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EPZ10^R catalyzed simple and efficient synthesis of flavanones

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ABSTRACT

An efficient synthesis of flavanones using Envirocat EPZ10^R as a heterogeneous catalyst under a solvent-free green procedure is described. This simple protocol offer advantages such as shorter reaction times, simple work-up, higher yield, and recovery and reusability of the catalyst.

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KEYWORDS

Flavanones;
Solvent-free reaction;
EPZ10^R;
Cyclization;
Microwave.

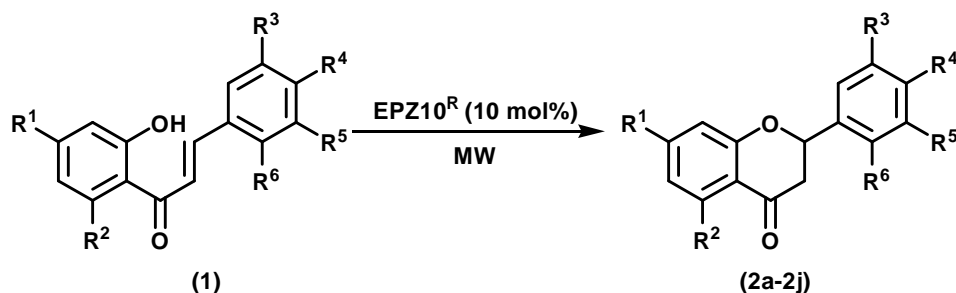
INTRODUCTION

Flavanones are a class of naturally occurring compounds that are widely distributed in plants and possess biological activities, such as antimicrobial^[1], anti-lungcancer^[2], anti-tuberculosis^[3], antifungal^[4], antiproliferative^[5], anti-inflammatory^[6], and anti-AIDS^[6]. The general method to obtain flavanones consists of an intramolecular conjugated addition of 2'-hydroxychalcones, which are prepared by aldol condensation of 2'-hydroxyacetophenones and benzaldehydes^[7]. The cyclization of 2'-hydroxychalcones can be performed using acids^[8], bases^[9], light^[10], heat^[11], Ni/K/Zn halides^[12], electrolysis^[13], and TFA/Silica^[14]. Other alternative procedures to synthesize flavanones include oxidation of flavan-4-ol^[15]. There are many drawbacks under these conditions including long reaction time, harsh reaction conditions, unsatisfactory yields, use of environmentally toxic reagents or solvents, use of large amount of solid supports, which result in the generation of a large amount of toxic waste, and tedious work-up. Hence, there is still a need to de-

velop efficient methods for the synthesis of flavanones.

In recent years, considerable attention has been paid to reactions done under solvent-free conditions^[16]. One of the areas of central attention in this field includes reactions between solids^[17]. These reactions are not only of interest from an economical point of view; in many cases they also offer considerable synthetic advantages in terms of yield, selectivity, and simplicity of the reaction procedure. Recently, significant progress has been made in the application of EPZ10^R to catalytic processes. EPZ10^R is non-toxic and recyclable solid acid catalyst, which is prepared by supporting ZnCl₂ on clay. EPZ10^R contain predominantly strong Lewis acid sites as well as weak Brønsted acid sites^[18]. EPZ10^R has been used as a catalyst for alkylation^[19], aromatic bromination^[19], addition^[19], benzylation^[19], and Friedel-Crafts acylation^[20]. EPZ10^R has also been used for the synthesis of 2,5-di-*t*-butyl-4-fluorophenol^[21], 3,4-dihydropyrimidin-2(1*H*)-ones^[22], and coumarins^[23]. EPZ10^R has continued to be exploited in organic synthesis because it is a non-toxic, eco-friendly, and easy handling catalyst.

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Scheme 1

Microwave assisted organic synthesis (MAOS) has emerged as a new “lead” in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. Important advantage of this technology include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of the product. Many reports that microwave-heated reactions typically proceed more cleanly, in higher yields and in less time than their conventionally heated counterparts have appeared^[24].

EXPERIMENTAL

General procedure

Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on Shimadzu 8400 instrument. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on Varian Mercury instrument using TMS as internal standard. Mass spectra were recorded on Shimadzu QP 5050. Elemental analysis was recorded on Flash E. A. 1112 Thermo instrument. Reactions were monitored by TLC on aluminum sheets precoated with silica gel 60F₂₅₄. Column chromatography was performed using silica gel (60–120 mesh size). For the microwave irradiation experiments, a microwave oven equipped with a turntable was used (Whirlpool 800T operating at 2450 MHz having maximum output of 1200 W).

Typical experimental procedure for the synthesis of 2-(4-chlorophenyl)chroman-4-one (2c)

A mixture of 3-(4-chlorophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (0.258g, 1 mmol) and EPZ10^R[19] (10 mol%) was irradiated in a microwave oven for 7 min and progress of reaction was

monitored by TLC. After completion of reaction, mass was cooled to room temperature, then the solid residue was dissolved in ethyl acetate and mixture stirred for 5 min. The catalyst was recovered and the solvent was evaporated to afford solid, which was purified by column chromatography (hexane/ethyl acetate, 8/2, v/v) using silica gel.

2-(4-chlorophenyl)chroman-4-one (2c)

Solid; Yield: 91%; m.p. 85–86°C; IR (KBr) cm^{-1} : 820, 1012, 1230, 1471, 1601, 1695 (C=O), 2900, 3033; ¹H NMR (TMS) δ ppm: 2.87 (dd, 1H), 3.05 (dd, 1H), 5.47 (dd, 1H), 7.04–7.10 (m, 2H), 7.38–7.44 (m, 4H), 7.49–7.52 (m, 1H), 7.93 (dd, $J = 7.7$ Hz, 1H); ¹³C NMR δ ppm: 44.3, 78.6, 118.1, 120.7, 121.5, 127.1, 127.5, 129.0, 134.4, 136.3, 137.2, 161.2, 190.2; Anal. Calcd for C₁₅H₁₁ClO₂: C 69.64, H 4.29%; Found: C 69.62, H 4.31%.

RESULTS AND DISCUSSION

In continuation of our work^[23,25] on the application of easily recyclable, heterogeneous, eco-friendly catalysts for the development of useful synthetic methodologies, we now show that flavanones can be produced using EPZ10^R as an efficient, non-toxic, recyclable heterogeneous catalyst (Scheme 1).

The effective amount of EPZ10^R as catalyst was investigated. Generally, the reaction rate and yield were increased over the amount of catalyst. It was found that 10 mol% of catalyst was appropriate amount for the reaction (TABLE 1, Entry 3). The fewer amounts gave a low yield even after long reaction time (TABLE 1, Entry 1-2), and the more amounts could not cause the obvious increase for the yield of product (TABLE 1, Entry 4-5).

Next, we prepared a range of flavanones under the

TABLE 1 : Effect of concentrations of EPZ10^R for the synthesis of flavanone (2a)

Entry	Catalyst (mol%)	Time (min)	Yield (%) ^a
1	0	15	Trace
2	5	15	52
3	10	8	92
4	15	8	91
5	20	8	92

^aisolated yield**TABLE 2 : EPZ10^R catalyzed simple and efficient synthesis of flavanones**

Entry	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Product ^a	Time (Min)	Yield (%) ^b
1	H	H	H	H	H	H	2a	8	92
2	H	H	H	OCH ₃	H	H	2b	8	90
3	H	H	H	Cl	H	H	2c	7	91
4	H	H	H	NO ₂	H	H	2d	9	86
5	H	H	H	OCH ₃	OCH ₃	OCH ₃	2e	7	89
6	H	H	OCH ₃	H	H	OCH ₃	2f	9	88
7	OCH ₃	H	H	H	H	H	2g	8	91
8	OCH ₃	H	OCH ₃	H	H	H	2h	8	93
9	OCH ₃	OCH ₃	Br	H	H	H	2i	9	89
10	H	H	H	H	H	Br	2j	8	90

^aAll products were characterized by ¹H NMR, ¹³C NMR and IR spectroscopic data and their m.p. compared with literature values^[8,14]. ^bisolated yield**TABLE 3 : The efficiency of recovered catalyst**

Run	No. of cycles	Yield (%) ^a
1	Cycle I	92
2	Cycle II	91
3	Cycle III	91
4	Cycle IV	90

^aisolated yield

optimized reaction conditions. The optimized results are summarized in TABLE 2. In all the cases, substituted 2'-hydroxychalcones reacted successfully and gave product in high yields. The present protocol considerably reduces the long reaction time usually encountered in traditional flavanone synthesis and affords the desired product in very good yields.

The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Thus, the efficiency of recovered catalyst (TABLE 3) was verified with the reaction of 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (TABLE 2, Entry 1). Using the fresh catalyst the yield of product

2-phenylchroman-4-one (2a) was 92% while with the recovered catalyst in the three subsequent recyclization the yields were 92, 91, 91, and 90%.

CONCLUSIONS

In summary, we have developed a simple, convenient, and effective method for facile synthesis of flavanones by the cyclization of 2'-hydroxychalcones using Envirocat EPZ10^R catalyst under solvent-free conditions. Present protocol offer very attractive features such as reduced reaction times, higher yields and reusability of catalyst for a number of times without appreciable loss of activity. When compared with conventional method as well as other catalysts, which will have wide scope in organic synthesis. The simple microwave irradiation procedure combined with easy of recovery and reuse of this catalyst make this method economic chemical process for the synthesis of flavanones.

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