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A New and Efficient Route to 4-Carboxymethylcoumarins Mediated by Vinyltriphenylphosphonium Salt

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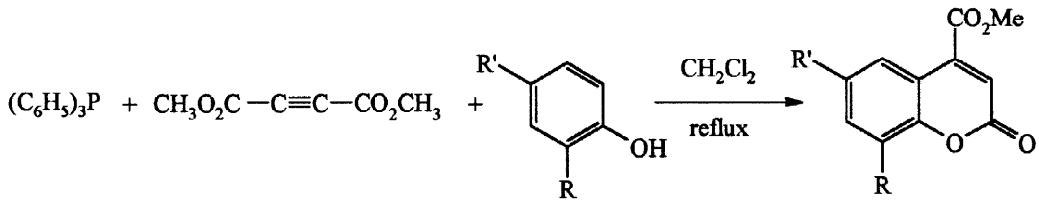
Abstract: Protonation of the reactive 1:1 intermediate produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate by substituted phenols leads to a vinyltriphenylphosphonium salt, which undergoes aromatic electrophilic substitution reaction with the phenolate conjugate base to produce 4-carboxymethylcoumarins in fairly high yields.

Coumarins are of interest because they constitute an important class of naturally occurring compounds, many of which exhibit useful and diverse biological activity.[1-3] In addition, other coumarins are of much interest as a result of their toxicity,[4] carcinogenicity,[5] and photodynamic effects.[6] The majority of the naturally occurring coumarins are highly oxygenated.[1] In this communication a direct, efficient, and operationally convenient approach to the synthesis of 4-carboxymethylcoumarins **2** based on the aromatic electrophilic substitution reaction between the conjugate base of substituted phenols **1** and a vinyltriphenylphosphonium salt will be presented. Thus, reaction of phenols **1** with dimethyl acetylenedicarboxylate (DMAD) in the presence of triphenylphosphine leads to the corresponding coumarins **2**.[7]



1 **2**

1,2	R	R'	%Yield of 2	1,2	R	R'	%Yield of 2
a	H	Me	65	h	H	F	83
b	H	*t*-Bu	72	i	H	CO_2Me	55
c	H	OMe	85	j	Cl	Cl	90
d	H	COMe	90	k	NO_2	NO_2	40
e	H	NO_2	70	l	Me	Cl	79
f	H	NHCOMe	75	m	OMe	CHO	60
g	H	CO_2H	70	n	OMe	CH_2-CH=CH_2	65

On the basis of the well established chemistry of trivalent phosphorus nucleophiles[8,9] it is reasonable to assume that coumarin **2** results[10] from the initial addition of triphenylphosphine to the acetylenic ester and a

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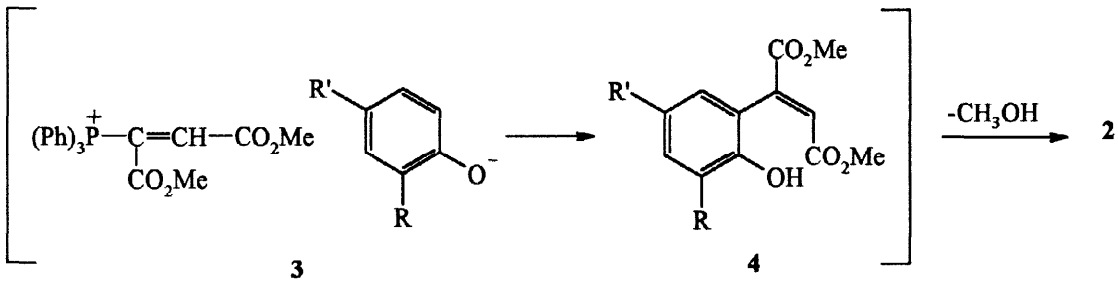
concomitant protonation of the reactive 1:1 adducts, followed by electrophilic attack of the vinyltriphenylphosphonium cation to the aromatic ring at *ortho* position relative to the strong activating group. The coumarin derivative **2** is presumably produced by intramolecular lactonization of **4**.



The structures of compounds **2a-n** were deduced from their elemental analyses and their ^{1}H and ^{13}C NMR data.[11] The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentations involved scission of the coumarin ring.

The present coumarin synthesis complements older established methods and offers significant advantages for the synthesis of coumarins having acid sensitive functional groups. In contrast, the well-known von Pechmann synthesis[12] entails strongly acidic conditions and frequently affords low and erratic yields.

Further investigation of the present method will be required to establish its utility and scope.

References and Notes

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4. Kadis, S., Ciegler, A. and Ajl, S. *Microb. Toxins*, **1972**, *7*, Chapter 1.
5. Ellis, G. P. and West, G. B. *Prog. Med. Chem.*, **1974**, *10*, 109.
6. Wells, P. and Morrison, H. *J. Am. Chem. Soc.*, **1975**, *97*, 154
7. Although, this work is not the first to have prepared coumarins from the reaction of a phenol with DMAD (Davies, S. G., Mobbs, B. E. and Goodwin, C. J. *J. Chem. Soc. Perkin Trans,1*, **1987**, 2597.), the yields are superior and the use of a vinyltriphenylphosphonium salt is unprecedented. We did not observe any of the corresponding chromone derivatives from these reactions by nucleophilic attack on the vinyltriphenylphosphonium salt *via* the phenolate oxygen itself. Thus, the present method appears to be selective for coumarins.
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9. Johnson, A. W. and Tebby, J. C. *J. Chem. Soc.*, **1961**, 2126. Caesar, J. C., Griffiths, D. V., Griffiths, P. A. and Tebby, J. C. *J.Chem. Soc. Perkin Trans. 1*, **1989**, 2425.
10. The typical process for the preparation of **2**: To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol) and **1** (2 mmol) in CH_2Cl_2 (8 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.284 g, 2 mmol) in CH_2Cl_2 (6 ml) at -5°C over 10 min. The reaction mixture was then refluxed for 120 hr. The solvent was removed under reduced pressure and the solid mass was purified by recrystalization from ethanol (95%).
11. Analytical and spectroscopic data (^{1}H and ^{13}C NMR, MS, IR) are in good agreement with the proposed structures.
12. Sethna, S. and Phadke, R. *Org. React. (N. Y.)*, **1953**, *7*, 1.