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Ion Exchange Resin Catalyzed Synthesis of Substituted-4-methyl-3-(substituted phenoxy)coumarins

M.V. RATHNAM*, CHITTARANJAN S. THATTE and ABHINAY C. PISE
B.N. Bandodkar College of Science, Chendani, Thane-400 601, India
E-mail: mnprgdrthnm3@gmail.com

Various substituted 2*H*-1-benzopyran-2-one-4-methyl-3-(substituted phenoxy)compounds have been successfully synthesized by the reaction of ethyl-2-(substituted phenoxy)-3-oxobutanoates (**Ia-Id**) with resorcinol, 4-chloro resorcinol and α-naphthol using ion exchange resins such as Amberlyst-35 and K-2641, with and without solvent. The catalyst was reused without much loss of yield. The homogeneity of these compounds was established by the HPLC analysis of pure compounds. The characterization of the compounds was done on the basis of ^{1}H NMR, IR, mass spectrometry and elemental analysis. The compounds have been tested for their antibacterial activity.

Key Words: Coumarin, Ion exchange resin, Catalyst, Antibacterial.

INTRODUCTION

2*H*-1-Benzopyran-2-one[1] (coumarin) form fascinating group of compounds not only because of their diverse structures but also due to their diverse biological activities, emerging from coumarin ring structure as possible drug carrier moiety. They are especially present in abundant in grasses, orchids, legumes and citrus fruits. The parent compound is the sweet smelling constituent of white clover and is present in the tonka bean[2] and in many other plants.

Amongst the simple monohydroxy coumarins having the hydroxy group in the coumarin nucleus, 7-hydroxycoumarin commonly called umbelliferone has been long known. The umbelliferone was obtained by the dry distillation of umbelliferous resin. It also occurs in the free condition in several plants. It is often regarded as the parent, both structurally and biogenetically of the more complex coumarins.

Recently some 3-substituted coumarins have also shown to possess interesting antituberculous properties[3-6]. In view of the importance of above observations and to study the general applicability of 3-substituted phenoxy coumarins, it was thought of interest to synthesize the 3-substituted phenoxy coumarins under Pechmann conditions and test their antibacterial properties. Substitution of groups at the α position of acetoacetic ester leads to the formation of 3-substituted coumarins[7]. It is generally been practice to use sulphuric acid as a condensing agent in the preparation of coumarins by von Pechmann reaction, sulphuric acid is used as a catalyst. Present

work is aimed to use of heterogeneous catalyst such as cation exchange resins (Amberlyst-35, K2641, Amberlyst-70) for their preparation. These compounds have been tested for their antibacterial activity.

EXPERIMENTAL

The melting points were taken in open capillaries on a Veego scientific melting point apparatus, Microanalysis was performed on FLASH EA 1112 series, IR spectra were determined in KBr on a Shimadzu model, ^{1}H NMR spectra were measured in (DMSO-d_6) using Varian 300 and 400 MHZ spectrometer. The mass spectra were recorded on Shimadzu spectrometer. HPLC was performed using HPLC (Agilent) and 5u silica, 100A, 250 μ × 4.6 μ × 5 μ column was used. The coumarin ethers were analyzed at 254 nm using DAD detector. The mobile phase for analyzing coumarin ethers (**IIIa-IIId** and **Iva-IVc**) was dichloromethane:methanol (99:1) and for coumarin ethers **Va-Vc** was dichloromethane.

The antibacterial activity was tested on gram +ve and gram -ve bacteria *e.g.*, *S. aureus* and *S. typhi*. The antibacterial activity testing was done at Hi Tech Analytical Works, Pune.

Procedure A: general method for the synthesis of substituted coumarin ethers

IIIa-Ivc (2*H*-1-benzopyran-2-one-4-methyl-3-(substituted phenoxy): In a three necked flask well equipped with magnetic stirrer cum heater, fitted with Dean and Stark water separator along with condenser, thermowell for temperature indication charged 12 g of *o*-xylene followed by the addition of 2 g (0.018 mol) resorcinol powder and 0.89 g, (10 % based on total reactants) amberlyst-35/K2641. The contents were heated under reflux at 135-140 °C. To the resulting mixture added ethyl-2-(2-chlorophenoxy)-3-oxobutanoate (0.027 mol 6.92 g) drop wise. The reaction was continued till water is completely eliminated from the reaction and separated in a Dean Stark. The contents were cooled, filtered to get solid mass containing product along with catalyst which is then extracted in hot dioxane and the solution is filtered to separate the catalyst. Finally the dioxane is flushed to obtain the residue, which is crystallized using appropriate solvent as listed in the Table-1 along with the purity by HPLC.

IIIb (Found C, 63.42, H, 3.60, Cl, 11.73 $C_{16}H_{11}O_4Cl$ requires C, 63.47, H, 3.63, Cl, 11.73). The IR (KBr, ν_{max}, cm^{-1}) spectrum of **IIIb** showed peaks at 1608 (lactonic keto), 3187 (OH), 1255-1235 (ether C-O-Ar) ^{1}H NMR (DMSO-d_6) spectrum of **IIIb** showed signals at 2.46 (3H, s, CH_3), 6.75-7.2 (5H, m, aromatic and coumarin), 7.5 (1H, d, aromatic), 7.63 (1H, d, C5H, J = 8.79), 10.5 (1H, s, OH), m/z (EI) 302, (M^+, $C_{16}H_{11}O_4Cl$ requires 302), 268.3 (100 %), 163.15(10.48), 133.7 (2.07), 107.15 (1.87), 91 (3.41), 75.1 (2.46).

IVa (Found C, 63.41, H, 3.59, Cl, 11.69 $C_{16}H_{11}O_4Cl$ requires C, 63.47, H, 3.63, Cl, 11.73). The IR (KBr, ν_{max}, cm^{-1}) spectrum of **IVa** showed peaks at 1693 (lactonic keto), 3302 (OH), 1260-1219 (ether C-O-Ar) ^{1}H NMR (DMSO-d_6) spectrum of

IVa showed signals at 2.3 (3H, s, CH_3), 6.7-7.4 (6H, m, aromatic and coumarin), 7.6 (1H, d, C5H), 10.5 (1H, s, OH), m/z (EI) 302, (M^+, $C_{16}H_{11}O_4Cl$ requires 302), 266 (8.1 %), 163.2 (100), 133.5 (9.66), 107.15 (31.36), 91.15 (21.34), 75.1 (39.96).

TABLE-1

Comp.	R	R'	R''	R'''	Yield	m.p. (ºC)	Catalyst used	Crystallizing solvent	HPLC Purity (area %)
IIIa	H	OH	OH	H	30	255	A-35	Ethanol	99.00
IIIb	2-Cl	OH	OH	H	44	280	A-35	Dioxane	98.68
IIIc	2-Cl	OH	OH	Cl	35	300d	A-35	Dioxane	96.31
IIId	2-Cl	OH	C_6H_5	H	32	203	A-35	Methanol	97.10
IVa	4-Cl	OH	OH	H	37	246	A-35	Methanol	98.06
IVb	4-Cl	OH	OH	Cl	34	240	A-35	Methanol	97.42
IVc	4-Cl	OH	C_6H_5	H	31	223	A-35	Acetone	98.81
Va	3-CH_3	OH	OH	H	35	205	K2641	Methanol	98.80
Vb	3-CH_3	OH	OH	Cl	26	231	K2641	Methanol	97.37
Vc	3-CH_3	OH	C_6H_5	H	25	182	K2641	Pet ether	98.15

Va (Found, C, 72.29, H, 4.92 $C_{17}H_{14}O_4$ requires) C, 72.34, H, 4.96) The IR (KBr, ν_{max}, cm^{-1}) spectrum of **Va** showed peaks at 1703 (lactonic keto), 3365 (OH), 1251-1 (ether C-O-Ar) ^1H NMR (DMSO-d_6) spectrum of **Va** showed signals at 2.02 (3H, s, CH_3), 2.24 (3H, s, CH_3), 6.7-7.2 (6H, m, aromatic and coumarin), 7.61 (1H, d, C5H, $J = 8.79$), 10.5 (1H, s, OH). On D_2O exchange of **Va** the peak at δ 10.5 disappears, which confirms the presence of OH group. m/z (EI) 282. (M^+, $C_{17}H_{14}O_4$ requires 282), 267.05 (14.68 %), 163.05 (100), 135.1 (15.96), 107.1 (25.03), 91 (68.62), 77 (45.51).

Procedure B: General method for the synthesis of substituted coumarin ethers

Va-Vc (2*H*-1-Benzopyran-2-one-4-methyl-3-(substituted phenoxy): In an oil bath preheated to 135-140 °C fitted with a three necked flask with guard tube, added of 2 g (0.018 mol) resorcinol powder and ethyl-2-(3-methylphenoxy)-3-oxobutanoate (6.37 g, 0.027 mol). The mixture was made homogeneous and added (2.67 g, 30 % based on total reactants) of K2641. The contents were heated for another 1 h. The contents were cooled and solid is then hot extracted in methanol. The solution is hot filtered to separate the catalyst, the solvent is flashed off and then it is recrystallised using appropriate solvent as listed in the Table-1 along with the purity by HPLC.

Antibacterial activity testing: Following compounds have been tested for their antibacterial activity on gram +ve and gram -ve bacteria *e.g.*, *S. aureus* and *S. typhi*. The approx. MIC (minimum inhibitory concentration) is = 1000 µg/mL.

Experimental conditions: Culture inoculum: freshly prepared (of 18 h age); Results taken: MIC after 48 h incubation along with positive and negative controls at 37 °C are tabulated in Table-2.

TABLE-2

Compounds used	*S. aureus*			*S. typhi*		
	Concentration (μg/mL)					
	250	500	1000	250	500	1000
2*H*-1-Bnzopyran-2-one,4-methyl-7-hydroxy-3-(2-chlorophenoxy) (**IIIb**)	+ +	+ +	+	+ +	+ +	+ +
2*H*-1-Benzopyran-2-one,4-methyl-7-hydroxy-3-(4-chlorophenoxy) (**IVa**)	+ +	+ +	+	+ +	+ +	+ +
2*H*-1-Benzopyran-2-one,4-methyl-7-hydroxy-3-(3-methylphenoxy) (**Va**)	+ +	+	P	+ +	+ +	+

Symbols: Total inhibition, no growth of organism = –, poor growth compared to controls = P, medium growth compared to controls = +, confluent growth, no inhibition = + +.

RESULTS AND DISCUSSION

Ethyl-2-(substituted phenoxy)-3-oxobutanoates required for the preparation of coumarin ethers were synthesized by the condensation of ethyl-α-chloroacetoacetate[8] with sodium salt of the respective phenol[9,10]. (phenol, *o*-chlorophenol, *p*-chlorophenol, *m*-methylphenol) using toluene as a solvent. The crude product was then distilled under vacuum to give semi pure product. The semi pure product was used as it is, since further purification led to the partial decomposition of the ester. The homogeneity of the esters was checked by gas chromatography. The yield and the boiling point of the respective ester are mentioned in the Table-3.

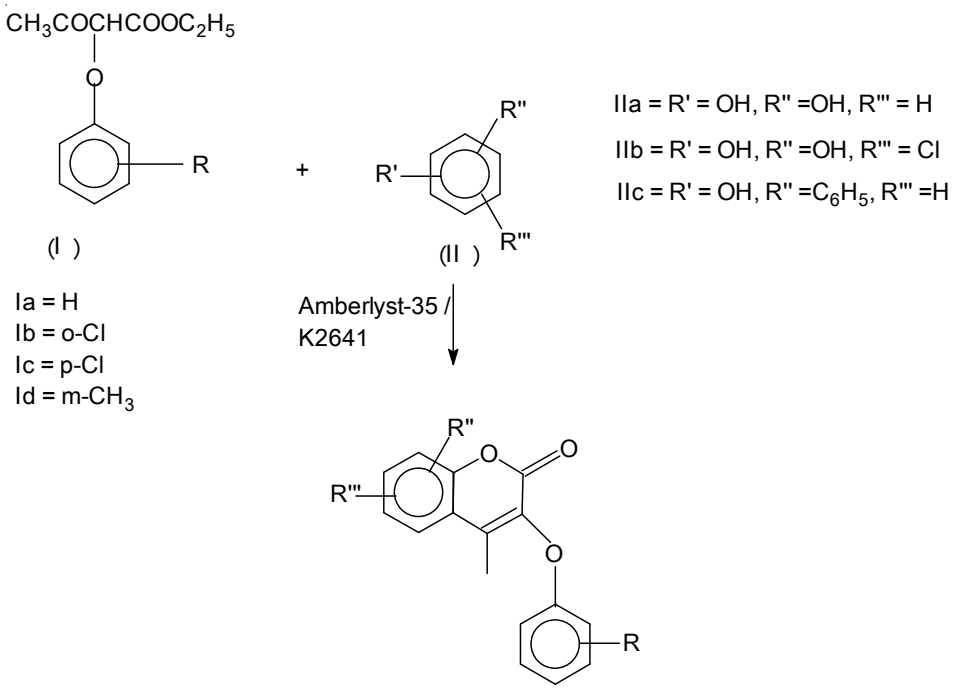
TABLE-3

Name of substituted esters	b.p. ºC/mmHg	Yield (%)
Ethyl-2-phenoxy-3-oxobutanoate (**1a**)	135-140/15	48
Ethyl-2-(2-chlorophenoxy)-3-oxobutanoate (**1b**)	145-150/15	45
Ethyl-2-(4-chlorophenoxy)-3-oxobutanoate(**1c**)	150-155/5	42
Ethyl-2-(3-methylphenoxy)-3-oxobutanoate(**1d**)	133-138/10	40

The initial work in the preparation of coumarin ethers began with the synthesis of 2*H*-1-benzopyrane-2-one-4-methyl-7-hydroxy-3-phenoxy, by the reaction of resorcinol with ethyl-2-phenoxy-3-oxobutanoate under Pechmann conditions. The reaction resulted in the formation of undesired product, which was found to be self cyclized product ethyl-3-methylcoumarillate of the corresponding ester, m/z, 204 (confirmed on the basis characterization of the compound). We thought that use of other suitable catalyst could avoid formation of cyclized product.

In the recent years, ion exchange resins have been used in organic reactions with some success[11,12]. Ion exchange resins like Zeocarb 225 and Amberlite IR-120 resins were crushed and used for the synthesis of coumarins[13]. The reaction involved use of acetoacetic ester as one of the reactants along with different phenols, however higher homologues have not been used for the synthesis of coumarins. In this context higher homologues of acetoacetic esters (ethyl-2-(substituted phenoxy)-3-oxobutanoates

was used for the preparation of 3-substituted coumarin ethers using cation exchange resins. When ion exchange resin was used as a catalyst, the product was found to be coumarin ether. Moreover ion exchange resin proved to be the promising catalyst for the preparation of coumarin ethers. The ethyl-2-(substituted phenoxy)-3-oxobutanoates were then reacted with different phenols using ion exchange resin as a catalyst to give substituted coumarin ethers. The synthesis of substituted coumarin ethers (**IIIa-d, IVa-c** and **Va-c**) was carried out as outlined in reaction **Scheme-I**.



Scheme-I

In the literature, preparation of compound **IIIa** has been reported with different method[14], whereas other compounds are not known. The purity of the crystallized coumarin ethers was established by HPLC using dichloromethane and methanol (99:1) as a mobile phase at $\lambda = 254$ nm. The purity of different coumarin ethers is included in Table-1.

Coumarin ether has also been synthesized using 80 % sulphuric acid as a catalyst, however the resin was found to be more advantageous over sulphuric acid when yield is compared. Coumarin **IIIa** was prepared using 80 % sulphuric acid as well as A-35 ion exchange resin and yield of 20 and 30 % was obtained, respectively. Moreover resin can be recycled without appreciable loss of yield. The waste effluent generation can also be avoided with the use of resin catalyst.

Various commercially available polymeric cation exchange resin catalysts like Amberlyst-35, Amberlyst-70, K2641 are acid catalysts typically used for alkylation, condensation type reactions and they also possess a maximum temperature stability (130-150 °C). These catalysts were screened for preparation of coumarin ethers by the reaction of ethyl-2-(2-chlorophenoxy)-3-oxobutanoate and resorcinol. The yield and purity obtained with different catalysts is given in Table-1. The catalysts were also used with and without solvent (toluene, *o*-xylene) and also with change in catalyst loading. The selected catalyst with most effective catalyst loading was then used for rest of the reactions. It was found that for preparation of (**Va-Vc**), the catalyst of choice was K2641.

Two procedures have been developed for the synthesis of coumarin ethers and regarded as procedure A (with solvent *o*-xylene) and procedure B (without any solvent). The selection of catalyst is summarized in Table-4.

TABLE-4
SELECTION OF CATALYST

Catalyst loading* and catalyst used	Solvent used	Temp. (ºC)	Yield (%)	Purity by HPLC (%)
10 %/Amberlyst-35	–	135-140	33.45	98.70
30 %/Amberlyst-35	–	135-140	39.63	98.68
30 %/K2641	–	135-140	35.00	98.65
10 %/Amberlyst-35	Toluene	110	10.00	97.40
10 %/Amberlyst-35	*o*-Xylene	130-135	30.00	96.20
10 %/Amberlyst-70	*o*-Xylene	130-135	27.00	95.40
10 %/K2641	Toluene	110	35.00	97.00

*Loading based on total wt. of reactants.

The catalyst can be recycled by drying the catalyst at 100 °C prior to recycle. The purity of coumarin ether obtained after recycle remains unaffected. Table-5 shows the use of catalyst and yield.

TABLE-5
CATALYST RECYCLE

Catalyst A-35	Yield (**IIIb**)	Purity(by HPLC) (**IIIb**)
1st use	39.63	98.68
2nd use	38.24	98.75

Various 4-methyl-3-(substituted phenoxy)-2*H*-1-benzopyran-2-one, compounds have been successfully synthesized using cation exchange resin A-35/K2641. The advantage in the synthesis of these compounds is a green recyclable catalyst.

The compound **Va** showed moderate antibacterial activity, hence it can be seen from the structure of this compound that methyl substituents in the phenoxy ring plays vital role in enhancing the activity. Therefore compounds with such type of substituents can be considered for further study.

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