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An efficient one-pot synthesis of coumarins mediated by propylphosphonic anhydride (T3P) via the Perkin condensation

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ABSTRACT

An efficient one-pot synthesis of coumarins mediated by T3P, a mild and low toxic peptide coupling agent, via the Perkin condensation has been demonstrated.

Coumarins and their derivatives are very important structural motifs that occur widely in natural products.[1] Their synthesis has attracted considerable attention from organic and medicinal chemists for many years as members of this family have wide applications in medicinal chemistry,[2] being known as anticancer,[3] antioxidants,[4] anti-HIV,[5] enzymatic inhibitors,[6] or vasorelaxants.[7] Besides the medicinal applications, coumarins have been used in fluorescent probes,[8] triplet sensitizers,[9] and cosmetic industries.[10]

Coumarins can be synthesized by one of such methods as the Witting reaction, Perkin reaction, Pechmann reaction as well as the Knoevenagel condensation.[11] The classical Perkin condensation is perhaps the most direct and simple method known for the preparation of substituted coumarins.[12] While this procedure is a suitable method, it suffers from drawbacks such as limited substrate scope, the use of strong acids and sometimes the necessity of multi-step reactions. In an attempt to improve on these procedures, Mashraqui et al. have described a convenient and single step alternative to the classical Perkin condensation to provide 3-substituted coumarins by using Mukaiyama esterification protocol.[13] Further optimization leading to practical methods having broad substrate and functional group tolerance is still essential and would extend the scope of coumarin synthesis.

Propylphosphonic anhydride (T3P) is a prevailing peptide coupling reagent having low toxicity.[14] Its versatility as a reagent in organic synthesis has generated innovative uses for this reagent beyond peptide synthesis.[15] There are quite a few examples, wherein, T3P is utilized in molecular rearrangements,[16] and dehydration chemistry.[17] Recently, T3P has been used as a reagent in the preparation of a range of functionalized heterocycles.[18] Herein, we report our results on the highly effective T3P mediated one-pot synthesis of functionalized coumarins via the Perkin condensation.

The preparation of **3a** from salicylaldehyde (**1a**) was chosen as a model reaction (Table 1). Accordingly, preliminary experiments were done in *n*-BuOAc with equimolar amounts of **1a**, cyanoacetic acid (**2a**), and T3P (50% solution in EtOAc) in the presence of 2.0 equiv of triethylamine (TEA) at room temperature (Table 1, entry 1). Under these conditions the reaction did not proceed beyond intermediate **4a**, and the mixture was then heated to 100 °C for 10 h to provide **3a** in 19% yield (Table 1, entry 2). Further raise in the reaction temperature (Table 1, entry 3) and amount of base (Table 1, entry 4) had no influence on the formation of **3a**. Interestingly, when 2.0 equiv of T3P were used (Table 1, entry 5), **3a** was obtained in 97% yield within 7 h of stirring at 100 °C. A comparable result was obtained in a shorter duration when the reaction was performed at 120 °C in the presence of 2.0 equiv of T3P, but could be limited to this substrate (Table 1, entry 6). Microwave irradiation did not prove beneficial for the preparation of **3a** (Table 1, entry 7) as it led to an incomplete reaction even after 2 h of irradiation at 150 °C. Further, formation of **3a** was not observed when the reaction was performed at 120 °C in the absence of T3P, instead, the Knoevenagel product **5a** was isolated in considerable amount (Table 1, entry 8).

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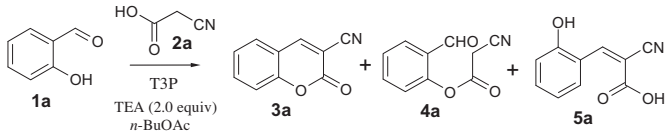
Table 1
Screening optimal reaction conditions



Entry[a]	T3P (mol %)	Time (h)	Temp (°C)	Yield (%)		
				3a	4a	5a
1	100	6	25	0	96	0
2	100	10	100	19	77	0
3	100	10	120	23	72	0
4[b]	100	10	100	21	76	0
5	200	7	100	97	0	0
6	200	5	120	97	0	0
7[c]	200	2	150	76	19	0
8[d]	0	10	120	0	0	61

[a] Reaction was monitored by LCMS.
[b] 3.0 equiv of TEA were used.
[c] Reaction was performed under MW irradiation.
[d] Reaction was performed in the absence of T3P.

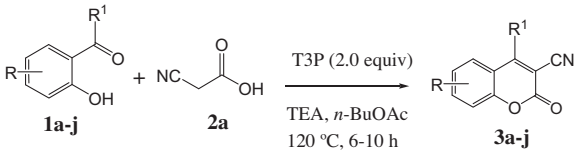
With optimal conditions in hand (Table 1, entry 5), various commercially accessible salicylaldehydes (**1a**–**f**) and 2-hydroxyarylketones (**1g**–**j**) were reacted with **2a** to evaluate the scope and limitations of T3P mediated coumarin synthesis (Table 2). As shown in Table 2, the conditions were compatible with various substituents on the aromatic ring and provided the respective coumarins in good yields. Electronic disparities between substrates had no influence on the rate of reaction or yield. While aldehydes were more reactive and produced the corresponding coumarins in 6–7 h (Table 2, entries 1–6), 7–10 h of heating was required for ketones to react to give the products in good yields (Table 2, entries 7–10). More importantly, this protocol could be applied to substrates having a labile functional group, such as **1j**, affording the corresponding coumarin **3j** without the loss of *N*-Boc group (Table 2, entry 10). Such novel coumarins are useful synthetic handles for further derivatization.

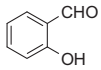
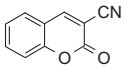
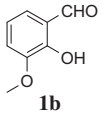
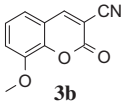
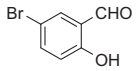
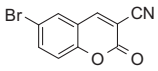
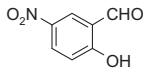
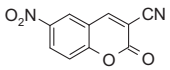
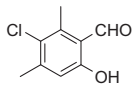
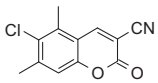
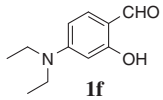
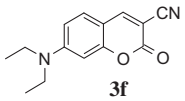
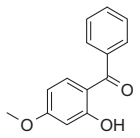
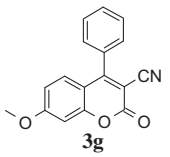
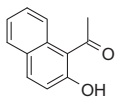
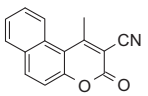
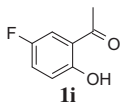
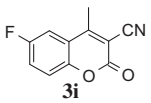
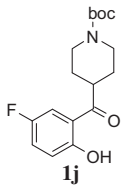
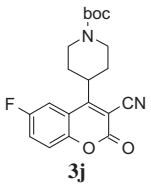
The substrate scope of the reaction was further extended to various substituted acetic acids (Table 3). Accordingly, **1b** was reacted with diverse carboxylic acids (**2b**–**j**) in the presence of T3P (2.0 equiv) under the optimized reaction conditions.[19] In general, as observed from Table 3, the reaction proceeded well for all acetic acids we tried, and gave good yields of respective coumarins. It is noteworthy that chloroacetic acid reacted well under the reaction conditions to give 3-chloro coumarin (**3l**) in moderate yield (Table 3, entry 3). Similarly, *N*-acetyl glycine produced the respective coumarin in 81% yield (Table 3, entry 6). However, the reaction did not tolerate the carboxamide functionality, instead, gave the corresponding nitrile following dehydration mediated by T3P[16a] (Table 3, entry 2). In addition to aryl and alkylsulfonyl acetic acids (Table 3, entries 4 and 5), arylacetic acids (Table 3, entries 7 and 8) as well reacted easily under the reaction conditions and gave excellent yields of corresponding 3-substituted coumarins. In most cases (Tables 2 and 3), the products were isolated by simple aqueous work-up, and purified by passing through a small plug of silica gel.

Trifluoromethyl substituted coumarins are known to be fluorescent markers.[20] Nevertheless, such applications are limited to 4-trifluoromethyl substituted coumarins due to their easy access.[21] Interestingly, the only two successful but low yielding preparations of 3-trifluoromethyl substituted coumarins reported so far involve the reaction of coumarins with bis(trifluoroacety1) peroxide[22] and that of coumarin-3-carboxylic acids with sulfur tetrafluoride.[23] As illustrated in Table 3, a convenient and high yielding synthesis of 3-trifluoromethyl substituted coumarins could be achieved by the reaction of 2-hydroxyarylcarbonyls with 3,3,3-trifluoropropionic acid (Table 3, entry 9).

In order to validate the position of T3P in coumarin synthesis, a control experiment was undertaken. Thus, **3p** was prepared via a stepwise procedure (Scheme 1). The reaction of **1b** with phenylacetic acid in the presence of T3P (1.0 equiv) and TEA (1.0 equiv) in *n*-BuOAc at room temperature for 4 h afforded the intermediate **4b** in 96% yield.[24] Subsequent heating of **4b** at 120 °C in the presence of

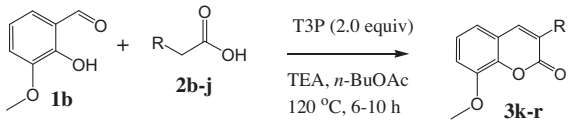
Table 2
T3P mediated coumarin synthesis

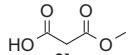
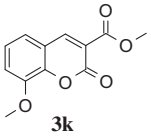
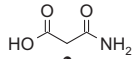
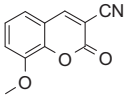
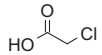
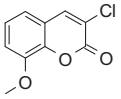
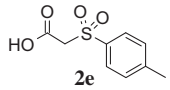
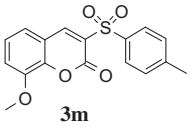
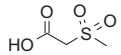
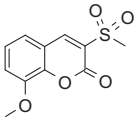
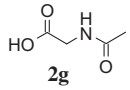
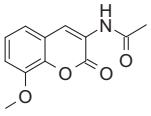
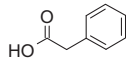
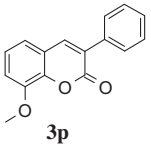
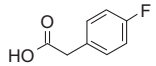
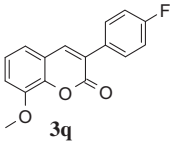
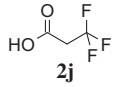
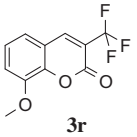


Entry	Substrate	Product	Yield[a] (%)
1	 1a	 3a	97
2	 1b	 3b	98
3	 1c	 3c	94
4	 1d	 3d	92
5	 1e	 3e	94
6	 1f	 3f	85
7	 1g	 3g	93
8	 1h	 3h	96
9	 1i	 3i	92
10	 1j	 3j	88

[a] Isolated yields.

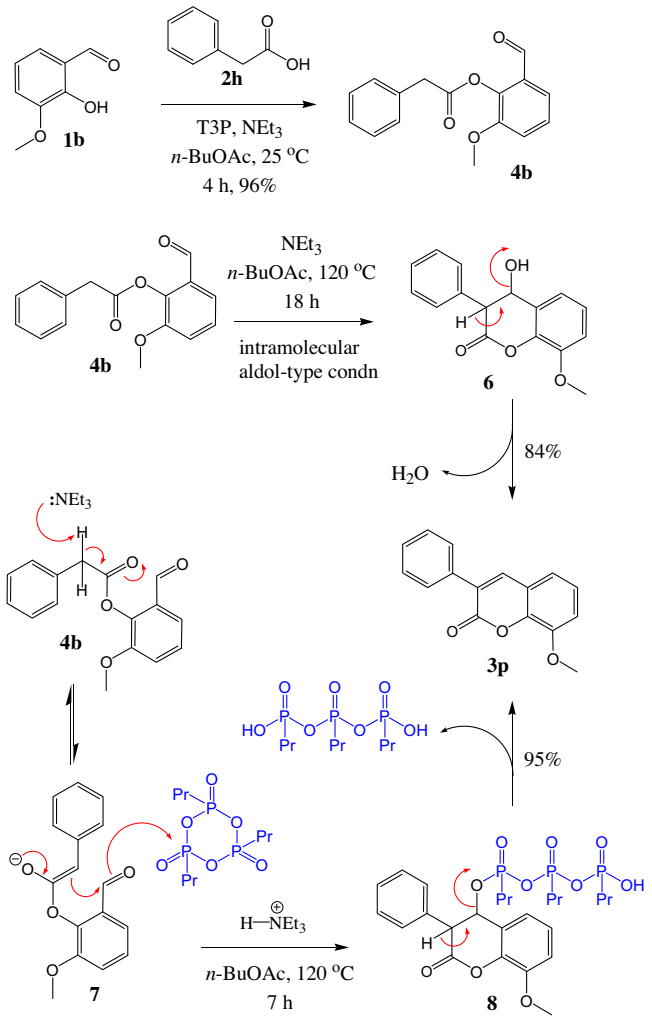
Table 3
T3P mediated coumarin synthesis: scope of acetic acids



Entry	Acid	Product	Yield[a] (%)
1	 2b	 3k	94
2	 2c	 3b	92[b]
3	 2d	 3l	44
4	 2e	 3m	89
5	 2f	 3n	94
6	 2g	 3o	81
7	 2h	 3p	95
8	 2i	 3q	88
9	 2j	 3r	91

[a] Isolated yields.
[b] Dehydration of amide was observed.

TEA (1.0 equiv) for 18 h afforded 84% conversion to **3p** via intramolecular aldol-type condensation as monitored by LC–MS (Scheme 1). However, when **4b** was heated at 120 °C in the presence of 1.0 equiv each of T3P and TEA, complete consumption of starting material was realized leading to the formation of **3p** in 95% yield within 7 h (Scheme 1). Accordingly, the formation of coumarin could be envisaged as a chronological coupling and cyclodehydration process mediated by T3P in one-pot via the



Scheme 1. Control experiment and probable mechanism of coumarin synthesis.

intermediates **4b, 7,** and **8** as shown in Scheme 1. The first equivalent of T3P could be involved in the generation of ester intermediate (**4b**) and subsequent cyclodehydration in the presence of another equivalent of T3P would lead to coumarin.[19]

In summary, a convenient and versatile method has been optimized for the synthesis of coumarins[25] via the Perkin condensation mediated by T3P, a mild and low toxic peptide coupling agent. The method not only employs readily accessible T3P, but also tolerates diverse 2-hydroxyarylcarbonyls and acetic acids giving access to distinctively substituted coumarins in good yields. Further, the reaction conditions are sufficiently mild that could tolerate sensitive functional groups and make the process a practical method for coumarin synthesis.

Supplementary data

Supplementary data (^{1}H NMR, ^{13}C NMR and LCMS report for **3a–r**, **4b** and ^{19}F NMR for **3i**, **3j**, **3q** and **3r**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.037.

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19. T3P has been known to regenerate in the reaction medium making it a green reagent or catalyst. Our previous studies involving T3P (see Ref. 16b,18e,16c,17b,18c) suggests that the regeneration is faster in the absence of an added base. Presence of a base such as triethylamine in the reaction mass could lead to further degradation of 'open' T3P which is produced in the reaction into *n*-propylphosphonic acid fragments. The need of 2.0 equiv of T3P for optimal yields in the coumarin synthesis could be attributed to its slow or no regeneration following the chronological coupling and cyclodehydration process in the basic reaction medium.
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24. Copies of ^{1}H NMR and ^{13}C NMR for compound **4b** are available in Supplementary data.
25. *T3P mediated synthesis of coumarins*: To a mixture of 2-hydroxyaryl aldehyde/ketone (1, 0.01 mol) and appropriate acetic acid (2, 0.01 mol) in *n*-BuOAc (10 mL) was added T3P (0.02 mol, 50% soln in EtOAc) followed by triethylamine (0.02 mol). The resulting reaction mixture was stirred at 120 °C for 6–10 h under conventional heating. When the reaction was completed (monitored by TLC), the mixture was cooled and washed with saturated $NaHCO_3$ solution (1 × 10 mL), water and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was passed through a small plug of silica to afford the coumarins (**3**) in good purity and yield.
Compound ***3c***: Yield 94%, yellow solid, mp 199.8–202.1 °C; IR (KBr): 3085, 2231, 1728, 1212 cm^{-1}; MS (ESI-APCI, negative mode) 251 $[M+2-H]^+$; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H = 7.50–7.47 (d, *J* = 8.8 Hz, 1H), 7.95–7.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 8.84 (s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ_C = 156.3, 153.1, 151.9, 137.4, 131.6, 119.2, 116.8, 114.2, 103.4.
Compound ***3o***: Yield 81%, white solid, mp 241.3–242.8 °C; IR (KBr): 3332, 1709, 1676, 1528, 1192 cm^{-1}; MS (ESI-APCI, negative mode) 232 $[M-H]^+$; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H = 2.15 (s, 3H), 3.89 (s, 3H), 7.18–7.16 (m, 1H), 7.27–7.20 (m, 2H), 8.57 (s, 1H), 9.76 (s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ_C = 170.2, 157.1, 146.2, 138.7, 124.8, 123.5, 120.1, 119.0, 111.9, 55.9, 23.9.