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AN EFFICIENT GREEN PROTOCOL FOR THE PRODUCTION OF 1,8-DIOXO-OCTAHYDROXANTHENES IN TRIETHYLAMMONIUM ACETATE (TEAA) A RECYCLABLE INEXPENSIVE IONIC LIQUID

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ABSTRACT

In-depth study is reported for the condensation of 5,5-dimethyl-1,3-cyclohexanedione with a variety of aldehydes to obtain title compounds and it is established Knoevenagel followed by Michael occurs without the need of any external catalyst to give bis-5,5-dimethyl-1,3-cyclohexanediones in this IL. Cyclization to title compounds 1,8-dioxo-octahydroxanthenes occurs only when external catalyst is used here catalytic amount of Ga(III)Chloride is employed.

Keywords: 1,8-dioxo-octahydroxanthenes, Triethylammonium acetate, Ga(III)Chloride, 5-5dimethyl-1,3-cyclohexanedione, aldehydes.

INTRODUCTION

Xanthenes are privileged class of organic compounds abundantly available in natural sources. Their analogues are of great importance to medicinal chemists and to chemists for their efficient production As such they posses large number of biological activities like antiviral[1], antibacteria[2], anti-inflammatory activities[3] as well as efficiency in photodynamic therapy[4] and antagonist for the paralyzing action of zoxazolamine[5]. Because of their significance attractive biological properties several synthetic procedures have been developed for their production using a variety of catalysts which include Bronsted acids as well as Lewis acids. To mention few these are InCl3.4H2O in ionic liquid[6], solid-state condensation by grinding at room temperature[7], diammonium hydrogen phosphate[8], p-dodecylbenzenesulfonic acid in water[9], Fe3+-montmorilonite[10], NaHSO4-SiO2 or silica chloride[11], amberlyst-15[12], silica sulfuric acid[13], tetrabutylammonium hydrogen sulfate[14], trimethylsilylchloride (TMSCl) [15], 1-methylimidazolium trifluroacetate[16], montmorillonite K-10-supported[17] and LiBr[18]. To mention all does not seem to be necessary here they are near to thirty or so. Several of these already reported methods suffer from drawbacks such as long reaction time, expensive catalyst systems, harsh reaction conditions, practicability, low product yields, these limitations necessitated search for a mild, inexpensive, and eco-friendly protocol for the synthesis of these molecules of high significance. Not only are this there differing reports that cyclised products / xanthones are obtained in water without adding any additives. No doubt expensive [bimim]PF6 and [bmim]BF4 ionic liquids are already used in this transformation along with mineral acids. Herein we wish to report use of readily accessible and inexpensive IL Triethylammonium acetate (TEAA) with the catalytic amount of Ga(III) Chloride.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Reagent-grade chemicals were purchased from a commercial source and used without further purification. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. 1H NMR spectra were recorded on a Varian Gemini 300 (300-MHz) spectrometer using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

Typical procedure of triethylammonium ionic liquid (TEAA) synthesis[19]

The synthesis of ionic liquid was carried out in a 250cm^3 round-bottomed flask, which was immersed in a water-bath and fitted with a reflux condenser. Acetic acid (1.5mol, 90.1 g, and 86.03 cm^3) was dropped into 101.2 g triethylamine (1mol, 139.4 cm^3) at 70°C within 1 h. After the addition, the reaction mixture was stirred for 2 h at 80°C to ensure that the reaction had proceeded to completion. The reaction mixture was then dried at 80°C in high vacuum (5mm Hg) until the weight of the residue remained constant. The yield of TEAA was 98%. ^{1}H NMR (DMSO-d$_6$): δ = 1.18 (t, 9H), 2.10 (s, 3H), 3.10 (m, 6H), 9.0 (s, 1H) ppm.

General procedure for the synthesis of bis-5,5-dimethyl-1,3-cyclohexanediones and 1,8-dioxo-octahydroxanthene derivatives:

A mixture of a substituted benzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), and TEAA (2mL) was stirred at r.t. for an appropriate time (Table 1). After completion of the reaction, as water (10ml) was added in reaction mixture precipitation of product is occurred. The products thus filtered, were pure and recrystallized with ethanol. Products thus obtained were bis-5,5-dimethyl-1,3-cyclohexanediones in very high yields . **For synthesis of 1,8-dioxo-octahydroxanthene:** Substituted benzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), TEAA (2mL) and catalytic amount of $GaCl_3$ was stirred at 65°C for an appropriate time (Table 2). After completion of the reaction, workup was done as mention earlier. Obtained products were recrystallized in ethanol: water (9:1). The mother liquor in both syntheses consisting of the IL was subjected to distillation at 80°C and 5mm Hg for 2h to remove water, leaving behind the IL, which was further, recycled. The conversion and the yield were not reduced after being reused more than 5 times.

bis(5,5-dimethyl-3-hydroxy-1-oxa-2-cyclohexen-2-yl)phenylmethane 3a: ^{1}H NMR ($CDCl_3$) δ : 1.13 (s, 6H, 2CH_3), 1.18 (s, 6H, 2CH_3), 2.30–2.48 (m, 8H, 4CH_2), 5.53 (s, 1H, CH), 6.52–6.81 (m, 5H, ArH), 9.44 (s, 1H, OH), 11.61 (s, 1H, OH); IR (KBr): 3000–2500, 2951, 2874, 1650,1586, 1373, 1260, 1240, 1165, 1073, 950, 829, 787 cm^{-1}.

bis(5,5-dimethyl-3-hydroxy-1-oxa-2-cyclohexen-2-yl)-2`-chlorophenylmethane (3c): ^{1}H NMR ($CDCl_3$) δ : 1.06(s, 6H, 2CH_3), 1.17 (s, 6H, 2CH_3), 2.25–2.51 (m, 8H, 4CH_2), 5.63 (s, 1H, CH), 7.09–7.39 (m, 4H, ArH), 9.76 (s, 1H, OH), 11.88 (s, 1H, OH); IR KBr): 3000–2500, 2956, 2929, 1610, 1470, 1380, 1289, 1230, 1140, 1070, 987, 745 cm^{-1}.

bis(5,5-dimethyl-3-hydroxy-1-oxa-2-cyclohexen-2-yl)benzo(3,4)dioxol-5-ylmethane 3f: ^{1}H NMR ($CDCl_3$) δ : 1.06 (s, 6H, 2CH_3), 1.24 (s, 6H, 2CH_3), 2.37–2.50 (m, 8H, 4CH_2), 5.44 (s, 1H, CH), 5.89 (s, 2H, OCH_2O), 6.49–7.06 (m, 3H, ArH), 9.70 (s, 1H, OH), 11.90 (s, 1H, OH); IR (KBr): 3000–2500, 2950, 2878, 1600, 1480, 1370, 1302, 1250, 1230, 1040, 940, 860, 810 cm^{-1}.

3,3,6,6-Tetramethyl-9-(phenyl)-1,8-dioxo-octahydroxanthene 4a: ^{1}H NMR ($CDCl_3$) δ : 0.98 (s, 6H, 2CH_3), 1.12 (s, 6H, 2CH_3), 2.20–2.45 (m, 8H, 4CH_2), 4.66 (s, 1H, CH), 7.20–7.40 (m, 5H, ArH); IR (KBr): 3030, 2980, 1687, 1670, 1470, 1360, 1200, 1170, 1142, 1005, 740, 700 cm^{-1}.

3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-1,8-dioxo-octahydroxanthene 4c: ^{1}H NMR ($CDCl_3$) δ : 1.02 (s, 6H, 2CH_3), 1.13 (s, 6H, 2CH_3), 2.21–2.53 (m, 8H, 4CH_2), 4.85 (s, 1H, CH), 7.42 (s, 1H, ArH), 7.88–7.95 (m, 3H, ArH); IR (KBr): 3030, 2980, 1680, 1675, 1628, 1535, 1366, 1340, 1210, 1175, 1145, 1005, 830, 765, 730, 700 cm^{-1}.

RESULTS AND DISCUSSION

When 1mmol of Benzaldehyde and 1mmol/2mmol of 5,5-dimethyl-1,3-cyclohexanedione, stirred at room temperature in ionic liquid triethylammonium acetate (Scheme1**a**) without any catalyst under solvent free condition on aqueous workup, only bis-5,5-dimethyl-1,3-cyclohexanedione products is formed in 95 % yields and reaction completed in short time 30min (see Table1). Reaction completion was checked via TLC. We stirred the same reaction mixture for long time i.e. 4h but no change in product **3a** occurred or stirred with heating at 65°C also produce same results did not yield xanthenedions. This reaction proceed via Knoevenagel condensation followed by Michael addition and yield bis-5,5-dimethyl-1,3-

cyclohexanediones but cyclization to 1,8-dioxo-octahydroxanthenes not occurred using above reaction condition.

To obtain title compound we catalysed above reaction mixture (benzaldehyde, dimedione and TEAA) with Gallium trichloride and stirred at 65°C under solvent free condition. Firstly, catalyst taken in minute quantity 5% mol, cyclisation occurred and product obtained was 1,8-dioxo-octahydroxanthenes but yield was not satisfactory. By repeating experiments we optimized the time (see table 2.) and quantity of catalyst i. e. 10% mol and titled compounds **4 a-g** were obtained in very good to excellent yield (Scheme 1). Encouraged by this observation, we extended this reaction to other aldehydes to investigate the scope of this procedure, from the table, it is clear present procedure is fairly general. Substitution on benzaldehyde does not affect much yield as well as time of reaction. The ionic liquid used in this protocol was recycled and reused for 5 times without apparent loss of reactivity and yield in the reaction of aromatic aldehydes and dimedione (Scheme 1). Triethylammonium acetate is air and water stable ionic liquid which is easy to synthesize by just neutralizing triethylamine and acetic acid, which are relatively inexpensive. It is needless to say that the synthesis of this unconventional TEAA ionic liquid is direct, simple, eco-friendly.

CONCLUSION

In conclusion, the present protocol employing a small amount of TEAA ionic liquid is an efficient, simple, convenient, and mild strategy for the synthesis of bis-5,5-dimethly-1,3-cyclohexanedione and with catalytic amount of $GaCl_3$ in TEAA yield 1,8-dioxo-octahydroxanthenes derivatives. The ionic liquid as well as catalyst used are eco-friendly, very mild, inexpensive, no harsh conditions are used and no corrosive by-products are formed during aqueous workup. The procedure is fairly general, high-yielding, and cost-effective. All these factors justify that it is superior over the existing methods.

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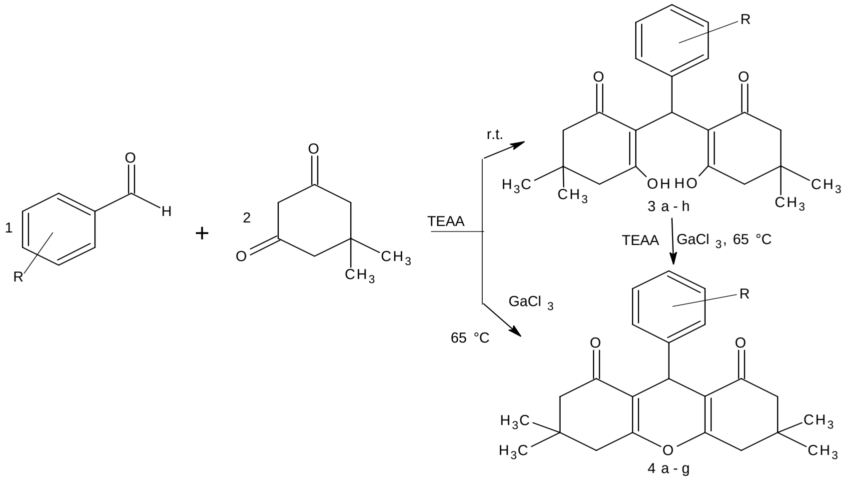

Scheme-1: Synthesis of bis-5,5-dimethyl-1,3-cyclohexanediones and 1,8-dioxo- octahydroxanthenes.

Table-1: Synthesis of bis-5,5-dimethyl-1,3-cyclohexanedione at r. t. in TEAA.

Product	R	Yield^a (%)	Time	Mp (°C) [Ref. 18]
3a	H	95	30	192–193
3b	3,4-$(CH_3)_2$	92	45	168–170
3c	2-Cl	93	35	196–197
3d	2,4-Cl_2	95	30	187–188
3e	4-F	88	40	184–185
3f	3,4-OCH_2O	86	45	165–166
3g	4-Cl	93	40	143–144
3h	3,4-Cl_2	96	30	167–168

[a] The products were characterized by comparison of their melting points and spectral (IR, ^{1}H NMR) data with those of authentic samples.

Table-2: Synthesis of 1,8-dioxo-octahydroxanthenes at 65°C using $GaCl_3$ with TEAA

Product	R	Time	Yield^a (%)	Mp (°C) [Ref. 18]
4a	H	25	93	202–203
4b	4-NO_2	20	95	225–226
4c	3-NO_2	30	92	168–170
4d	3,4-OCH_2O	25	90	223–225
4e	4-Cl	20	93	227–229
4f	3-Cl	25	90	181–182
4g	2,4-Cl_2	20	95	252–253

[a] The products were characterized by comparison of their melting points and spectral (IR, ^{1}H NMR) data with those of authentic samples.

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