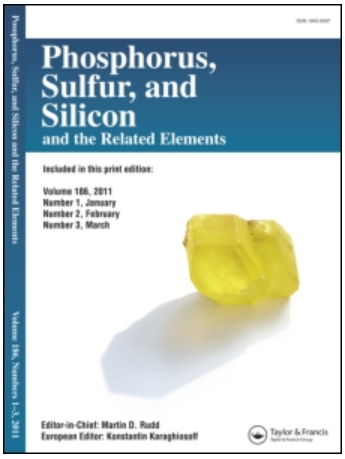


## Phosphorus, Sulfur, and Silicon and the Related Elements

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# A One Pot, Facile, and Convenient Synthesis of Some Coumarin Derivatives

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# A ONE POT, FACILE, AND CONVENIENT SYNTHESIS OF SOME COUMARIN DERIVATIVES

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*Protonation of the reactive 1:1 intermediate produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate by substituted phenols lead to vinyl triphenylphosphonium salt, which undergoes aromatic electrophilic substitution reaction with the phenolate conjugated base to produce coumarin derivatives.*

*Keywords:* Coumarin derivatives; dimethyl acetylenedicarboxylate (DMAD); triphenylphosphine

Coumarins are simple molecules, with most of the derivatives having been known for more than a century. Coumarins constitute an important class of natural products, many of which exhibit useful drug activity. Moreover, coumarins are a group of compounds that have important roles as food constituents, antioxidants, stabilizers, and immunodualatory substances, such as fluorescent markers for use in analysis, lasers, and in clinical use.[1–9] To date, naturally occurring coumarins have been isolated from over 800 species of plants and microorganisms, and more than 1,000 coumarin derivatives have been described.[10]

In view of the natural occurrence and useful range of biological activity associated with these coumarins, various methods have been developed for their synthesis.[11] The history of coumarin synthesis began in the mid-19th century with Perkin's discovery of the famous synthesis, which now bears his name.[12]

A variant of the Perkin reaction, in which a coumarin is formed under much milder conditions, utilizes malonic acid. Another variant,

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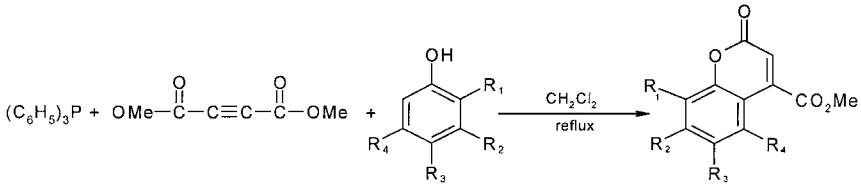
the Kostanecki-Robinson reaction,[13] can be used to prepare 3- and 4-substituted coumarins.

Fifteen years after Perkin discovered his coumarin synthesis, von Pechmann reported an alternative method.[14] We now report a new synthetic approach to coumarin derivatives which is a one-pot reaction, facile, and convenient.

This article presents a direct, efficient, and operationally convenient approach to the synthesis of some 4-carboxymethyl coumarins based on the aromatic electrophilic substitution reaction between the conjugated base of substituted phenols (**1**) and a vinyl triphenylphosphonium salt. Thus, reaction of phenols (**1**) with dimethyl acetylene dicarboxylate (DMAD) in the presence of triphenylphosphine leads to the corresponding coumarins (**2**) (Scheme 1). The compounds that have been prepared are summerized in Table I.




1 2

**SCHEME 1**

On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[15–17] it is reasonable to assume that compounds **2a–g** apparently result from initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the reactive 1:1 adduct, followed by electrophilic attack of the vinyl triphenylphosphonium cation at the aromatic ring in the ortho position relative

**TABLE I** List of Phenols **1**, and the Prepared Compounds **2**

| **1,2** | $R_1$ | $R_2$ | $R_3$ | $R_4$ | m.p. °C of 2 | % Yield of 2 |
|---|---|---|---|---|---|---|
| **a** | H | H | Cl | H | 104–105 | 92 |
| **b** | H | H | CHO | H | 116 | 85 |
| **c** | OMe | H | H | H | 134 | 70 |
| **d** | H | H | Br | H | 129–131 | 90 |
| **e** | H | COOMe | H | H | 120 | 80 |
| **f** | Cl | Cl | H | H | 146 | 95 |
| **g** | H | CH=C(H)–C(=O)–OMe | H | H | 177–178 | 82 |

**TABLE II** Proton and Carbon-13 NMR Data for Compounds **2a–g**

| Compound | $^1H/^{13}C$ | $\delta$ (ppm) ($CDCl_3$—$Me_4Si$) |
|---|---|---|
| **2a** | $^1H$ | 4.1 (3H, s, OMe), 7 (1H, s), 7.2 (1H, s), 7.5 (1H, dd), 8.4 (1H, dd) |
| | $^{13}C$ | 53.3 (OMe), 116.7 (CH), 116.4 (C), 120.6 (CH), 126.5 (CH), 130.2 (C), 132.3 (CH), 140.8 (C), 152.2 (C), 159.2 (C═O), 163.6 (C═O) |
| **2b** | $^1H$ | 4.15 (3H, s, OMe), 7.1 (1H, s), 7.45 (1H, d), 8.15 (1H, dd), 8.85 (1H, d), 10.1 (1H, s) |
| | $^{13}C$ | 53.3 (OMe), 115.9 (C), 116.08 (CH), 120.5 (CH), 130.4 (CH), 131.7 (CH), 132.767 (CH), 141 (C), 157.5 (C), 158.6 (C═O lacton), 163 (C═O ester), 190 (HC═O) |
| **2c** | $^1H$ | 3.85 (3H, s, OMe), 4.1 (3H, s, OMe), 6.9 (1H, s, CH vinilic), 7.2 (1H, t), 7.45 (1H, dd), 7.8 (1H, dd) |
| | $^{13}C$ | 53.2 (OMe), 56.3 (OMe), 114.2 (CH), 116.5 (C), 118 (CH), 119 (CH), 124.5 (CH), 142.8 (C), 144.1 (C), 147.4 (C), 159.4 (C═O), 164.3 (C═O) |
| **2d** | $^1H$ | 4 (3H, s, OMe), 6.9 (1H, s), 7.2 (1H, s), 7.7 (1H, dd), 8.45 (1H, d) |
| | $^{13}C$ | 53 (OMe), 117 (C), 116.5 (CH), 119.5 (CH), 125.5 (CH), 129.4 (C), 131.7 (CH), 139.6 (C), 151.4 (C), 158.3 (C═O), 162.9 (C═O) |
| **2e** | $^1H$ | 3.96, 4.06 (3H, s, OMe), 7 (1H, s), 7.4 (1H, s), 8.2 (1H, d), 9 (1H, d) |
| | $^{13}C$ | 52.3 (OMe), 53.2 (OMe), 115.3 (C), 117.2 (CH), 120 (CH), 128 (C), 131.3 (CH), 133 (CH), 141.5 (C), 156.6 (C), 158.8 (C), 164.2 (C═O), 165.3 (C═O) |
| **2f** | $^1H$ | 4.1 (3H, s, OMe), 7 (1H, s), 7.4 (1H, d), 8.2 (1H, d) |
| | $^{13}C$ | 53.3 (OMe), 115.4 (CH), 119.7 (CH), 125.1 (CH), 125.7 (CH), 137.3 (C), 141.3 (C), 180.8 (C), 188.2 (C), 163.5 (C═O lacton), 171.5 (C═O ester) |
| **2g** | $^1H$ | 3.8 (3H, s, OMe), 4 (3H, s, OMe), 6.4 (1H, s), 6.65 (1H, s), 7 (1H, s), 7.4 (1H, s), 7.7 (1H, dd), 8.4 (1H, d) |
| | $^{13}C$ | 52.5 ($CH_3$), 53.7 ($CH_3$), 116.2 (CH), 117 (CH), 121.3 (CH), 126 (CH), 127.5 (C), 129.5 (C), 130.2 (C), 133 (C), 137.4 (C), 142.3 (CH), 164.2 (C═O), 167.5 (C═O), 178.1 (C═O) |

to the strong activating group. The coumarin derivative **2** is presumably produced by intramolecular lactonization.

The structures of compounds **2a–f** were deduced from their elemental analyses and their IR, $^1H$, and $^{13}C$ NMR data (Table II). The mass spectra of these compounds displayed a molecular ion peak at appropriate m/e values. Initial fragmentations involved sission of the coumarin ring. Although, this work is not the first to have prepared coumarins from the reaction of a phenol, the yields are superior and the use of vinyl triphenyl phosphonium salt is unprecedented.

## EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected; elemental analyses were performed using a Heraeus CHN–O rapid analyzer; IR spectra were recorded on a Philips PU 9800 FT-IR spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were measured with JEOL EX-90 spectrometer at 90 and 22.6 MHz respectively. Mass spectra were recorded on a Finnigan-MaH8430 mass spectrometer operating at an ionization potential of 70 ev. Dimethyl acetylenedicarboxylate, substituted phenols **1**, and triphenylphosphine were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

### General Procedure

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 $-5^{\circ}C$ over 10 min. The reaction mixture was then refluxed for 100 h the solvent was removed under reduced pressure and the solid mass was purified by recrystallization from ethanol (95%).



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