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Envirocat EPZ-10: An efficient catalyst for the synthesis of 3-acetoacetylcoumarins

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ABSTRACT

A simple, efficient and ecofriendly procedure has been developed for the synthesis of 3-acetoacetylcoumarins from salicylaldehyde(s) and 4-hydroxy-6-methyl-2*H*-pyran-2-one using EPZ-10 as a catalyst in ethanol medium at reflux condition. The present methodology offers several advantages such as excellent yields, short reaction time and use of EPZ-10 as an eco-friendly catalyst.

1. Introduction

Recently, organic chemists have focused their attention towards the development of novel methodologies for the synthesis of heterocycles possessing sites for annulation. Amongst them, coumarin derivatives are becoming popular due to their wide pharmacological properties such as antioxidants, anti-HIV, anticancer, vasorelaxants and enzymatic inhibitors [1]. The 3-(N-substituted) aminocoumarins have found applications as fluorescent markers and are also known to exhibit photochemical properties [2]. 3-Benzamidocoumarin derivatives *viz* Novobiocin, Clorobiocin (Fig. 1) are used as antibiotics [3]. Novobiocin also inhibits a well-validated drug target (DNA gyrase) [4] and is an exciting new target in the cancer drug discovery [5]. Warfarin, Coumachlor, Dicoumarol and Acenocoumarol (3-substituted coumarin derivatives) are clinically used as blood anticoagulants as well as rodenticides [6]. Other than their biological importance, some coumarin derivatives are used in the preparation of polymers having applications in electroluminescent devices [7], while some derivatives are used as fluorescent chemosensors [8]. Sesquiterpenes bearing a coumarin skeleton are used in synthesis of natural products *viz* gumosides B (Fig. 1), cauferoside, feselol, conferoside, ferilin, ferocaulidin, ligupersin A, conferol, and daucosterol possessing cytotoxic activity [9]. These unique properties have triggered a renewed interest in developing ecofriendly synthetic methods which enable rapid access to 3-acetoacetylcoumarins.

2. Results and discussion

An intriguing line in the development of ecofriendly methodologies is being fueled by the basic paradigm shift from use of traditional catalysts to clay [10] as a catalyst because they have many advantages such as ease of handling, non-corrosiveness, low cost and regeneration. EPZ-10 is a clay catalyst commercially available from Contract Chemicals, England (www.contract-chemicals.com).

It is prepared by supporting $ZnCl_2$ on clay containing predominantly strong Lewis acid sites as well as weak Bronsted acid sites and provides a high surface area for the reactions. As a part of our research aimed at exploring envirocat EPZ-10 for developing new synthetic methods [10,11a] and preparation of heterocyclic compounds

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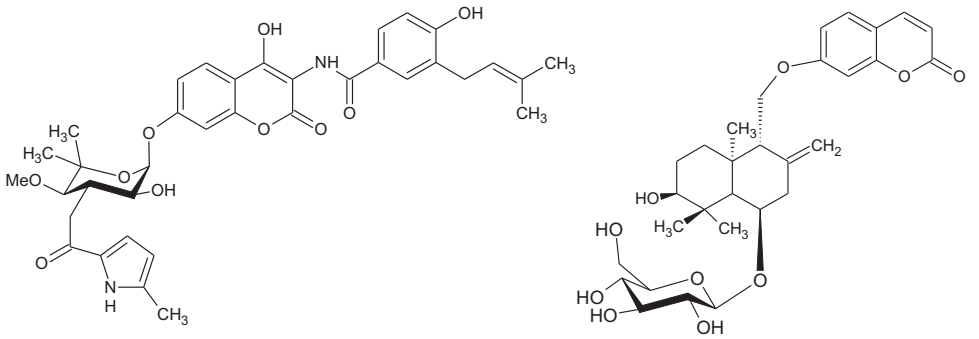
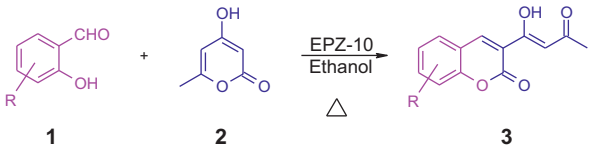


Fig. 1. Biologically active coumarin derivatives.



Scheme 1. EPZ-10 catalyzed synthesis of 3-acetoacetylcoumarins.

[11(b–d)], we report herein an efficient and simple synthesis of acetoacetylcoumarins in high yields from salicyldehyde(s) (**1**) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**) in the presence of envirocat EPZ-10 as a catalyst in EtOH medium (Scheme 1).

Initially, the reaction of salicylaldehyde (1) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (2) was carried using EPZ-10 in ethanol medium at reflux conditions and gratifyingly, the corresponding 3-acetoacetylcoumarin (3) (Scheme 1) was obtained in 89% yield in 3 h. After this success, we focused our attention towards optimization of reaction conditions.

From Table 1, it is found that 10 mol % of envirocat EPZ-10 is sufficient for carrying out the present transformation. The catalytic efficiency of other clays compared with the EPZ-10 is not sufficient. So by using these optimized reaction conditions, the scope and efficiency of this approach was explored for the synthesis of a wide variety of substituted acetoacetylcoumarins and results are summarized in Table 2. It is worthwhile to note that variation in the electronic nature of the substituent on the aromatic ring of salicyldehyde does not affect the rate of formation of reaction. Both electron-rich as well as electron-deficient salicylaldehydes reacted effectively with 4-hydroxy-6-methyl-2*H*-pyran-2-one in ethanol medium and yielded corresponding coumarins in good to excellent yields (Table 2**,** entries a–k).

Table 1
Optimization of reaction conditions for synthesis of 3-acetoacetylcoumarins.

Catalyst	Cat. (relative mol %)	Yield (%)
–	–	10
Montmorillonite K-10	10	78
Montmorillonite KSF	10	80
EPZG	10	82
EPZ-10	10	87
EPZ-10	20	89
EPZ-10	30	89
EPZ-10	40	88
EPZ-10	50	90

Reaction conditions: Salicylaldehyde (1 mmol); 4-hydroxy-6-methyl-2*H*-pyran-2-one; (1 mmol); solvent: ethanol; temperature: reflux, time: 3 h.

Table 2
EPZ-10 catalyzed an efficient synthesis of 3-acetoacetylcoumarins.

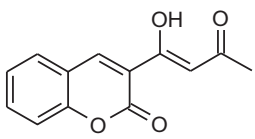
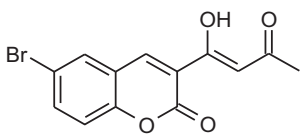
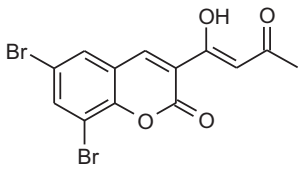
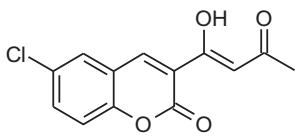
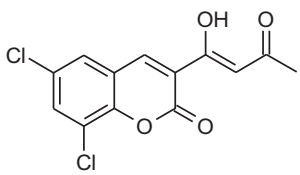
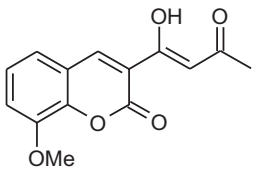
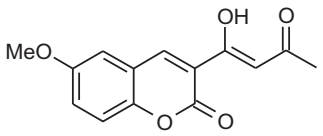
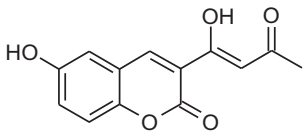
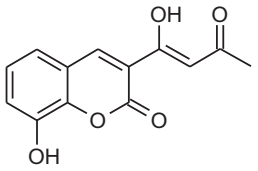
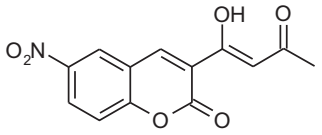
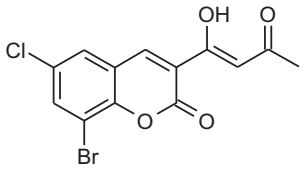
Entry	Product (3)	Time (min)	Yield (%)[a,b]
a		45	87
b		30	91
c		50	94
d		50	91
e		50	90

Table 2 (*Continued*)

Entry	Product (3)	Time (min)	Yield (%)[a,b]
f		60	87
g		60	93
h		45	89
i		60	91
j		60	92
k		60	91

[a] Yields refer to pure isolated products.
[b] All products gave satisfactory spectroscopic (IR, ^{1}H and ^{13}C NMR, MS) analysis.

3. Conclusion

In conclusion, a convenient and environmentally benign methodology for the synthesis of 3-acetoacetylcoumarins using salicylaldehyde(s) and 4-hydroxy-6-methyl-2*H*-pyran-2-one has been developed using a catalytic amount of EPZ-10. The attractive features of this protocol are simple reaction procedure, use of a commercially available green catalyst, short reaction time, easy product separation and purification.

4. Experimental

Various substituted salicylaldehydes (Sigma-Aldrich), 4-hydroxy-6-methyl-2*H*-pyran-2-one (Alfa Aesar) were used as received. Melting points were determined an open capillary and are uncorrected. IR spectra were recorded on Perkin-Elmer [FT-IR-783] spectrophotometer. NMR spectra were recorded on Bruker AC-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard and δ values are expressed in ppm. Mass spectra were recorded on a Shimadzu QP2010 GCMS.

4.1. General procedure for synthesis of acetoacetylcoumarins

A mixture of a salicylaldehyde (1 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol) in ethanol (5 mL) was stirred at reflux condition using EPZ-10 (10 mol %) as a catalyst and the progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was filtered in ice cold water. The product was recrystallized from 95% ethanol. These products were characterized by spectral techniques (i.e. IR, ^{1}H and ^{13}C NMR, MS).

4.2. Spectral data of unknown compounds

6-Hydroxy-3-acetoacetylcoumarin (**3 h**, Table 2): mp. 220 °C, IR (KBr): 3402, 3211, 1725, 1560, 1112, 1022, 825 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 6.89 (s, 1H, CH), 7.14–7.32 (m, 3H, Ar-CH), 8.73 (s, 1H, CH), 9.94 (s, 1H, Ar-OH), 15.80 (s, 1H, OH); ^{13}CMR (75 MHz): 27.44, 101.44, 114.22, 117.47, 119.26, 120.10, 123.29, 146.53, 147.91, 154.52, 158.07, 173.77, 199.37; MS (EI): *m/z* 246 (M^+).

8-Hydroxy-3-acetoacetylcoumarin (**3i**, Table 2): mp. 235 °C, IR (KBr): 3420, 3124, 1745, 1611, 1411, 1108, 847 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 6.90 (s, 1H, CH), 7.19 (d, 2H, *J* = 6.0 *Hz*, Ar-CH), 7.34 (t, 1H, *J* = 6.0 *Hz*, Ar-CH), 8.74 (s, 1H, CH), 10.41 (s, 1H, Ar-OH), 16.03 (s, 1H, OH); ^{13}CMR (75 MHz): 27.46, 101.41, 119.68, 119.99, 120.68, 120.95, 125.39, 143.07, 144.88, 147.01, 157.75, 173.61, 199.37; MS (EI): *m/z* 246 (M^+).

6-Chloro, 8-Bromo-3-acetoacetylcoumarin (**3k**, Table 2): mp. 195 °C, IR (KBr): 3419, 3057, 1747, 1609, 1577, 1182, 1008, 829 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH_3), 6.99 (s, 1H, CH), 7.57 (d, 1H, *J* = 2.4 *Hz*, Ar-CH), 7.82 (d, 1H, *J* = 2.1 *Hz*, Ar-CH), 8.51 (s, 1H, CH), 15.74 (s, 1H, OH); ^{13}CMR (75 MHz): 27.73, 102.14, 110.87, 120.19, 122.49, 127.68, 130.41, 136.41, 143.48, 149.71, 156.40, 170.33, 200.33; MS (EI): *m/z* 343 (M^+).

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