A Rapid, Simple and Efficient Synthesis of 4*H*-chromene-3-carboxylates

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Abstract:
In this course of synthetic program, we report an efficient and ecofriendly synthetic method to synthesize substituted 4H-chromene-3-carboxylate derivatives. We utilize Dimedone as a building block and methyl isobutyryl acetate along with substituted aldehydes, and ethanol as a solvent to achieve desired product with excellent yield. The structures of all the newly synthesized compounds are elucidated by various spectroscopic techniques like FT-IR, mass spectra, ^{1}H NMR and elemental analysis.

Keywords: *4H-chromene-3carboxylates, dimedone, isobutyryl acetate, spectroscopic techniques*

1. Introduction

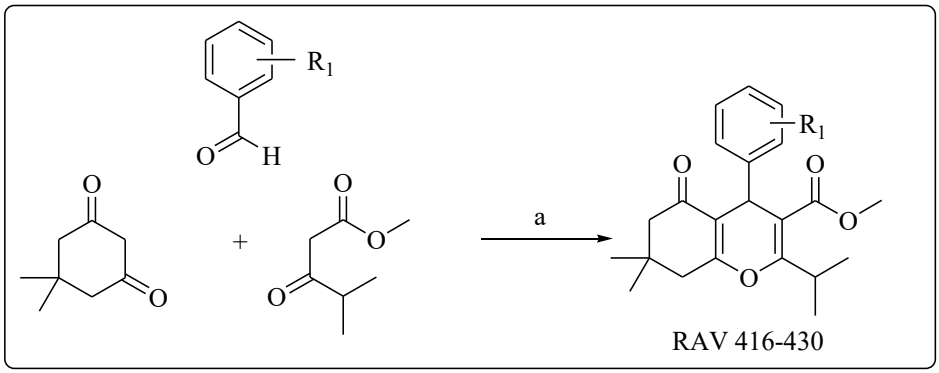
Numerous methods have been developed for the synthesis of substituted chromenone molecules. The two most important methods for the synthesis of chromenone derivatives are due to Perkin W. H.[1] and Pechmann V[2]. the naturally occurring chromenones[3] have been obtained either (i) by the closure of the lactonic ring with the necessary substitutents in the benzene nucleus, or (ii) by the introduction of the aliphatic acid and its anhydride on an *o*-hydroxy aldehyde with the intermediate formation of the *o*-hydroxy cinnamic acid (perkin's method) and the action of malic acid on phenols in the presence of sulphuric acid (Pechmann's method) have been very convenient methods for the synthesis of naturally occurring chromenones. The *o*-hydroxy cinnamic acids have also been prepared by other methods and them easily lactonize to chromenones.

The phenols have been used by Ruhemann S.[4] and Simonis H.[5] for the synthesis of chromone derivatives. Ruhemann condensed sodium phenolates with ethyl chloro fumarate, ethyl phenyl propiolate and ethyl *β*-chloro crotonate and treated the intermediate products, thus obtained, with con. H_2SO_4 or better with PCl_5 and $AlCl_3$ whereby the desired chromones were obtained.

The chromenone and its derivatives have attracted considerable interest to medicinal and synthetic organic chemists because of a wide range of biological activities. So it was thought worthwhile to design a synthetic program to achieve substituted 4*H*-chromene-3-carboxylate to explore pharmacological potential of these classes of compounds. Moreover, Chromenones bearing carboxylate functionality at C3, afford the possibility of further modifications through which, one can generate, a large number of pharmacologically important compounds. Given the biological significance of 2,3-substituted chromenones, several routes are reported in the literature for the synthesis of substituted chromenone *via* [4+2] annulations [45], [5+1] addition [36, 46], [4+1+1] addition reaction [47], or electrophilic substitution reactions over the preconstructed chromone motifs. However, these potentially useful methods have not been thoroughly explored. Furthermore, the existing few examples are rather limited in scope and suffer from several practical disadvantages such as extremely vigorous conditions or low yields [48]. Therefore synthetic program constisting simple

and effective method to synthesize substituted 4*H*-chromene-3-carboxylate via readily available starting material is expected.

Scheme 1: Synthesis of 4H-chromene-3-carboxylates



Reagents & Conditions: (a) EtOH, Stirring, 30-40 min.

2. Experimental

Melting points were determined in open glass capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by Iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR were determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Synthesis of methyl 4-(aryl)-5,6,7,8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4H-chromene-3-carboxylate (4a-j)

A mixture of the dimedone (0.01 mol), methyl isobutyl acetate (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in 8-10 mL of EtOH was stirred for 30 to 40 min. After completion of the reaction, the reaction mixture was filtered to give the solid products **(4a-j)**, which were recrystallized from ethanol.

Table 1: Physical data for synthesized compounds (4a-j)

Code	R_1	M.F.	M.W.	M.P. ºC	Yield %
4a	4-OCH_3	$C_{23}H_{29}O_5$	384	145-148	85
4b	4-CH_3	$C_{23}H_{29}O_4$	368	150-152	81
4c	4-F	$C_{22}H_{26}FO_4$	372	151-153	77
4d	4-Cl	$C_{22}H_{26}ClO_4$	388	152-154	83
4e	3-Cl	$C_{22}H_{26}ClO_4$	388	181-183	69
4f	4-Br	$C_{22}H_{26}BrO_4$	432	158-161	75
4g	2-Cl	$C_{22}H_{26}ClO_4$	388	167-168	80
4h	2-Br	$C_{22}H_{26}BrO_4$	432	140-143	75
4i	3,4-OCH_3	$C_{24}H_{31}O_6$	414	174-176	88
4j	2,5-OCH_3	$C_{24}H_{31}O_6$	414	119-121	73

Methyl 5, 6 ,7, 8-tetrahydro-2-isopropyl-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-chrom-ene-3-carboxylate (4a)

IR (cm^{-1}): 3066 (C-H stretching of aromatic ring), 2891 (C-H stretching of alkane), 1695 (C=O stretching of carbonyl group of ester), 1649 (C=O stretching of carbonyl group of cyclohexanone),

1267 (C-O-C- stretching of ester) 1070 (C-H in plane bending of aromatic ring), 840 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.85 (s, 3H, H_a), 1.03 (s, 3H, H_b), 1.13-1.15 (d, 3H, H_c), 1.20-1.22 (d, 3H, H_d), 1.97-2.01 (d, 1H, H_e), 2.15-2.19 (d, 1H, H_f), 2.41-2.42 (d, 1H, H_g), 3.54 (s, 3H, H_h), 3.68 (s, 3H, H_i), 4.08-4.15 (m, 1H, H_j), 4.84 (s, 1H, H_k), 6.68-6.72 (dd, 2H, $H_{ll'}$, J = 11.48 Hz), 7.06-7.10 (dd, 2H, $H_{mm'}$, J = 11.48 Hz); MS: *m/z* 384; Anal. Calcd. for $C_{23}H_{29}O_5$: C, 71.85; H, 7.34. Found: C, 71.72; H, 7.21%.

Methyl 5, 6 ,7, 8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4-p-tolyl-4H-chromene-3-carbo-xylate (4b)

IR (cm^{-1}): 3014 (C-H stretching of aromatic ring), 2872 (C-H stretching of alkane), 1695 (C=O stretching of carbonyl group of ester), 1649 (C=O stretching of carbonyl group of cyclohexanone), 1269 (C-O-C- stretching of ester), 1068 (C-H in plane bending of aromatic ring), 837 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.86 (s, 3H, H_a), 1.01 (s, 3H, H_b), 1.13-1.15 (d, 3H, H_c), 1.20-1.22 (d, 3H, H_d), 1.98-2.02 (d, 1H, H_e), 2.15-2.19 (d, 1H, H_f), 2.22 (s, 3H, H_g), 2.34 (s, 3H, H_h), 2.41-2.43 (d, 3H, H_i), 4.07-4.13 (m, 1H, H_j), 4.86 (s, 1H, H_k), 6.94-6.96 (d, 2H, $H_{ll'}$, J = 7.92 Hz), 7.05-7.07 (d, 2H, $H_{mm'}$, J = 8.04 Hz); MS: *m/z* 368; Anal. Calcd. for $C_{23}H_{29}O_4$: C, 74.97; H, 7.66. Found: C, 74.83; H, 7.53%.

Methyl 4-(4-fluorophenyl)-5, 6, 7, 8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4H-chrom-ene-3-carboxylate (4c)

IR (cm^{-1}): 3078 (C-H stretching of aromatic ring), 2874 (C-H stretching of alkane), 1707 (C=O stretching of carbonyl group of ester), 1647 (C=O stretching of carbonyl group of cyclohexanone), 1265 (C-O-C- stretching of ester), 1068 (C-H in plane bending of aromatic ring), 850 (C-H out of plane bending for 1,4-disubstituted aromatic ring); MS: *m/z* 372; Anal. Calcd. for $C_{22}H_{26}FO_4$: C, 70.95; H, 6.77. Found: C, 70.79; H, 6.59%.

Methyl4-(4-chlorophenyl)-5,6,7,8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4H-chrom-ene-3-carboxylate (4d)

IR (cm^{-1}): 2956 (C-H stretching of aromatic ring), 2877 (C-H stretching of alkane), 1710 (C=O stretching of carbonyl group of ester), 1647 (C=O stretching of carbonyl group of cyclohexanone), 1265 (C-O-C- stretching of ester), 1068 (C-H in plane bending of aromatic ring); MS: *m/z* 388; Anal. Calcd. for $C_{22}H_{26}ClO_4$: C, 67.95; H, 6.48. Found: C, 67.78; H, 6.30%.

Methyl4-(3-chlorophenyl)-5,6,7,8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4H-chrom-ene-3-carboxylate (4e)

IR (cm^{-1}): 2960 (C-H stretching of aromatic ring), 2873 (C-H stretching of alkane), 1714 (C=O stretching of carbonyl group of ester), 1643 (C=O stretching of carbonyl group of cyclohexanone), 1269 (C-O-C- stretching of ester), 1064 (C-H in plane bending of aromatic ring); MS: *m/z* 388; Anal. Calcd. for $C_{22}H_{26}ClO_4$: C, 67.95; H, 6.48. Found: C, 67.72; H, 6.28%.

Methyl4-(4-bromophenyl)-5,6,7,8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4H-chrom-ene-3-carboxylate (4f)

IR (cm^{-1}): 3076 (C-H stretching of aromatic ring), 2874 (C-H stretching of alkane), 1705 (C=O stretching of carbonyl group of ester), 1647 (C=O stretching of carbonyl group of cyclohexanone), 1267 (C-O-C- stretching of ester), 1068 (C-H in plane bending of aromatic ring), 840 (C-H out of plane bending for 1,4-disubstituted aromatic ring); MS: *m/z* 432; Anal. Calcd. for $C_{22}H_{26}BrO_4$: C, 60.98; H, 5.82. Found: C, 60.77; H, 5.71%.

Methyl4-(2-chlorophenyl)-5,6,7,8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4H-chrom-ene-3-carboxylate (4g)

IR (cm^{-1}): 3010 (C-H stretching of aromatic ring), 2876 (C-H stretching of alkane), 1719 (C=O stretching of carbonyl group of ester), 1653 (C=O stretching of carbonyl group of cyclohexanone), 1262 (C-O-C- stretching of ester), 1061 (C-H in plane bending of aromatic ring); MS: *m/z* 388; Anal. Calcd. for $C_{22}H_{26}ClO_4$: C, 67.95; H, 6.48. Found: C, 67.79; H, 6.21%.

Methyl4-(2-bromophenyl)-5,6,7,8-tetrahydro-2-isopropyl-7,7-dimethyl-5-oxo-4H-chrome-ne-3-carboxylate (4h)

IR (cm^{-1}): 3071 (C-H stretching of aromatic ring), 2879 (C-H stretching of alkane), 1709 (C=O stretching of carbonyl group of ester), 1641 (C=O stretching of carbonyl group of cyclohexanone), 1262 (C-O-C- stretching of ester), 1063 (C-H in plane bending of aromatic ring); MS: *m/z* 432; Anal. Calcd. for $C_{22}H_{26}BrO_4$: C, 60.98; H, 5.82. Found: C, 60.73; H, 5.60%.

Methyl 5,6,7,8-tetrahydro-2-isopropyl-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-4H-ch-romene-3-carboxylate (4i)

IR (cm^{-1}): 3074 (C-H stretching of aromatic ring), 2871 (C-H stretching of alkane), 1702 (C=O stretching of carbonyl group of ester), 1647 (C=O stretching of carbonyl group of cyclohexanone), 1261 (C-O-C- stretching of ester), 1068 (C-H in plane bending of aromatic ring); MS: *m/z* 414; Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.31; H, 7.15%.

Methyl5,6,7,8-tetrahydro-2-isopropyl-4-(2,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-4H-ch-romene-3-carboxylate (4j)

IR (cm^{-1}): 3069 (C-H stretching of aromatic ring), 2868 (C-H stretching of alkane), 1713 (C=O stretching of carbonyl group of ester), 1641 (C=O stretching of carbonyl group of cyclohexanone), 1259 (C-O-C- stretching of ester), 1070 (C-H in plane bending of aromatic ring); MS: *m/z* 414; Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.34; H, 7.12%.

3. Results and Discussion

The mechanism reaction occurs *via* an *in situ* initial formation of the arylidene of substituted ester, containing the electron-poor C=C double bond, from the Knoevenagel condensation between aromatic aldehydes and substituted ester by loss of water molecules. Finally, Michael addition of dimedone to the initially formed unsaturated intermediate, i.e. nucleophilic attack of hydroxyl moiety to the aryliedine moiety affords desired chromene-3-carboxylates.

Systematic fragmentation pattern was observed in mass spectral analysis. Molecular ion peak was observed in agreement with molecular weight of respective compound. For synthesized compounds, confirmatory bands for carbonyl groups were observed at 1600-1750 cm^{-1} which suggested formation of desired products. ^1H NMR spectra confirmed the structures of chromenes **(4a-j)** on the basis of following signals: a singlet for the methine proton of pyran ring at 4.70-5.20 δ ppm. The aromatic ring protons and J value were found to be in accordance with substitution pattern on phenyl ring.

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