Original Article: Regioselective One-Pot Tranformation of 2'-Hydroxy Chalcones to 3,5-Diphenylisoxazole Via Dehydrogenation of Dihydroisoxazolines Using Copper Salt in DMF

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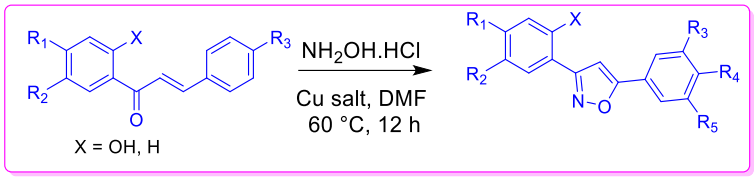
ABSTRACT

A synthesis of series of 3, 5-diaryl isoxazoles has been described. The Cu salt in DMF with DBU base inducing oxidative dehydrogenation of 2-(5-phenyl-4,5-dihydroisoxazol-3-yl) phenol resulted in the formation of 2-(5-phenylisoxazol-3-yl) phenol in a excellent yields under mild reaction conditions.



Introduction

Isoxazoles belong to an important aromatic heterocycles class having five-membered with two electronegative heteroatoms, nitrogen and oxygen N-O in a 1,2-relationship [1]. These scaffolds are found to be key constituents in various synthetic products in daily use and also present as a pharmacophore essential for biological activity in many drugs and bioactive natural products [2] (Figure 1). Besides, isoxazoles have demonstrated their ability to exhibit important precursors for agricultural applications. Apart from this, isoxazoles also show potent analgesic [3], COX-2 inhibitory [4], antinociceptive [5],

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anticancer [7], antitubercular, antimicrobial, antifungal[8]activities. Since the last decade, the synthesis of isoxazoles has been perfumed by using 2-alkyn-1-one-o-methyl oximes[9], sonogashira coupling of acid chlorides with terminal alkynes [10], dehydration of primary nitro compounds with organic bases [11], α-Halohydrazones/ketoximes are transformed into trisubstituted pyrazoles/disubstituted isoxazoles by treatment with phosphine, acyl chloride, and a base [12]. The synthesis of isoxazoles is broadly based on two major approaches including utilization of 1,3-dipolar cycloadditions as a general route to isoxazoles[13]. The second most popular approach to isoxazoles depends on the reaction of hydroxylamine with a 1,3 carbonyl compound, such as 1,3-diketone or an *α*, *β*-unsaturated ketones [14].

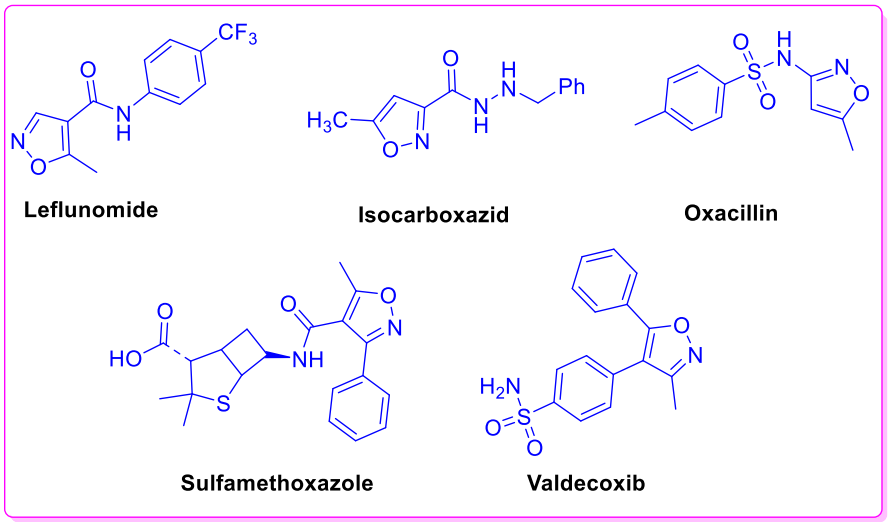


Figure 1. Bioactive isoxazoles in natural products

Over the last decade, researchers have made efforts for the synthesis of regioselective isoxazoles. According to Praveen *et al.,* $AuCl_3$-catalyzed cycloisomerization of *α,β*-acetylenic oximes leads to substituted isoxazoles in very good yields [15]. In*Himoet al.,* report, Cycloadditions of copper (I) acetylides to azides and nitrile oxides provide ready access to 1,4-disubstituted 1,2,3-triazoles and 3,4-disubstituted isoxazoles [16]. According to *Kadam et al.,* the use of either *tert*-butyl nitrite or isoamyl nitrite enables an efficient, one-pot approach for the synthesis of 3,5-disubstituted isoxazoles from substituted aldoximes and alkynes under conventional heating conditions [17]. According to*Gayon et al.,* the sequential use of iron and palladium catalysts in an uninterrupted four-step sequence allows the synthesis of trisubstituted isoxazoles from readily available propargylic alcohols[18]. Using cheap and eco-friendly iron(III) nitrate as the nitration and cyclization reagent and KI as an additive for the synthesis of isoxazoles from alkynes, both self-coupling and cross-coupling products could be successfully prepared [19]. Cu (I)-free cyclization of nitrile oxides with terminal amides provides isoxazoles [20].The first synthesis of isoxazole-4-carboxylic acid derivatives by domino isoxazole-isoxazole isomerization has been reported [21]. We have always been interested in bleaching clay [22], $CuCl_2.H_2O$ [23] iodine in DMSO [24] mediated aromatization, dehydrogenation for medicinally important heterocycles [25-26]. Herein, in this report we have described a simple efficient practical benign one-pot oxidative synthesis of 3,5-diaryl isoxazoles from isoxazoline by using Cu salt – in DMF with 90% yields without the need of any special reaction conditions.

Experimental

General

All reactions were carried out in oven-dried glassware and starting material was obtained from commercial suppliers (Aldrich, Merck,

Spectrochem, and Fisher), and used without further purification. Some reactions were performed under an atmosphere of Nitrogen gas. Analytical thin-layer chromatography (TLC) was performed on Merck DC pre-coated TLC plates with 0.25mm kieselgel 60F_{254}. Silica gel column chromatography was carried out with Flash silica gel (60-120 Mesh) from Spectrochem. IR spectra are recorded on a Perkin- Elmer 683 spectrometer. Optical rotation was obtained on a Jasco Polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Spectrometer in $CDCl_3$. Chemical shift is expressed in parts per million (d) using residual solvent protons as internal standard (δ= 7.26 ppm for $_{1}H$, δ= 77.0 ppm for 13 C). Coupling constant (*J*) are reported in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiple), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet). Combination of gas chromatography and low resolution mass spectroscopy was obtained on in Agilent. Gas Chromatogrphy (30 m 0.25 mm column with 0.25 mm HP-5 MS coating, He carrier gas) and Agilent mass spectrometer (Ion source: EI, 70 eV, 230°C; Interface: 300°C. All melting points and Boiling Points were measured on Buchi 501 apparatus and were uncorrected.

General procedure for synthesis of 3,5-diphenylisoxazole

Following the general procedure to a solution of compound dihydroisoxazolines(2A) (1 equiv) in DMF, CuCl(0.25equiv.), DBU(1 equiv.) was added. The resulting mixture was heated at 60°C temperature for 12. The reaction mixture was allowed to cool at room temperature and quenched in ice cold water, the crude product extract with ethyl acetate/hexane, the organic layer dry under vacuum, the crude compound purified by column chromatography provides the desired compound with 82% yield.

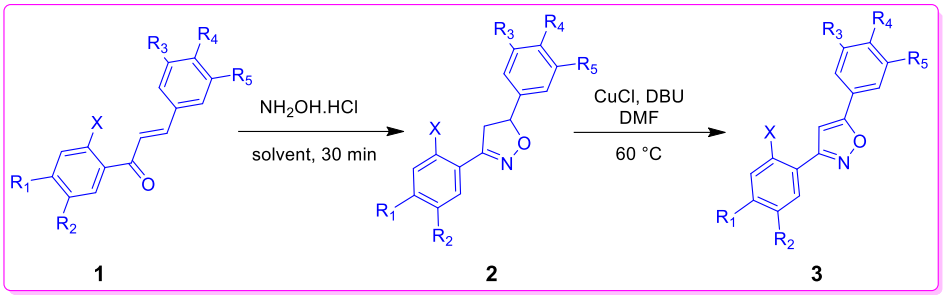
1)2-(5-phenylisoxazol-3-yl)phenol(**3A**); Light yellow solid, yield; mp 206°C. FTIR; cm^{-1}: 1218, 1560, 1594, 1661, 3010; ^{1}H NMR(300MHz, $CDCl_3$) δ, ppm: 6.24 s (1H,), 6.95 dd (1H, J = 8.16, 7.98'), 7.16 dd (2H, J = 8.1, 1.8 Hz,), 7.23–7.15m (1H), 7.39 d (2H, J = 8.12Hz,), 7.51 d.d.d (1H, J = 7.64, 6.4, 1.2 Hz'), 7.84 d (2H, J = 7.86 Hz,), 7.92 d.d (1H, J = 8.4, 1.8 Hz), 12.78 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 99.18, 117.14, 118.18, 121.40, 123.34, 126.43, 127.50, 127.78, 128.35, 128.92, 129.77, 131.93, 155.22, 163.21, 169.22. EIMS (m/z): 237 $[M]^{+}$

2) 5-(4-chlorophenyl)-3-phenylisoxazole(**3B**); white solid; R*f*=0.34 (ethyl acetate:*n*-Hexane, 1:4); mp = 180.9-178.8 °C.FTIR;cm^{-1}: 3110, 1413, 1098, 828; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.94-7.86 (m, 2H), 7.78 (d, *J*= 8.6 Hz, 2H), 7.56-7.48 (m, 5H), 6.86 (s, 1H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 169.81, 164.15, 137.3, 131.17, 129.34, 129.10, 128.93, 127.16, 126.84, 125.93, 97.87.

3)2-(5-(3-chlorophenyl)isoxazol-3-yl)phenol(**3C**); white solid, mp = 136.1-139.9 °C, FT-IR**;** cm^{-1} 3112, 1574, 1419, 1088, 799, 697,^{1}H NMR(400 MHz, $CDCl_3$) δ 7.93-7.83 (m, 2H), 7.82 (s, 1H), 7.74 (t, *J*= 4.3 Hz, 1H), 7.54-7.48 (m, 3H), 7.45-7.49 (m, 2H), 6.87 (s, 1H). ^{13}C NMR(100 MHz, $CDCl_3$) δ;169.70, 164.11, 136.21, 130.72, 130.51, 130.82, 129.21, 128.99, 128.92, 126.82, 125.92, 124.2, 98.32.; HRMS (ESI) for $C_{15}H_{11}ClNO$, $[M+H]^{+}$ (256.0529) found: 256.0534.

Result and Discussion

We started our research to prepare 2-(5-phenyl-4,5-dihydroisoxazol-3-yl) phenol by the reaction of by reacting 2'-hydroxy chalcones and chalcone with hydroxylamine hydrochloride in DMF as a solvent were readily converted to appropriate 3,5-diphenyl-4,5-dihydroisoxazole (Scheme 1).Thus, 3,5-diphenyl-4,5-dihydroisoxazole was further treated with catalytic amount CuBr in DMF to afford desired product.



Scheme 1. Comparison of the yield of isoxazoline in different solvents

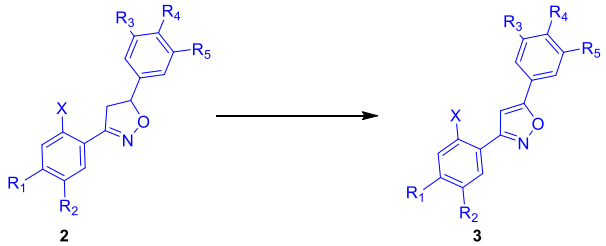
When 2'-hydroxy chalcone was treated with hydroxylamine hydrochloride in a one-pot fashion, it afforded the substrate **2a-i** in excellent yield which was further aromatized using CuBr to afford the product **3a-3i** in excellent yield. To select the best reaction solvent condition, the reaction was performed by using substrate **1a** as a model reaction in numerous solvents (Table 1). It was found that the reaction proceeded MeCN, PEG and DMF solvent with good to moderate yield. The reaction did not proceed in methanol, and diethyl ether whereas a very low yield was observed in toluene under reflux conditions. Among the solvents examined, PEG, DMSO and DMF were found to be efficient solvents for this oxidative aromatization system (Table 1, Entry 3).

Table 1. Comparison of the yield of isoxazoline in different solvents

Entry	Solvent	% Yield 3
1	DMSO	72
2	PEG	65
3	DMF	76
4	MeCN	52
6	CH_3OH	25

To select the best reaction condition, the reaction was optimized by using substrate **1a** as a model reaction performed in the DMF solvent. Our research was initiated with the optimization of reaction conditions for the Cu-catalyzed oxidative conversion of dihydroisoxazolines 2a to 3,5-diphenylisoxazole 3a. With the oxidative conversion of dihydroisoxazolines 2ato 3,5-diphenylisoxazole 3a as the model reaction, various conditions have been tested, and results are summarized in Table 1. At the beginning of optimization of conditions, reaction was performed in the absence of a copper catalyst (Table 2, entry 1) and no reaction happened. Then, we moved to perform the reaction using a reagent. We have tested reaction conditions in the absence of copper catalysts such as cupric bromide, CuCl, $CuCl_2$. H_2O, cupric acetate, cupric carbonate, cupric sulfate, copper(II) oxide, and copper powder have been tested as catalysts for the model reaction (Table 2, entries 2–8).

Table 2. Optimization of Reaction Conditions for dihydroisoxazolines**2a**to 3,5-diphenylisoxazole **3a**.



entry	Catalyst	Equiv.	Additive	Solvent	t(h)	Temp/ C	Yield(%)
1	No		Et_3N	DMF	12	60 °C	

2	NO		DBU	DMF	12	60 °C	
3	CuBr	0.05	Et_3N	DMF	12	60 °C	25
4	CuBr	0.05	DBU	DMF	12	60 °C	35
5	CuBr	0.10	DBU	DMF	12	60 °C	45
6	CuBr	0.15	DBU	DMF	12	60 °C	57
7	CuBr	0.20	DBU	DMF	12	60 °C	64
8	CuBr	0.25	DBU	DMF	12	60 °C	77
9	CuBr	0.50	DBU	DMF	12	60 °C	80
10	CuCl	0.10	DBU	DMF	12	60 °C	25
11	CuCl	0.25	DBU	DMF	12	60 °C	82
12	CuCl	0.50	DBU	DMF	12	60 °C	84

We started our statergy with Cu-catalyzed oxidative conversion of dihydroisoxazolines2a to 3,5-diphenylisoxazole3a in DMF, and the results are summarized in Table 2. Initially, dihydroisoxazolines 2a treated with 0.05 Equiv. of CuBr with Et_3N and DBU base in DMF at 60 °C, 3a was isolated in 25 to 35% yield (Table 1, entry 3,4). While the starting moiety was treated with 0.10, 0.15, and 0.20 equiv. CuBr in DMF with DBU base at 60 °C, the yield of reaction increased to 45 to 64% (Table 1, entry 5,6,7). When the reaction was performed at 60°C, with 0.25, 0.50 equiv. Cuin DMF at afforded 3a with 80–82% yield (Table 1, entry 8, 9). Similarly, dihydroisoxazolines 2a was treated with 0.10, 0.25 and 0.50 Equiv. Of CuCl with DBU base in DMF at 60 °C, 3a was isolated in 25 to 80% yield (Table 1, entry 10-12). The isolated product was confirmed by ^{1}H NMR, ^{13}CNMR, and mass spectroscopy techniques.

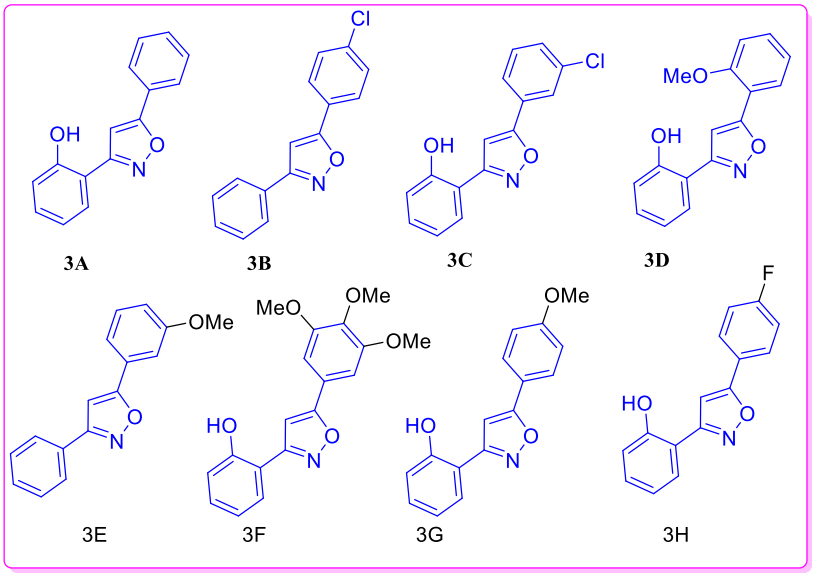


Table 3. Synthesis of 3,5-diaryl isoxazole via isoxazoline

The scope of the subtracte reaction is very broad; approximately all of the treated dihydroisoxazolines could be nicely converted to 3,5-diphenylisoxazolein a excellent yields. We have observed that the dihydroisoxazolines with electron-withdrawing at 3,5-phenyl ring position could undergo oxidation aromatization in DMF at 60 °C to afford 3,5-diphenylisoxazolein a excellent yield. While the electron-donating group present at 3 and 5 sites of phenyl group undergoes oxidative dehydrogenation gives desire product with good yield(Table3).

Therefore, for the this converstation the substituents effect does not play an important role for the dehydrogenation of dihydroisoxazolines. The practical methods involve simple efficient, eco-friendly, laboratory convenient, rapid and show ability

to endure a variety of electron releasing and electron withdrawing functional groups, such as NO_2, COOMe, OH and Cl.

Conclusion

In conclusion, we have developed a novel method for the selective oxidative dehydrogenation of dihydroisoxazolines to 3,5-diphenylisoxazole by using Cu salt in the presence of DBU base in DMF solvent. The advantages of this method is its tolerance of dihydroisoxazolines. The practical simplicity and low cost viability of this method explain additional research of this reaction. This is a metal free light condition; practical simplicity and low temperature reaction are some of the important features that render this protocol to be a best option to the regular organic synthesis.

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