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A Green Synthesis of xanthone and thioxanthone Derivatives by $ZrCl_4$ in Ionic liquid under Microwave Irradiation

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Abstract

A mild and green procedure is presented for the preparation of biologically interesting hydroxyl xanthones and hydroxyl thioxanthones via condensation of salicylic acid / thiosalicylic acid with phenol derivatives in the presences of $ZrCl_4$ under microwave-assisted ionic liquid (MAIL) condition. This procedure offers several advantages including high yields, short reaction time, clean reaction and easy work-up which make it a useful and attractive strategy for the synthesis of xanthones and thioxanthones derivatives.

Keywords: Green Chemistry, Ionic Liquid, Hydroxy xanthone, Hydroxy thioxanthone, $ZrCl_4$.

Contents

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1. Introduction

The xanthone ring is the core structure of a wide variety of naturally occurring and manmade compounds that exhibit extraordinary anti-inflammatory, anti-oxidant and anti-cancer activity. Some xanthone-containing plant extracts are directly used in traditional medicines. Analogous thioxanthone derivatives are also potential anti-cancer drugs [1-4]. The interesting structural scaffold and biological efficacy of xanthones enforced many scientists to isolate or synthesize these compounds for the development of prospective new drug candidates [5]. Several methods for the synthesis of xanthones and thioxanthones have been reported [6-10]. Most of these reported methods suffer from long reaction times, harsh reaction conditions, strong acids or toxic metals. The chemical and pharmaceutical industries are trying to find environmentally green organic reaction methodologies. Ionic liquids have emerged as a set of green reaction media with unique properties such as high polarity, good thermal stability, good dissolving ability, negligible vapor pressure, excellent microwave (MW) absorbing ability and recyclability ability and high ionic conductivity, etc [11,13]. From the perspective of microwave chemistry, one of the key important advantages

of RTILs is the presence of large organic positive ions with a high polarizability. Therefore, RTILs are good media for absorbing microwaves, leading to a high heating rate. Recently, by combining the advantages of both RTILs and microwave heating, a new microwave-assisted ionic liquid (MAIL) method for the fast controlled synthesis has been developed [14-17]. Herein, we demonstrated that the MAIL method is a fast, highly efficient, and environmentally friendly green route for the production of hydroxyxanthone and hydroxythioxanthone by use $ZrCl_4$ as an ideal lewis acid.

2. Experimental

Salicylic acids, thiosalicylic acids, phenol derivatives and zirconium tetrachloride were purchased from Fluka and Merck chemical companies. ^{1}HNMR and ^{13}CNMR spectra were measured on a Bruker DPX-250 Avance instrument at 250 MHz and 62.9 MHz in $CDCl_3$ or DMSO-d_6 with chemical shift given in ppm relative to TMS as internal standard. IR spectra were taken on a Perkin Elmer 781 spectrometer in KBr pellets and reported in cm^{-1}. Melting points were taken on an Electrochemical 9100. GC-MS spectra were recorded with Shimadzu GC-MS-QP5050. Purity determination of the products were accomplished by TLC on silica-gel polygram SILG/UV254 plates. Chromatography was carried out on column over silica gel 60, 0.063-0.200 mm. (70–230 mesh ASTM).

***General procedure for the preparation of hydroxythioxanthone and hydroxyxanthone derivatives*:**
Zirconium tetrachloride (20 mol %) was placed in a mortar followed by salicylic acid (0.138 gr, 1 mmol) or thiosalicylic acid (0.154 gr, 1 mmol) and phenolic compounds (1 mmol). These materials were then mixed using a pestle. The homogenized mixture was placed in vessel microwave and [Bmim][PF_6] (0.3 mL) was added to mixture reaction. The reaction mixture was irradiated in the microwave at power level of 80 w for appropriated time, which was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was allowed to cool and extracted with diethyl ether (3×15 mL). Then, the organic phase dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude products were purified by column chromatography over silica gel eluted with n-hexane/ EtOAc to give yellow or orange crystalline products. The products were characterized by comparison of their NMR, IR, MS, and UV spectra.

Spectral data of the product

1-Hydroxy-3-methylxanthone (3b)
Yield: 90%; yellow cubes; mp 137–138 °C; IR (KBr): 2400-3100 (br, OH), 2900 (m, CH_3), 1640 (s,C=O), 1600 (s), 1470 (s), 1450 (s), 1350 (m), 1265 (s), 1200 (s), 1145 (s), 104 (s), 805 (s), 760 (s); ^{1}H NMR ($CDCl_3$, 400 MH) δ: (ppm): 2.44 (s, 3H, Me), 6.64 (s, 1H), 6.76 (s, 1H), 7.39-7.74 (m, 2H), 7.84 (s, 1H), 8.26 (m,1H), 12.58 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 21.5, 106.9, 107.4, 111.2, 117.8, 120.5, 120.5, 123.9, 125.5, 135.2, 156.1, 161.5, 181.6; ms: *m*/*z* (%) = 227 (14, M+1), 226 (100, M^+), 197 (34), 169 (4), 141(8), 121 (17), 115 (11), 105 (4), 91 (12), 77 (12); UV: λ max = 268, 313, 405 nm.

1, 3-Dihydroxythioxanthone (3l)
Yield: 70%; orange cubes; mp 232–233 °C. IR (KBr): 3250 (s), 1640 (s), 1590 (s), 1440 (s), 1270 (s), 1200 (s), 1160 (s), 1020 (s), 900 (s), 840 (s), 750 (s) cm^{-1}; ^{1}H NMR (DMSO-*d*6): d = 6.31 (s, 1 H), 6.50 (s, 1 H), 7.52 (t, 1 H), 7.72 (m, 2 H), 8.70 (d, 1 H), 11.05 (s, 1 H), 14.36 (s, 1 H); ^{13}C NMR (DMSO-*d*6): d = 101.4, 103.3, 107.8, 126.0, 126.9, 127.6, 128.7, 133.4, 136.6, 140.3, 164.2, 166.9, 183.3; ms: *m*/*z* (%) = 244 (10) [M+], 216 (5), 187 (10), 115 (11), 85 (17), 69 (50), 43 (100); UV: λ max = 267, 39

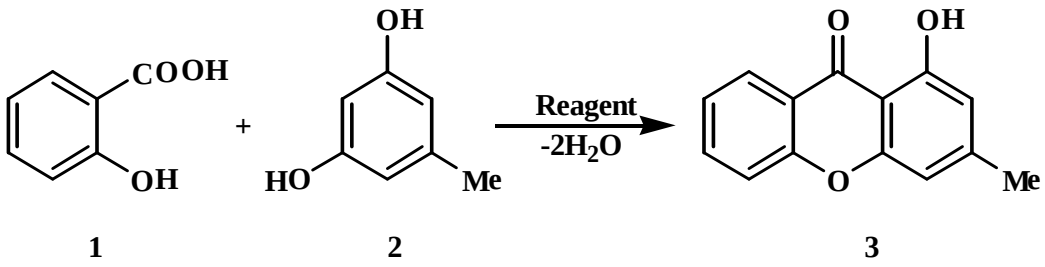
1-Hydroxy-3-methylthioxanthone (3m)
Yield: 85%; orange cubes; mp 148-150 °C; IR (KBr): 2840-3420 (br, OH), 2950 (m, CH_3), 1615 (s, C=O), 1565 (s), 1550 (s), 1470 (s), 1450 (s), 1440 (s), 1385 (s), 1345 (s), 1170 (s), 1070 (s), 800 (s), 760 (s), 705 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: (ppm): 2.35 (s, 3H), 6.75 (s, 1H), 6.85 (s. 1H), 7.5 (m, 3H), 8.6 (d,1H), 14.05 (s, H); ^{13}C NMR ($CDCl_3$) δ: 22.7, 115.5, 116.5, 118.3, 125.7, 126.3, 128.1, 129.5, 133.1, 137.4, 144.3, 147.8, 164.0, 184.2; ms: *m*/*z* (%) = 243 (17, M+1), 242 (100, M^+), 213 (25), 184 (15); UV: λ max = 267, 390 nm.

1,4-Dihydroxytioxanthone (3o)
Yield: 65%; red needles; mp 276–278 °C. IR (KBr): 1630 (s), 1580 (s), 1480 (s), 1450 (s), 1350 (s), 1220 (s), 910 (s), 800 (s), 740 (s), 710 (s) cm^{-1}; ^{1}H NMR (DMSO-*d*6): d = 6.87 (d, 1 H), 7.24 (d, 1 H), 7.60 (t, 1 H), 7.81 (t, 1 H), 7.98 (d, 1 H), 8.48 (d, 1 H), 10.43 (s, 1 H), 13.35 (s, 1H); ^{13}C NMR (DMSO-*d*6): d = 113.37, 114.01, 121.55, 124.32, 127.07, 127.30, 127.62, 128.88, 133.88, 138.13, 144.14, 157.34, 185.53; ms: *m*/*z* = 244 (100) [M+], 187 (18), 115 (16); UV: λ max = 255, 273, 339, 439 nm.

2-Hydroxy-1,4-dimethylthioxanthone (3p)
Yield: 70%; yellow needles; mp 210–212 °C. IR (KBr): 1610 (s), 1590 (s), 1450 (s), 1400 (s), 1320 (s), 1270 (s), 1080 (s), 950 (s), 930 (s) cm^{-1} . ^{1}H NMR (DMSO-*d*.): d = 2.41 (s, 3 H), 2.57 (s, 3 H), 7.17 (s, 1 H) 7.51 (t, 1 H), 7.67 (d, 1 H), 7.75 (t, 1 H), 8.25 (d, 1 H), 9.78 (s, 1 H)): d = 17.9, 20.9, 118.9, 123.0, 126.4, 128.7, 129.1, 129.6, 13o.6, 131.5, 132.2, 135.9, 136.2, 149.8, 183.2.^{13}C NMR (DMSO-*d)* MS: *m*/*z* (%) = 256 (43) [M+], 135 (32), 107(100), 77 (53), 43 (51). UV: λ max = 205, 255, 405 nm.

3. Results and Discussion

In an initial endeavor for synthesis of hydroxyxanthones, salicylic acid (**1**) and 3-hydroxy-5-methylphenol (**2**) were taken as the model substrates (Scheme **1**).



Scheme 1: Preparation of 1-hydroxy-3-methyl xanthone

The reaction was examined by various solvents (CH_2Cl_2, EtOH, DMSO, CH_3CN, EtOAc, and H_2O). In refluxing solvents, after 72 h, the yields of products were low (<10%) with large amounts of starting materials remaining. Also, it was observed that this reaction did not proceed in the presence of different Lewis acids by using solvent-free system at 110 °C for 12 h. In addition, this reaction in ionic liquid at 110 °C for 12 h was carried out by low yield. Nevertheless it seems noteworthy to mention that the reaction was not successful in the absence of catalyst under ionic liquid and microwave. Therefore, to improve the yield and to optimize the reaction conditions, the same reaction was carried out in the presence of $ZrCl_4$ as an efficient and stable Lewis acid catalyst and RTIL under microwave irradiation conditions. The majority of starting materials were consumed and a 93% yield of 1-hydroxy-3-methyl xanthone (3) was isolated.

The reaction was carried out by different ILs types, the various amounts of ILs and catalyst, the different durations of irradiation and power level of microwave instrument. All of these parameters had critical effect on the yield of reaction (Tables **1** and **2**). Increasing the reaction time did not affect the yield of the products. It is interesting to mention that ILs which are highly polar media, efficiently absorb microwave energy and transfer it to heat. When the amount of IL was high, the mixture of reaction turned to dark color and burned. It seems this increasing raised polarity of mixture reaction and increased absorption of microwave energy rate. In conclusion, the amounts of production destroyed and decreased yield of reaction, due to thermal concentration. Therefore, the shorter period and lower microwave power level were quite necessary. Controlling experiments indicated that in the absence of the catalyst, the reaction at the same condition gave 1-hydroxy-3-methyl xanthone in a rather low yield of 5% (Table **1**, entry 10).

Table 1: Effect of power level, temperature and the amount of catalyst on the synthesis of 1-hydroxy-3-methyl xanthone in the presence of $ZrCl_4$ in [Bmim][PF_6] [a]

Entry	Catalyst (mol%)	Power(w)	Time(s)	Yield (%)[b]
1	5	40	60	20
2	5	60	50	20
3	5	80	30	25
4	10	40	40	30
5	10	60	40	30
6	10	80	30	45
7	20	40	50	55
8	20	60	20	80
9	20	80	20	90
10	-	80	60	trace

[a]The reactions were run under microwave irradiation and the molar ratio of salicylic acid/ phenols was 1: 1.
[b]Yields are related to isolated pure products.

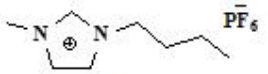
Table 2: synthesis of 1-hydroxy-3-methyl xanthone in the presence of $ZrCl_4$ and different type and amount of ionic liquid [a]

Entry	Amounts of IL (ml)	Media	Yield (%)[b]
1	0.1	[Bmim][PF_6]	80
2	0.1	[Bmim][BF_4]	65
3	0.1	[Bmim][Br]	55
4	0.3	[Bmim][PF_6]	90
5	0.3	[Bmim][BF_4]	72
6	0.3	[Bmim][Br]	60
7	0.5	[Bmim][PF_6]	85
8	0.5	[Bmim][BF_4]	70
9	0.5	[Bmim][Br]	56
10	-	None	Trace

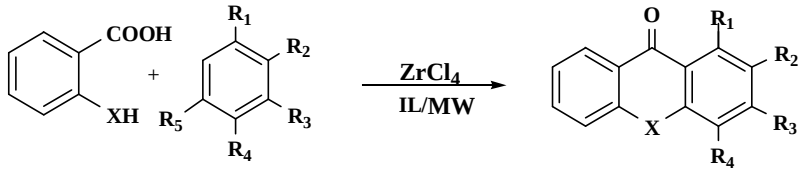
[a]The reactions were run under microwave irradiation and the molar ratio of salicylic acid/ phenols/ $zrcl_4$ was 1: 1: 20 mol%.
[b]Yields are related to isolated pure products.

The optimum conditions which were obtained have been applied for the preparation of 1-hydroxy-3-methyl xanthone and the results are demonstrated in Table **3**.

Table 3: Optimum condition for the preparation of 1-Hydroxy-3-methyl xanthone

Suitable IL	
Amount of IL (ml)	0.3
Amount of catalyst (mol%)	20
Power level (%)	80
Reaction time (s)	20

We showed here that it is possible to greatly accelerate the rate of reactions performed in ionic liquids as media for the synthesis of hydroxyxanthones or hydroxythioxanthones by reaction of salicylic acid or thiosalicylic acid with phenol derivatives using microwave irradiation (scheme 2).To ascertain the scope and limitation of the present reaction, salicylic acid and phenol compounds were reacted under optimized condition to produce the corresponding hydroxyxanthone in good to excellent yields. We were pleased to find that all substrates were converted to the corresponding products in good to excellent yields (60-90%). The results are listed in table **4**, entries 1-16.



(a-i) x=o
(j-p) x=s

2a-o **3a-n**

Scheme 2: Preparation of hydroxyxanthones and hydroxythioxanthones

Not only salicylic acid but also thiosalicylic acid (Table **4**, Entries 10-16) afforded the desired products in good to excellent yields (60-85%) in short reaction time and under given condition.

The reactivity of different phenols was influenced by the nature and position of the substituent on the aromatic ring. The phenol derivatives having an electron-donating substituent were highly reactive and gave the products in excellent yields (Table **4**). As illustrated in table **3**, when salicylic acid and thiosalicylic acid with both 3-hydroxy-5-methyl phenol (**2b**) and 3,5-dihydroxy phenol (**2c**) were employed, 1-hydroxy-3-methyl xanthone (**3b**), 1,3-dihydroxy xanthone (**3c**) and 1-hydroxy-3-methyl thioxanthone (**3m**), 1,3-dihydroxy thioxantone (**3l**) were proceeded well within a short reaction time and were isolated as regiospecific isomers by 93%, 90% and 85%, 82% respectively (Table **4**, Entries 2, 3, 12 and 13).

Table 4: Synthesis of hydroxyxanthone and hydroxythioxanthone in presence of $zrcl_4$ and [bmim][PF_6] under microwave irradiation

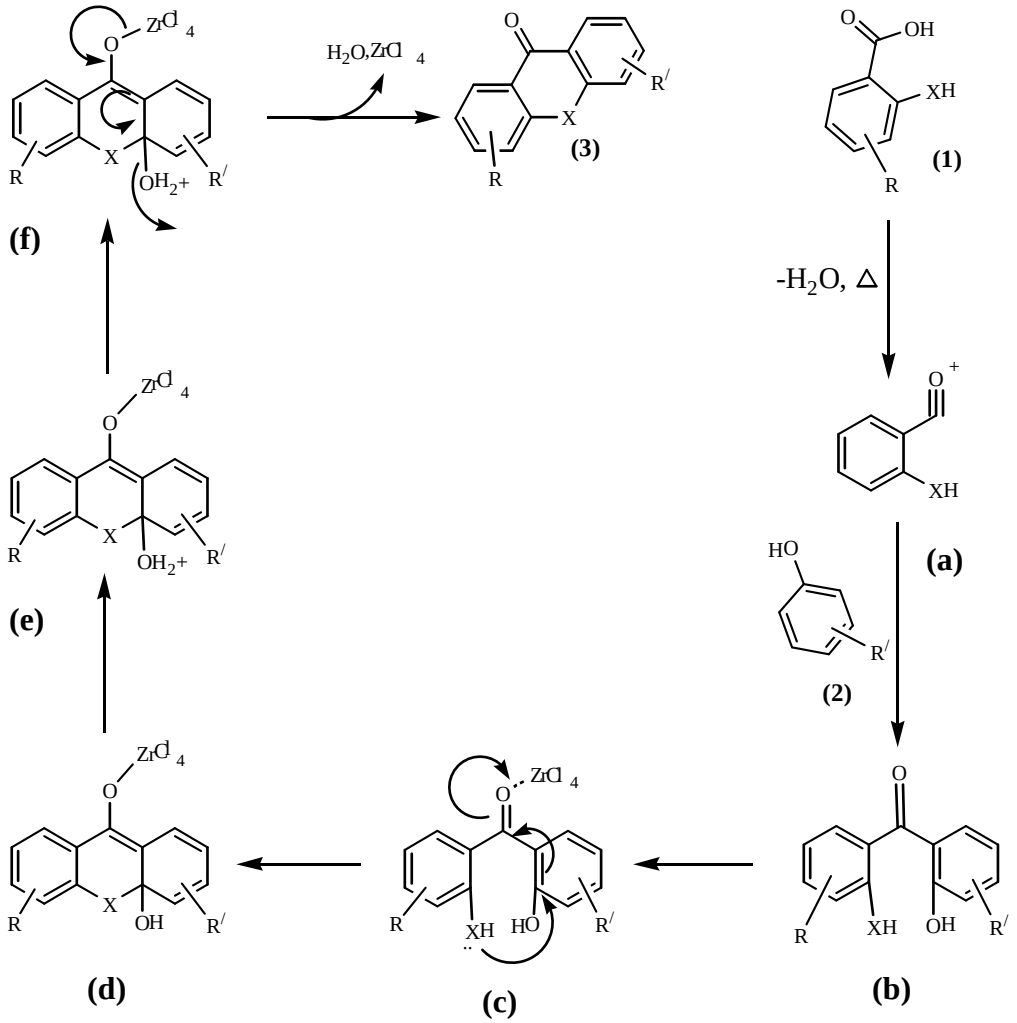
Entry	acid	Phenol						Product					Time (s)	Yield (%)[b]
	X		R_1	R_2	R_3	R_4	R_5		R_1	R_2	R_3	R_4		
1	O	2a	OH	H	OH	H	H	3a	OH	H	H	H	20	65
2	O	2b	OH	H	Me	H	OH	3b	OH	H	Me	H	20	93
3	O	2c	OH	H	OH	H	OH	3c	OH	H	OH	H	20	90
4	O	2d	OH	H	H	OH	H	3d	OH	H	H	OH	45	70
5	O	2e	OH	OH	H	H	H	3e	OH	OH	H	H	25	65
6	O	2f	OMe	H	OH	H	H	3f	OMe	H	H	H	20	75
7	O	2g	OH	H	Me	Me	H	3g	OH	H	Me	Me	25	60
								3g*	Me	Me	H	OH		10
8	O	2h	OH	H	H	NO_2	H	No reaction					18	
9	O	2i	OH	H	H	Cl	H	No reaction					18	
10	S	2j	OH	OH	H	H	H	3j	OH	OH	H	H	25	60
11	S	2k	OH	H	OH	H	H	3k	OH	H	H	H	20	62
12	S	2l	OH	H	OH	H	OH	3l	OH	H	OH	H	20	82
13	S	2m	OH	H	Me	H	OH	3m	OH	H	Me	H	20	85
14	S	2n	OMe	H	OH	H	H	3n	OMe	H	H	H	45	65
15	S	2o	OH	H	H	OH	H	3o	OH	H	H	OH	40	65
16	S	2p	Me	OH	H	Me	H	3p	Me	OH	H	Me	25	70

[a] Reaction condition: salicylic acid / thiosalicylic acid (1mmol), phenols (1mmol), $zrcl_4$ (20mol%) and [bmim][PF_6] (0.3 cc) under microwave irradiation.
[b] Yields are related to isolated pure products.

not only salicylic acid but also thiosalicylic acid (Table **4**, Entries 10-16) afforded the desired products in good to excellent yields (60-85%) in short reaction time and under given.

Hydroxyxanthones which can produce two compound, product is preferred that has one hydroxyl group in position 1 (Table 4, entry 7). This behavior could result from formation of hydrogen-bond between the hydroxyl and the carbonyl group in xanthones. The ^{1}H NMR signal of the H-bonded OH group was observed at d= 14 ppm. Phenols

bearing electron-withdrawing groups such as 2-Cl and 4-NO_2 phenol under similar conditions remained almost intact in appropriate reaction time. Based on the experimental results, a plausible mechanism was proposed in Scheme **3**.



Scheme 3: Plausible mechanism of synthesis of Hydroxyxanthone and Hydroxythioxanthone by using $ZrCl_4$

After dehydration of salicylic acid or thiosalicylic acid (1), the intermediate (b) generated by coupling of (a) and (2) undergoes intramolecular nucleophilic cyclization to afford the intermediate (d) which converted to desire hydroxyxanthone or hydroxythioxanthone (3) after dehydration. In this hypothesis, $ZrCl_4$ might be served as the Lewis-acid catalyst for several stages.

4. Conclusion

In conclusion, we have described a new and green method for synthesis of hydroxyxanthone and hydroxythioxanthone derivatives via microwave-assisted ionic liquid in the presences of $ZrCl_4$. The operational simplicity, very fast reaction, high yields of products, ecofreindly approach, and clean reaction conditions have marked it as a green and economically superior methodology.

5. Acknowledgment

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