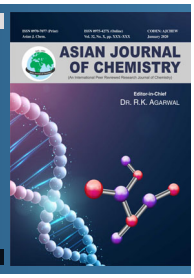
Asian Journal of Chemistry; Vol. 32, No. 10 (2020), 2611-2616

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22849



Zirconium(IV) Oxychloride: A Simple and Efficient Catalyst for the Synthesis of Chromen-2-one Derivatives

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Received: 9 June 2020; *Accepted*: 17 July 2020; *Published online*: 25 September 2020; AJC-20078

The present work explores a highly efficient, environmental friendly, green protocol for the synthesis of chromen-2-one derivatives (**3a-m**) by the condensation of salicylaldehydes with various active methylene compounds using zirconium (IV) oxychloride as catalyst. This is a convenient and rapid method for Knoevenagel condensation and this methodology offers several advantages including shorter reaction time, milder conditions, inexpensive catalyst, simple operational procedure and allowed to achieve the desired products in excellent yields. The structures of all the synthesized compounds were confirmed by spectral data.

Keywords: Zirconium (IV) oxychloride, Chromen-2-one derivatives, Salicylaldehydes, Active methylene compounds.

INTRODUCTION

Chromen-2-one or 2*H*-[1]-benzopyran-2-one or simply coumarin and its derivatives are present in various natural products, especially in alkaloids and often used for the design of many synthetic compounds with diverse pharmacological properties [1]. Beside, biological activites *viz*. antimicrobial [2-5], antidepressant [6], antioxidant [7], anti-inflammatory [8], antinociceptive [9], antitumor [10], antiasthmatic [11], antiviral [12,13], antituberculosis [14], anti-influenza [15], anti-Alzheimer [16,17], antihyperlipidemic [18], antipyretic [19], *etc*. a wide range of chromen-2-one scaffolds have also been found to possess various therapeutic activities such as anti-proliferative [20], anticancer [21], anti-HCV [22], anti-HIV [23], anti-alzheimer [24], antimalarial [25,26], antibacterial [27,28], antifungal [29,30], antioxidant [31], anticonvulsant [32], anti-inflammatory [33] and anti-TB [34,35]. Furthermore, they are also widely used as additives in food, perfumes, agro-chemicals, cosmetics, pharmaceuticals [36] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable laser dye [37].

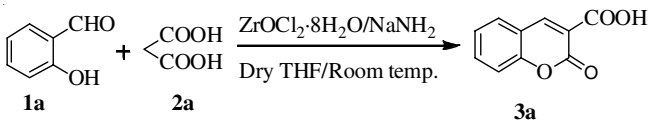
There are several established protocols for the synthesis of these pharmacologically active chromen-2-one scaffolds including Perkin reaction [38], Pechmann reaction [39], Knoevenagel reaction [40] and Baylis-Hilmanreaction [41]. They have also been synthesized by various catalysts such as *p*-TsOH [42], $ZnCl_4$ [43], $Yb(OTf)_3$ [44], PPA [45], $BiCl_3$ [46], $InCl_3$ [47]. However, in spite of their potential utility, many of these methods have certain disadvantages such as hazardous and carcinogenic solvents, longer reaction time and less yield of the product, which limit the use of these reactions in industrial process. Therefore, the development of environmentally benign organic synthesis to minimize the economic cost and environmental impact has become mandatory. As a consequence, the reaction of salicylaldehydes with various active methylene compounds in the presence of an efficient, ecofriendly and inexpensive zirconium(IV) oxychloride catalyst is reported.

EXPERIMENTAL

A commercially available reagents were used of analytical grade and employed without further purification. The products were purified using column chromatography wherever needed. All synthesized compounds identified by spectroscopic data, melting points and by comparison with available standards. FTIR spectra were obtained with a Shimadzu 8000 spectro-

photometer. ^{1}H & ^{13}C NMR spectra were recorded on Varian spectrometer. Chemical shifts (δ) are reported in ppm and with 60 F_{254} plates and spots were rendered visible by exposing to UV light and iodine. Melting points were determined with an electro thermal model 9100 apparatus and are uncorrected.

General procedure for the synthesis of chromen-2-one derivatives from salicylaldehydes and active methylene compounds (3a-m): A mixture of salicylaldehyde (**1**, 1 mmol), active methylene compound (**2**, 1.2 mmol), $ZrOCl_2$-THF (0.048 g, 0.15 mmol) and sodium amide (0.005 g, 0.15 mmol) was stirred for 30 min at room temperature. The progress of the reaction was monitored by TLC. After the completion of reaction, the crude mixture was diluted with moist ether (20 mL). The resultant reaction mixture was washed with water (3 × 25 mL) to discharge the colour, $ZrOCl_2$ and sodium amide. The ethereal solution obtained after extraction was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Finally, this reaction mixture was purified by passing through a silica gel column chromatography to get pure product (**Scheme-I**).



1a **2a** **3a**

Scheme-I: Synthesis of coumarin-3-carboxylic acid (**3a**)

Coumarin-3-carboxylic acid (3a): Colorless solid, m.p.: 189-191 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450 (-OH), 1676 (-C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.74 (s,1H), 7.90 (d, 1H, *J* = 7.6 Hz), 7.73 (m, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.39, 157.13, 154.85, 148.75, 134.70, 130.59, 125.25, 118.74, 118.37, 116.53. Elemental analysis for $C_{10}H_6O_4$: C, 63.14 (63.16); H, 3.16 (3.18).

2-Oxo-2*H*-chromene-3-carbonitrile (3b): White solid, m.p.: 175-176 ºC; IR (KBr, ν_{max}, cm^{-1}): 2229 (-C≡N), 1774 (-C=O group of lactone). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 4.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9, 135.6, 129.3, 125.8, 117.5, 113.5, 106.8, 101.0. Elemental analysis of calcd. (found) % for $C_{10}H_5NO_2$: C, 70.14 (70.18); H, 2.92 (2.94); N, 8.16 (8.18).

6-Bromocoumarin-3-carboxylic acid (3c): White solid, m.p.: 193-195 ºC; IR (KBr, ν_{max}, cm^{-1}): 3474 (-OH), 2914 (-C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s,1H), 8.15 (d, *J* = 2 Hz, 1H), 7.86 (dd, *J* = 8.8 and 2.4 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.14, 156.52, 153.91, 147.32, 136.80, 132.37, 120.25, 119.93, 118.82, 116.64. Elemental analysis of calcd. (found) % for $C_{10}H_5O_4Br$: C, 44.62 (44.64); H, 1.84 (1.87).

6-Bromo-2-oxo-2*H*-chromene-3-carbonitrile (3d): White solid, m.p.: 196-197 ºC; IR (KBr, ν_{max}, cm^{-1}): 2372 (-C≡N), 1753 (-C=O group of lactone). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.59 (s, 1H), 7.28 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4, 137.1, 130.2, 118.0, 117.4. Elemental analysis of calcd. (found) % for $C_{10}H_4NO_2Br$: C, 48.01 (48.03); H, 1.59 (1.61); N, 5.58 (5.60).

Ethyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate (3e): White solid, m.p.: 164-166 ºC; IR (KBr, ν_{max}, cm^{-1}): 1753 (-C=O group of lactone), 1705 (-C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.24 (s, 1H), 7.70-7.78 (m, 2H), 4.43 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 161.7, 155.1, 153.0, 149.6, 146.2, 137.2, 136.0, 130.6, 130.5, 118.5, 118.4, 118.2, 117.6, 116.4, 61.3, 13.3. Elemental analysis of calcd. (found) % for $C_{12}H_9O_4Br$: C, 48.49 (48.51); H, 3.02 (3.05).

4-Methyl-2-oxo-2*H*-chromene-3-carbonitrile (3f): White solid; m.p.: 120-122 ºC; IR (KBr, ν_{max}, cm^{-1}): 2204 (-C≡N), 1720 (-C=O group of lactone). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 7.8 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 162.2, 156.7, 136.5, 130.7, 118.9, 118.4, 26.7. Elemental analysis of calcd. (found) % for $C_{11}H_7NO_2$: C, 71.33 (71.35); H, 3.79 (3.81); N, 7.52 (7.56).

Ethyl 2-oxo-4-phenyl-2H-chromene-3-carboxylate (3g): White solid, m.p.: 117-119 ºC; IR (KBr, ν_{max}, cm^{-1}): 1733 (-C=O group of lactone), 1706 (-C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.1 Hz, 3H, CH_3), 4.07 (q, *J* = 7.1 Hz), 7.18-7.26 (m, 2H), 7.34-7.40 (m, 3H), 7.48-7.50 (m, 3H), 7.57 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 61.9, 117.3, 119.3, 121.7, 124.8, 128.3, 128.5, 128.8, 129.8, 133.0, 133.2, 153.2, 153.8, 158.0, 164.1. Elemental analysis of calcd. (found) % for $C_{18}H_{14}O_4$: C, 73.42 (73.46); H, 4.75 (4.79).

3-Acetyl-6-bromo-2*H*-chromen-2-one (3h): White solid; m.p.: 281-282 ºC; IR (KBr, ν_{max}, cm^{-1}): 1687, 1625. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.35 (s, 1H), 6.95 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 162.5, 148.4, 132.7, 132.3, 125.2, 118.5, 117.2, 116.9, 112.4,21.7. Elemental analysis of calcd. (found) % for $C_{11}H_7O_3Br$: C, 49.45 (49.47); H, 2.62 (2.64).

4-Methyl-2-oxo-2*H*-chromene-3-carboxamide (3i): Brown solid; m.p.: 100-105 ºC; IR (KBr, ν_{max}, cm^{-1}): 1778 (-C=O group of lactone), 1716 (-C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 6.31(s, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 130.9, 123.6, 123.3, 116.2, 114.2, 17.7. Elemental analysis of calcd. (found) % for $C_{11}H_9NO_3$: C, 65.01 (65.02); H, 4.44 (4.46); N, 6.87 (6.89).

3-Oxo-3*H*-benzo[*h*]chromene-2-carbonitrile (3j): White solid; m.p.: 96-97 ºC; IR (KBr, ν_{max}, cm^{-1}): 2310 (-C≡N), 1743 (-C=O group of lactone). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.31 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 9.0Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 6.9 Hz,1H), 7.46 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$): δ 162.7, 156.0, 155.0, 143.6, 135.2, 129.3, 128.9, 128.8, 128.5, 128.3, 128.2, 125.7, 120.6, 115.7, 115.5, 111.3. Elemental analysis of calcd. (found) % for $C_{14}H_7NO_2$: C, 76.01; H, 3.19; N, 6.33.

Ethyl 3-oxo-3*H*-benzo[*h*]chromene-2-carboxylate (3k): Yellow solid; m.p.: 115-117 ºC; IR (KBr, ν_{max}, cm^{-1}): 1745 (-C=O group of lactone), 1697 (-C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H),

7.60 (t, *J* = 7.5 Hz,1H), 7.44 (d, *J* = 9.0 Hz, 1H), 4.47 (q, *J* = 10.5 Hz, 2H), 1.45 (t, *J* = 10.5 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 162.7, 155.0, 143.6, 135.2, 129.3, 128.5, 128.3, 128.2, 125.6, 120.6, 115.7, 115.5, 111.4, 61.2, 13.4. Elemental analysis of calcd. (found) % for $C_{16}H_{12}O_4$: C, 71.62 (71.64); H, 4.49 (4.51).

3-Oxo-1 phenyl-3*H*-benzo[*h*]chromene-2-carbonitrile (3l): White solid; m.p.: 196-197 ºC; IR (KBr, ν_{max}, cm^{-1}): 2222 (-C≡N), 1724 (-C=O group of lactone). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.94 (d, *J* = 8.8 Hz, 1H), 7.24 (m, 1H), 7.50-7.54 (m, 3H), 7.67-7.72 (m, 3H), 7.74 (d, *J* = 7.7 Hz, 1H), 8.08 (d, *J* = 7.0 Hz, 1H), 8.44 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (125MHz, DMSO-d_6): δ 102.21, 112.08, 114.23, 117.20, 124.37, 126.01, 127.04, 128.02, 128.70, 129.61, 129.74, 130.27, 131.10, 136.49, 137.92, 155.44, 156.71, 163.90. Elemental analysis of calcd. (found) % for $C_{20}H_{11}NO_2$: C, 80.78 (80.80); H, 3.71 (3.73); N, 4.69 (4.71).

3-Oxo-3*H*-benzo[*h*]chromene-2-carboxylic acid (3m): Pale orange solid, m.p.: 194-196 ºC; IR (KBr, ν_{max}, cm^{-1}): 3440 (-OH), 1744 (-C=O group of lactone). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (s, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.25 (dd, *J* = 8.4 and 2.8 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.64-7.59 (m, 1H), 7.54 (dd, *J* = 8.4 and 2.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.74, 155.34, 143.93, 138.8, 136.17, 130.15, 129.68, 126.80, 124.63, 122.57, 119.01, 117.67,116.79, 112.42. Elemental analysis of calcd. (found) % for $C_{14}H_8O_4$: C, 70.00 (70.01); H, 3.32 (3.32).

RESULTS AND DISCUSSION

An efficient and simple protocol is reported for the synthesis of chromen-2-one derivatives (**3a-m**) by one pot condensation of salicyladehydes (**1a-m**) with various active methylene compounds (**2a-m**) in the presence of $ZrOCl_2$/$NaNH_2$ in THF at room temperature with constant stirring. In the preliminary stage of investigation, a systematic evaluation of different catalysts is focussed. For this purpose, a reaction of compound **1a** (1 mmol) with compound **2a** (1.2 mmol) in the presence of $ZrOCl_2$ (0.048 g, 0.15 mmol) and sodium amide (0.005 g, 0.15 mmol) in THF (5 mL) was chosen as a model reaction (**Scheme-I**) and the results are presented in Table-1.

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF **3a**

Entry	Catalyst	Time (h)	Yield (%)[a]
1	$ZnCl_2$	6.0	70
2	$FeCl_3$	6.0	70
3	*p*-TsOH	7.0	80
4	Nano-ZnO	2.5	91
5	L-Proline	6.0	70
6	$SnCl_2$	7.0	60
7	K10	5.0	50
8	$ZrOCl_2{\cdot}8H_2O$	0.5	95

[a]Yields of the isolated products.

When the model reaction was performed under a wide variety of catalysts including of $ZnCl_2$, $FeCl_3$, *p*-TsOH, nano ZnO, L-proline, $SnCl_2$ and K10 (Table-1) the reaction took a longer time with moderate yield of the product. Interestingly, when the same reaction was carried out in the presence of $ZrOCl_2$/sodium amide it led to yield the desired product in 95% yield in 30 min only (Table-1, entry 8). To get the optimum concentration of catalyst, the model reaction investigated at 0, 5, 10, 15 and 20 mol% of $ZrOCl_2$/sodium amide (Table-2, entries 1, 2, 3, 4, 5). The yield product was obtained in 10%, 65%, 80%, 95%, and 95%, respectively. This indicates that 15 mol% of $ZrOCl_2$/sodium amide is sufficient for the best result.

TABLE-2
OPTIMIZATION OF THE CONCENTRATION OF CATALYST

Entry	$ZrOCl_2.8H_2O$ (mol %)	Yield (%)[a]
1	0	10
2	5	65
3	10	80
4	15	95
5	20	95

[a]Yields of the isolated products.
Reaction condition: Reaction of **1a** (1 mmol) with **2a** (1.2 mmol) in the presence of $ZrOCl_2$ (0.048 g, 0.15 mmol), and sodium amide (0.005 g, 0.15 mmol) in THF (5 mL) at room temperature.

During the optimization of reaction condition, the effect of temperature was monitored at 25 ºC and chosen as an optimum temperature. Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 25 ºC did slow down the reaction rate (Table-3).

TABLE-3
EFFECT OF TEMPERATURE ON THE REACTION

Entry	Temperature (°C)	Yield (%)[a]
1	0	40
2	5	50
3	10	55
4	15	67
5	20	85
6	25	95
7	30	95
8	35	90

[a]Yields of the isolated products.
Reaction condition: Reaction of **1a** (1 mmol) with **2a** (1.2 mmol) in the presence of $ZrOCl_2$ (0.048 g, 0.15 mmol), and sodium amide (0.005 g, 0.15 mmol) in THF (5 mL) at room temperature.

Various solvents were also screened to test their efficiency at 25 ºC and the results are summarized in Table-4. When the condensation carried out under solvent free condition. The yield was not high, because the reaction mixture could not stirred well (Table-4, entry 1). In order to improve the yield, water as a solvent was chosen (Table-4, entry 2), however, the product was obtained in trace amount only. In other solvents like ethanol, methanol, chloroform, acetonitrile and dichloromethane (Table-4, entries 3, 4, 5, 6, 7), the reaction took a longer time with moderate yield of the product. However, the model reaction was carried out in dry tetrahydrofuran (Table-4, entry 8) there was significant increase in the yield of the product in a shorter time period. Therefore, the best results were obtained from the reaction of compound **1a** (1 mmol) with compound **2a** (1.2

TABLE-4
SCREENING OF VARIOUS SOLVENTS

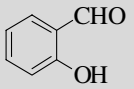
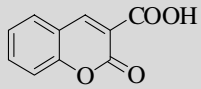
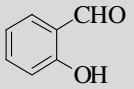
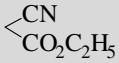
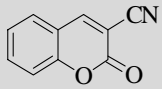
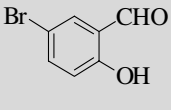
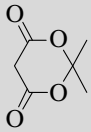
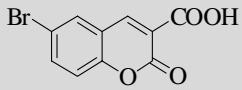
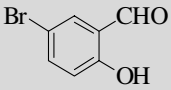
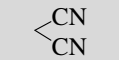
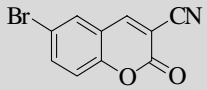
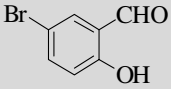
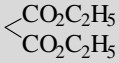
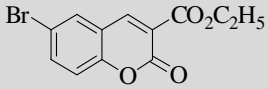
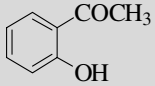
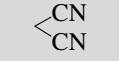
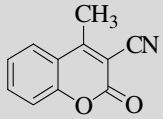
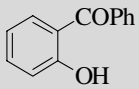
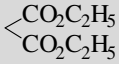
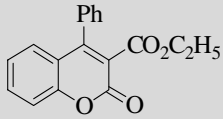
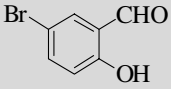
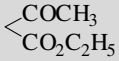
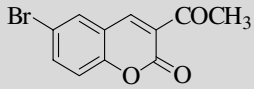
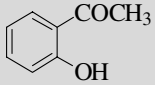
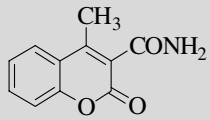
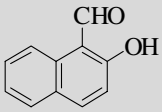
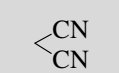
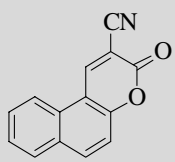
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	–	25	5	35
2	Water	80	3	40
3	Ethanol	70	3	80
4	Methanol	60	3	80
5	Chloroform	60	3	65
6	Acetonitrile	70	3	60
7	Dichloromethane	35	4	60
8	Tetrahydrofuran (dry)	25	0.5	95

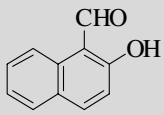
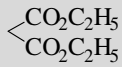
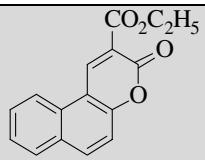
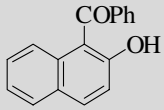
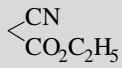
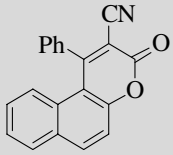
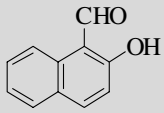
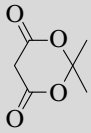
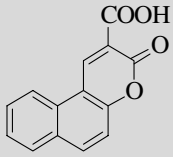
[a]Yields of the isolated products.
Reaction condition: Reaction of **1a** (1 mmol) with **2a** (1.2 mmol) in the presence of $ZrOCl_2$ (0.048 g, 0.15 mmol), and sodium amide (0.005 g, 0.15 mmol) in THF (5 mL).

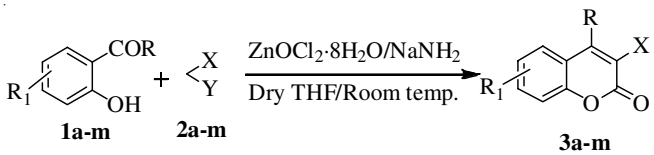
mmol) in the presence of 15 mol % zirconium(IV) oxychloride as catalyst and dry tetrahydrofuran solvent by stirring at room temperature.

To study the substrate scope, the optimized reaction conditions were applied to various aromatic aldehydes and ketones bearing electron releasing as well as electron withdrawing groups (**Scheme-II**) and the results are summarized in Table-5. It is found that aromatic aldehydes were more reactive and produces corresponding chromen-2-one derivatives than the ketone in good yield. Reaction of malononitrile with salicylaldehyde bearing a strong electron withdrawing group at *para* position of aldehyde and strong electron releasing group at *para* position of hydroxyl took place smoothly (Table-5, entry 18-20). Reaction with Meldrum′s acid required less time to

TABLE-5
SYNTHESIS OF VARIOUS CHROMEN-2-ONES

Entry	Substrates 1	Substrates 2	Product 3	Yield (%)
1				95
2				98
3				92
4				90
5				88
6				90
7				91
8				80
9				88
10				85

11				84
12				90
13				91



Scheme-II: Synthesis of chromen-2-one derivatives (**3a-m**)

complete the conversion compared to other active methylenes. It was observed that yields obtained from malononitrile and ethyl acetoacetate were less than those obtained with ethyl cyanoacetate and diethyl malonate, respectively (Table-5, entry 5-6, 10). However, in the most cases the products were isolated either by simple aqueous workup or purified by column chromatography.

Conclusion

In conclusion, an expedient, simple and improved protocol for the synthesis of chromen-2-one derivatives from the condensation of salicylaldehydes with various active methylene compounds using zirconium (IV) oxychloride as catalyst was developed. This efficient and clean protocol offers advantages in terms of simplicity, mild reaction conditions, easy workup, high product yields, short reaction times and high atom economy.

ACKNOWLEDGEMENTS

This work was supported by the Dean of Scientific Research, King Khalid University for the financial support is greatly appreciated for the General Research Project under grant number [R.G.P2/83/41]. The authors are thankful to Dean of Scientific Research, King Khalid University and the College of Pharmacy, Department of Pharmaceutical Chemistry for providing facilities to carry out the research work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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