

A Mild and Efficient Procedure for the Preparation of Chromone-2-carboxylates

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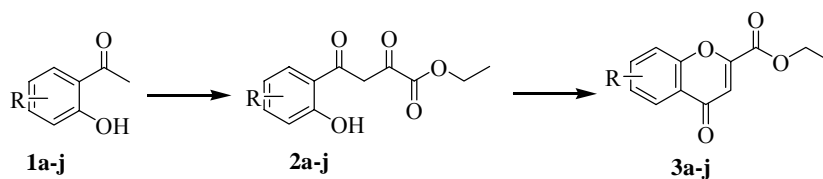
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Abstract: A mild and efficient procedure to build up various chromone-2-carboxylates was developed. Condensation of diverse 2-hydroxyacetophenones with *tert*-butyl oxalate in the presence of sodium ethoxide could be accomplished rapidly under mild condition. Cyclodehydration was carried out to achieve chromone-2-carboxylates in one-pot with impressive yield. Advantages over conventional methods with diethyl oxalate were observed in yield and reaction time.

Keywords: Chromone-2-carboxylates, *tert*-butyl ethyl oxalate, diethyl oxalate.

Chromone-2-carboxylates are widely used for the pharmacological activity of several of its derivatives¹. The general synthesis of such chromone derivatives includes two steps (**Scheme 1**): a Claisen condensation of dialkyl oxalate with 2-hydroxyacetophenones in the presence of NaH, NaOEt, or NaOMe; cyclodehydration of the alkyl 3-(2-hydroxyaryl)-3-oxopropanoates to obtain chromones under acid condition. The total yield of the two steps is quoted in a wide range of 60-85%², which depends on the structure of the substrate and the reaction conditions. In our investigation, attempts to reproduce these procedures gave inconsistent results with much lower yields, especially for halide-substituted 2-hydroxyacetophenones and hindered analogues. Furthermore, the reported oxalating reaction occurs in harsh condition (refluxing or long time)². The reported methods have limitation in the preparation of various chromones for further developments of their diverse function.

Scheme 1 Synthesis of chromone-2-carboxylates



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To improve the efficiency of building chromone-2-carboxylates with various substitutions on the phenyl ring, we introduced a *tert*-butyl group into the oxalation reagent. Thus *tert*-butyl ethyl oxalate³ was examined in comparison with diethyl oxalate. The condensation of 2-hydroxyacetophenones with *tert*-butyl ethyl oxalate occurred efficiently at room temperature, using 1 equiv. of 2-hydroxyacetophenone, 2 equiv. of *tert*-butyl ethyl oxalate and 2.0 equiv. of sodium ethoxide. According to the same examples with diethyl oxalate, the quantity of sodium ethoxide was increased to 3 equiv. in order to achieve a reasonable yield. Cyclodehydration was finished in a short time at refluxing in one-pot in the presence of concentrated HCl. The optimized mixed solvent of THF and DME (3:1) was used for the two-step procedure to obtain the desired product. A range of substituted 2-hydroxyacetophenones bearing electron-donating and electron-withdrawing groups, as well as sterically hindered groups, were screened. The results are shown in **Table 1**.

In all cases, far shorter oxalating time was needed and much better cyclodehydration yields were achieved for the 2-hydroxyacetophenones coupling with *tert*-butyl ethyl oxalate, compared with those using diethyl oxalate as oxalic source. Halide- and electron-donating group substituted hydroxyacetophenones (**1b-e**, **1g**, **1f**) exhibited an overwhelming preference for *tert*-butyl ethyl oxalate over diethyl oxalate in the condensation reactions. The bulky substituents on the aryl (**1h**, **1j**) or hindered hydroxyacetophenone (**1g**) did not retard the inclination. Taking *tert*-butyl ethyl oxalate as oxalic source, hydroxyacetophenones containing electron-withdrawing group (**1i**) resulted in a yield of 45%, but the difference of reactivity between the two oxalates still stays significant.

In summary, we have developed a mild and efficient procedure to build up various chromone-2-carboxylates. Condensation of diverse 2-hydroxyacetophenones with *tert*-butyl ethyl oxalate in the presence of sodium ethoxide could be accomplished rapidly under mild condition. Cyclodehydration was carried out to achieve chromone-2-carboxylates in one-pot in impressive yield. This optimized procedure may remove the limitation in the preparation of various chromones for further developments of their diverse function.

Procedure A for the preparation of chromone-2-carboxylates: To a mixed solution of NaOEt (2.0 equiv.) and *tert*-butyl ethyl oxalate (2.0 equiv.) in anhydrous THF under nitrogen at room temperature was added dropwise the solution of substituted 2-hydroxyacetophenone (1.0 equiv.) in anhydrous DME. The resulting mixture was stirred at room temperature for proper time. Solution of 10% HCl was added to adjust the pH of the system to about 5.0. Concentrated HCl solution (2.0 equiv.) was added before the reaction was heated to reflux for 20 min. Solvent was removed in vacuum. Water was added to the residue and extracted with ether. The organic layer was washed with saturated sodium carbonate solution and DI water, respectively, then dried. Solvent was removed in vacuum to get a solid. The residue was subject to silica gel chromatography to furnish the desired product.

Procedure B for the preparation of chromone-2-carboxylates: This procedure was similar to procedure A except for the use of 3 equiv. of NaOEt to the 2-hydroxy arylketone.

Table 1 Coupling of variously substituted 2-hydroxyacetophenone with *tert*-butyl ethyl oxalate or diethyl oxalate in the presence sodium ethoxide

Compd.	starting compound	Isolated yield ^a (%) / (oxalating reaction time)	
		<i>tert</i> -butyl methyl oxalate ^b	dimethyl oxalate ^c
1a		88/(45 min)	60/(10 h)
1b		96/(45 min)	45/(10 h)
1c		91/(40 min)	51/(10 h)
1d		89/(1 h)	26/(15 h)
1e		95/(30 min)	35/(15 h)
1f		95/(1 h)	59/(12 h)
1g		92/(20 min)	60/(10 h)
1h		84/(40 min)	40/(15 h)
1i		45/(1 h)	28/(15 h)
1j		55/(2 h)	29/(10 h)

a. Yields calculated after cyclodehydration.

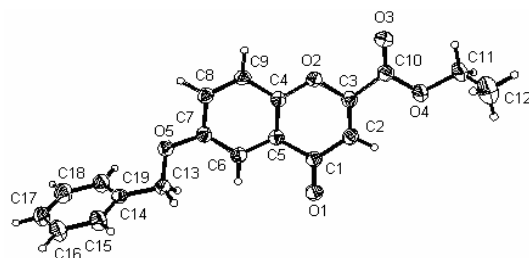
b. The preparation was achieved according to procedure A.

c. The preparation was achieved according to procedure B.

References and Notes

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 - Analytical data for compound **3 h**: Mp 117-118°C. ¹H NMR (CDCl₃, δ ppm): 1.43(t, 3H J=7.15Hz), 4.46(q, 2H, J=7.15Hz), 5.15(s, 2H), 7.11(s, 1H), 7.39(m, 5H), 7.46(d, 1H, J=7.28Hz), 7.57(d, 1H, J=9.21Hz), 7.65(d, 1H, J=3.02Hz). ¹³C NMR(CDCl₃, δ ppm): 178.2, 160.5, 156.5, 151.9, 150.9, 135.9, 128.6(×2), 128.2, 127.6(×2), 125.3, 125.1, 120.3, 113.8, 105.7, 70.6, 62.9, 14.0. Anal. Calcd. For C₁₉H₁₆O₅ : C, 70.36; H, 4.97. Found: C, 70.36; H, 5.04. HRMS: *m/z* calcd. For C₁₉H₁₆O₅: 324.0998; found: 324.1002.
 - The single crystal X-ray structure of **3 h**.



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