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CuX_2 (X =Cl, Br) as catalysts for Pechmann reaction: synthesis of 4-substituted coumarins

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CuX_2 (X=Cl, Br) are found to be efficient catalysts (10 mol%) for the Pechmann condensation reaction of phenols and β-ketoesters to give 4-substituted coumarins under solvent-free conditions. The yields of coumarin derivatives obtained via this new protocol, were equal or higher than those using the conventional method and the reaction time was reduced to a few minutes.

Keywords: coumarins, Pechmann reaction, CuX_2, catalysis, heterocycles

Coumarins (2*H*-1-benzopyran-2-one) and their derivatives are important natural products. In addition, they have a broad range of applications in the pharmaceutical, perfume, and cosmetic industries. They have been used successfully as additives to food, optical brightening agents, and as dispersed fluorescent and tunable laser dyes. They have varied bioactivities, for example, inhibition of platelet aggregation,[1] anti-cancer agents,[2] steroid 5α-reductase inhibitors.[3] Coumarins also act as intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols.[4] Consequently, coumarins and their derivatives are interesting targets for organic chemists.

Coumarins have been synthesised by several routes including the Pechmann,[5] Perkin,[6] Knoevenagel,[7] Reformatsky,[8] and Wittig reactions[9] and by flash vacuum pyrolysis.[10] The Pechmann reaction is a simple procedure for the synthesis of 4-substituted coumarins in good yields by reacting phenols and β-ketoesters in the presence of acidic catalyst. Various acidic catalysts including H_2SO_4, $HClO_4$, CF_3COOH, PPA, $ZrOCl_2$, $Sm(NO_3)_3 \cdot 6H_2O$, $FeCl_3$, $ZnCl_2$, $AlCl_3$, $TiCl_4$, $InCl_3$, $ZrCl_4$, Montmorillonite, cation exchange resins, microwave irradiation, ionic liquids and a polyaniline supported acid catalyst, are known to affect this condensation.[11-22] However, some of these catalysts have to be used in large amounts. Moreover, in some cases, long reaction times were needed, undesired side products were isolated and often high reaction temperatures up to 150 °C were required.

Recently, CuX_2 has emerged as a powerful Lewis acid catalyst for various chemical transformations. The new interest in CuX_2 is easily justified by its favourable ecological properties. Recently considerable emphasis has been placed on improvement in the environmental impact of industrial chemical processes. Cupric halides are relatively nontoxic, inexpensive, insensitive to air and no special care is required in handling them. In connection with our research on developing new methods using CuX_2 as catalyst,[23] we have studied their use in the Pechmann condensation, to produce the coumarins derivatives.

Result and discussion

The substituted phenols and ethyl acetoacetate or ethyl benzoylacetate undergo condensation in the presence of Lewis acid CuX_2 catalysts under solvent-free condition to produce the 4-substituted coumarins in excellent yields (Scheme 1).

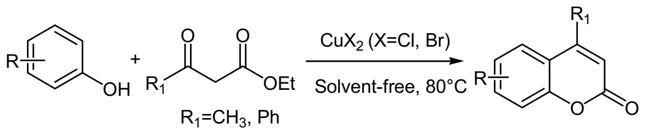
This is novel, one-pot condensation not only preserves the simplicity of the Pechmann condensation reaction but also consistently produces excellent yields of the coumarin derivatives and greatly decreases environmental pollution. In the presence of CuX_2 (X =Cl, Br) (10 mol%), the reaction of ethyl acetoacetate (6 mmol) and phloroglucinol (5 mmol) was carried out under solvent-free condition for 5 min at 80 °C, and gave 5,7-dihydroxy-4-methylcoumarin (**5**) in 96% (X =Cl) and 98% (X = Br) yields. Similarly, phloroglucinol was treated with ethyl benzoylacetate in the presence of CuX_2 (X =Cl, Br) (10 mol%) for 10 min to furnish coumarins (**6**) in 89% yields for $CuCl_2$ and 91% yields for $CuBr_2$ respectively (Table 1, entries 1 and 2). The melting point of these products (in Table 1) was in good agreement with the corresponding literature values.

Encouraged by the above results, other phenolic substrates were subjected to the Pechmann reaction using CuX_2 (X =Cl, Br) as catalysts. Resorcinol, 5-methylresorcinol, α-naphthol and pyrogallol were subjected to the reaction with different β-ketoesters as shown in Table 1 to give the corresponding coumarin derivatives. The reaction was found to be adaptable to a variety of substrates and the yields, in general, were high (80–98%). Short reaction times were observed (5–20 min) regardless of structural variations in the phenols or β-ketoesters. Different substitution patterns on the aromatic ring could be introduced with high efficiency. For most of the substrates, the reaction time was reduced substantially even under mild reaction conditions in contrast to reported procedures[24,25] and gave an excellent yield of the coumarin derivatives.

In conclusion, we have demonstrated an efficient and simple alternative for the preparation of substituted coumarins via the CuX_2 (X =Cl, Br) catalysed Pechmann reaction in solvent-free conditions. Prominent among the advantages of this new method are operational simplicity, good yields, short reaction times and an easy work-up.

Experimental

Staring materials were obtained from commercial suppliers and were used without further purification. Melting points were determined with X-5 apparatus in open glass capillaries and were uncorrected. IR spectra were recorded on EQUINX 55 FT-IR spectrometer using



Scheme 1 Preparation of coumarins catalysed by CuX_2 under solvent free conditions.

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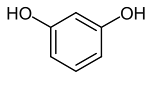
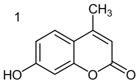
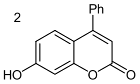
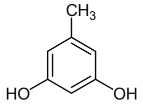
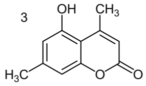
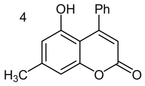
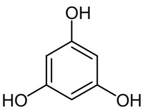
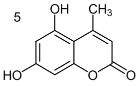
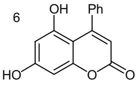
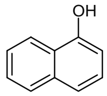
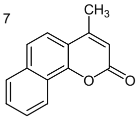
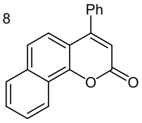
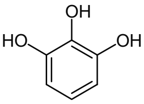
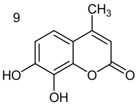
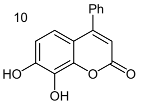
Table 1 CuX_2 (X=Cl, Br) catalysed synthesis of 4-substituted coumarin

Entry	Phenol	Ethyl acetoacetate	Product[a]	Time [c]/min	Yield [b]/%
1	Resorcinol 	$CH_3COCH_2CO_2Et$	1 	5	92 ($CuCl_2$) 94 ($CuBr_2$)
2		$PhCOCH_2CO_2Et$	2 	10	88 ($CuCl_2$) 87 ($CuBr_2$)
3	5-methylresorcinol 	$CH_3COCH_2CO_2Et$	3 	10	90 ($CuCl_2$) 93 ($CuBr_2$)
4		$PhCOCH_2CO_2Et$	4 	20	86 ($CuCl_2$) 97 ($CuBr_2$)
5	Phloroglucinol 	$CH_3COCH_2CO_2Et$	5 	10	96 ($CuCl_2$) 98 ($CuBr_2$)
6		$PhCOCH_2CO_2Et$	6 	15	89 ($CuCl_2$) 81 ($CuBr_2$)
7	1-naphthol 	$CH_3COCH_2CO_2Et$	7 	15	86 ($CuCl_2$) 87 ($CuBr_2$)
8		$PhCOCH_2CO_2Et$	8 	30	No product
9	Pyrogallol 	$CH_3COCH_2CO_2Et$	9 	15	85 ($CuCl_2$) 89 ($CuBr_2$)
10		$PhCOCH_2CO_2Et$	10 	20	80 ($CuCl_2$) 83 ($CuBr_2$)

[a] All products were characterised by comparison of their m.p., IR, and ^1H NMR spectra with those of authentic samples.
[b] Isolated yields.
[c] All reactions were carried out at 80 °C.

KBr pellets. NMR spectral data were collected on an AVANCF 300 MHz spectrometer in DMSO-d_6 with TMS as an internal standard. Elemental analyses were performed with a Vario ELIII instrument.

Gerenal experimental procedure

The CuX_2 (X=Cl, Br) (0.5 mol) was added to the phenol (5 mmol) and β-ketoester (6 mmol), in a 50 mL round bottom flask and the contents were stirred in a pre-heated oil-bath at 80 °C. After completion of the reaction (monitored by TLC, the time indicated in Table 1), the reaction mixture was cooled to room temperature and the viscous contents were poured into water. The products were collected by filtration, washed with water and dried. They were further purified by silica column chromatography for analysis.

All the coumarin derivatives are well-known. Compound (**1**) was selected as the representative product and was fully characterised (melting point, IR, ^1H NMR and elemental analysis). Other compounds were identified by their melting point and IR and by comparison of their physical and spectral data with literature.

7-hydroxy-4-methyl-2H-chromen-2-one (**1**): Solid; m.p. 186–187 °C (Lit.[26], 182–184 °C), IR: υ_{max} 3500, 3156, 2807, 1677, 1598, 1449, 1390, 1273, 1239, 1156, 1131, 1065 cm^{-1}. ^1H NMR: δ 2.36 (s, 3H, $-CH_3$), 6.08(s, 1H, C=CH), 6.75(d, 2H, ArH), 7.57(s, 1H, ArH), 10.52(s, H, –OH). Anal. Calcd for $C_8H_{10}O_3$: C, 68.18%; H, 4.58. Found: C, 68.15%; H, 4.56%.

7-hydroxy-4-phenyl-2H-chromen-2-one (**2**): Solid; m.p. 256–258 °C (Lit.[12], 256–257 °C), IR: υ_{max} 3157, 2983, 2806, 1680, 1588, 1433, 1389, 1263, 1241, 1150, 1108 cm^{-1}.

5-hydroxy-4,7-dimethyl-2H-chromen-2-one (**3**): Solid; m.p.259–260 °C (Lit.[27], 257–258 °C), IR: υ_{max} 3440, 3047, 2929, 1658, 1612, 1513, 1448, 1409, 1380, 1339, 1295, 1252, 1150, 1099 cm^{-1}.

5-hydroxy-7-methyl-4-phenyl-2H-chromen-2-one (**4**): Solid; m.p. 225–226 °C (Lit.[12], 226 °C), IR: υ_{max} 3439, 3064, 2983, 1674, 1657, 1611, 1450, 1369, 1339, 1313, 1276, 1174, 1106, 1070 cm^{-1}.

5,7-dihydroxy-4-methyl-2H-chromen-2-one (**5**): Solid; m.p. 281–283 °C (Lit.[26], 284–285 °C), IR: υ_{max} 3449, 2926, 2686, 1667, 1622, 1587, 1552, 1473, 1388, 1362, 1301, 1237, 1159, 1099, 1076 cm^{-1}.

5,7-dihydroxy-4-phenyl-2H-chromen-2-one (**6**): Solid; m.p. 245–246 °C (Lit.[12], 246–247 °C), IR: υ_{max} 3416, 3163, 2983, 1688, 1670, 1587, 1552, 1450, 1389, 1364, 1276, 1161, 1074, 1027 cm^{-1}.

4-methyl-2H-benzo[h]chromen-2-one (**7**): Solid; m.p. 154–155 °C (Lit.[26], 153–154 °C), IR: υ_{max} 3436, 3197, 1683, 1628, 1572, 1554, 1469, 1380, 1271, 1147, 1082 cm^{-1}.

7,8-dihydroxy-4-methyl-2H-chromen-2-one (**9**): Solid; m.p. 240–241 °C (Lit.[15], 241–243 °C), IR: υ_{max} 3413, 3232, 2984, 1646, 1727, 1619, 1596, 1513, 1448, 1389, 1335, 1307, 1230, 1138, 1061, 1007 cm^{-1}.

7,8-dihydroxy-4-phenyl-2H-chromen-2-one (**10**): Solid; m.p. 197–198 °C (Lit.[12], 195–197 °C), IR: υ_{max} 3411, 3221, 2983, 1717, 1646, 1600, 1490, 1403, 1308, 1275, 1184, 1107, 1062, 1028 cm^{-1}.

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