl/$FeCl_3$-catalyzed cross-dehydrogenative-coupling of 1,4-benzoxazinones with various indoles

Ali Sharifi[1] · Maryam Moazami[1] · M. Saeed Abaee[1] · Mojtaba Mirzaei[1]

Received: 30 October 2019 / Accepted: 22 April 2020

Abstract
A novel C(sp^3)–C(sp^2) cross-dehydrogenative-coupling procedure was developed for the reaction of benzoxazin-2-ones with indole derivatives. Thus, ionic liquid-mediated coupling of 1,4-benzoxazinone derivatives with indoles were observed in which [Omim]Cl/$FeCl_3$ acted as both the solvent and the catalyst. Under [Omim]Cl/$FeCl_3$-TBHP conditions, derivatives of **1** coupled at room temperature with indoles bearing various substituents to give the target products in good yields and within 0.5–2 h time period. The procedure is relatively environmentally friendly and is applicable to several derivatives of both reactants to access the desired products.

Keywords Ionic liquids · CDC reactions · Benzoxazinones · Heterocycles

Introduction

Carbon–carbon (C–C) and carbon–heteroatom (C–X) bond formations are of fundamental reactions and are among the most important processes in synthetic organic chemistry to quickly build up complex molecules from simpler reactants [1]. In this context, direct coupling of C–H bonds with other C–H or X–H bonds via cross-dehydrogenative-coupling (CDC) reactions provides a useful route to form C–C or C–X bonds to construct various target molecules, where X would be heteroatoms such as oxygen, sulfur or nitrogen [2–6]. A major advantage achieved by direct CDC reactions is that the introductory steps for the preparation of reactants containing carbon-leaving groups and carbon–metal bonds are avoided [7–10]. In addition, CDC reactions are very useful methods for oxidation of amines [11–14]. This is because the undesired in situ oxidation of the starting amines to their respective iminium ions is avoided. Therefore, addition of nucleophiles of choice to the intermediate iminium to access the desired final structures is facilitated [15–17]. As a consequence of this strategy, several natural products and biologically active compounds have been synthesized so far [18].

Many biologically active compounds are known which have 1,4-benzoxazinone skeleton in their structure [19–22]. 1,4-Benzoxazinone are also synthetically manipulated to access more complex molecules with desired pharmaceutical properties [18, 23]. Some related illustrative examples are presented in Fig. 1. These chemical transformations are usually performed through derivatization of the carbon atom next to the amine functional group in the benzoxazinone ring. Despite the efficiency of this method, only a few related studies are carried out so far. Two recent investigations are the oxidative cross-dehydrogenative-coupling by Zhang [24] and the iron-catalyzed oxidative carbon–hydrogen bond functionalization by Huo [18]. Although these studies provided new methods for the synthesis of 3,4-dihydro-1,4-benzoxazin-2-one derivatives, there is still demands for the development of sustainable methods capable of functionalizing C–H bonds of benzoxazinone rings.

In the framework of increasing worldwide demands for more severe environmental protection, ionic liquids (IL's) have been introduced in recent decades as useful surrogates for traditional solvents in various chemical processes. This is because IL's have higher thermal stability, much low vapor pressure, increased tendency to dissolve various reactants and reagents and higher shelf lives [25–29]. One particular application is furnished by altering the cationic or anionic

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13738-020-01941-y) contains supplementary material, which is available to authorized users.

✉ Ali Sharifi
sharifi@ccerci.ac.ir

[1] Faculty of Organic Chemistry and Natural Products, Chemistry and Chemical Engineering Research Center of Iran, Pajohesh Blvrd., Tehran 1496813151, Iran

Published online: 05 May 2020

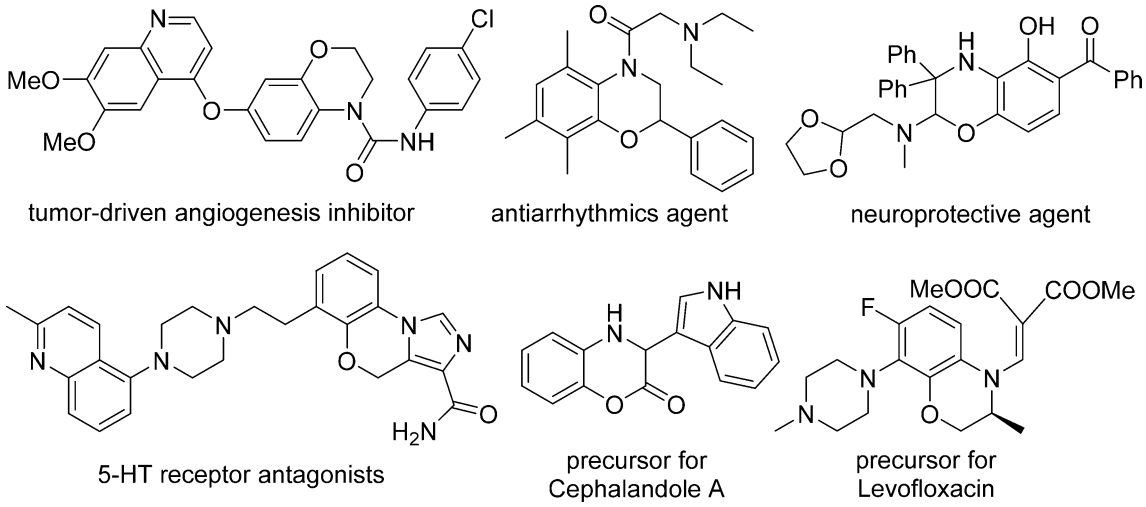


Fig. 1 Examples of important 1,4-benzoxazinone structures

components of IL's to access improved selectivity and reactivity in various synthetic transformations [30–33]. This is practically feasible by tailoring IL's with desired physical and chemical characteristics [34, 35].

Based on our previous studies on the development of environmentally friendly procedures [36–39], here we report a convenient procedure for IL-mediated coupling of 1,4-benzoxazinone **1** with 1*H*-indole derivatives **2** in the presence of [Omim]Cl/$FeCl_3$. The ionic liquid acts as both the solvent and the catalyst of the process (Scheme 1). The procedure presents a one-pot reaction which is mild and takes place at room temperature and incorporates various derivatives of the reactants.

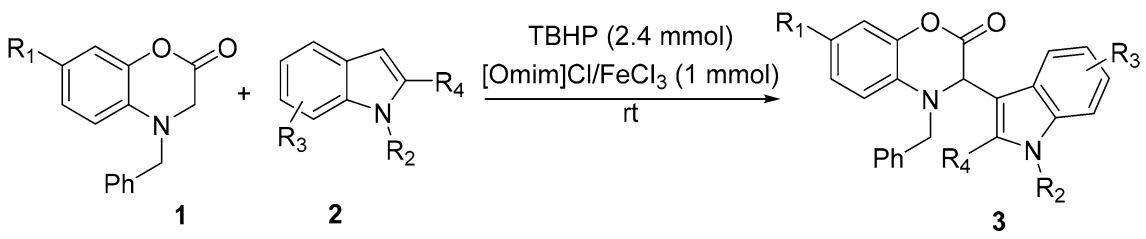
Experimental

General

Reactions were monitored by TLC using silica gel-coated plates and EtOAc/hexanes solutions as the mobile phase. Melting points are uncorrected. FT-IR spectra were 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 were obtained on a FT-NMR Bruker Ultra Shield™ instrument as $CDCl_3$ solutions, and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. Reagents and starting materials were purchased from commercial sources and were freshly used after being purified by standard procedures. The identities of the known products were confirmed by the comparison of their melting points and their ^{1}H NMR data with those reported in the literature [18]. New products were characterized by their ^{1}H NMR, ^{13}C NMR, IR, and mass spectra, and their purity were confirmed by elemental analyses.

Typical procedure for the synthesis of derivatives of 1 [40]

2-Aminophenol (2.2 gr, 20 mmol) and KF (2.9 gr, 50 mmol) were dissolved in dry DMF (100 mL). To this mixture was added ethyl 2-bromoacetate (2.2 mL, 20 mmol), and the



Scheme 1 General reaction for the synthesis of 1,4-benzoxazinones

mixture was stirred for 6 h at 60 °C. Then, the volatiles of the mixture were removed under reduced pressure and the residue was extracted by EtOAc (100 mL). The extract was washed by water (40 mL), dried over Na_2SO_4 and the volatile portion was removed under reduced pressure. The intermediate was fractionated by column chromatography using EtOAc/hexanes (1/10) as the eluent. Next, a mixture of the intermediate (1.95 gr, 10 mmol), glacial $MeCO_2H$ (0.9 mL, 15 mmol), and benzaldehyde (1.2 mL, 12 mmol) in CH_2Cl_2 (50 mL) was cooled in an ice bath for 30 min. To this mixture was added $NaBH(OAc)_3$ (3.18 gr, 15 mmol) and the mixture was stirred for 24 h. The mixture was washed with water (40 mL) and extracted with CH_2Cl_2 (60 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was fractionated by column chromatography using EtOAc/hexanes (1/10) as the eluent to obtain **1a** (1.56 gr, 65%).

Typical procedure for the synthesis of products 3

1*H*-Indole (**2a**, 0.14 gr, 1.2 mmol) was added to a mixture of **1a** (0.24 gr, 1.0 mmol) in [Omim]Cl/$FeCl_3$ (0.4 gr, 1.0 mmol). *tert*-Butyl hydroperoxide (TBHP) (0.3 gr, 2.4 mmol) was added to this mixture, and it was stirred for 0.5 h at room temperature. The mixture was extracted with EtOAc (10 mL), the extract was washed with water (15 mL) and dried over Na_2SO_4, and the volatile portion was removed under reduced pressure. The residue was fractionated by column chromatography using EtOAc/hexanes (1/10) as the eluent to obtain **3a** (0.32 gr, 93%).

Structural data of products 3

4-Benzyl-3-(1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (3a) [18]

Yellow solids in 93% yield; mp 63–66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.39–7.25 (m, 6H), 7.21 (t, J = 7.0 Hz, 1H), 7.13 (t, J = 7.5 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 5.41 (s, 1H), 4.62 (d, J = 15.0 Hz, 1H), 4.16 (d, J = 15.0 Hz, 1H).

4-Benzyl-3-(5-bromo-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (3b) [18]

Yellow solid in 68% yield; mp 152–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.56 (s, 1H), 7.41–7.24 (m, 6H), 7.18 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 5.31 (s, 1H), 4.63 (d, J = 14.5 Hz, 1H), 4.07 (d, J = 14.5 Hz, 1H).

4-Benzyl-3-(5-bromo-1-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (3c)

White solid in 75% yield; mp 192–194 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.32–7.42 (m, 3H), 7.32–7.25 (m, 3H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.0 Hz, 2H), 6.96 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.58 (s, 1H), 6.30 (s, 1H), 4.62 (d, J = 14.5 Hz, 1H), 4.07 (d, J = 14.5 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 141.8, 135.8, 135.3, 134.1, 128.9, 128.4, 128.3, 128.1, 127.9, 125.5, 125.3, 121.9, 120.1, 116.6, 114.1, 113.5, 110.9, 106.8, 55.3, 51.5, 33.1; MS (70 eV) m/z (%) 446, 418, 327, 248, 221, 196, 91; IR (KBr, cm^{-1}) 2859, 1756, 1371, 1239, 1198, 756. Anal. Calcd for $C_{24}H_{19}BrN_2O_2$: C, 64.44; H, 4.28; N, 6.26. Found: C, 64.35; H, 4.11; N, 6.05.

4-Benzyl-3-(1-benzyl-5-bromo-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (3d)

White solid in 80% yield; mp 159–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 1.5 Hz, 1H), 7.42–7.33 (m, 3H), 7.32–7.27 (m, 5H), 7.25 (dd, J = 1.5, 9.0 Hz, 1H), 7.14 (dd, J = 1.0, 7.9 Hz, 1H), 7.12–7.04 (m, 2H), 6.98–6.91 (m, 3H), 6.85 (d, J = 8 Hz, 1H), 6.68 (s, 1H), 5.33 (s, 1H), 5.11 (s, 2H), 4.63 (d, J = 14.5 Hz, 1H), 4.09 (d, J = 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 141.9, 136.2, 135.8, 134.9, 134.1, 128.9, 128.8, 128.6, 128.2, 128.1, 127.9, 127.8, 126.7, 125.5, 122.2, 120.3, 116.6, 114.2, 113.8, 111.6, 107.3, 55.4, 51.7, 50.4; MS (70 eV) m/z (%) 522, 496, 403, 325, 298, 196; IR (KBr, cm^{-1}) 3062, 1760, 1499, 1452, 1203, 1160, 742. Anal. Calcd for $C_{30}H_{23}BrN_2O_2$: C, 68.84; H, 4.43; N, 5.35. Found: C, 68.98; H, 4.21; N, 5.30.

4-Benzyl-3-(6-chloro-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (3e) [18]

White solid in 78% yield; mp 40–42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.45–7.32 (m, 4H), 7.29 (s, 3H), 7.18–7.04 (m, 3H), 6.95 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 5.36 (s, 1H), 4.64 (d, J = 15.0 Hz, 1H), 4.11 (d, J = 15.0 Hz, 1H).

4-Benzyl-3-(5-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (3f) [18]

White solid in 75% yield; mp 69–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.42–7.28 (m, 5H), 7.27 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 7.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 5.4 (s, 1H), 4.63 (d, J = 15.0 Hz, 1H), 4.15 (d, J = 15.0 Hz, 1H), 2.43 (s, 3H).

4-Benzyl-3-(2-phenyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3 g) [18]

White solid in 70% yield; mp 86–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.2 (s, 1H), 7.52 (s, 2H), 7.44–7.32 (m, 4H), 7.25–7.16 (m, 3H), 7.15–7.07 (m, 3H), 7.07–6.99 (m, 2H), 6.99–6.93 (m, 2H), 6.92–6.85 (m, 1H), 6.72 (d, J = 8.0 Hz, 1H), 5.6 (s, 1H), 4.45 (d, J = 16.0 Hz, 1H), 3.90 (d, J = 16.0 Hz, 1H).

4-Benzyl-3-(2-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3 h) [18]

Yellow solid in 85% yield; mp 194–197 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.33–7.24 (m, 3H), 7.18 (dd, J = 31.0, 8.0 Hz, 4H), 7.13–7.07 (m, 3H), 6.98 (t, J = 7.0 Hz, 1H), 6.92 (t, J = 7.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.36 (s, 1H), 4.60 (d, J = 16.0 Hz, 1H), 3.98 (d, J = 16.0 Hz, 1H), 1.90 (s, 3H).

Table 1 Optimization of the conditions for the synthesis of **3a**

Entry	Solvent	Conditions	Time (h)	Yield (%)[a,b]
1	[Omim]Cl/$FeCl_3$	TBHP	0.5	93
2	–	TBHP	0.5	0
3	MeCN	TBHP/$FeCl_3$	0.5	45
4	MeCN	TBHP/$FeCl_2.4H_2O$	0.5	50
5	MeCN	TBHP	0.5	0
6	[Omim]Cl/$FeCl_2$	TBHP	0.5	55
7	–	TBHP/$FeCl_3$	0.5	0
8	–	TBHP/$FeCl_2.4H_2O$	0.5	0
9	[Omim]PF_6	TBHP	0.5	0
10	[Omim]PF_6	TBHP/$FeCl_2.4H_2O$	0.5	65
11	[Omim]PF_6	TBHP/$FeCl_3$	0.5	70
12	[Omim]Cl/$CuCl_2$	TBHP	0.5	15
13	[Omim]Cl/$AlCl_3$	TBHP	0.5	50
14	[Emim]Cl/$FeCl_3$	TBHP	0.5	60
15	[Bmim]Cl/$FeCl_3$	TBHP	0.5	62
16	[C_{10}mim]Cl/$FeCl_3$	TBHP	0.5	70
17	[C_{12}mim]Cl/$FeCl_3$	TBHP	0.5	72
18	[Omim]Cl/$FeCl_3$	O_2	0.5	5
19	[Omim]Cl/$FeCl_3$	H_2O_2	0.5	35
20	[Omim]Cl/$FeCl_3$	$(NH_4)_2S_2O_8$	0.5	5

[a]Isolated yields

[b]Room temperature

4-Benzyl-3-(1-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3i) [18]

White solid in 84% yield; mp 194–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8 Hz, 1H), 7.42–7.32 (m, 5H), 7.32–7.26 (m, 2H), 7.21–7.14 (m, 2H), 7.11 (t, J = 8.0 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 5.45 (s, 1H), 4.65 (d, J = 15.0 Hz, 1H), 4.19 (d, J = 15.0 Hz, 1H), 3.65 (s, 3H).

4-Benzyl-3-(1-benzyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3j) [18]

Yellow solid in 93% yield; mp 146–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0, 1H), 7.40–7.33 (m, 3H), 7.33–7.26 (m, 5H), 7.26–7.18 (m, 2H), 7.14 (m, 2H), 7.07 (t, J = 8.0 Hz, 1H), 6.97–6.95 (m, 2H) 6.92 (t, J = 7.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 5.43 (s, 1H), 5.17 (s, 2H), 4.62 (d, J = 15.0 Hz, 1H), 4.18 (d, J = 15.0 Hz, 1H).

4-Benzyl-3-(1,2-dimethyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3 k) [18]

Brown solid in 79% yield; mp 197–199 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 4H), 7.23–7.15 (m, 4H), 7.14 (d, J = 8.0 Hz, 1H), 7.11–7.05 (m, 1H), 7 (t, J = 7.0 Hz, 1H), 6.94–6.88 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.42 (s, 1H), 4.6 (d, J = 16.0 Hz, 1H), 4.02 (d, J = 16.0 Hz, 1H), 3.66 (s, 3H), 2.15 (s, 3H).

4-Benzyl-3-(1-benzyl-2-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3l)

White solid in 85% yield; mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.43–7.19 (m, 9H), δ 7.19–7.08 (m, 4H), 7.07–7.01 (m, 1H), 7.01–6.92 (m, 3H), 6.89 (d, J = 8.0 Hz, 1H), 5.43 (s, 1H), 5.34 (d, J = 17.0 Hz, 1H), 5.23 (d, J = 17.0 Hz, 1H), 4.69 (d, J = 16.0 Hz, 1H), 4.04 (d, J = 16.0 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 140.8, 137.5, 137.2, 136.9, 136.7, 134.9, 128.9, 128.8, 127.6, 127.4, 126.1, 125.7, 121.8, 120.4, 119.2, 118.9, 117.2, 113.4, 109.6, 106.3, 56.1, 50.1, 46.7, 10.3; MS (70 eV) m/z (%) 458, 430, 339, 261, 237, 221, 91, 65; IR (KBr, cm^{-1}) 3498, 3031, 1762, 1603, 1494, 1021, 747. Anal. Calcd for $C_{31}H_{26}N_2O_2$: C, 81.20; H, 5.72; N, 6.11. Found: C, 81.39; H, 5.57; N, 6.22.

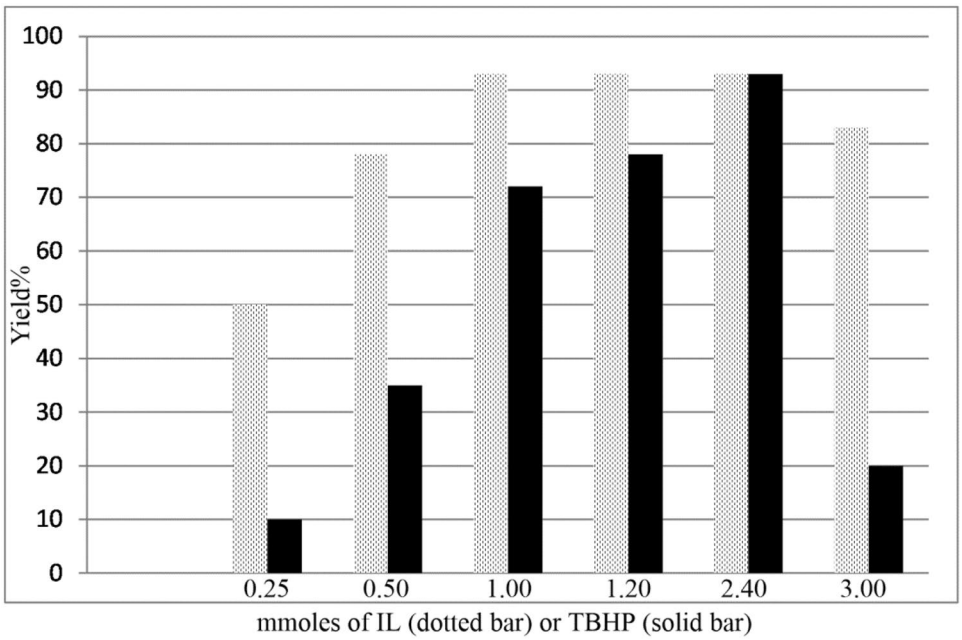


Fig. 2 Effect of the concentration of the IL (dotted bar) and the oxidant (solid bar) on the synthesis of **3a** (after 0.5 h reaction time)

4-Benzyl-3-(1*H*-indol-3-yl)-7-methyl-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3m) [18]

Orang solid in 70% yield; mp 174–175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.38–7.30 (m, 6H), 7.16 (t, J = 7.0 Hz, 1H), 6.96 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.76–6.71 (m, 2H), 5.40 (s, 1H), 4.58 (d, J = 15.0 Hz, 1H), 4.15 (d, J = 15.0 Hz, 1H), 2.35 (s, 3H).

4-Benzyl-7-methyl-3-(1-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3n)

White solid in 90% yield; mp 214–216 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.52 (d, J = 8.0 Hz, 1H), δ 7.38–7.24 (m, 7H), 7.17–7.12 (m, 1H), 6.97 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.61 (s, 1H), 5.39 (s, 1H), 4.57 (d, J = 15.0 Hz, 1H), 4.1 (d, J = 15.0 Hz, 1H), 3.64 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 140.9, 135.7, 135.5, 130.7, 128.8, 127.8, 126.8, 126.7, 126.2, 125.9, 124.7, 121.3, 118.9, 118.3, 116.1, 112.9, 108.4, 106.2, 55.1, 50.8, 31.9, 19.6; MS (70 eV) m/z (%) 382, 354, 263, 171, 143, 91; IR (KBr, cm^{-1}) 3046, 1757, 1513, 1448, 1227, 1153, 739. Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.48; H, 5.70; N, 7.43.

4-Benzyl-7-methyl-3-(2-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-one (3o)

White solid in 69% yield; mp 185–187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.30–7.22 (m, 4H), 7.17–7.08 (m, 4H), 7.03–6.96 (m, 2H), 6.8 (d, J = 8.0 Hz, 1H), 6.7 (d, J = 8.0 Hz, 1H), 5.31 (s, 1H), 4.57 (d, J = 16.0 Hz, 1H), 3.97 (d, J = 16.0 Hz, 1H), 2.35 (s, 3H), 2.06(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 140.6, 136.9, 135.4, 135.2, 132.3, 129.1, 128.6, 127.2, 126.7, 125.9, 121.7, 120.2, 118.8, 117.5, 117.4, 113.3, 110.5, 106.1, 55.9, 50.1, 20.5, 11.7; MS (70 eV) m/z (%) 382, 354, 263, 171, 130, 91; IR (KBr, cm^{-1}) 3386, 3058, 1741, 1254, 737. Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.52; H, 5.75; N, 7.49.

Results and discussion

We first optimized the reaction of **1a** (R_1 = H) with **2a** ($R_2 = R_3 = R_4$ = H) under various conditions (Table 1). The best results were obtained when a 1.0:1.2:2.4 mixture of **1a**, **2a** and TBHP was dissolved in [Omim]Cl/$FeCl_3$ and stirred at room temperature to obtain **3a** in 93% yield after 0.5 h (entry 1). Conducting the reaction in the absence of an IL and a catalyst (entry 2) gave no product and reactants remained intact. Lower yields of **3a** were obtained when the conditions reported by Huo et al. [18] were simulated (entries 3–4). Moreover, catalyst-free reaction in MeCN (entry 5) gave no product proving the need for either a

Table 2 Synthesis of various derivatives of **3**

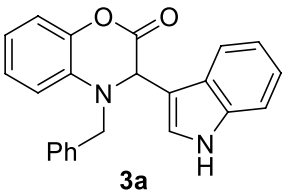
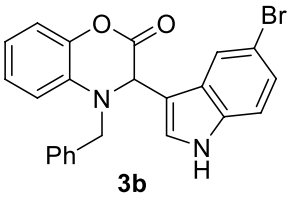
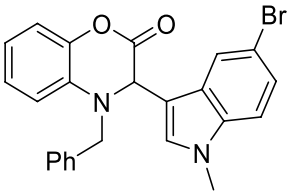
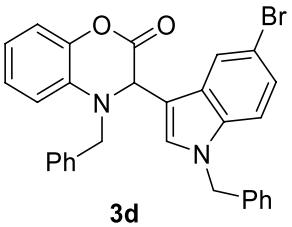
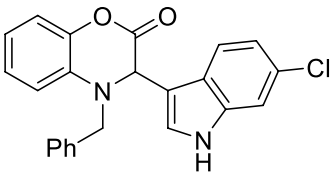
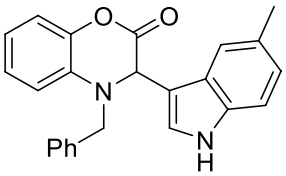
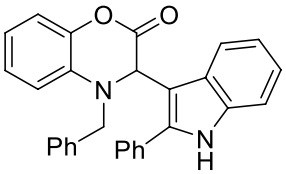
Entry	Reactants	Product	T (°C)	Time (h)	Yield (%)[a]
1	**1a** (R_1 = H) **2a** (R_2 = R_3 = R_4 = H)	 **3a**	25	0.5	93
2	**1a** (R_1 = H) **2b** (R_2 = R_4 = H, R_3 = Br)	 **3b**	25	1.5	68
3	**1a** (R_1 = H) **2c** (R_2 = Me. R_3 = Br, R_4 = H)	 **3c**	25	1.5	75
4	**1a** (R_1 = H) **2d** (R_2 = CH_2Ph, R_3 = Br, R_4 = H)	 **3d**	25	1	80
5	**1a** (R_1 = H) **2e** (R_2 = R_4 = H, R_3 = Cl)	 **3e**	25	1	78
6	**1a** (R_1 = H) **2f** (R_2 = R_4 = H, R_3 = Me)	 **3f**	25	0.5	75
7	**1a** (R_1 = H) **2 g** (R_2 = R_3 = H, R_4 = Ph)	 **3g**	25	1.5	70

Table 2 (continued)

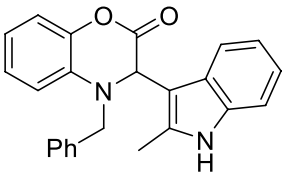
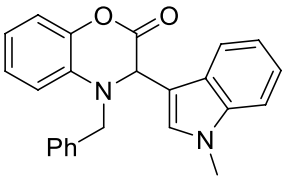
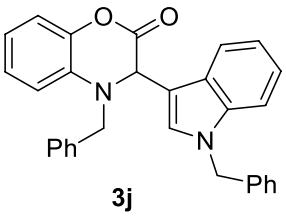
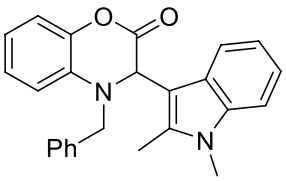
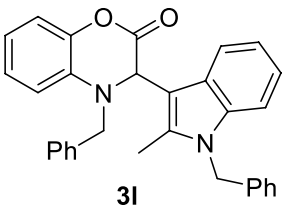
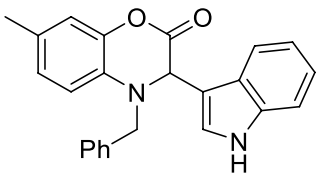
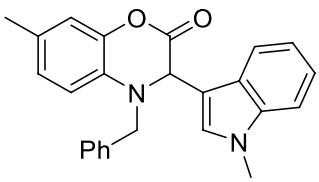
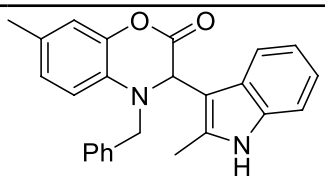
Entry	Reactants	Product	T (°C)	Time (h)	Yield (%)[a]
8	**1a** (R_1 = H) **2 h** (R_2 = R_3 = H, R_4 = Me)	 **3h**	25	1	85
9	**1a** (R_1 = H) **2i** (R_3 = R_4 = H, R_2 = Me)	 **3i**	25	1	84
10	**1a** (R_1 = H) **2j** (R_3 = R_4 = H, R_2 = CH_2Ph)	 **3j**	25	1	93
11	**1a** (R_1 = H) **2 k** (R_2 = R_4 = Me, R_3 = H)	 **3k**	25	1.5	79
12	**1a** (R_1 = H) **2 l** (R_2 = CH_2Ph, R_3 = H, R_4 = Me)	 **3l**	25	1	85
13	**1b** (R_1 = Me) **2a** (R_2 = R_3 = R_4 = H)	 **3m**	25	2	70
14	**1b** (R_1 = Me) **2i** (R_3 = R_4 = H, R_2 = Me)	 **3n**	25	1.5	90

Table 2 (continued)

Entry	Reactants	Product	T (°C)	Time (h)	Yield (%)[a]
15	**1b** (R_1 = Me) **2 h** (R_2 = R_3 = H, R_4 = Me)	 **3o**	25	2	69

[a]Isolated yields

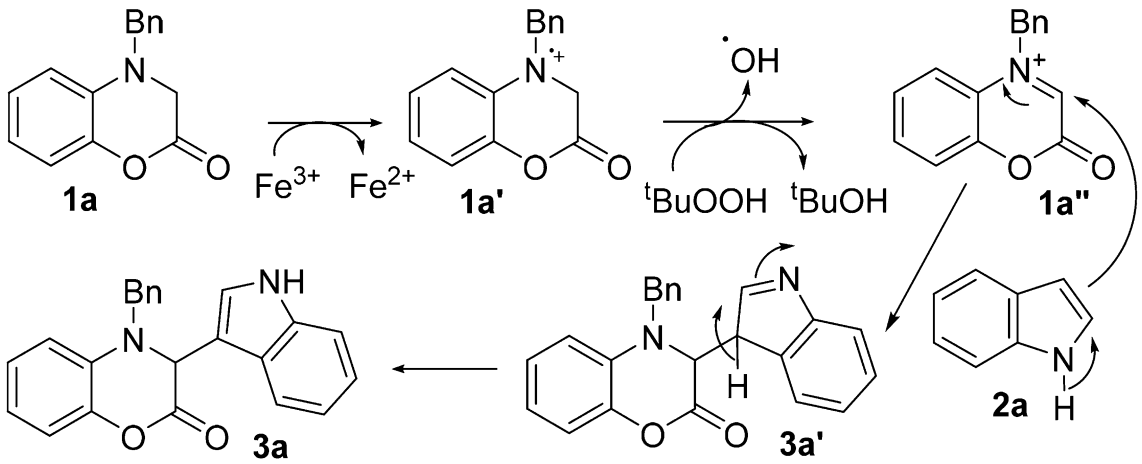


Fig. 3 A plausible mechanism for the reaction

Table 3 Comparison of the present work (synthesis of **3a**) with recent related procedures

Catalyst	Additive	Solvent	Oxidant	Conditions	T (h)	Yield %
$Zn(OTf)_2$	9,10-Phenanthrenequinone	MeCN	–	White LED	10	75 [41]
$Ru(bpy)_3Cl_2$	–	MeCN	–	Fluorescent bulb	10	50[24]
$FeCl_2$	–	MeCN	TBHP	–	1	65[18]
–	–	[Omim]Cl/$FeCl_3$	TBHP	–	0.5	93 (This work)

catalyst or an IL so that the reaction can proceed. Conducting the reaction in [Omim]Cl/$FeCl_2$ led to 55% formation of **3a**, implying that the Fe(III)-containing IL has a better catalytic effect on the process (entry 6). Alternatively, when either $FeCl_3$ (entry 7) or $FeCl_2$•$4H_2O$ (entry 8) was used instead of an IL, no **3a** was formed to further illustrate the catalytic effect of the IL on the process.

These results convinced us that [Omim]Cl/$FeCl_3$ behaves as both a dissolving medium and a catalyst for the reaction. Therefore, we decided to use other catalytic systems to further evaluate the role of counter ions. While [Omim]PF_6 alone caused no reaction (entry 9), [Omim]PF_6-$FeCl_2$•$4H_2O$ (entry 10) or [Omim]PF_6-$FeCl_3$ improved the outcome (entry 11). Alternatively, [Omim]Cl/$CuCl_2$ (entry 12) or [Omim]Cl/$AlCl_3$ (entry 13) gave **3a** in lower yields, supporting that $FeCl_4^-$ ($[Cl/FeCl_3]^-$) ion causes better conversion of the reactants to the product. Finally, change of the cationic part of the IL proved that [Omim] has a better performance on the progress of the reaction (entries 14–17). In addition, the role of the oxidizing agent was studied, where TBHP showed by far a much better effect on the coupling process (entries 18–20).

Next, we investigated the effect of the concentration of both the IL and the oxidant on the progress of the model reaction (Fig. 2). For the IL, the yield of **3a** increased as the amount of the IL reached to 1.00 equivalent and remained

unchanged at a higher concentration (dotted bar). Similar trend was observed for the amount of TBHP until 2.4 equivalents of the oxidant were used and the yield dropped to lower amounts for higher concentrations of TBHP (solid bar). It should be noted that the reaction can be performed with equimolar amounts of TBHP as well. However, it takes longer time (more than 3 h) to reach to about 80% yield.

We then evaluated the generality of the reaction by coupling various derivatives of the two reactants **1** and **2** under the optimized conditions (Table 2). Therefore, reaction of **1a** with the parent 1*H*-indole derivative **2a** (entry 1) or other derivatives of **2** bearing electron withdrawing or electron donating groups with different substitution patterns gave the desired products **3a**–**3l** in high yields within 0.5–2 h mixing at room temperature (entries 1–12). Similar results were observed when a methyl substituted derivative of **1** was reacted with derivatives of **2** to get products **3m**–**o** (entries 13–15). The structure of the products was elucidated by various spectroscopic methods. Particularly, in the ^{1}H NMR spectrum, the presence of a singlet proton at about 5.5 ppm was attributed to the CH of the position 3 of the benzoxazinone ring, showing the substitution of the indolyl residue. In addition, two diastereotopic doublet hydrogens appearing at about 4.5 and 4.0 ppm with $^{2}J = 16$ Hz, respectively, were an additional support for desymmetrization of the benzoxazinone ring as a result of the CDC process.

Based on these observations, a mechanism is proposed for reactions catalyzed by [Omim]Cl/$FeCl_3$, as shown in Fig. 3 for coupling of **1a** with **2a.** Initially, reduction in the ferric ion by the starting 1,4-benzoxazinone gives cation–radical **1a′**. Further oxidation of **1a′** by TBHP leads to iminium ion **1a″**. This ion is then nucleophilicly attacked by the second reactant to give **3a′**. Then, hydrogen rearrangement in **3a′** provides the final product **3a**. To support this mechanism, the reaction was repeated in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), which acts as a radical scavenger. Under these conditions, no product was obtained, suggesting that the reaction is perhaps going through a radical pathway.

Conclusions

In summary, a convenient procedure is developed for room temperature synthesis of indolyl-benzoxazin-2-one derivatives through coupling of 1,4-benzoxazinones with various indoles. The reaction chemoselectively leads to 3-indolyl derivatives and gives high yields of products in relatively short times. The IL is used in minimum quantities, and the reaction scope is general to prepare various products with different substituents. For a better conclusion, a comparison of the present work with other recent related studies is summarized in Table 3.

Acknowledgements CCERCI is gratefully acknowledged for financial support of this work.

References

1. T.W. Lyons, M.S. Sanford, Chem. Rev. **110**, 1147–1169 (2010)
2. X. Li, Y. Li, Y. Huang, T. Zhang, Y. Liu, B. Yang, C. He, X. Zhou, J. Zhang, Green Chem. **19**, 2925–2930 (2017)
3. P. Ghaderi-Shekhi Abadi, E. Rafiee, M. Joshaghani, J. Iran. Chem. Soc. **15**, 1513–1525 (2018)
4. C.-L. Sun, B.-J. Li, Z.-J. Shi, Chem. Rev. **111**, 1293–1314 (2011)
5. A. Tanoue, W.-J. Yoo, S. Kobayashi, Org. Lett. **16**, 2346–2349 (2014)
6. F. Feizpour, M. Jafarpour, A. Rezaeifard, New J. Chem. **42**, 807–811 (2018)
7. C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, Chem. Rev. **115**, 12138–12204 (2015)
8. N. Kuhl, N. Schröder, F. Glorius, Adv. Synth. Catal. **356**, 1443–1460 (2014)
9. C.S. Yeung, V.M. Dong, Chem. Rev. **111**, 1215–1292 (2011)
10. L. Wan, K. Qiao, X.N. Sun, Z.C. Di, Z. Fang, Z.J. Li, K. Guo, New J. Chem. **40**, 10227–10232 (2016)
11. D.B. Freeman, L. Furst, A.G. Condie, C.R.J. Stephenson, Org. Lett. **14**, 94–97 (2012)
12. Y.-H. He, Y. Xiang, D.-C. Yang, Z. Guan, Green Chem. **18**, 5325–5330 (2016)
13. Y. Pan, C.W. Kee, L. Chen, C.-H. Tan, Green Chem. **13**, 2682–2685 (2011)
14. C.-J. Wu, J.-J. Zhong, Q.-Y. Meng, T. Lei, X.-W. Gao, C.-H. Tung, L.-Z. Wu, Org. Lett. **17**, 884–887 (2015)
15. M.O. Ratnikov, X. Xu, M.P. Doyle, J. Am. Chem. Soc. **135**, 9475–9479 (2013)
16. H. Bartling, A. Eisenhofer, B. König, R.M. Gschwind, J. Am. Chem. Soc. **138**, 11860–11871 (2016)
17. S. Cai, X. Zhao, X. Wang, Q. Liu, Z. Li, D.Z. Wang, Angew. Chem. Int. Ed. **51**, 8050–8053 (2012)
18. C. Huo, J. Dong, Y. Su, J. Tang, F. Chen, Chem. Commun. **52**, 13341–13344 (2016)
19. D.S. La, J. Belzile, J.V. Bready, A. Coxon, T. DeMelfi, N. Doerr, J. Estrada, J.C. Flynn, S.R. Flynn, R.F. Graceffa, S.P. Harriman, J.F. Larrow, A.M. Long, M.W. Martin, M.J. Morrison, V.F. Patel, P.M. Roveto, L. Wang, M.M. Weiss, D.A. Whittington, Y. Teffera, Z. Zhao, A.J. Polverino, J.-C. Harmange, J. Med. Chem. **51**, 1695–1705 (2008)
20. E.N. Koini, P. Papazafiri, A. Vassilopoulos, M. Koufaki, Z. Horváth, I. Koncz, L. Virág, G.J. Papp, A. Varró, T. Calogeropoulou, J. Med. Chem. **52**, 2328–2340 (2009)
21. S.M. Bromidge, R. Arban, B. Bertani, S. Bison, M. Borriello, P. Cavanni, G. Dal Forno, R. Di-Fabio, D. Donati, S. Fontana, M. Gianotti, L.J. Gordon, E. Granci, C.P. Leslie, L. Moccia, A. Pasquarello, I. Sartori, A. Sava, J.M. Watson, A. Worby, L. Zonzini, V. Zucchelli, J. Med. Chem. **53**, 5827–5843 (2010)
22. E. Blattes, B. Lockhart, P. Lestage, L. Schwendimann, P. Gressens, M.-B. Fleury, M. Largeron, J. Med. Chem. **48**, 1282–1286 (2005)
23. K. Sato, T. Yagi, K. Kubota, A. Imura, Inventors, Oblon, McClelland, Maier & Neustadt, P.C., assignee, United States Patent 20040077060, April 22 (2004)
24. G.-Y. Zhang, K.-X. Yu, C. Zhang, Z. Guan, Y.-H. He, Eur. J. Org. Chem. **2018**, 525–531 (2018)

25. B. Chan, N. Chang, M. Grimmett, Aust. J. Chem. **30**, 2005–2013 (1977)
26. F.H. Hurley, T.P. Wier, J. Electrochem. Soc. **98**, 203–206 (1951)
27. P. Wasserscheid, W. Keim, Angew. Chem. Int. Ed. **39**, 3772–3789 (2000)
28. H. Zhao, S. Xia, P. Ma, J. Chem. Technol. Biotechnol. **80**, 1089–1096 (2005)
29. A.R. Hajipour, F. Rafiee, J. Iran. Chem. Soc. **6**, 647–678 (2009)
30. S. Nunomoto, Y. Kawakami, Y. Yamashita, H. Takeuchi, S. Eguchi, J. Chem. Soc. Perkin Trans. **1**, 111–114 (1990)
31. C. Chiappe, D. Capraro, V. Conte, D. Pieraccini, Org. Lett. **3**, 1061–1063 (2001)
32. Z.-L. Shen, H.-L. Cheong, Y.-C. Lai, W.-Y. Loo, T.-P. Loh, Green Chem. **14**, 2626–2630 (2012)
33. H. Singh, J. Sindhu, J.M. Khurana, J. Iran. Chem. Soc. **10**, 883–888 (2013)
34. D.J. Eyckens, L.C. Henderson, Front. Chem. **7**(263), 1–15 (2019)
35. H. Li, P.S. Bhadury, B. Song, S. Yang, RSC. Adv. **2**, 12525–12551 (2012)
36. A. Sharifi, F. Hosseini, N. Ghonouei, M.S. Abaee, M. Mirzaei, A.W. Mesbah, K. Harms, J. Sulfur Chem. **36**, 257–269 (2015)
37. M.M. Mojtahedi, M.S. Abaee, H. Abbasi, J. Iran. Chem. Soc. **3**, 93–97 (2006)
38. A. Sharifi, M.S. Abaee, M. Mirzaei, R. Salimi, J. Iran. Chem. Soc. **5**, 135–139 (2008)
39. A. Sharifi, M. Barazandeh, M.S. Abaee, M. Mirzaei, Tetrahedron Lett. **51**, 1852–1855 (2010)
40. N. Zidar, D. Kikelj, Tetrahedron **64**, 5756–5761 (2008)
41. J. Rostoll-Berenguer, G. Blay, J.R. Pedro, C. Vila, Catalysts **8**(653), 1–21 (2018)