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A novel synthesis of coumarins employing triphenyl(α-carboxymethylene)-phosphorane imidazolide as a C-2 synthon

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ABSTRACT

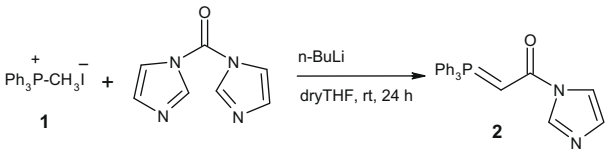
A novel one-pot synthesis of coumarins via intramolecular Wittig cyclization from the reaction of phenolic compounds containing *ortho*-carbonyl group and triphenyl(α-carboxymethylene)phosphorane imidazolide is described.

Coumarins 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] They also represent the core structure of several molecules of pharmaceutical importance. A number of coumarin derivatives have been isolated from natural sources, and their pharmacological and biochemical properties depend upon the pattern of substitutions. Coumarins have been reported to exhibit antibacterial, anticarcinogenic and analgesic activity.[2] In addition, they also serve as anti-oxidant, anti-inflammatory agents and HIV protease inhibitors.[2]

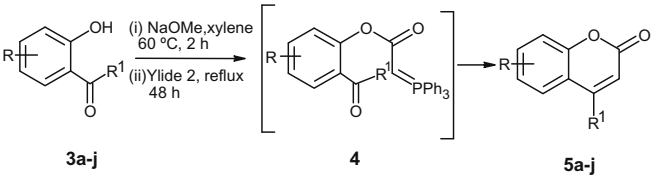
Because of the utmost significance of this heterocyclic system and their diverse pharmacological properties, many strategies for the synthesis of substituted coumarins have been developed.[3] Classical routes[4] to coumarins incorporate Pechmann, Knoevenagel, Perkin, Reformatsky and Wittig condensation reactions. However, most of these methods suffer from expensive catalyst, harsh reaction conditions, multistep synthesis or low chemical yield.

The intramolecular Wittig reaction has been extensively used as an excellent method for the C–C bond-forming process in the synthesis of natural products.[5] As part of our ongoing programme for developing a methodology employing phosphacumulene and (trimethylsilyl) methylene triphenyl phosphorane and their subsequent application to the biologically useful compounds,[6] triphenyl (α-carboxymethylene)phosphorane imidazolide **2**[7] is envisaged as a versatile reagent offering considerable opportunity for synthetic manipulation. The synthetic utility of **2** is hitherto unknown in the literature, and herein we report for the first time the application of triphenyl (α-carboxymethylene)phosphorane imidazolide as a C-2 synthon for the one-pot synthesis of biologically relevant coumarins. The generality of this concept has been established with several examples.

Ylide **2**[8] was prepared by the reaction of carbonyl diimidazole and methylenetriphenyl phosphorane generated from the corresponding phosphonium salt **1** as depicted in Scheme 1. Since the carbanion in ylide **2** is stabilized by the amide carbonyl, one would



Scheme 1. Synthesis of ylide **2**.



Scheme 2. One-pot synthesis of substituted coumarins.

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expect low reactivity of this ylide in a nucleophilic reaction. At the same time, imidazole being a good leaving group would facilitate reaction at the carbonyl centre. Thus, the hydroxy carbonyl compound **3** was first heated with NaOMe in xylene at 60 °C for 2 h, and then reacted with ylide **2** under reflux conditions to afford phosphoranes **4** which underwent intramolecular Wittig cyclization to furnish the desired coumarin **5** in good yields (Scheme 2).

Taking into consideration the low nucleophilicity of ylide **2,** it was necessary to use an equimolar amount of an additional base such as sodium methoxide to generate an alkoxy anion from hydroxy carbonyl compound **3**. The reaction is then followed by a nucleophilic attack of the alkoxy anion on the carbonyl of ylide **2,** ultimately leading to the formation of the intermediate **4** with the extrusion of imidazole as a by-product. The phosphorane **4** thus formed immediately undergoes ring closure via an intramolecular Wittig reaction to afford the desired coumarin **5** in good yields.

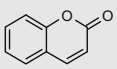
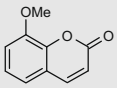
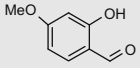
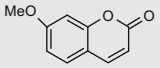
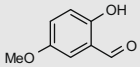
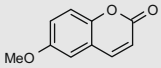
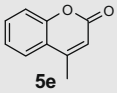
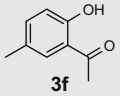
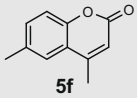
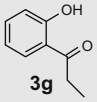
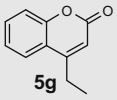
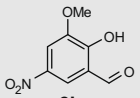
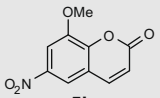
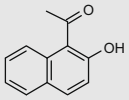
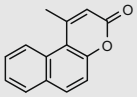
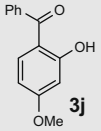
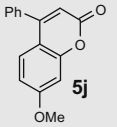
To support our mechanism, the intermediacy of **4** has been established by spectroscopic means. Although the treatment of **3e** with **2** in xylene in the presence of NaOMe at room temperature did not show any progress in the reaction, the extrusion of imidazole and the formation of phosphorane **4e** could be observed when the reaction was performed at reflux temperature. Interestingly, compound **4e**[9] was found to be stable enough to be isolated after 3 h of the reaction, and was further identified by its spectral data. Compound **4e** on subsequent heating in refluxing xylene for 48 h gave the desired coumarin **5e**. Thus, the above finding indicates that compound **4e**, which results from the extrusion of imidazole, is an intermediate that undergoes subsequent intramolecular Wittig cyclization at reflux temperature to furnish the desired product **5e**.

As is apparent from Table 1, the intramolecular Wittig cyclization involving phosphorus ylide and carbonyl is general for the preparation of a variety of coumarin derivatives. While the electron-donating or electron-withdrawing substituents in the aromatic rings (entries 2–4 and 8, respectively) do not have any considerable effect in terms of the yields of the products obtained, the steric effect during Wittig cyclization resulting from substitution in aromatic rings appears to be significant. Thus, propionyl and benzoyl groups (entries 7 and 10) have pronounced steric hindrance due to their close proximity to the carbonyl group, and hence a longer time (55 h) is required for completion of the reaction affording relatively low yields of the products, **5g** and **5j**, respectively. It may be pertinent to mention here that a few applications of transition-metal catalyzed reactions for coumarin synthesis have been reported, but most of these are of limited scope.[10,11] For example, palladium-catalyzed carbonylative annulation of internal alkynes by *o*-iodophenols is known to give varying proportions of two regioisomers of substituted coumarins.[12]

In this connection, the present methodology for the synthesis of coumarins is noteworthy.

In conclusion, an efficient annulation protocol for a variety of coumarins has been developed. To the best of our knowledge, this is the first report of coumarin synthesis via intramolecular Wittig carbonyl olefination using triphenyl (α-carboxymethylene) phosphorane as a C-2 synthon. Currently, work is in progress to extend the synthetic potential of ylide **2** for the construction of nitrogen and sulfur heterocycles as well.

Table 1
One-pot synthesis of substituted coumarins

Entry no.	Hydroxy carbonyl compounds	Products[a]	Yield (%)
1	 **3a**	 **5a**	85
2	 **3b**	 **5b**	70
3	 **3c**	 **5c**	72
4	 **3d**	 **5d**	70
5	 **3e**	 **5e**	75
6	 **3f**	 **5f**	72
7	 **3g**	 **5g**	62
8	 **3h**	 **5h**	70
9	 **3i**	 **5i**	75
10	 **3j**	 **5j**	60

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

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References and notes

1. (a) *Heterocyclic Chemistry*, 4th ed.; Joule, J. A., Mills, K., Eds.; Blackwell Science Ltd: Oxford, 2006; p 170; (b) Murrray, R. D. H. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 199; (c) Green, G. R.; Evans, J. M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II*, 1st ed.; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press Ltd: Oxford, 1984; Vol. 5, pp 469–500.
2. (a) Feuer, G. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; North-Holland: New York, 1974; (b) Deana, A. A.; Stokker, G. E.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J.; Russo, H. F., Jr.; Waston, L. S. *J. Med. Chem.* **1983**, *26*, 580; (c) Wenkert, E.; Buckwalter, B. L. *J. Am. Chem. Soc.* **1972**, *94*, 4367; (d) Kostova, I. *Curr. Med. Chem. Anticancer Agents* **2005**, *5*, 29.
3. For recent publications on coumarin synthesis, see: (a) Koenigs, P.; Neumann, O.; Hackeloer, K.; Kataeva, O.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2008**, 343 and references cited therein; (b) Ramesh, E.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 1812; (c) Ye, F.-F.; Gao, J.-R.; Sheng, W.-J.; Jia, J.-H. *Dyes Pigments* **2008**, *77*, 556 and references cited therein; (d) Trost, B. M.; Toste, F. D.;

Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518; (e) Oyamada, J.; Jia, C.; Fujiwara, Y.; Kitamura, T. *Chem. Lett.* **2002**, 380.

4. (a) Brufola, G.; Fringue, lli F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257; (b) Elnagdi, M. H.; Abdallah, S. O.; Ghoneim, K. M.; Ebied, E. M.; Kawser, N. K. *J. Chem. Res. Synop.* **1997**, 44; (c) Harayama, T.; Nakatsuka, K.; Katsuro, K.; Nishioka, H.; Murakami, K.; Fuji, M. *Chem. Express* **1993**, *8*, 245; (d) Narasimhan, N. S.; Mal, R. S.; Barve, M. V. *Synthesis* **1979**, 906; (e) Jones, G. *Org. React.* **1967**, *15*, 204.
5. For reviews on intramolecular Wittig reaction, see: (a) Heron, B. M. *Heterocycles* **1995**, *41*, 2357; (b) Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 3049.
6. (a) Kumar, P.; Pandey, B. *J. Chem. Soc., Chem. Commun.* **1992**, 1580; (b) Kumar, P.; Dinesh, C. U.; Pandey, B. *Tetrahedron Lett.* **1994**, *35*, 922; (c) Kumar, P.; Saravanan, K. *Tetrahedron* **1998**, *54*, 2161; (d) Kumar, P.; Bodas, M. S. *Org. Lett.* **2000**, *2*, 3821.
7. (a) Bestmann, H. J.; Sommer, N.; Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 270; (b) Staab, H. A.; Sommer, N. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 270.
8. *Preparation of ylide* **2**: To a solution of Wittig salt (10.0 g, 0.025 mol) in dry THF, *n*-BuLi (15% in hexane) (10.55 ml, 0.025 mol) was added under argon atmosphere and stirred for 2 h, and then carbonyldiimidazole (2.0 g, 0.0124 mol) was added at rt and stirred for 24 h. After completion of the reaction, the solvent was removed and the crude product was purified by recrystallization from dry CH_2Cl_2–THF (1:1.5) to give the ylide **2** (14.7 g, 80% yield) as a white solid, mp 185–187 °C; (lit.[7]mp 185 °C). I.R. ν_{max}/cm^{-1} ($CHCl_3$): 3460, 3063, 2934, 2365, 1613; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.12 (d, J = 13 Hz, 1H), 7.66–7.84 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 67.3, 117.6, 118.8, 128.8, 129.9, 130.0, 132.3, 132.6, 132.7, 134.7, 190.1; mass (ESI): 371 (277 + CH_3COONH_4 + H_2O).
9. *Synthesis of phosphorane* **4e**: To a solution of 2-hydroxy acetophenone (500 mg, 0.0037 mol) in dry xylene, NaOMe (0.2 g, 0.0037 mol) was added under argon atmosphere. After being stirred under heating for 2 h, ylide **2** (2.72 g, 0.0037 mol) was added and refluxed for 3 h. The progress of reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under rotavapour and the crude solid residue was purified by silica gel column chromatography using ethyl acetate and pet ether as eluent (98:2) to give the phosphorane **4e** in excellent yield, (1.45 g, 90% yield) as a red colour solid. Mp 180–182 °C; I.R. ν_{max}/cm^{-1} ($CHCl_3$): 1683, 1736, 3073; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.0 (s, 3H), 3.10 (d, J = 13 Hz, 1H),7.36–7.76 (m, 19H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.0, 60.3, 117.6, 119.3, 128.6, 128.9, 130.3, 130.6, 131.7 132.0, 132.3, 132.5, 133.0, 133.2, 135.2,176.2; MS (LC–MS): [M + H^+] 439, 301, 277, 267, 245, 239, 229, 223; Anal. Calcd for $C_{28}H_{23}O_3P$ (438.43): C, 76.70; H, 5.29. Found: C, 76.48; H, 5.58.
10. An, Z.-W.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1989**, *371*, C51.
11. (a) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5919; (b) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5923; (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305.
12. (a) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643; (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423.