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SYNTHESIS OF 3-CARBOXYCOUMARINS USING PHASE TRANSFER CATALYSIS

M.S Lamba[a] , J.K Makrandi[b] and Suresh Kumar[*]

[*]Department of Chemistry, Kurukshetra University, Kurukshetra-India-136119
[a]Ordnance Factory Chanda, Ministry of Defence, India-442501
[b]Department of Chemistry, M.D.University, Rohtak-India
**Email-suresh_dua47@rediffmail.com*

ABSTRACT
The condensation of suitably substituted salicylaldehydes with diethylmalonate in biphase medium using phase transfer catalyst results in to the formation of ethylcoumarin-3-carboxylates. Ethylcoumarin-3-carboxylates so formed on hydrolysis gives coumarin-3-carboxylic acid in high yield.

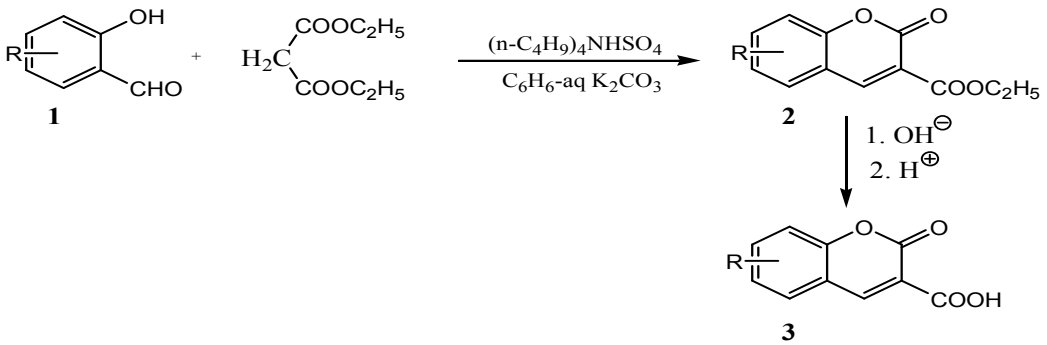
Keywords: 3-Carboxycoumarins, ethylcoumarin-3-carboxylate, phase transfer catalysis, salicylaldehyde, diethylmalonate.

INTRODUCTION
Majority of synthetic organic reactions yields large amounts of byproducts, which lower the atom efficiencies of the processes, thus waste valuable starting materials and reduce overall economics. Phase Transfer catalysis is a well established technique, widely used in laboratory synthesis and chemical industry [I,II]. By this technique reactions can be carried out in a biphase system consisting of aqueous and organic phase of almost negligible miscibility [I,II]. This technique does not require costly anhydrous solvent or non polar solvent. The use of phase transfer catalyst as 'Green' catalysts has also been well established [III,IV], as it results in waste minimization, safer operating conditions and easier product workup.
Coumarins constitute an important class of naturally occurring compounds with useful pharmacological activities like antitumor [V], antibacterial [VI], antifungal [VII], diuretic [VIII], anticoagulant [IX] and anti-inflammatory [X]. Selected coumarins are also used as photographic sensitizer and solar collectors [XI]. Coumarin-3-carboxylic acid is used in synthesis of cephalosporins [XII], pencillins [XIII], isoureas [XIV], esters and amides which exhibit specific inhibitors of α- chymotripsin and human leukocyte elastase [XV]. Coumarin carboxylic acid and its derivatives also display a broad range of biological properties [XVI].
Earlier methods used for synthesis of 3-carboxycoumarins includes condensation of salicylaldehyde with Meldrums' acid [XVII], condensation of salicylaldehyde with malonic acid in presence of montmorillonite KSF clay [XVIII] , condensation of salicylaldehyde with malononitrile followed by hydrolysis [XIX] , reaction of salicylaldehyde with malonate ester [XX] , treating salicylaldehyde with ethylcyanoacetate [XXI] , refluxing salicylaldehyde with 2,2-pentamethylene-1,3-dioxane-4,6-dione in acetic acid in presence of pyridine [XXII]. Though the above methods

used are suitable for synthesis of 3-carboxycoumarin but above procedures involves the use of organic and inorganic bases like piperidine, pyridine, acetic acid or refluxing at high temperature for long period (24 hours), resulting in generation of large amount of toxic waste. In continuation of our work for the development of significant and alternative routes for the synthesis of oxygen heterocyclic compounds [III, IV, XXIII, XXIV] herein we wish to report an, efficient and significant approach for the synthesis of 3-carboxycoumarins using phase transfer catalysis in high yields.

RESULTS AND DISCUSSION

Salicylaldehyde (2-Hydroxybenzaldehyde) on magnetically stirring with diethylmalonate in a biphase medium consisting of benzene and saturated aqueous potassium carbonate, in presence of tetra-n-butylammonium hydrogen sulphate, a phase transfer catalyst, at 80-90^{0}C for specified period, gave ethylcoumarin-3-carboxylates **2a-f (Table 1)**. The resulting compounds were refluxed with 20% NaOH for 1.5-2.5 h followed by hydrolysis with conc. HCl, which gave the title compound **3a-f (Table 2)** in high yield **(Scheme 1)**. The identity of the compound was confirmed from their ^{1}H-NMR spectral data and CO-IR data. The earlier method of synthesis affords these title compounds in low yield and also requires long reaction time.



Scheme: I

Here in this method, coumarin-3-carboxylic acids have been prepared, using phase transfer catalysis in high yield and short reaction times. The reaction was performed under very mild conditions and products were obtained in pure and high yields using simple workup procedure. The advantages of the present method may be summarized as use of commercially available catalysts, mild reaction conditions and high yields of the desired products.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin- Elmer 781 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO with spectrometer at 90 MHz using TMS as internal reference.

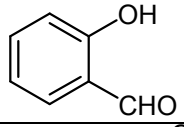
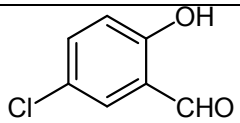
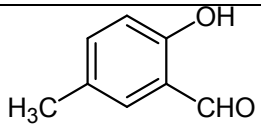
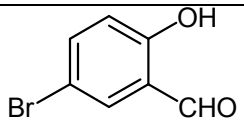
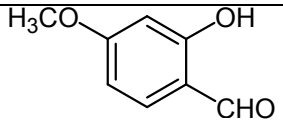
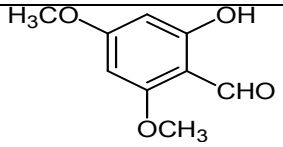
General procedure

Ethylcoumarin-3-carboxylates (2a-f)

A solution of salicylaldehyde (5 mmole) in benzene (20 ml), diethylmalonate (5 mmole), saturated aqueous potassium carbonate solution (20 ml) and tetra-n-butylammonium hydrogen sulphate (1.2 mmole) were stirred magnetically in an oil bath at 80-90^{o}C for the time specified in Table 1. The completion of the reaction was checked on TLC. The organic layer was separated,

washed with water and benzene was separated by distillation under vacuum. The residue thus obtained was crystallized from methanol to give (**2a-f)**.

Table 1. Condensation of salicylaldehyde with diethylmalonate in presence of PTC to give ethylcoumarin-3-carboxylate (2)

Sr No.	Reactant	Time (T_1) Hrs	Ethylcoumarin-3-carboxylates (2)		
			Yield (%)	M.P.	Lit. M.P.
1a		1.5	85	92-93	95-96[XX]
1b		3.5	80	141-42	145-47[XXV]
1c		3.0	80	136-38	-----
1d		3.0	75	165-67	168-69[XX]
1e		4.5	70	118-20	120-25[XXV]
1f		6.0	70	151-52	147-49[XXV]

7-Methoxycoumarin-3-carboxylic acid ethyl ester (**2e)**
M. pt.118-20 ^{0}C,
IR (KBr),ν (cm^{-1}): 1765 (C=O), 1690 (C=O),1600 (C=C),
^{1}H-NMR/(DMSO),δ (ppm): 1.34 (t, 3H, CH_3-CH_2), 3.80 (s, 3H, OCH_3), 4.35 (q, 2H, CH_2-CH_3), 6.72-7.48 (m, 3H, Ar-H), 8.36(s, 1H, H-4).

Coumarin-3-carboxylic acids (3a-f)

Solution of ethylcoumarin-3-carboxylate **2a-f** (2 mmole) in 50 ml of 20% NaOH was refluxed with stirring on an oil bath for time specified in Table 2. The solution was cooled at 0^0C and Conc. HCl was added till the pH reached to acidic (2 to 4). The colorless precipitates were filtered off. The residue was washed with diethyl ether and dried to give titled compound **(3a-f)** in high yield.

Table 2. Synthesis of 3-Carboxycoumarin (3)

Reactant	Time (T_2) Hrs	Coumarin-3-carboxylic acids (3)		
		Yield (%)	M.P.	Lit. M.P.
2a	1.5	75	189-90	191-92[XX]
2b	1.0	74	194-95	198[XXV]
2c	1.5	76	168	166[XVIII]
2d	1.5	70	195-97	199[XX]
2e	2.0	55	178	176-77[XXV]
2f	2.5	50	232-33	234-37[XXV]

7-Methoxycoumarin-3-carboxylic acid (3e)
M.pt.178^{0}C,
IR (KBr),ν (cm^{-1}): 1725 (C=O), 1690 (C=O), 1610 (C=C),
^{1}H-NMR/ (DMSO),δ (ppm): 3.98 (s, 3H, OCH_3), 7.01-7.84 (m, 3H, Ar-H), 8.75 (s, 1H, H-4), 12.90 (s, 1H, COOH).

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