

Copper (II) chloride: A regioselective catalyst for oxidative aromatization of pyrazoline, isoxazoline and 3-methyl flavanones

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A new protocol has been reported in which a series of pyrazoline, isoxazoline and 3-methyl flavanone has been conveniently aromatized by using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in DMSO within a short reaction time in excellent yields. The attraction of this new protocol is regioselective aromatization of substrate **3i-j** and **5a-e** which has been carried out to afford the aromatized product with O-allyl group intact in excellent yield.

Keywords: Copper (II) chloride, 3-methyl flavone, pyrazole, isoxazole, flavone, aromatization

In heterocyclic chemistry, substituted pyrazole is an important part of biologically active natural products as well as the part of commercially available pharmaceuticals due to its significant properties like anti-inflammatory¹, analgesic², anesthetic², antimicrobial³ and insecticidal⁴. Even more important is that the pyrazole ring is present in many compounds that possess a variety of pharmacological properties such as high binding affinity for estrogen receptor⁵, HIV protease inhibition⁶, antitumor activity⁷, inhibition of protein kinase C- β (Ref 8), 5HT₂ and 5HT₃ receptor antagonism⁹.

Similarly, “flavones” the subgroup of flavonoids are also a major constituent which are distributed from ferns to higher plants possessing various biological activities such as antioxidant, antifungal, antibacterial, anti-inflammatory, antitumor, antiasthmatic, antiviral, antihypertensive, estrogenic, antiangiolytic, diuretic activity and inhibition of hormone dependent proliferation of cancer cells^{10,11}.

Literature evaluation reveals many methods for the conversion of substituted pyrazoline to the respective pyrazole which include $\text{Pb}(\text{OAc})_4$, MnO_2 (Ref 12), KMnO_4 (Ref 13), Pd/C (Ref 14), $\text{Zn}(\text{NO}_3)_4$ (Ref 15) and $\text{PhI}(\text{OAc})_2$ (Ref 16). Out of these, MnO_2 and $\text{Pb}(\text{OAc})_4$ suffer from excess use of reagent and longer reaction time whereas Pd/C, $\text{Zn}(\text{NO}_3)_4$ catalyst causes formation of the side products. In the same way various heterogenous catalysts are also used for the oxidation of flavanones to flavones such as molecular iodine loaded on neutral alumina under microwave condition¹⁷ and CuI catalyzed cascade oxa-Michael oxidation mediated by the ionic liquid

[bmim] [NTf₂] (Ref 18) but these methods require longer time and higher temperature to complete the reaction.

Owing to its high chemical stability and less hindered nature, allyl group is commonly employed as protecting group for various functionalities especially alcohol, acid and less frequently, for amines during the synthesis of carbohydrates¹⁹, peptides²⁰, nucleotides²¹ and other natural products²². Despite its stability there are many reported protocols of pyrazoline and flavanone in which deallylation with aromatization has been carried out, for example treatment of pyrazoline with I₂-DMSO at 100°C afforded pyrazole with O-deallylation²³, I₂-DMSO at 130°C causes deallylation followed by cyclization of 2'-allyloxy chalcone to get flavanones, and I₂-DMSO-H⁺ at 80-90°C causes deallylation followed by oxidative cyclization to produce 5-methyl-3-phenylfuran-2-(5H)-one²⁴.

Copper (II) chloride is a versatile oxidant in organic synthesis and plays various roles like oxidizing agent for selective oxidation of benzyl alcohol to benzaldehyde using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ -DMSO (Ref 25) and oxidation of alcohol to aldehyde and ketone using CuCl_2 -TBHP (Ref 26), oxidative coupling agent for the synthesis of heterocyclic compounds²⁷, halogenating agent like chlorination, acts as a Lewis acid catalyst to promote iodination reaction, dehydrogenation of indoline to indole using anhydrous CuCl_2 in pyridine²⁸, coupling agent for the coupling of terminal alkynes in PEG (Ref 29) and reducing agent for the reduction of alkyl mesylate, dimesylate and triflate to the corresponding hydrocarbon using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ -Li and

DTBB in THF (Ref 30). Besides its versatile applicability in organic synthesis it is inexpensive, convenient to handle and simple to work up with no side products.

In continuation to the oxidation studies especially in the field of aromatization reactions, herein is explored the $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in DMSO system as an efficient oxidizing reagent for the selective aromatization of substituted pyrazoline, isoxazoline and 3-methyl flavanone to the corresponding pyrazole, isoxazole and 3-methyl flavone selectively without forming any side products.

Results and Discussion

The initial endeavor was to synthesis pyrazole and isoxazole scaffold from 2'-hydroxy chalcone. The 2'-hydroxy chalcone was prepared by treating 2'-hydroxy acetophenone and benzaldehyde with 40% NaOH in methanol as solvent. When 2'-hydroxy chalcone was treated with phenyl hydrazine or hydrazine hydrate and hydroxyl amine hydrochloride in one pot fashion, it afforded the substrate **1a-i** in excellent yield which was further aromatized using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ to afford the product in excellent yield as shown in **Table I**.

To choose the best reaction medium, the reaction was optimized by using substrate **1a** as a model reaction in various solvents. The reaction did not proceed in methanol, dichloromethane and diethyl

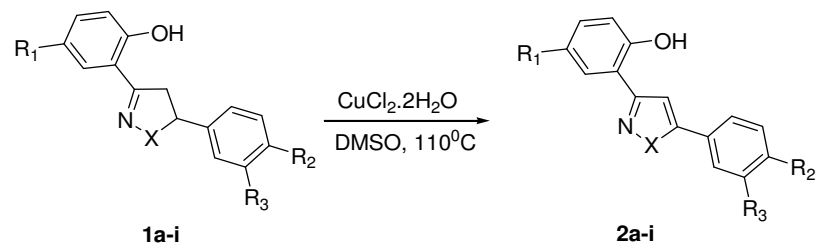
ether whereas very low yield was observed in toluene under reflux conditions. Among the solvents examined, DMSO was found to be an efficient solvent for this oxidative aromatization system (**Table II, Entry h**).

Initially, the system was studied at ambient temperature and no change could be observed after 20 h. At 80°C , the product could be obtained 50% yield with regeneration of the starting substrate in 8 h. As the temperature of the reaction increased, a greater portion of the reactant converted into the product. Consequently, the time required for completion of the reaction was reduced. Therefore, the best result was found at 110°C , whereas the product started decomposing above 140°C (**Table III**).

Thereafter, the amount of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ required to catalyze the aromatization of the substrate **1a** was investigated. Decreasing the amount of catalyst to half equivalent, afforded the product in 45% yield after 8 hr with the regeneration of the starting substrate. Further increase of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ to three equivalents does not affect the yield of product. Therefore, the best results were obtained by use of two equivalents of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$.

To validate the generality of the method and check the versatility of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, substrates **1a-i** was employed successfully and remarkable influence of electron withdrawing and electron donating group could be observed on the yield of the product. The

Table I — Oxidative aromatization of **1a-i** using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in DMSO solvent



Entry	X ^a	Product			Time (min)	m.p. ($^\circ\text{C}$)	Yield ^b (%)
		R ₁ ^a	R ₂ ^a	R ₃ ^a			
2a	NH	H	H	H	40	144-45	90
2b	NH	H	H	OCH ₃	40	104-105	92
2c	NH	Cl	H	H	40	169-70	92
2d	NH	Cl	OCH ₃	OCH ₃	40	181-82	92
2e	<i>p</i> -CHO-Ar-N	H	H	H	40	189-90	91
2f	<i>p</i> -CHO-Ar-N	H	OCH ₃	H	45	197-98	94
2g	O	CH ₃	H	H	40	119-20	87
2h	O	OCH ₃	H	H	45	208-09	89
2i	O	Cl	H	H	40	121-22	89

^asubstituent for **1a-i**

^bisolated yield of the product

presence of electron withdrawing group increased the yield while electron donating group decreased the yield of the aromatized product.

To explore the utility of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ mediated aromatization reaction, this methodology has been extended to the other heterocyclic moiety such as

flavanones shown in **Table IV**. Substrates **3a-j** were synthesized by the cyclization of substituted 2'-hydroxy chalcone in presence of sulphuric acid with silica gel support at RT in dichloromethane.

With this compound in hand, the oxidative aromatization reaction was examined by treatment of substrates **3a** in DMSO as solvent with two equivalents of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ at 110°C to afford 3-methyl flavones with 94% yield without forming any side product. Thereafter, a series of substituted 2,3-dihydro-3-methylchromen-4-one **3b-j** were employed to check the versatility of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and to afford the product **4b-j** in 90-94% yield. There was no remarkable influence of electron withdrawing and electron donating groups on the yield of product **4a-i**.

Previously, aromatization of pyrazoline and isoxazoline was carried out using catalytic amount of iodine in DMSO to afford the corresponding pyrazole and isoxazole. In this report, simultaneous deallylation as well as aromatization was carried out²⁰. In order to avoid the previous limitation and to check the selectivity of the present methodology, the 2'-hydroxyl group of pyrazoline, isoxazoline and 3-methyl flavanones was protected with allyl bromide using K_2CO_3 in DMF solvent. Reaction was carried out by using allylated substrates **5a-e**, **3i-j** with two equivalents of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in DMSO at 110°C which afforded the aromatized products **6a-e**, **4i-j** in excellent yields with O-allyl group intact (**Table V**).

Table II — Optimization of the substrate **1a** by using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in various solvents

Entry	Solvent	Time	Yield (%)
a	Methanol	8 h	No reaction
b	Dichloromethane	8 h	No reaction
c	Diethylether	8 h	No reaction
d	Acetonitrile	8 h	57
e	Tetrahydrofuran	8 h	25
f	Toluene	8 h	10
g	Dimethyl formamide	5 h	69
h	Dimethyl sulphoxide	45 min	92

Table III — Effect of temperature of aromatization reaction on the yield of substrate **1a** in dimethylsulphoxide solvent

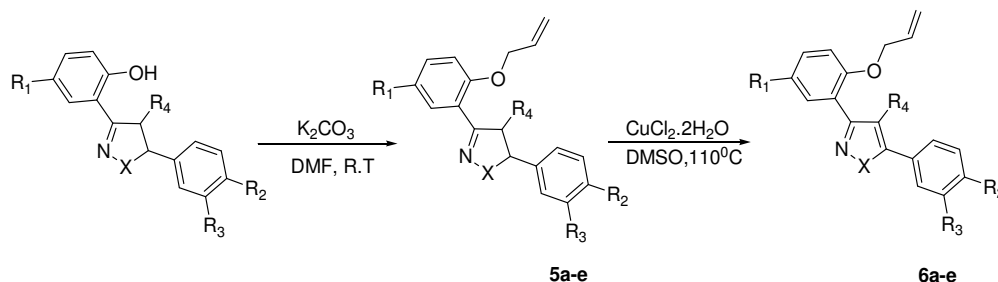
Entry	Temperature ($^\circ\text{C}$)	Time	Yield (%)
a	50	20 h	No reaction
b	80	8 h	50
c	110	40 min	92
d	130	35 min	91
e	140	30 min	80

Table IV — Aromatization of flavanones **3a-j** in presence of active O-allyl group

Entry	Product		Time (min)	m.p. ($^\circ\text{C}$)	Yield ^b (%)
	R_1^a	R_2^a			
4a	H	Cl	40	153-54	94
4b	H	Cl	40	198-99	92
4c	Cl	Cl	35	165-66	90
4d	Cl	Cl	40	168-69	91
4e	Cl	Cl	40	175-76	94
4f	Cl	Cl	45	187-88	91
4g	Cl	Cl	35	210-11	90
4h	Br	Cl	40	181-82	93
4i	H	H	40	135-36	91
4j	H	Cl	45	148-50	93

^asubstituent for **3a-j**

^bisolated yield of the product

Table V — Oxidative aromatization of **5a-e** using CuCl₂·2H₂O in DMSO solvent

Entry	X ^a	Product				Time (min)	m.p. (°C)	Yield ^b (%)
		R ₁ ^a	R ₂ ^a	R ₃ ^a	R ₄ ^a			
6a	<i>p</i> -CHO-Ar-N	H	H	H	H	40	189-90	91
6b	<i>p</i> -CHO-Ar-N	H	OCH ₃	H	H	45	197-98	94
6c	O	CH ₃	H	H	H	40	119-20	87
6d	O	Cl	OCH ₃	H	CH ₃	45	188-89	90
6e	O	Cl	Cl	H	CH ₃	40	214-15	91

^asubstituent for **5a-e**^bisolated yield of the product

Experimental Section

TLC was performed on E-Merck 60 F₂₅₄ precoated plates and the spots were rendered visible by exposing to UV light and iodine vapour. Melting points were determined with an Electro-Thermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 8000 spectrophotometer. The ¹H and ¹³C NMR spectra were recorded on a Varian spectrometer. Chemical shifts (δ) are reported in ppm with reference to tetramethyl silane as internal standard. Mass spectra (GCMS) were recorded on a Shimadzu Q-5050 spectrometer.

General procedure for the synthesis of substrates **2 a-i**, **4a-j**, **6a-e**

A mixture of substrates **1a-i**, **3a-j**, **5a-e** (0.1 mmol) and CuCl₂·2H₂O (0.2 mmol) in 10 mL DMSO solvent was stirred at 110°C for 40-45 min. The completion of the reaction was monitored by TLC. The resultant reaction mixture was poured onto crushed ice. The precipitated compound was filtered and purified by recrystallization from ethanol.

4-(3-(2-Hydroxyphenyl)-5-phenyl-1H-pyrazol-1-yl) benzaldehyde, 2e. Yield 91%; m.p. 189-91°C; IR (KBr): 3419, 3123, 2917, 2848, 1701, 1585, 1510 cm⁻¹; ¹H NMR (CDCl₃): δ 6.98 (1H, s), 6.95 (t, 1H, *J* = 7.8 Hz), 7.07 (1H, d, *J* = 7.8 Hz), 7.24 – 7.31 (3H, m), 7.35 – 7.42 (3H, m), 7.52 (2H, d, *J* = 8.7 Hz), 7.61 (1H, dd, *J*₁ = 7.8 Hz, *J*₂ = 1.8 Hz), 7.92 (2H, d, *J* = 8.7 Hz), 10.11 (1H, s), 10.43 (1H, s); ¹³C NMR

(CDCl₃): δ 105.7, 115.3, 118.5, 118.8, 120.8, 127.3, 127.9, 128.0, 128.7, 129.7, 133.3, 133.8, 141.6, 142.1, 152.1, 158.3, 191.1; MS: *m/z* (%) 340 (M⁺) (100), 208.42.

4-(3-(2-Hydroxyphenyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzaldehyde, 2f. Yield 94%; m.p. 197-98°C; IR (KBr): 3446, 3103, 3059, 2839, 2744, 1693, 1600, 1581, 1496 cm⁻¹; ¹H NMR (CDCl₃): δ 3.85 (3H, s), 6.86 (1H, s), 6.91 (2H, d, *J* = 8.7 Hz), 6.96 (1H, t, *J* = 7.5 Hz), 7.07 (1H, d, *J* = 8.4 Hz), 7.24 (2H, d, *J* = 8.4 Hz), 7.28-7.31 (1H, m), 7.51 (2H, d, *J* = 8.7 Hz), 7.64 (1H, dd, *J*₁ = 7.8 Hz, *J*₂ = 1.5 Hz), 7.88 (2H, d, *J* = 7.8 Hz), 10.02 (1H, s), 10.68 (1H, s); ¹³C NMR (CDCl₃): δ 55.3, 105.4, 114.3, 115.7, 117.2, 119.4, 121.6, 124.5, 126.6, 129.9, 130.2, 130.4, 134.6, 143.8, 144.2, 152.7, 156.1, 160.2, 190.9; MS: *m/z* (%) 370 (M⁺) (100), 238 (45).

6-Chloro-2-(4-methoxyphenyl)-3-methyl-4H-chromen-4-one, 4a: Yield 94%, m.p. 153-54°C; IR (KBr): 3067, 2965, 1639, 1608, 1511, 1461 cm⁻¹; ¹H NMR (CDCl₃): δ 2.19 (3H, s), 3.90 (3H, s), 7.04 (2H, d, *J* = 9 Hz), 7.42 (1H, d, *J* = 8.7 Hz), 7.57-7.63 (3H, m), 8.21 (1H, d, *J* = 2.1 Hz); ¹³C NMR: δ 11.9, 55.4, 113.8, 116.9, 119.5, 123.3, 125.1, 125.3, 130.3, 130.5, 133.4, 154.3, 161.1, 161.2, 177.7; MS: *m/z* (%) 300 (M⁺), 299 (100), 285, 269, 257, 222, 205, 194, 178, 146, 126, 103, 77, 63.

6-Chloro-2-(4-chloro phenyl)-3-methyl-4H-chromen-4-one, 4b. Yield 92%; m.p. 198-99°C; IR (KBr): 3054, 2956, 1642, 1611, 1526, 1461 cm⁻¹; ¹H NMR

(CDCl₃): δ 2.15 (3H, s), 7.41 (1H, d, $J = 9$ Hz), 7.42 (1H, d, $J = 8.7$ Hz), 7.51 (2H, d, $J = 8.4$ Hz), 7.58 – 7.62 (3H, m), 8.21 (1H, d, $J = 2.4$ Hz); ¹³C NMR: δ 11.8, 114.2, 117.1, 125.2, 126.8, 128.9, 129.1, 130.3, 131.3, 131.4, 134.1, 135.6, 154.9, 160.8, 178.3; MS: m/z (%) 304 (M⁺), 289 (100), 269, 258, 224, 193, 150, 111(10), 77, 61.

6,8-Dichloro-2-3-methyl-2-phenyl-4H-chromen-4-one, 4c. Yield 90%; m.p. 165-66°C; IR (KBr): 3072, 1647, 1618, 1597, 1458, 1357, 1182, 1130, 1078, 891, 773 cm⁻¹; ¹H NMR (CDCl₃): δ 2.15 (3H, s), 7.41 (3H, d, $J = 9$ Hz), 7.42 (1H, d, $J = 8.7$ Hz), 7.51 (2H, d, $J = 8.4$ Hz), 7.58 – 7.62 (3H, m), 8.21 (1H, d, $J = 2.4$ Hz); ¹³C NMR: δ 11.8, 114.2, 117.1, 125.2, 126.8, 128.9, 129.1, 130.3, 131.3, 131.4, 134.1, 135.6, 154.9, 160.8, 178.3; MS: m/z (%) 304 (M⁺), 289 (100), 269, 258, 224, 193, 150, 111 (10), 77, 61.

6,8-Dichloro-2-(4-methoxyphenyl)-3-methyl-4H-chromen-4-one, 4d. Yield 91%; m.p. 168-69°C; IR (KBr): 3074, 1641, 1610, 1568, 1458, 1356, 1265, 1182 cm⁻¹; ¹H NMR (CDCl₃): δ 2.22 (3H, s), 3.90 (3H, s), 7.05 (2H, dd, $J_1 = 6.9$ Hz, $J_2 = 1.8$ Hz), 7.67-7.71 (3H, m), 8.11 (1H, d, $J = 2.7$ Hz); ¹³C NMR: δ 12.3, 55.6, 113.7, 116.4, 123.1, 127.5, 127.6, 127.9, 129.1, 131.4, 139.2, 151.5, 161.8, 162.2, 178.1; MS: m/z (%) 334 (M⁺), 319, 303, 227 (100), 192, 147, 93, 77, 56.

6,8-Dichloro-2-(3,4-dimethoxyphenyl)-3-methyl-4H-chromen-4-one, 4e. Yield 94%; m.p. 175-76°C; IR (KBr): 3092, 1652, 1561, 1502, 1467, 1351, 1255, 1182 cm⁻¹; ¹H NMR (CDCl₃): δ 2.24 (3H, s), 3.96 (3H, s), 3.98 (3H, s), 7.01 (1H, d, $J = 8.4$ Hz), 7.28 (1H, d, $J = 1.8$ Hz), 7.33 (1H, dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 7.74 (1H, d, $J = 3$ Hz), 8.12 (1H, d, $J = 3$ Hz); ¹³C NMR (CDCl₃): δ 11.6, 55.1, 56.4, 110.8, 113.7, 118.1, 118.8, 125.1, 126.9, 127.3, 129.7, 132.1, 134.3, 148.8, 151.0, 161.8, 176.1; MS: m/z (%) 364 (M⁺), 349, 333 (100), 314, 302, 227, 187, 176, 145, 101, 63, 41.

6,8-Dichloro-2-(3,4,5-trimethoxyphenyl)-3-methyl-4H-chromen-4-one, 4f. Yield 91%; m.p. 187-88°C; IR (KBr): 3071, 1646, 1595, 1506 cm⁻¹; ¹H NMR (CDCl₃): δ 2.24 (3H, s), 3.93 (6H, s), 3.95(3H, s), 6.94 (2H, s), 7.71 (1H, d, $J = 2.4$ Hz), 8.12 (1H, d, $J = 2.4$ Hz); ¹³C NMR (CDCl₃): δ 11.9, 56.3, 60.9, 106.6, 117.5, 123.8, 123.9, 127.6, 130.2, 133.3, 133.3, 140.1, 150.2, 153.1, 160.8, 177.0; MS: m/z (%) 394 (M⁺), 379, 363 (100), 349, 323, 321, 295, 293, 265, 249, 230, 191, 160, 148, 133, 97, 77, 63.

6,8-Dichloro-2-(4-chlorophenyl)-3-methyl-4H-chromen-4-one, 4g. Yield 90%; m.p. 210-11°C; IR (KBr): 3076, 1651, 1612, 1597, 1568, 1498, 1460, 1359, 1186, 1130, 869, 783 cm⁻¹; ¹H NMR (CDCl₃): δ 2.19

(3H, s), 7.52 (2H, d, $J = 9$ Hz), 7.66 (2H, d, $J = 9$ Hz), 7.71(1H, d, $J = 2.4$ Hz), 8.12(1H, d, $J = 2.4$ Hz); ¹³C NMR (CDCl₃): δ 11.9, 56.3, 60.9, 106.6, 117.5, 123.8, 123.9, 127.6, 130.2, 133.3, 133.3, 140.1, 150.2, 153.1, 160.8, 177.0; MS: m/z (%) 394 (M⁺), 379, 363 (100), 349, 323, 321, 295, 293, 265, 249, 230, 191, 160, 148, 133, 97, 77, 63.

8-Bromo-6-chloro-2-(4-methoxyphenyl)-3-methyl-4H-chromen-4-one, 4h: Yield 93%; m.p. 182-82°C; IR (KBr): 3076, 1647, 1612, 1566, 1510, 1452, 1365, 1176, 1124, 1030, 879, 775 cm⁻¹; ¹H NMR (CDCl₃): δ 2.23 (3H, s), 3.90 (3H, s), 7.06 (2H, dd, $J_1 = 7.8$ Hz, $J_2 = 2.1$ Hz), 7.72 (2H, dd, $J_1 = 6.6$ Hz, $J_2 = 2.1$ Hz), 7.85 (1H, d, $J = 2.4$ Hz), 8.16 (1H, d, $J = 3$ Hz); ¹³C NMR (CDCl₃): δ 12.1, 55.6, 113.7, 113.9, 119.0, 123.1, 128.5, 129.0, 133.2, 138.9, 153.4, 160.9, 162.2, 179.4; MS: m/z (%) 378 (M⁺), 363, 328, 299, 297, 271, 146 (100), 101, 77.

2-(4-(Allyloxy)-3-methoxy phenyl)-6-chloro-3-methyl-4H-chromen-4-one, 4i: Yield 91%; m.p. 135-36°C; IR (KBr): 3078, 1702, 1645, 1612, 1564, 1445, 1348, 1296, 1245, 1132, 1064, 1005, 929, 864, 818, 756 cm⁻¹; ¹H NMR (CDCl₃): δ 8.12 (1H, d, $J = 2.1$ Hz), 7.60 (1H, dd, $J_1 = 2.7$, $J_2 = 2.4$ Hz), 7.49 (2H, d, $J = 12.6$ Hz), 7.32 (1H, s), 6.96 (1H, d, $J = 8.4$ Hz), 6.12 (1H, m), 5.46 (2H, dd, $J_1 = 3.3$ Hz, $J_2 = 10.5$ Hz), 4.69 (2H, d, $J = 5.4$ Hz), 3.96 (3H, s), 1.93 (s, 3H); ¹³C NMR (CDCl₃): δ 155, 119.5, 135.5, 129.2, 130.8, 125.5, 183.2, 104.4, 160.2, 123.8, 119.9, 115.2, 149.2, 149.7, 111.6, 56.2, 6.2; MS: m/z (%) 356.08 (100), 358, 357.

2-(2-Allyloxyphenyl)-6-chloro-3-methyl-4H-chromen-4-one, 4j: Yield 93%; m.p. 148-50°C; IR (KBr): 3652, 3080, 1708, 1647, 1610, 1566, 1454, 1346, 1299, 1249, 1136, 1062, 1004, 927, 860, 815, 75 cm⁻¹; ¹H NMR (CDCl₃): δ 8.17 (1H, d, $J = 2.4$ Hz), 7.84 (1H, d, $J = 9.3$ Hz), 7.61 (1H, dd, $J_1 = 2.7$ Hz, $J_2 = 2.7$ Hz), 7.47 (2H, dd, $J_1 = 9.0$, $J_2 = 1.2$ Hz), 7.10 (2H, m), 7.02 (1H, d, $J = 8.1$ Hz), 6.09 (1H, m), 1.98 (3H, s), 5.43 (2H, dd, $J_1 = 17.1$, $J_2 = 10.5$ Hz), 4.68 (2H, d, $J = 4.8$ Hz); ¹³C NMR (CDCl₃): δ 155.4, 119.3, 135.6, 129.3, 130.6, 125.2, 183.1, 104.5, 160.2, 110.2, 127.4, 121.3, 129.0, 114.2, 157.5, 72.4, 133.4, 116.4; MS: m/z (%) 326 (100), 328, 327.

4-(3-(2-Allyloxy)phenyl)-5-phenyl-1H-pyrazol-1-yl) benzaldehyde, white solid 6a: Yield 92%; m.p. 174-75°C; IR (KBr): 3123, 2917, 2848, 1701, 1585, 1510, 1655 cm⁻¹; ¹H NMR (CDCl₃): δ 6.98 (1H, s), 6.95 (t, 1H, $J = 7.8$ Hz), 7.07 (1H, d, $J = 7.8$ Hz), 7.24 – 7.31(3H, m), 7.35 – 7.42 (3H, m), 7.52 (2H, d, $J = 8.7$ Hz), 7.61 (1H, dd, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz), 7.92 (2H, d, $J = 8.7$ Hz), 5.44 (dd, $J = 17.1$, 10.5 Hz, 2H), 4.69 (d, $J = 4.8$

Hz, 2H), 6.05 (m, 1H) 10.11 (1H, s), 10.43 (1H, s); ^{13}C NMR (CDCl_3): δ 105.7, 115.3, 118.5, 118.8, 120.8, 127.3, 127.9, 128.0, 128.7, 129.7, 133.3, 133.8, 141.6, 142.1, 152.1, 158.3, 191.1, 72.3, 133.6, 116.4; MS: m/z (%) 340 (M^+) (100), 208.42.

4-(3-(2-Allyloxy) phenyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl benzaldehyde, 6b: Yield 93%; m.p. 183-84°C; IR (KBr): 3103, 3059, 2839, 2744, 1658, 1693, 1600, 1581, 1496 cm^{-1} ; ^1H NMR (CDCl_3): δ 3.85 (3H, s), 6.91 (2H, d, $J = 8.7$ Hz), 6.96 (1H, t, $J = 7.5$ Hz), 7.07 (1H, d, $J = 8.4$ Hz), 7.24 (2H, d, $J = 8.4$ Hz), 7.28-7.31 (1H, m), 7.51 (2H, d, $J = 8.7$ Hz), 7.64 (1H, dd, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz), 7.88 (2H, d, $J = 7.8$ Hz), 10.02 (1H, s), 5.43 (dd, $J = 17.1$, 10.5 Hz, 2H), 4.68 (d, $J = 4.8$ Hz, 2H), 6.09 (m, 1H), 10.68 (1H, s); ^{13}C NMR (CDCl_3): δ 55.3, 105.4, 114.3, 115.7, 117.2, 119.4, 121.6, 124.5, 126.6, 129.9, 130.2, 130.4, 134.6, 143.8, 144.2, 152.7, 156.1, 160.2, 190.9, 72.3, 133.6, 116.4; MS: m/z (%) 370 (M^+) (100), 238 (45).

5-(2-(Allyloxy)-5-chlorophenyl)-3-(4-methoxyphenyl)-4-methylisoxazole, 6d: Yield 90%; m.p. 188-89°C; IR (KBr): 3028, 2992, 1645, 1608, 1029, 1063 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.27 (3H, s), 3.88 (3H, s), 7.01-7.06 (3H, m), 7.33 (1H, dd, $J_1 = 9$ Hz, $J_2 = 2.7$ Hz), 7.42 (1H, d, $J = 2.7$ Hz), 7.63 (2H, d, $J = 8.7$ Hz), 5.44 (dd, $J = 17.1$, 10.5 Hz, 2H), 4.69 (d, $J = 4.8$ Hz, 2H), 6.05 (m, 1H); ^{13}C NMR (CDCl_3): δ 8.7, 54.8, 110.3, 113.8, 116.2, 117.1, 121.3, 122.6, 128.9, 129.0, 130.5, 153.8, 159.9, 161.6, 162.9, 72.3, 133.6, 116.4; MS: m/z (%) 355.10 (M^+), 357, 356, 358.

5-(2-Allyloxy)-5-chlorophenyl)-3-(4-chlorophenyl)-4-methylisoxazole, 6e: Yield 91%; m.p. 214-15°C; IR (KBr): 3021, 2991, 1619, 1645, 1608, 1032, 1065 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.25 (3H, s), 7.02 (1H, d, $J = 8.7$ Hz), 7.34 (1H, dd, $J_1 = 8.85$ Hz, $J_2 = 8.1$ Hz), 7.63 (2H, d, $J = 8.7$ Hz) 5.44 (dd, $J = 17.1$, 10.5 Hz, 2H), 4.69 (d, $J = 4.8$ Hz, 2H), 6.05 (m, 1H); ^{13}C NMR (CDCl_3): δ 8.3, 10.98, 116.9, 122.4, 125.1, 127.5, 127.6, 128.1, 129.8, 133.8, 153.4, 159.0, 162.1, 72.3, 133.6, 116.4; MS: m/z (%) 359.05 (100), 361.05, 360.06, 362, 363, 364.05.

Conclusion

In conclusion a facile and convenient pathway has been successfully developed for the aromatization of pyrazoline, isoxazoline and 3-methyl flavanone by use of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in DMSO solvent in excellent yield with easy work-up. The main advantage of the current methodology is high regioselective oxidative aromatization of pyrazoline, isoxazoline and 3-methyl flavanone in presence of active O-allyl group. The operational simplicity and economic viability of this method broadens the purview for further study in this area.

References

- Mishriky N, Fahmy M A, Yehia A I & Adel S G, *Indian J Chem*, 35B, **1996**, 935; (b) Shridhar R, Perumal P T, Shanmugam S E G, Ponnuswamy M N, Prabhayathy V R & Mathivanan N, *Bioorg Med Chem Lett*, 14, **2004**, 6035.
- Bruno O, Ranise A, Schenone P, Donnoli D, Cenicola M L, Matera C, Russo S & Bondavalli M E, *Il Farmaco*, 44 (7-8), **1989**, 655; (b) Banoglu E, Sukuroglu M, Caliskan B, Nacak S, Ayapar E & Ark M, *Turk J Chem*, 14, **2007**, 677.
- Siqqiqi Z N, Musthafa T N M, Ahmad A & Khan A U, *Bio Med Chem Lett*, 21, **2011**, 2860.
- Sammelton R E, Caboni P, Durkin K A & Casida J E, *Bio Med Chem Lett*, 12, **2004**, 3345.
- Steffen R J, Matelan E, Ashwell M A, Moor W J, Solvibar W R, Trbulski E, Chadwick C C, Mosyak X & Harnish D, *J Med Chem*, 47, **2004**, 6435.
- Han W, Pelleuer J & Hodge C N, *Biorg Med Chem Lett*, 8, **1998**, 3615.
- Showalter H D H, Angelo M M, Berman E M, Kanter G D, Orwine D F, Ross Keston S G, Sercel A D, Turner W R, Werbel N M, Worth D F, Elslager E F, Leopald W R & Shillis G H, *J Med Chem*, 31, **1988**, 1527.
- Zhang H C, Derian C K, McComsey D F, White K B, Ye H, Heckar L R, Li J, Addo M F, Croll D, Eckardt A J, Smith C E, Li Q, Cheung W M, Conway B R, Emaneul S, Demarest K I, Andrade Gordon P, Damiano B P & Mavyanooff B E, *J Med Chem*, 48, **2005**, 175.
- Fludzinski P, Evard D A, Bloanquist W E, Lacefield W B, Peifer W, Jones N D, Deeter J B & Cohen M L, *J Med Chem*, 30, **1987**, 1535; (b) Harada H, Morie T, Hirokawa Y & Kato S, *Tetrahedron Asymmetry*, 8, **1997**, 2367; (c) Ma J A, Danta Narayana A P, Zinke P W, McLaughlin M A & Shant N A, *J Med Chem*, 49, **2006**, 318.
- Cimanga K, Ying L, DeBruyne T, Apers S, Cos P, Hermans N, Bakana P, Tona L, Kambu K, Kalenda D T, Pieters L, Vanden B D & Vlietinck A J, *Il Farmaco*, 64, **2001**, 96; (b) Khan M S Y & Hasan S M, *Indian J Chem*, 42B, **2003**, 1970.
- Wang Y, Tan W, Li W & Li Y, *J Nat Prod*, 64, **2001**, 196; (b) Nijveldt R J, Nood E, Hoorn D, Baelens P G, Nooren K & Leeuwen P, *Am J Clin Nutrition*, 74, **2001**, 418.
- Bhatnagar I & Georgem M V, *Tetrahedron*, 24, **1968**, 1293.
- Smith L I & Howard K L, *J Am Chem Soc*, 65, **1943**, 159.
- Nakamichi N, Kawashita Y & Hayashi M, *Org Lett*, 22, **2002**, 3955.
- Gowravam S, Kiran G S, Reddy K, Reddy C S, Fatima N & Yadav J S, *Synthesis*, 8, **2003**, 1267.
- Singh S P, Kumar D, Prakash O & Kapoor R P, *Synth Commun*, 27, **1997**, 2683.
- Pawar R P, Sarda S R & Jadhve W N, *Int J Chem Technol Res*, 1, **2009**, 539.
- Wang J, Du Z, Ng H, Zhang K & Zeng H, *Org Biomo Chem*, 9, **2011**, 11.
- Spijker N M, Keuning C A, Hooglugt M, Veeneman G H & Vanboeckel C A A, *Tetrahedron*, 52, **1996**, 5945; (b) Hayashi M, Tanaka M, Itoh M & Miyauchi H, *J Org Chem*, 61, **1996**, 2938; (c) Alzeer J, Cai, C & Vasella A, *Helv Chim Acta*, 78, **1995**, 242; (d) Mayer T G, Kratzer B & Schmidt R R, *Angew Chem Int Ed Engl*, 33, **1994**, 2177; (e) Nakayama K, Uoto K, Higashi K, Soga T & Kusama T, *Chem Pharm Bull*, 40, **1992**, 1718.
- Kaljuste K, Unden A, *Tetrahedron Lett*, 37, **1996**, 3031; (b) Waldmann H, Nagele E, *Angew Chem, Int Ed Engl*, 34,

- 1995, 2259; (c) Ueno Y, Suda F, Taya Y, Noyori R, Hayakawa Y & Hata, *Bioorg Med Chem Lett*, 5, **1995**, 823; (d) Beugelmans R, Neuville L, Bois-Choussy M, Chastanet J & Zhu J, *Tetrahedron Lett*, 36, **1995**, 3129.
- 21 Bergmann F, Kueng E, Iaiza P & Bannwarth W, *Tetrahedron*, 51, **1995**, 6971; (b) Nishiyama S, Yamamura S, Kato K & Takita T, *Tetrahedron Lett*, 29, **1988**, 4739; (c) Hayakawa Y, Kato H, Uchiyama M, Kajino H & Noyori R, *J Org Chem*, 51, **1986**, 2402.
- 22 Roush W R & Lin X, *J Am Chem Soc*, 117, **1995**, 2236; (b) Raymond J C, Kelly D H, DiMichele L M, Shuman R F & Grabowski E J J, *J Org Chem*, 59, **1994**, 7704; (c) Jones R J & Rapoport H, *J Org Chem*, 55, **1990**, 1144; (d) Paquette L A, Macdonald D, Anderson L G & Wright J, *J Am Chem Soc*, 111, **1989**, 8037; (e) Hanessian S & Alpegiani M, *Tetrahedron*, 45, **1989**, 941; (f) Boeckmann R K & Perni R B, *J Org Chem*, 51, **1986**, 5486.
- 23 Humne V T, Zadeh K H & Lokhande P D, *Res Chem Intermed*, 39, **2013**, 585.
- 24 Lokhande P D, Sakate S S, Taksande K N & Nawghare B R, *Tetrahedron Lett*, 46, **2005**, 1573; (b) Lokhande P D & Nawghare B R, *Synth Commun*, **2012**, DOI: 10.1080/00397911.2012.667490; (c) Lokhande P D & Nawghare B R, *Indian J Chem*, 51B(1), **2012**, 328; (d) Lokhande P D, Nawghare B R & Sakate S S, *J Heterocycl Chem*, 51, **2013**, 291; (e) Lokhande P D, Nawghare B R, Funde S G & Raheem A, *Chinese J Chem*, 30, **2012**, 1695.
- 25 Lokhande P D, Waghmare S, Gaikwad H & Hankare P P, *J Korean Chem Soc*, 56, **2012**, 05.
- 26 Ferguson G & Ajjou A N, *Tetrahedron Lett*, 44, **2003**, 9139.
- 27 Liu Y & Sun J W, *J Org Chem*, 77, **2012**, 1191.
- 28 Gurevich P A & Yaroshevskaya V A, *Chem Heterocycl Compd*, 36, **2000**, 1361.
- 29 Li Y L, Wan J L & He L N, *Tetrahedron Lett*, 52, **2011**, 3485.
- 30 Radivoy G, Francisco A, Moglie Y, Vitale C & Yus M, *Tetrahedron*, 61, **2005**, 3859.