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An Efficient Microwave-Assisted Propylphosphonic Anhydride (T3P®)-Mediated One-Pot Chromone Synthesis via Enaminones

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Abstract An efficient synthesis of 4*H*-chromene-4-ones via enamino ketones, with cyclization by using T3P® under microwave heating is described. This is the first report for the synthesis of chromones by using T3P®. Significant features of this method include short reaction times and high-purity products.

Keywords cyclization, chromenones, enamino ketones, propylphosphonic anhydride, microwave heating, hydroxybenzophenones

Propylphosphonic anhydride (T3P®) has been widely used as a water scavenger and as a coupling reagent for the synthesis of amides.[1] It is available as an ethyl acetate solution, and is easy to handle. It has a broad functional-group tolerance and low toxicity, and its use results in easy work-up procedures.[2] Because of these features, applications continue to be developed for this reagent.[3] For instance, T3P® has been used in dehydration chemistry that involves the conversion of carboxylic acids and amides into nitriles, as well as in the syntheses of alkenes, isonitriles, and substituted heterocycles.[4] More recently, a convenient microwave-assisted, T3P®-mediated, one-pot pyrazolone synthesis has been reported.[5]

Chromone derivatives have a wide range of biological activities,[6] and they have been shown to be inhibitors of tyrosine and protein kinases[7,8] and to act as antiinflammatory,[9] antiviral,[10] antioxidant,[11] and antihypertensive agents.[10] Compounds containing the chromone moiety are also active as benzodiazepine receptors,[12] and on lipooxygenase and cyclooxygenase.[13] In addition, they have been shown to be anticancer agents,[14] and to activate the cystic fibrosis transmembrane conductance regulator.[15] The vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure.[16]

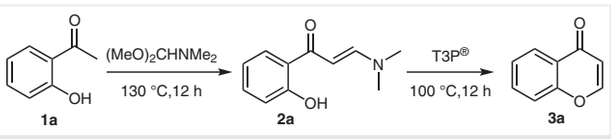
In general, chromones are synthesized under acidic or basic conditions.[17] One of the first methods for the synthesis of chromone, introduced by Heywang and Kostanecki, involved the decarboxylation of chromone-2-carboxylic acid.[18] The classical 2,3-disubstituted benzopyranone synthesis utilizes acidic conditions, proceeding through an intramolecular condensation of 3-aryl-1-(2-hydroxyphenyl)propane-1,3-dione derivatives. These 1,3-dione derivatives are usually obtained through a Bayer–Venkataraman rearrangement or through a Claisen ester condensation reaction. Most syntheses require acidic conditions in the final step. On the other hand, syntheses utilizing basic conditions require several hours to effect the ring closure, and are far less common than those under acidic conditions.

Enaminones (β-acylated enamines) are polyfunctional reagents that have been extensively used as building blocks for the synthesis of heterocycles;[19] they have been used for the preparation of chromone scaffolds, as well as for the construction of their 3-halogenated analogues.[20] Recently, an efficient synthesis of 3-substituted chromones via enaminones was reported.[21] Silver triflate was employed for the activation of the electrophile to react with enaminone. Similarly, 3-benzylated chromones have been prepared through a cyclobenzylation reaction between enaminones and benzyl bromide in the presence of sodium iodide.[22] Compared with the synthesis of 3-substituted chromones, there are few reports on the preparation of 2,3-unsubstituted chromones by using enaminones.[23] For example, TMSCl/DMF has been used for the cyclodeamination reaction of enaminone **2a**(see Scheme 1) to form chromone **3a**.[24] Engelhart and Aldrich reported that chromone **3a** was formed while they were screening various sulfamoylating reagents for the preparation of chromone-3-sulfonamide from enaminone **2a**.[25] However, the reported methods

involve use of harsh reaction conditions and elevated temperatures, so the development of new methods for the synthesis of 2,3-unsubstituted chromones is still required.

In our continuing efforts to develop novel synthetic methods for the synthesis of natural products and derivatives,[26] we needed to synthesize a number of chromone derivatives, and we surmised that T3P® might be used for the cyclization of enaminoacetophenones, suitably substituted with a hydroxy group, to prepare the chromones. Here, we report the synthesis of chromones by using T3P® under microwave irradiation. This is the first example of the use of T3P® as a deamination reagent for the synthesis of chromones.

Initially, the enamino ketone **2a** was prepared by the reaction of 1-(2-hydroxyphenyl)ethanone (**1a**) with *N*,*N*-dimethylformamide dimethyl acetal [(dimethoxymethyl)dimethylamine, $(MeO)_2CHNMe_2$] in refluxing toluene (Scheme 1). Compound **2a** was characterized by ^1H NMR and LC-MS analyses; in particular, the peak at δ = 8.2 ppm in the ^1H NMR spectrum was assigned to the olefinic proton.



Scheme 1 Preparation of chromones by using T3P®

The conversion of enamino ketone **2a** into chromone (4*H*-chromen-4-one; **3a**) in the presence of T3P® was taken as a model reaction. On treating enaminone **2a** in the presence of a 50% solution of T3P® in EtOAc (1.0 equiv) at room temperature for 24 hours, we are pleased to find that T3P® mediated the cyclization, resulting in a 25% conversion of **2a** into **3a** (Table 1, entry 2). Chromone (**3a**) was characterized by means of IR and ^1H and ^{13}C NMR spectroscopy, as well as by elemental analysis. The reaction was allowed to continue at room temperature as no byproducts were formed (as evidenced by LC-MS analysis), but even after 48 hours, there was no increase in product formation (entry 3). We therefore attempted to optimize the reaction by changing the reaction temperature (entries 4–6) and the solvent (entries 6–8), and by using microwave heating (entries 11–14).[27]

Performing the cyclization under microwave-heating conditions at 90 °C in the presence of T3P® (0.2 equiv) in ethyl acetate for ten minutes afforded a 65% yield of chromone (**3a**; Table 1, entry 13). When the amount of T3P® was increased to 1.0 equiv, the yield of **3a** increased to 92% (entry 14), but the use of an excess of T3P® under the same conditions led to a decrease in the yield (entry 15). Finally, to confirm that the ring-closing deamination was mediated by T3P®, a control experiment was conducted. As expected,

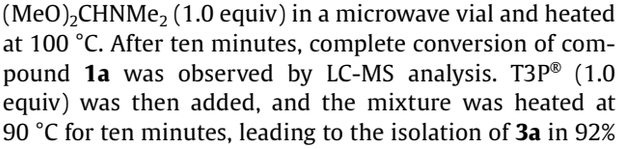
Table 1 Screening of Optimal Cyclization Conditions

Entry	Reaction conditions[a]	Yield[b] (%)
1	EtOAc, RT, 24 h	0
2	T3P® (1.0 equiv), EtOAc, RT, 24 h	25
3	T3P® (1.0 equiv), EtOAc, RT, 48 h	54
4	T3P® (1.0 equiv), EtOAc, 100 °C, 16 h	76
5	T3P® (2.0 equiv), EtOAc, 100 °C, 12 h	85
6	T3P® (1.0 equiv), DCE, 80 °C, 5 h	60
7	T3P® (1.0 equiv), toluene, RT, 16 h	30
8	T3P® (1.0 equiv), DMF, RT, 24 h	35
9	T3P® (1.0 equiv), 1,4-dioxane, 100 °C, 16 h	78
10	PPA(1.0 equiv), 100 °C, 16 h	74
11	PPA (1.0 equiv), 60 °C, 10 min, MW	63
12	EtOAc, 90 °C, 10 min, MW	0
13	T3P® (0.2 equiv), EtOAc, 60 °C, 10 min, MW	65
14	T3P® (1.0 equiv), EtOAc, 90 °C, 10 min, MW	92
15	T3P® (2.0 equiv), EtOAc, 90 °C, 10 min, MW	73

[a] Reaction conditions: **2a** (1.0 equiv), solvent (1 mL).
[b] Isolated yield.

heating compound **2a** in EtOAc at 100 °C without T3P® for ten minutes with microwave irradiation resulted in no conversion (entry 12).

After optimizing the reaction conditions for the cyclization of **2a** to obtain chromone (**3a**), we were interested in exploring a one-pot procedure for the synthesis of **3a** (Scheme 2). Compound **1a** was treated with $(MeO)_2CHNMe_2$ (1.0 equiv) in a microwave vial and heated at 100 °C. After ten minutes, complete conversion of compound **1a** was observed by LC-MS analysis. T3P® (1.0 equiv) was then added, and the mixture was heated at 90 °C for ten minutes, leading to the isolation of **3a** in 92% yield, a comparable yield with that of the two-step procedure.[28]



Scheme 2 One-pot synthesis of chromone using T3P®

To prove the generality of this method, the reactions of various aryl and hetaryl acetophenones were examined, and the results are summarized in Table 2. Higher yields were observed for substrates having electron-donating groups on the aromatic ring (**3g**, **3h**) compared with those with electron-withdrawing groups (**3d**, **3i**). Importantly, previously inaccessible naphthalene analogues and substituted pyrazole analogues were synthesized in good yields

(**3o**, **3p**),[29] and the acid-sensitive benzodioxole ring was not affected during the two-step one-pot procedure using T3P®. Acetophenones having bulky substituents (**3m**, **3o**) were also converted into the corresponding chromones in good yields.

Table 2 Synthesis of Substituted Chromones with T3P® under Microwave Irradiation

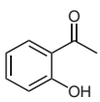
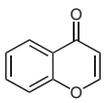
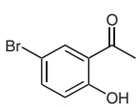
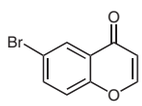
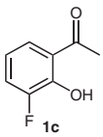
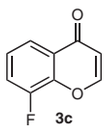
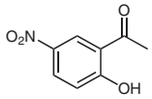
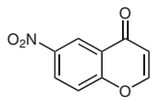
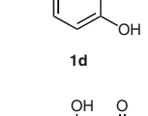
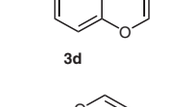
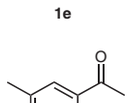
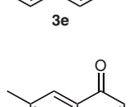
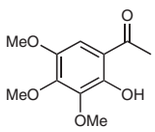
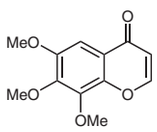
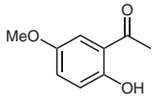
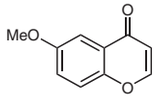
Entry	Acetophenone	Product	Yield (%)
1	 **1a**	 **3a**	92
2	 **1b**	 **3b**	90
3	 **1c**	 **3c**	80
4	 **1d**	 **3d**	75
5	 **1e**	 **3e**	92
6	 **1f**	 **3f**	70
7	 **1g**	 **3g**	89
8	 **1h**	 **3h**	95

Table 2 (continued)

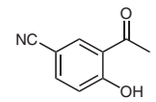
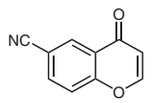
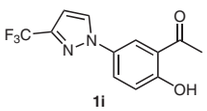
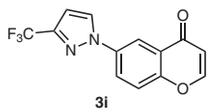
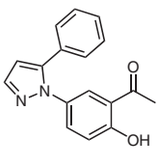
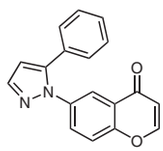
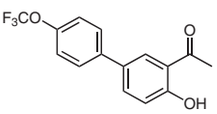
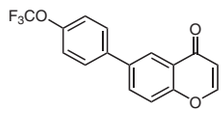
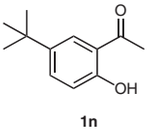
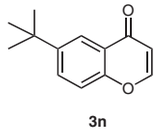
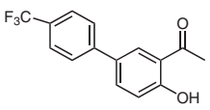
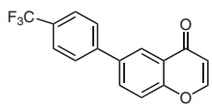
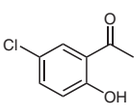
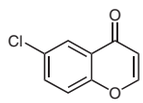
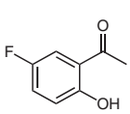
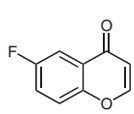
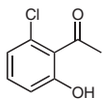
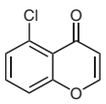
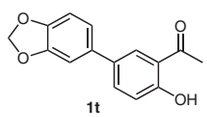
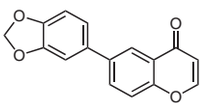
Entry	Acetophenone	Product	Yield (%)
9	 **1i**	 **3i**	85
10	 **1i**	 **3i**	85
11	 **1k**	 **3k**	91
12	**1l**	**3l**	90
13	 **1m**	 **3m**	87
14	 **1n**	 **3n**	90
15	 **1o**	 **3o**	90
16	**1p**	**3p**	83
17	 **1q**	 **3q**	87
18	 **1r**	 **3r**	80

Table 2 (continued)

Entry	Acetophenone	Product	Yield (%)
19	 1s	 3s	74
20	 1t	 3t	80

A one-step synthesis of chromone was also attempted, but when 1-(2-hydroxyphenyl)ethanone (**1a**) was treated with $(MeO)_2CHNMe_2$ in the presence of T3P® in ethyl acetate, and the mixture was heated to 110 °C for 16 hours or subjected to microwave irradiation, no product was formed, as evidenced by LC-MS analysis.

In summary, we have developed a novel, efficient and easily reproducible T3P®-mediated formation of chromones from readily available *o*-hydroxyacetophenones under microwave irradiation. This protocol offers a useful alternative to the strongly acidic conditions that are generally required for this conversion. The reaction conditions are simple and sufficiently mild to tolerate various functionalities that can serve as platforms for further functionalization of the chromone products. We believe that this methodology will find widespread application in the synthesis of chromone derivatives.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591898.

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(28) **6-(1,3-Benzodioxol-5-yl)-4*H*-chromen-4-one (3t); Typical Procedure**

A mixture of acetophenone derivative **1t** (100 mg, 0.39 mmol) and $(MeO)_2CHNMe_2$ (0.051 mL, 0.39 mmol) was introduced into a 2–5 mL pressure-resistant vial, and the mixture was subjected to microwave irradiation for 10 min at 100 °C. The mixture was then cooled to RT, a 50% solution of T3P® in EtOAc (0.25 mL, 0.39 mmol) was added, and the mixture was irradiated for a further 10 min at 90 °C until the reaction was complete (TLC; 30% EtOAc–PE). The crude mixture was diluted with EtOAc (10 mL) and washed with H_2O (5 mL) and brine (4 mL), then dried (Na_2SO_4). After filtration and removal of the solvent, the crude product was purified by column chromatography (silica gel, EtOAc–hexane) to give a white solid; yield: 83 mg (80%); mp 177–179 °C. FTIR (KBr): 3072, 1645, 1463, 1305, 1224, 1120, 1024, 921, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 2.4 Hz, 1 H), 7.87–7.81 (m, 2 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 7.13–7.12 (m, 2 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 6.37 (d, *J* = 6 Hz, 1 H), 6.01 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6, 155.6, 155.2, 148.3, 147.5, 138.1, 133.5, 132.3, 124.9, 123.1, 120.8, 118.6, 112.9, 108.7, 107.6, 101.3. MS (EI): *m/z* (%) = 267 $[M + 1]^+$ (100). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{10}O_4$: 267.0654; found: 267.0657.

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