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Choline chloride: 2 $ZnCl_2$ catalyzed efficient one-pot regioselective synthesis of dihydrobenzofuro[2,3-b]benzofuran

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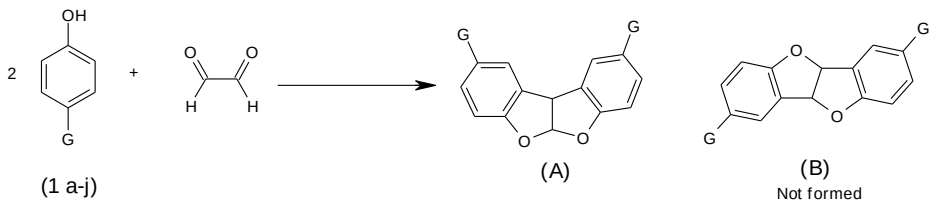
Abstract

The reaction of 2-naphthol and also para-substituted phenols with glyoxal in presence of choline chloride: 2 $ZnCl_2$ [ChCl: 2$ZnCl_2$], a deep eutectic solvent (DES), as a green catalyst was studied. The amount of catalyst, solvent type, temperature, and time on the yield of reaction were investigated. It was found that the optimal condition included 10% mol ratio of catalyst (mol percentage of DES to glyoxal), solvent-free condition (60 °C) and the time about one hour. Under these conditions, products are obtained in good yield (80%). The products were characterized on the basis of FT-IR, ^{1}H-NMR, ^{13}C-NMR spectra and comparison of melting point with authentic sample. The NMR spectra indicated that of the two probable isomers with an acetal and ether structure; the aforementioned reaction, regioselectively, furnished compounds with acetal linkage, rather than ether.

Keywords: Regioselective synthesis; benzofuro[2,3-b]benzofuran; deep eutectic solvent; choline chloride: 2 $ZnCl_2$.

Introduction

Condensation of glyoxal with phenols gave a network and insoluble resin with ethylenic or acetalic linkage [1,2], while *p*-substituted phenols have been reported to yield dimeric products in which the acetal or ether linkage may exist between the two benzene rings [3-9] (Scheme 1). Previous reports suggested that the condensation of *p*-substituted phenols with glyoxal yielded a product assigned ether structure (B) rather than the alternate acetal structure (A). However, the later studies displayed that the product of this reaction was the 5a,10b-dihydro benzofuro[2,3-b]benzofuran derivative (A) with acetal linkage.



Scheme 1. Condensation of *p*-substituted phenol with glyoxal

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The 5a,10b-dihydrobenzofuro[2,3-b]benzofuran derivatives have been prepared by the condensation of *p*-substituted phenols or anisols with dihloroacetal, followed by cyclization of products [10-12]. Also, these compounds have been synthesized in one-step by the reaction of *p*-substituted phenols or 2-naphthol with glyoxal in different acidic media such as: in acetic acid as solvent and presence of H_2SO_4, CH_3SO_3H or CF_3CO_2H as catalyst. In some studies, glyoxal bisulfite has been used instead of glyoxal. Also, Kito *et al*. performed reaction of 2-naphthol with glyoxal in alkaline condition [13].

The most convenient synthetic approach of dihydrobenzofuro[2,3-b]benzofuran derivatives is one-pot condensation of glyoxal with 2-naphthol or *p*-substituted phenols in presence of sulfuric acid as catalyst [14-17]. However, a large amount of sulfuric acid has to be used in this method (8 mole sulfuric acid for 1 mole product).

In recent years, the use of ionic liquids (ILs) in organic synthesis, electrochemistry, extraction and separation processes, and various other fields has been considered [18]. One class of ILs with special properties is the deep eutectic solvent (DES), defined by Abbot as solvent based on mixture of a hydrogen bond donor (HBD) and hydrogen bond acceptor molecules [19].

Deep eutectic solvents are systems formed from a eutectic mixture of Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species [20] while most DESs include a quaternary ammonium ion as the cationic component and hydrogen bond acceptor. Choline chloride has been used widely in preparation of DESs. It is bifunctional, containing both quaternary ammonium salt (HBA) and an alcohol (HBD). Abbott *et al*. found DESs by mixing choline chloride with hydrated transition metal salts [21], or with anhydrous zinc(II) chloride or tin(II) chloride [19,22].

Promoted by these findings and because of different useful properties of benzofurobenzofuran derivatives [8,23-25], in this article, we wish to report an efficient approach to the synthesis of benzofurobenzofurans using choline chloride: 2 $ZnCl_2$, a deep eutectic solvent, as a green and reusable catalyst.

Experimental

All chemicals were commercially available and used without further purification. ChCl: 2 $ZnCl_2$ was prepared according to the literature procedures [22]. Melting points were recorded on a Stuart SMP3 electrothermal type 9100 melting point apparatus. The FT-IR spectra were obtained from a Bruker Tensor 27 spectrophotometer, Germany, using the KBr pellet mode in the region of 4000-400 cm^{-1}. The ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker Avance DRX-300 spectrophotometer, Germany, with tetramethylsilane (TMS) as the internal standard and DMSO-d_6 as the deuterated solvents.

Synthesis of dihydrobenzofuro[2,3-b]benzofuran derivatives; (general procedure)

In a 10 mL round bottomed flask, 25 mmol *p*-substituted phenol or 2-nahthol (1a-j), (13 mmol, 1.5 mL) glyoxal solution 40 wt. % in H_2O, and (0.49 g, 10 mol% based on the glyoxal) ChCl: 2 $ZnCl_2$ was heated on an oil bath at 60 °C. Progress of the reaction was monitored by TLC. After completion the reaction, the reaction mixture was cooled to room temperature, cold ethanol (2×5 mL) was added to the

mixture and the precipitate was filtered off, washed with ethanol, and dried at 80 ℃ for 1 h to give the products. The filtrate was collected for separation and reusing of catalyst.

Reusability of the catalyst

The deep eutectic solvent as catalyst, [ChCl: 2 $ZnCl_2$], was soluble in ethanol; therefore, it is retrievable from reaction mixture. Then, the filtrate was washed with diethyl ether, dried in vacuum oven at 60 °C for 2 h, and reused in another reaction. The recycled catalyst was reused in four more cycles without significant loss in activity.

Results and discussion

In order to determine the most appropriate reaction conditions and evaluate the catalytic efficiency, initially, a model study was carried out on the synthesis of 2,9-dimethyl-5a,10b-dihydrobenzofuro[2,3-b]benzofuran in different solvents and under solvent-free conditions (Table 1). The best result was obtained when the reaction was carried out at 60 °C in acetic acid with 10 mol% of the ChCl:2$ZnCl_2$ catalyst (Table 1, Entry 6). The yield of the reaction with 10% mole ratio of the catalyst to glyoxal under solvent-free condition was comparable with Entry 15. Solvent-free condition offers several advantages over the solution techniques, including facile workup, environmentally friendly conditions and the absence of any hazardous organic solvents, so we choose solvent-free condition.

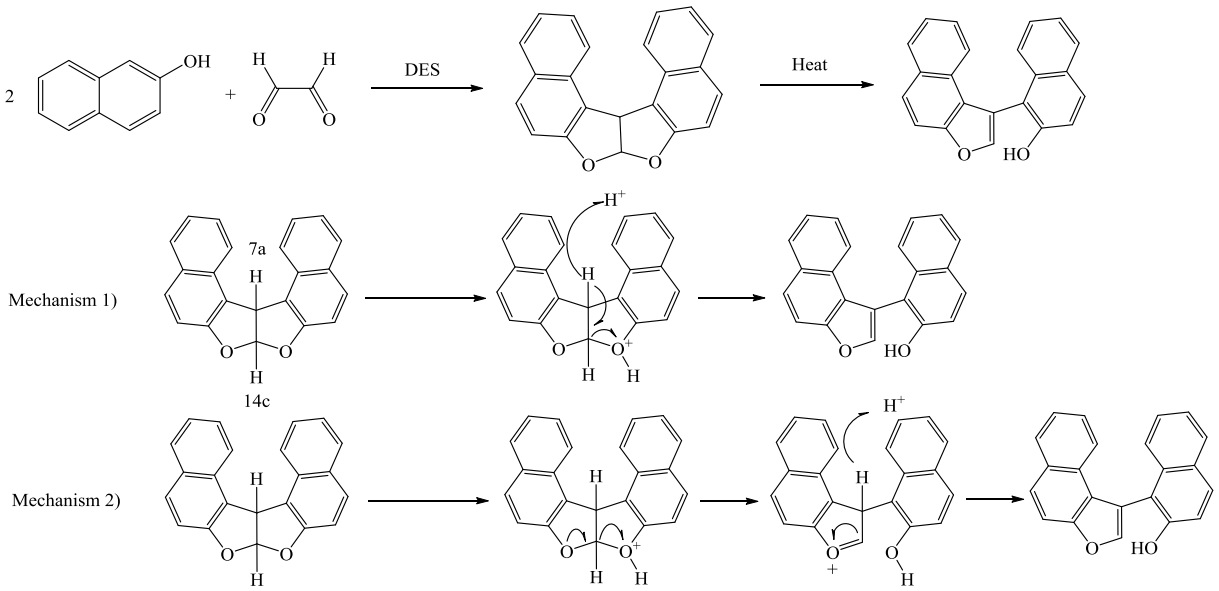
To evaluate and optimize the catalytic system, the effect of the catalyst to substrate molar ratio on the reaction was investigated in the model reaction. It was found that the use of 5 % mole ratio of catalyst gave low yield even after longer reaction duration. In comparison, 10% mole ratio of the catalyst led to an 85% yield of product. Increasing the amount of catalyst could not bring much better results (Table 1).

Table 1. Reaction of p-cresol (0.1 mol) with glyoxal (0.05 mol) at different condition

Entry	Dialdehyde	Solvent (mL)	Catalyst (mol% of catalyst to glyoxal)	Temperature (°C)	Time (Min.)	Yield (%)	Reference
1	Glyoxal	HOAc (100)	H_2SO_4 (800)	30	60	53	[5]
2	Glyoxal bisulfite	HOAc:H_2O (150:75)	H_2SO_4 (1800)	90	90	53	[6]
3	Glyoxal	HOAc (100)	CH_3SO_3H (912)	35	60	86	[6]
4	Glyoxal	HOAc (100)	ChCl: $ZnCl_2$ (5)	60	60	40	
5	Glyoxal	HOAc (100)	ChCl: 2 $ZnCl_2$ (5)	60	60	60	
6	Glyoxal	HOAc (100)	ChCl: 2 $ZnCl_2$ (10)	60	60	90	
7	Glyoxal	HOAc (100)	ChCl: 2 $ZnCl_2$ (15)	60	60	90	
8	Glyoxal	HOAc (100)	ChCl: 2 $ZnCl_2$ (10)	80	60	60	
9	Glyoxal	HOAc (100)	ChCl: 2 $ZnCl_2$ (10)	100	60	30	

10	Glyoxal	Toluene (100)	ChCl: 2 $ZnCl_2$ (10)	60	60	40
11	Glyoxal	CH_3CN (100)	ChCl: 2 $ZnCl_2$ (10)	60	60	60
12	Glyoxal	DMF (100)	ChCl: 2 $ZnCl_2$ (10)	60	60	68
13	Glyoxal	DMSO (100)	ChCl: 2 $ZnCl_2$ (10)	60	60	75
14	Glyoxal	-	ChCl: 2 $ZnCl_2$ (5)	60	120	50
15	Glyoxal	-	ChCl: 2 $ZnCl_2$ (10)	60	60	85
16	Glyoxal	-	ChCl: 2 $ZnCl_2$ (10)	80	60	80
17	Glyoxal	-	ChCl: 2 $ZnCl_2$ (10)	100	60	45

The effect of temperature on the yield of reaction was investigated. At the temperature higher than 60 °C, the products appeared to result in an opening of the heterocycles (Scheme 2).



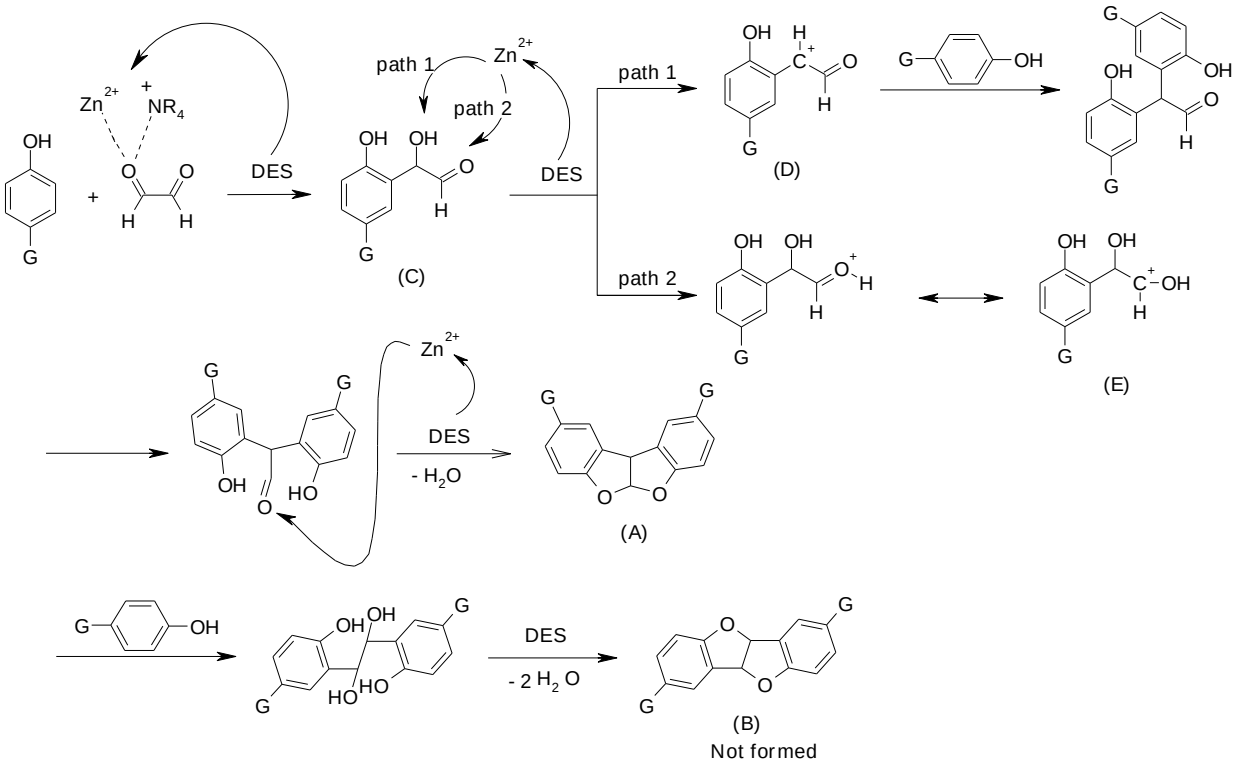
Scheme 2. Ring opening reaction at high temperature

The reaction of *p*-substituted phenol derivatives and also naphthol was carried out under particular conditions with glyoxal; the results are reported in Table 2. According to the results, this reaction is highly dependent on the nature of substituent and dose not proceed with the electron deficiency phenol (Entry 8). If 1-naphthol is used instead of phenols, since 1-naphthol has several active sites for the electrophilic substitution, a mixture of products is produced that could not be separated, but 2-naphthol reacted successfully with glyoxal to give the corresponding naphthofuronaphthofuran product in high yield over short reaction time. In addition, 3-hydroxy-2-naphthoic acid which contains the electron-withdrawing group of carboxylic acid reacted with glyoxal to give the desired product, while 4-hydroxybenzoic acid did not react with glyoxal.

Table 2. The reaction of *p*-substituted phenol derivatives with glyoxal at different conditions

Entry	Phenol (1a-j)	Time (min.)	m.p. (°C)		Yield (%)	
			Found	Reported	Found	Reported
1	*p*-cresol	60	195-196	194-195	85	53 [5]
2	4-chlorophenol	60	234-235	234-236	60	28 [6]
3	4-bromophenol	90	256-257	255-256	55	29 [26]
4	4-methoxyphenol	60	177-179	177-177.5	90	11 [6]
5	2,4-dimethylphenol	60	250-251	250-251	85	56 [5]
6	3,4-dimethylphenol	60	233-235	233-234	85	83 [6]
7	4-chloro-3-methylphenol	60	255-256	255-256	80	80 [27]
8	4-hydroxybenzoic acid	90	-	-	-	-
9	2-naphthol	30	238-240	236.5-238	95	79 [8]
10	3-hydroxy-2-naphthoic acid	90	216-218	210-220	60	60 [8]

According to the mechanism, the reaction proceeds *via* electrophilic substitution of one carbonyl group of glyoxal with two moles of phenol, followed by intramolecular acetalization reaction of phenolic OH with another carbonyl of glyoxal (Scheme 3), so electron-donating group on aromatic ring causes easier electrophilic substitution on the phenol ring, also the penolic OH is more nucleophilic and can easily attack to carbonyl group. Based on the mechanism and structure of catalyst, we were secured that ChCl: $2ZnCl_2$ can play a triple role. Thus, we propose that the ammonium ion in choline $[(CH_3)_3N^+(CH_2CH_2OH)]$ induces the polarization of the carbonyl groups, the OH group in choline actives carbonyl group by hydrogen bond formation and Zn^{2+} as Lewis acid can promote the necessary reactions. A comparison of ChCl: $2ZnCl_2$ with ChCl: $ZnCl_2$ reveals that the role of Zn^{2+} is more important than ammonium ion in choline.



Scheme 3. Mechanism of the reaction

Depending on the mechanism, there are two pathways for proceeding of the reaction, thus two isomers are possible. In the pathway (A), the benzylic carbocation intermediate is stabilized by resonance by the two aromatic ring, whereas in the pathway (B), for the carbocation intermediate is not possible such resonance forms. For this reason, this reaction regioselectively furnished compounds with acetal linkage rather than ether. These two isomers can be distinguished by NMR. For instance, the ^{1}H NMR spectrum of 7a,14b-dihydronaphtho[2,1-b]naphtho[2',3':4,5] furo[3,2-d]furan (DHNF) was shown in Figure 1. The number of peaks, multiplicities and integration of 2:2:2:2:2:2:1:1 for a total of 14 protons are in agreement with the acetal structure. The ^{1}H NMR spectrum shows eight distinct peaks, the peaks at 8.30 (d, 2H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.1 Hz), 7.77 (d, 2H, J = 8.7 Hz), 7.56 (t, 2H, J = 7.2 Hz), 737 (t, 2H, J = 7.5 Hz), and 7.27 (t, 2H, J = 8.7 Hz) ppm corresponded to the aromatic protons, the two duplets at 7.12 (d, 1H, J = 6 Hz) and 5.52 (d, 1H, J = 6 Hz) ppm corresponded to 7a and 14c, respectively. In the ether structure, both aliphatic hydrogens are identical and should appear as a singlet peak.

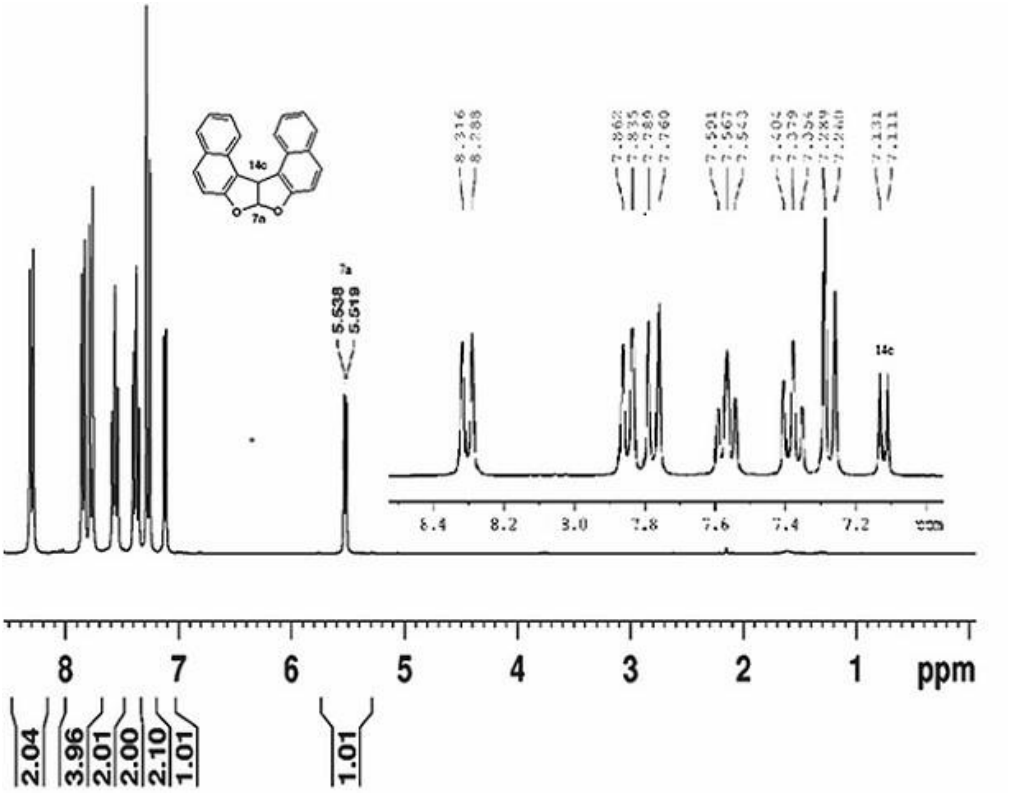


Figure 1. ^{1}H NMR spectrum of naphthofurofuran derivative (DHNF)

In addition, the ^{13}C NMR spectrum of (DHNF) showed twelve peaks, the peaks at δ=49.5 ppm and δ=112.3 ppm corresponded to carbon atoms of 14c and 7a, respectively. These findings confirm that the structure of product is acetal rather than ether (Figure 2). For the ether structure, due to symmetry, the carbon atoms of 14c and 7a must appear as one peak at δ≈90 ppm.

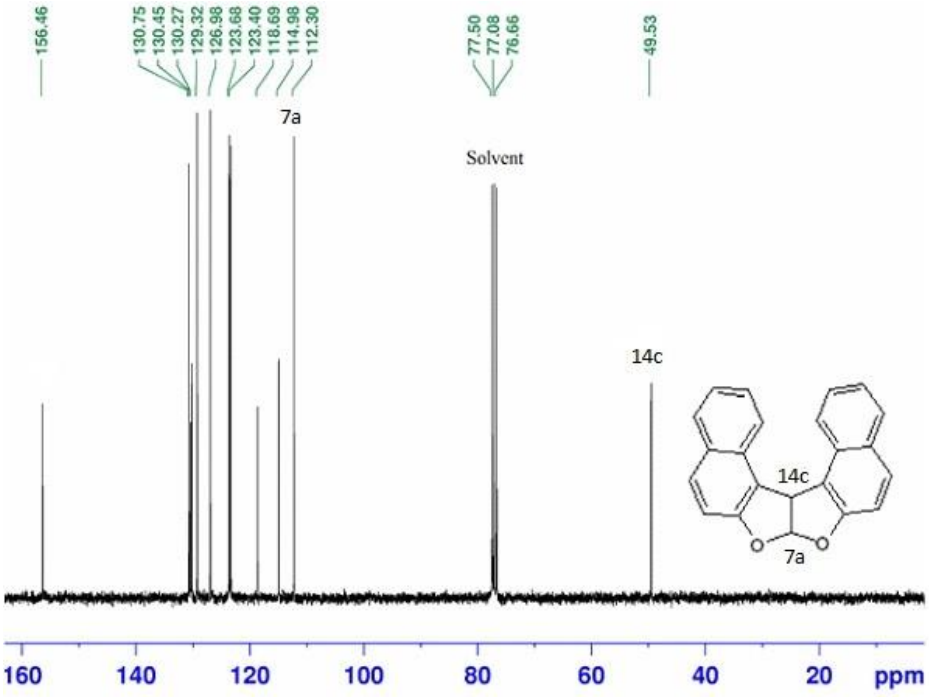


Figure 2. ^{13}C NMR spectrum of naphthofurofuran derivative (DHNF)

Conclusion

Different methods have been reported for synthesis of dihydrobenzofuro[2,3-b]benzofuran derivatives so far, and most of the methods use large amount of acidic solvents such as acetic acid formic acid and expensive catalyst like methanesulfonic acid or triflouroacetic acid. In addition, some of these methods use glyoxal bisulfite or dry glyoxal instead of glyoxal, which have to be synthesized first, so these methods are relatively expensive. Our method has several advantages including mild conditions, good yields, use of inexpensive, recyclable and reusable catalyst, utilizing cheap available 40% aqueous of glyoxal, the simplicity of separation and purification of products, and the elimination of volatile and hazardous organic solvents.

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