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Envirocat EPZ-10: A Solid Acid Catalyst for the Synthesis of 1,8-Dioxooctahydroxanthenes in Aqueous Medium

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ENVIROCAT EPZ-10: A SOLID ACID CATALYST FOR THE SYNTHESIS OF 1,8-DIOXO-OCTAHYDROXANTHENES IN AQUEOUS MEDIUM

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An efficient method for synthesis of 1,8-dioxo-octahydroxanthenes using EPZ-10 as a heterogeneous catalyst is developed. In this method, aldehydes and dimedone l cyclohexane-1,3-dione are heated at 70°C in the presence of a catalytic amount of EPZ-10 in water as a universal solvent, affording the corresponding 1,8-dioxo-octahydroxanthenes in moderate to excellent yields. Also, domino Knoevenagel l hetero-Michael-addition reaction is described in water without any catalyst with excellent yields. The major advantages of this method are excellent yields, short reaction time, and ease of operation. This green protocol works well with dimedone as well as cyclohexane-1,3-dione.

Keywords: 1,8-Dioxo-octahydroxanthenes; domino reaction; Envirocat EPZ-10; heterogeneous catalyst; xanthenedione derivatives

Xanthene derivatives such as octahydroxanthenes have attracted the attention of synthetic organic chemists and are becoming increasingly popular because they are frequently occurring motifs in a number of natural products^[1] and have been used as versatile synthons because of the inherent reactivity of the pyran ring.^[2] The synthesis of 1,8-dioxo-octahydroxanthenes (Scheme 1) is an useful reaction that involves the condensation between an aldehyde and dimedone or cyclohexane-1,3-dione in the presence of Lewis acids.^[3] However, most of these reported procedures have disadvantages including poor yields, prolonged reaction times, use of an excess of reagents and catalysts, and use of toxic organic solvents. Therefore, an environmentally benign protocol for synthesis of 1,8-dioxo-octahydroxanthenes is highly desirable.

An intriguing line in the development of ecofriendly methodologies is being fueled by basic paradigm shift from use of traditional catalysts to clay as catalysts because they fulfill the principles of green chemistry. Envirocat EPZ-10, a clay catalyst, has received considerable attention as a versatile catalyst because of its high reactivity, stability, ease of handling, easy preparation, and low toxicity. [Envirocats catalysts are available from Contract Chemicals, England (www.contract-chemicals. com).] EPZ-10, which is prepared by supporting ZnCl₂ on clay, is known to contain

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Scheme 1. Synthesis of 1,8-dioxo-octahydroxanthenes.

Table	1.	Synthesis	of	product 3	in	water at	100 °C	without	any	catalyst
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Entry	Product (3)	Time (h)	Yield (%) ^a	
a	R=R'=H	3	86	
b	R = H; R' = 4-OMe	3	96	
с	R = H; R' = 4-Me	3.5	90	
d	R = H; R' = 4-Cl	3.5	84	
e	R = H; R' = 3-OMe, 4-OH	3	86	
f	R = H; R' = 4-CN	2.5	90	
g	$R = CH_3; R' = H$	2.5	95	
h	$R = CH_3$; $R' = 4$ -OMe	3.0	89	
i	$R = CH_3; R' = 4-CH_3$	2.5	88	
j	$R = CH_3; R' = 4-Cl$	3.0	96	
k	$R = CH_3; R' = 4-NO_2$	2.5	92	
1	$R = CH_3; R' = 4-CN$	2.5	93	
m	$R = CH_3$; $R' = 3,4-(OMe)_2$	2.5	93	
n	$R = CH_3; R' = 4-N, N-(CH_3)_2$	3.0	95	
0	$R = CH_3; R' = 2-NO_2$	3.0	95	
p	$R = CH_3; R' = 3,4-O_2CH_2$	3.0	84	

^aYields refer to pure isolated products.

Table 2. EPZ-10-catalyzed synthesis of 1,8-dioxo-octahydroxanthenes



Entry	Product (4)	Time (h)	Yield (%) ^{<i>a,b</i>}
a	R = R' = H	2	82
b	R = H; R' = 4-Cl	2.5	84
c	R = H; R' = 4-OMe	2.5	91
d	R = H; R' = 4-Me	3	87
e	$R = H; R' = 4-NO_2$	3.0	80
f	$R = H; R' = 4-N, N-(CH_3)_2$	2	95
g	R = H; R' = 3-OMe, 4-OH	2	86
h	$R = CH_3; R' = H$	2.5	92
i	$R = CH_3$; $R' = 4$ -OMe	2.5	89
j	$R = CH_3; R' = 4-Me$	2.5	84
k	$R = CH_3; R' = 4-Cl$	2.5	88
1	$R = CH_3; R' = 4-NO_2$	3.0	86
m	$R = CH_3; R' = 4-N, N-(CH_3)_2$	2.5	92
n	$R = CH_3; R' = 3-OMe, 4-OH$	2.0	91
0	$R = CH_3; R' = 2-NO_2$	3	82
р	$R = CH_3; R' = 3-NO_2$	3	83
q	$R = CH_3; R' = CN$	2.5	85
r	$R = CH_3; R' = Ph-CH = CH-$	2	87
S	$R = CH_3; R' = 3,4-(OMe)_2$	2.5	86
t	$R = CH_3$; $R' = thienyl$	2	94

^{*a*}Yields refer to pure isolated products.

^bAll products gave satisfactory spectroscopic (IR, ¹H NMR, MS) analysis.

predominantly strong Lewis acid sites as well as weak Brønsted acid sites.^[4] It has been used as a catalyst for several transformations such as the Friedel–Crafts alkylation, aromatic bromination and benzylation, Biginelli reaction,^[5a] synthesis of 3-carboxycoumarins,^[5b] and synthesis of geminal diacetates.^[5c] As a part of our program aimed at developing selective and environmental friendly methodologies,^[6] we report herein the synthesis of 1,8-dioxo-octahydroxanthene derivatives using a catalytic amount of EPZ-10 at 70 °C in water as a solvent (Scheme 1).

Initially, the reaction of dimedone and *p*-chlorobenzaldehyde was carried out without any catalyst in an aqueous medium at 100 °C and, as expected, product **3** was formed. No traces of cyclized product **4** was observed, to allude that the acid is essential for cyclodehydration of **3** to **4**.

A series of aldehydes were then studied for undergoing domino Knoevenagel/ hetero-Michael-addition reaction in water without any catalyst at 100 °C. We observed that product **3** is formed in moderate to excellent yields as shown in Table 1.

After these initial scrutinizes, we then extended our attention to the synthesis of 1,8-dioxo-octahydroxanthenes. We studied the condensation of dimedone and

p-chlorobenzaldehyde in water using EPZ-10 as a catalyst under elevated temperature to obtain the product **4**. The versatility of this reaction to other aldehydes is reported in Table 2.

CONCLUSION

In this report, we have described an elegant protocol for the synthesis of 1,8-dioxo-octahydroxanthenes *via* domino Knoevenagel/hetero-Michael-addition reaction followed by dehydration in water using a catalytic amount of EPZ-10.

EXPERIMENTAL

General Procedure

Domino Knoevenagel / hetero-Michael-addition reaction. 1,3-Diketone (10 mmol) was added to a solution of an aldehyde (5 mmol) in water (10 mL) and heated at reflux until completion of the reaction. Progress of the reaction was monitored by testing with thin-layer chromatography (TLC). On completion of the reaction, the formed solid product was filtered and dried.

EPZ-10-Catalyzed synthesis of 1,8-dioxo-octahydroxanthenes. A mixture of an aldehyde (2.5 mmol), 1,3-diketone (5 mmol) in water (15 mL), and EPZ-10 (10 mol%) was stirred at 70 °C, and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ether (30 mL) and dried over anhydrous sodium sulfate. The ether was evaporated to obtain the desired 1,8-dioxo-octahydroxanthenes. These products were characterized by the usual elemental analysis and spectral techniques [i.e., infrared (IR), ¹H NMR, mass spectrometry (MS)].

Spectral Data of Unknown Compounds

Compound 3m: 2,2'-(3,4-dimethoxyphenyl)methylene-bis (3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one). Mp 180 °C; IR (KBr): 3009, 2963, 1588, 1463, 1375, 1239, 1147, 1027, 868 cm⁻¹; ¹H NMR (200 MHz, CDC1₃): δ 12 (s, 1H), 6.61–6.85 (3H, m), 5.51 (1H, s), 3.85 (3H, s), 3.78 (3H, s), 2.40 (4H, s), 2.27 (4H, s), 1.06 (6H, s), 1.02 (6H, s); EIMS: m/z 428 (M+), 288, 273, 257, 201, 176, 140, 91, 76, 65, 55, 40. CHN analysis calcd. for C₂₅H₃₂O₆: C, 70.07; H, 7.53. Found: C, 69.80; H, 7.68.

Compound 4s: 3,3,6,6-tetramethyl-9-(3,4-dimethoxy phenyl)-1,8-dioxo-octahydroxanthene. Mp 170 °C; IR (KBr): 2960, 1596, 1514, 1375, 1252, 1238, 1146, 1027, 871 cm⁻¹; ¹H NMR (200 MHz, CDC1₃): δ 6.90 (1H, s), 6.71 (2H, s), 4.67 (1H, s), 3.86 (3H, s), 3.80 (3H, s), 2.45 (4H, s), 2.21 (4H, s), 1.11 (6H, s), 1.01 (6H, s); EIMS: *m/z* 410 (M+), 379, 273, 217, 161, 105, 91, 77, 55, 41. CHN analysis calcd. for C₂₅H₃₀O₅: C, 73.15; H, 7.37. Found: C, 73.01; H, 7.49.

Compound 4t: 3,3,6,6,-tetramethyl-9-(2-thienyl)-1,8-dioxo-octahydro xanthene. Mp 145 °C; IR (KBr): 2960, 2928, 2870, 1594, 1375, 1311, 1260, 1166, 868, 702 cm^{-1} ; ¹H NMR (200 MHz, CDC1₃): δ 6.92 (1H, dt), 6.77 (1H, t), 6.64

(1H, m), 5.08 (1H, s), 2.39 (4H, s), 2.20 (4H, s), 1.04 (6H, s), 0.99 (6H, s); EIMS: m/z 356 (M+), 339, 323, 272, 217, 188, 161, 83, 55. CHN analysis calcd. for C₂₁H₂₄O₃S: C, 70.76; H, 6.79; S, 8.99. Found: C, 70.48; H, 6.95; S, 8.89.

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