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A Novel Synthesis of 4*H*-Chromen-4-ones via Intramolecular Wittig Reaction

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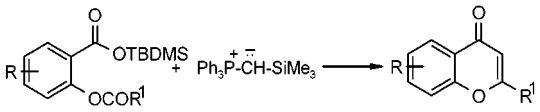
ABSTRACT



The acylphosphoranes formed in a sequential manner from the reaction of the silyl ester of *O*-acyl(aroyl)salicylic acids and (trimethylsilyl)-methylenetriphenylphosphorane undergo intramolecular Wittig cyclization on the ester carbonyl to afford the 4*H*-chromen-4-ones in good to excellent yields.

Chromones constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents.[1] As part of our ongoing program for developing methodologies using phosphacumulene[2] and their subsequent application to biologically useful compounds, the (trimethylsilyl)methylenetriphenylphosphorane is envisaged as a versatile reagent offering considerable opportunities for synthetic manipulations.[3] In general, chromones are synthesized by the cyclodehydration of 1-(*o*-hydroxyaryl)-1,3-diketone or equivalent intermediates catalyzed by strong acids or strong bases.[4] They have been also prepared on a large scale by the Allan−Robinson synthesis involving acylation, rearrangement, and subsequent cyclization.[5] In the Baker−Venkataraman synthesis,[6] internal claisen condensation of 2-aryloxy-1-acetylarenes is employed as a key step. While a variety of synthetic methodologies for chromones have been developed,[7] the literature describing novel one-pot cyclization methods based on a consecutive process is rather scarce. Also, most of these methods suffer either from harsh reaction conditions, poor substituent tolerance, or low chemical yields. We now report a new and simple route to 4*H*-chromen-4-ones via intramolecular ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane.

Salicylic acid or its substituted derivative **1** was converted into its *O*-acyl(aroyl) derivatives **2** by reaction with the corresponding acid chloride or anhydride. Compound **2** was

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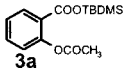
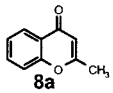
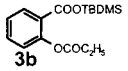
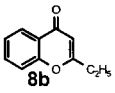
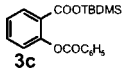
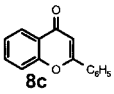
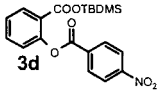
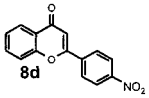
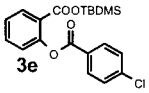
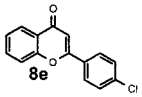
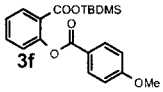
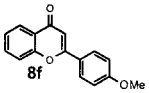
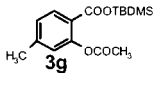
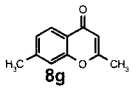
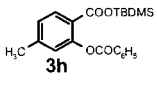
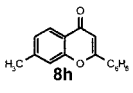
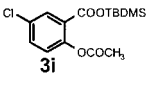
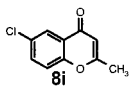
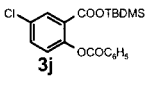
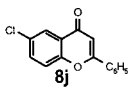
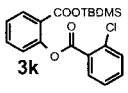
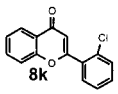
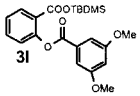
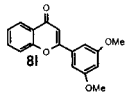
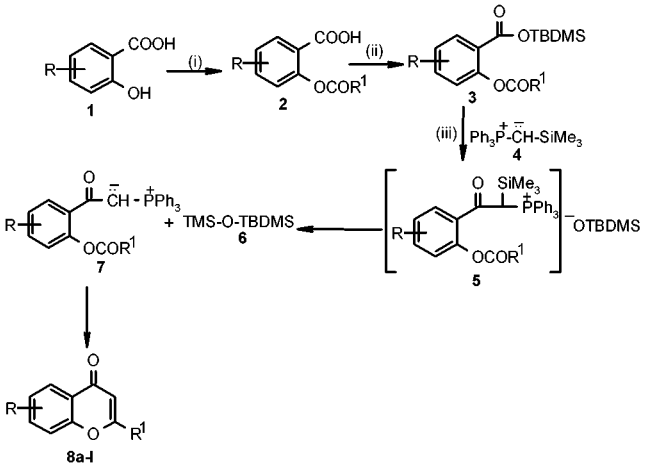
then treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole to furnish the corresponding silyl ester **3** in excellent yields. When a mixture of compound **3** and (trimethylsilyl)methylenetriphenylphosphorane[3] **4** was heated in refluxing THF, the desired chromones **8** were obtained in 55−80% yields (Table 1). The formation of product **8** could be explained by a sequence of reaction as depicted in Scheme 1. A possible reaction pathway for the conversion of **3** into **8** involves acylation of (trimethylsilyl)methylenetriphenylphosphorane **4** by **3** to the resulting phosphonium salt **5**. There is then migration of the trimethylsilyl group from C to O, followed by the extrusion of silyl ether **6** and ultimately leading to the acylphosphorane **7**, which subsequently undergoes ring closure via the intramolecular Wittig reaction on the ester carbonyl to afford the desired chromones **8**.

Table 1. One-Pot Synthesis of 4*H*-1-Chromen-4-ones **8** from **3** and **4** via Intramolecular Wittig Cyclization

Entry	Substrate	Product[a]	Reaction time(h)	Yield (%)
1	 **3a**	 **8a**	14	75
2	 **3b**	 **8b**	16	75
3	 **3c**	 **8c**	18	76
4	 **3d**	 **8d**	28	60
5	 **3e**	 **8e**	22	74
6	 **3f**	 **8f**	20	80
7	 **3g**	 **8g**	16	72
8	 **3h**	 **8h**	18	71
9	 **3i**	 **8i**	21	73
10	 **3j**	 **8j**	23	73
11	 **3k**	 **8k**	43	55
12	 **3l**	 **8l**	40	57

[a] All products were characterized by their satisfactory IR, ^{1}H NMR, and mass spectral data and also by comparison with literature data.

Scheme 1. Syntheses of Chromones **8**



Reagents and conditions: (i) $(R^1CO)_2O$, conc. sulfuric acid(5drops) or R^1COCl, aq.KOH, 0°C-room temp., 0.5h, 75-80%; (ii) TBDMS-Cl, imidazole (1.5 eq.), CH_2Cl_2, 0°C-room temp.,7-8h, 65-70%; (iii) 14-43h in THF, reflux, 55-80%.

To support our suggested mechanism, the intermediacy of compound **7** has been established by spectroscopic means. Although the treatment of **3b** with **4** in THF at room temperature did not show any progress of reaction, the extrusion of silyl ether **6** and formation of acylphosphorane **7** could be observed when the reaction was performed at higher temperature (50 °C). Interestingly, compound **7b** was found to be stable enough to be isolated and was further identified by its spectral data. Compound **7b**, on heating in refluxing THF, gave the desired chromone **8b**. Even though we could not isolate the phosphonium salt **5b**, presumably as a result of its fast rearrangement into the acylphosphorane, the above finding indicates that compound **7b**, which results from **5b** after the cleavage of silyl ether **6**, is one of the intermediates that undergoes subsequent intramolecular Wittig cyclization at reflux temperature to furnish the desired product **8b**.

As is apparent from Table 1, the intramolecular Wittig cyclization involving phosphorus ylide and ester carbonyl is general for the preparation of a variety of chromone derivatives. However, steric effect during the Wittig cyclization resulting from the substitution in aroyl group appears to be significant. Thus an *ortho*-substituent such as the chloro group in **3k** and *meta*-substituent such as the methoxy group

in **3l** have pronounced steric hindrance due to their close proximity to the carbonyl group, and hence a longer time is required to complete the reaction, affording relatively low yield of the products **8k** and **8l**, respectively (Table 1, entries 11 and 12). It may be mentioned that for the synthesis of 2-alkyl chromones, the utilization of a large excess of esters as acylating reagent is reported to be the only acceptable method.[8] Also, the conventional methods employing *o*-hydroxy acetophenone as starting material failed to give the substituted flavones, particularly with methoxy substituents.[9] Similarly, few reports employing palladium-catalyzed carbonylative coupling of 2-hydroxyaryliodides with ethynylarenes are known to give a mixture of flavones and aurones.[1,10] In this connection, the present methodology for the synthesis of chromones is noteworthy.

In summary, an efficient annulation protocol for a variety of chromones has been developed. To the best of our knowledge, this is the first report of chromone synthesis via intramolecular Wittig ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane. Currently studies are in progress to extend the synthetic potential of mono- and bis-silylated phosphorus ylides for the construction of a variety of carbocyclic and several other heterocyclic compounds.

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Supporting Information Available: Experimental procedures for **2**, **3**, **7b**, and **8** and the spectroscopic data for compounds **7b** and **8a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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