Ph_3P Catalyzed One-Pot Synthesis of Heterocyclic Derivatives of Biological Active Curcumin

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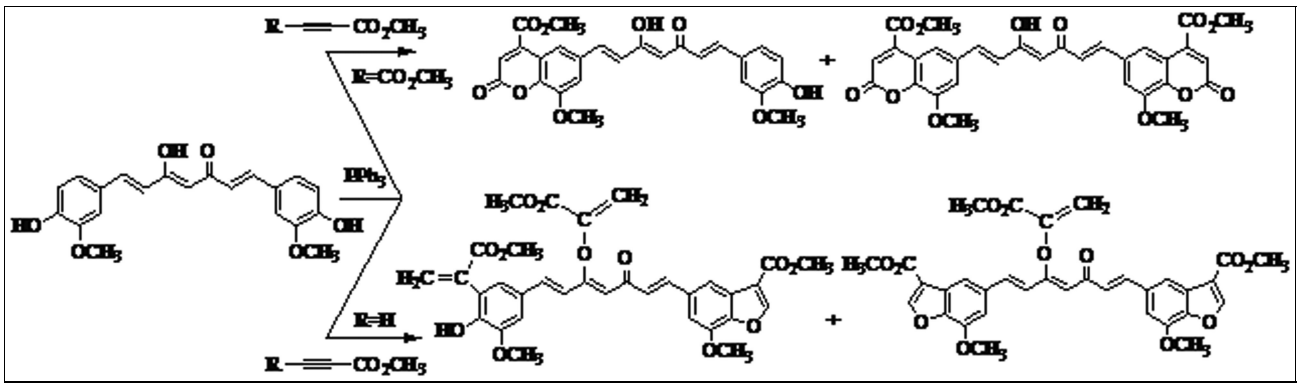

The natural product curcumin with different biological activity reacts smoothly with electron–deficient acetylenic compounds in the presence of Ph_3P to produce different new curcumin derivatives which is containing coumarin and furan functional fragments in moderate yields. The reaction based on the aromatic electrophilic substitution reaction between phenol moieties of curcumin and vinyltriphenylphosphonium salts under mild conditions.

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INTRODUCTION

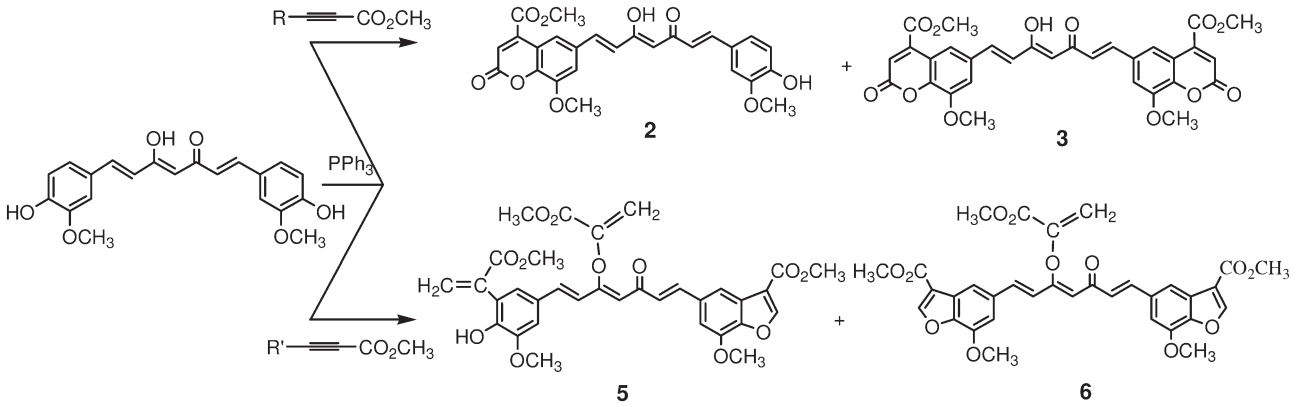
Curcumin as a turmeric yellow-orange pigment (*Curcuma longa*) [1–3], is used as a spice in South Asian cooking and a herbal medicine. It is known to exhibit different biological activities such as bilious regulating functions [4,5], reducing cholesterol level [6], anti-inflammatory [7–9], antiarthritic effects [10] and anti-oxidant properties [11]. In addition, curcumin inhibits the proliferation of a variety of tumor cells [12–14], and it has been shown to be active in both the prevention and treatment of Alzheimer's disease [15,16]. Despite the extensive investigations on the possible medicinal applications of curcumin have been done, information about the precise reactions mechanism of this compound is still scant [17]. The various activities of curcumin can be related to these factors: the ring substituents, the enone functionality, the presence of conjugated double bonds in the aliphatic chain, or the position of the phenolic hydroxyl groups [17]. So, curcumin analogs have been used in recent studies to examine the effective site for each property [13]. The present work reports an operationally convenient reaction between curcumin and π-deficient acetylenic reagents to show curcumin reactivity under neutral conditions. Furthermore, coumarin and furan moieties of the synthesized compounds have long been recognized for their broad spectrum of applications [18–21].

EXPERIMENTAL

Compounds **1**, **4**, and triphenylphosphine were obtained from Fluka (Buchs, Switzerland). Curcumin was purchased from sigma (St. louis, MO). Melting points were measured on an Electrothermal 9100 apparatus are uncorrected. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^1H and ^{13}C spectra were measured with a Bruker DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500 and 125.7 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure. To a magnetically stirred solution of triphenylphosphine (3.14 g, 12 mmol) and dimethoxycurcumin (1.47 g, 4 mmol) in 1,4-dioxane (10 mL) was added, dropwise, a mixture of dimethylacetylenedicarboxylate (1.44 mL, 12 mmol) or methylacetylene carboxylate (1.01 mL, 12 mmol) in 1,4-dioxane at −5°C over 5 min. The reaction mixture was then allowed to warm up to room temperature and refluxed for

Scheme 1. Synthesis of curcumin derivatives **2**, **3** and **5**, **6**.



72 h. The solvent was removed under reduced pressure, and the residue was purified by Column chromatography (silica gel, Merck 230–400 mesh) using 1:2:3 CH_2Cl_2/$CHCl_3$/*n*-hexane mixtures as eluent for compounds **2**, **3** and CH_2Cl_2/*n*-hexane 6: 1 mixture for compounds **5**, **6**.

6-(1E,3Z,6E)-3-Hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(methyl-8-methoxy-2-oxo-2H-chromene-4-carboxylate)-5-oxohepta-1,3,6-triene (2). Yellow powder, 0.65 g (34%), m.p. 271–273°C; IR (potassium bromide): 3470 (O—H), 1735, 1680 and 1670 (C=O). ^{1}H NMR (deuteriochloroform): δ 3.68, 3.73 and 3.82 (3s, 9H, 3 OCH_3), 5.87 (s, 1H, keto-enol CH), 6.84–7.05 (d, 4H, $^3J_{HH}$ = 15 Hz, 4 CH), 7.43–7.83 (m, 6H, 6 CH), 9.87 (s, 1H, PhOH), 10.06 (s, 1H, enol OH); ^{13}C NMR (deuteriochloroform): δ 54.83 (CO_2CH_3), 66.32 and 67.02 (2 OCH_3), 104.08 (keto-enol CH), 124.08–129.11 (Ar), 168.02 (ester C=O), 170.38 (lactone C=O), 185.12 (ketone C=O); ms: *m/z* 478 (M^+, 4), 401 (10), 327(11), 281(20), 207(70), 83 (100), 69 (70); *Anal*. Calcd. for $C_{26}H_{22}O_9$: C, 65.27; H, 4.60. Found: C, 65.2; H, 4.5.

6-(1E,3Z,6E)-3-Hydroxy-1,7-bis(methyl-8-methoxy-2-oxo-2H-chromene-4-carboxylate)-5-oxohepta-1,3,6-triene (3). Yellow crystals, 0.90 g (47%), m.p. 342–343°C; IR (potassium bromide): 1724, 1722, and 1675 (C=O). ^{1}H NMR (deuteriochloroform): δ 4.18, 4.20, 4.22 and 4.24 (4s, 12H, 4 OCH_3), 6.02 (s, 1H, keto-enol CH), 7.08–7.20 (bs, 4H, 4 CH), 7.52–7.54 (m, 3H, 3CH), 7.69–7.71 (m, 3H, 3 CH), 10.15 (s, 1H, enol OH); ^{13}C NMR (deuteriochloroform): δ 53.69 (2 CO_2CH_3), 68.16 (2OCH_3), 106.62 (keto-enol CH), 126.67–130.87 (Ar), 167.67 (2 ester C=O), 171.90 (2 lacton C=O), 187.63 (ketone C=O). ms: *m/z* 588 (M^+, 2), 503 (20), 458 (35), 352 (50), 281 (30), 207 (80), 83 (100), 69 (70). *Anal*. Calcd. for $C_{31}H_{24}O_{12}$: C, 63.26; H, 4.08. Found: C, 63.2; H, 4.0.

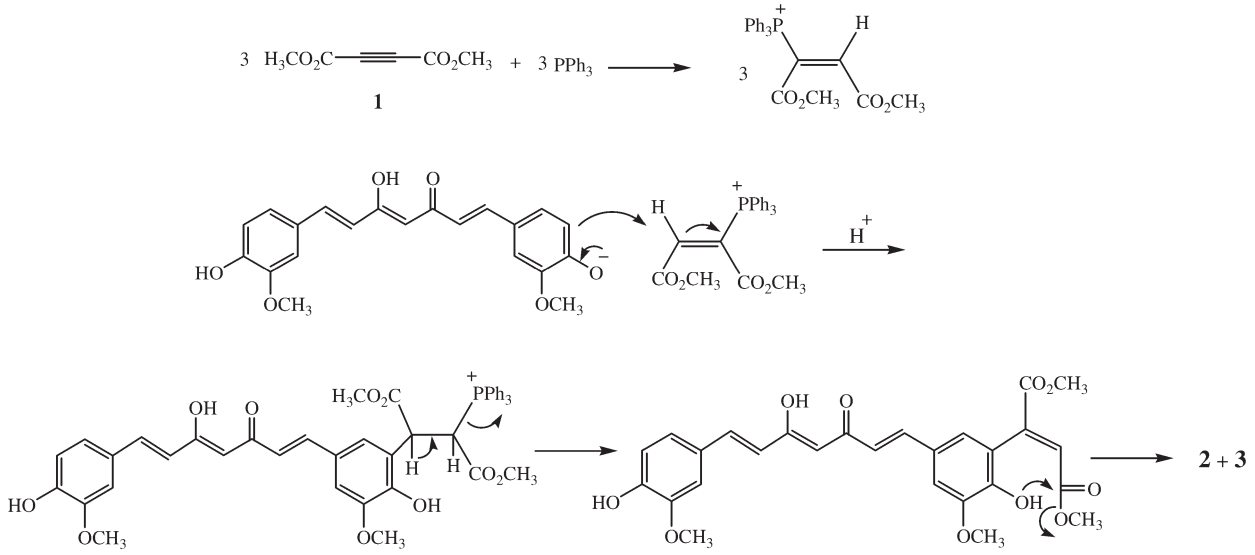
Methyl-2-((1E,3Z,6E)-1-(methyl-2-(2-hydroxy-3-methoxyphenyl) acrylat)-7-(methyl-7-methoxybenzofuran-3-carboxylate)-5-oxohepta-1,3,6-trien-3-yloxy) acrylate (5). Yellow powder, 0.90 g (36%), m.p. 323–325°C; IR (potassium bromide): 3323 (O—H), 1773, 1735, 1700, 1680 (C=O). ^{1}H NMR (deuterioaceton): δ 3.86, 3.88, 3.92, 3.95 and 3.96 (5 s, 15H, 5 OCH_3), 5.81 and 6.10 (d, 2H, $^2J_{HH}$ = 4Hz, O—C=CH_2), 6.90 (bs, 1H, CH), 6.97 and 7.04 (bs, 2H, C=CH2), 7.51–7.97 (m, 9H, 9 CH), 8.75 (s, 1H, PhOH), ^{13}C NMR (deuterioaceton): δ 51.26, 52.38, 52.63, 52.92 and 53.79 (5 OCH_3), 100.53 (CH), 111.57 and 115.60 (O—C=CH_2), 115.37 and 116.91 (C=CH_2), 123.84–134.60 (Ar), 160.28, 161.62 and 165.01 (ester C=O), 186.23 (ketone C=O). ms: *m/z* 618 (M^+, 2), 533 (20), 447 (10), 330 (20), 204 (20), 172 (65), 153 (50), 84 (100), 68 (60). *Anal*. Calcd for $C_{33}H_{30}O_{12}$: C, 64.08; H, 4.85. Found: C, 64.0; H, 4.8.

Methyl-2-((1E,3Z,6E)-1,7-(methyl-7-methoxybenzofuran-3-carboxylate)-5-oxohepta-1,3,6-trien-3-yloxy) acrylate (6). Yellow powder, 0.98 g (40%), m.p. 270–272°C; IR (potassium bromide): 1789, 1725 and 1660 (C=O). ^{1}H NMR (deuteriochloroform): δ 3.69, 3.70 and 3.71 (3 s, 15H, 5 OCH_3), 5.19 and 5.21 (bs, 2H, O—C=CH_2), 5.30 (bs, 1H, CH), 7.05–7.47(s, 10H, 10 CH), ^{13}C NMR (deuteriochloroform) δ 65.28, 68.17, and 69.17(5 OCH_3), 103.62 (CH), 111.07 and 111.12 (O—C=CH_2), 127.62–133.88 (Ar), 165.43 and 173.32 (ester C=O), 192.46 (ketone C=O). ms: *m/z* 616 (M^+, 2), 531 (10), 499 (10), 326 (20), 204 (30), 172 (70), 153 (50), 84 (100), 68 (50). *Anal*. Calcd for $C_{33}H_{28}O_{12}$: C, 64.29; H, 4.54. Found: C, 64. 2; H, 4.5.

Analyses and spectra. There have been many studies on the reactions between trivalent phosphorus nucleophiles and α-β-unsaturated carbonyl compounds in the presence of a proton-donor source such as a phenol or a CH-acid [22–24]. As curcumin has a relatively simple bis-phenolic structure, we could represent a route to the synthesis of heterocyclic curcumin derivatives *via* the reaction of its phenolic groups with π-deficient acetylenic reagents in the presence of Ph_3P at reflux temperature (Scheme 1). The structures of products **2**, **3** and **4**, **5** were deduced from their elemental analyses and their ^{1}H, ^{13}C NMR, IR, and mass-spectral data. These compounds displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentations involve complete loss of the side chains and scission of the heterocyclic ring units.

The vinyltriphenylphosphonium salt results from the initial addition of vinyltriphenylphosphine to the acetylenic compounds and subsequent protonation of the reactive 1:1 adduct by curcumin. Then, the positively charged ion is attacked by the conjugate base of the phenol moiety. The product is presumably produced by intramolecular lactonization of unsaturated diester **2** and **3** (Scheme 2). Compound **3** was isolated as

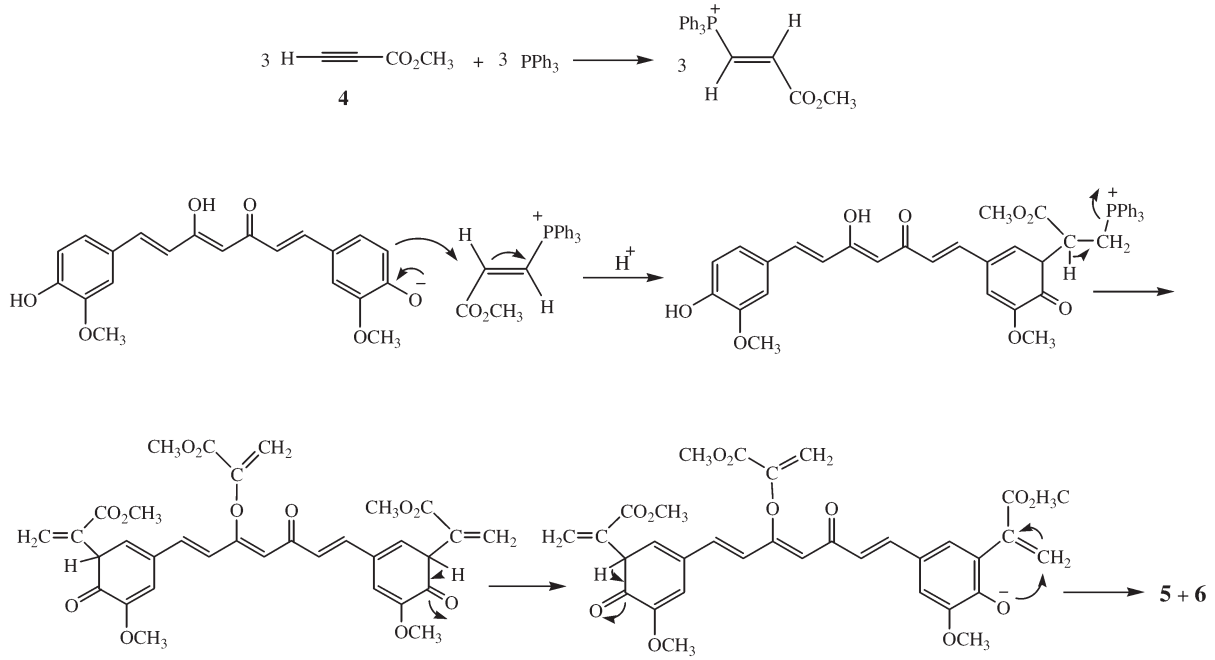
Scheme 2. Proposed mechanism for the synthesis of compounds **2** and **3**.



the major product in the reaction. The ^{1}H NMR spectrum of **2** displayed a characteristic six singlet line identified as three methoxy (δ = 3.68, 3.73 and 3.82) protons, one methyne proton of keto-enol tautomer (δ = 5.87). Phenolic and enol hydroxyl groups (δ = 9.87 and δ = 10.06) along with the aromatic protons, which appear at δ = 7.43–7.83. The ^{13}C NMR spectrum of **2** showed resonances in agreement with the proposed structures. Partial assignment of these resonances is given in Experimental section. The ^{1}H and ^{13}C NMR spectra of **3** are similar to those of **2** except for the phenolic —OH group, which has been omitted, and the number of ^{13}C NMR signals of product **3** is reduced because of the molecular symmetry. The structural assignments made on the basis of ^{1}H and ^{13}C NMR data of structure **2** and **3** were supported by measurement of their IR spectra. Of special interest is the carbonyl absorption at 1670–1730 cm^{-1}, and the stretching vibration of the hydroxyl groups are observed around 3400 cm^{-1}.

As curcumin exists in equilibrium between the diketo and keto-enol from which especially this phenomenon is strongly favored by intramolecular H-bonding, when we used methyl propiolate in aforementioned route, the products of this reaction (**5** and **6**) were differentiated. Compound **5** apparently resulted from the same mechanism but the keto-enol unit of curcumin treated with the less-hindered vinyltriphenylphosphonium salt, which underwent a conjugate addition then followed by elimination of triphenylphosphine. Furthermore, the furan ring closure

Scheme 3. Proposed mechanism for the synthesis of compounds **5** and **6**.



has been preffered to the lactonization (Scheme 3). Also, the amount of the product **6** was more than the compound **5**. The ^{1}H NMR spectrum of **5** exhibited some characteristic lines arising from five methoxy (δ = 3.86–3.96) protons, methyne (δ = 6.90) proton for keto-enol system, vinyl (δ = 5.81 and 6.10) protons with a doublet ($^2J_{HH}$ = 4 Hz) for enolate moiety and phenolic hydroxy group (δ = 8.75) proton with the aromatic protons, which appear at δ = 7.51–7.97. The ^{13}C NMR spectra of **5** displayed distinct signals for carbonyl groups at δ = 160.28, 161.62, 165.01 and at δ = 186.23 for another carbonyl group of keto-enol system. The sharp signal due to methoxy carbon were discernible at δ = 51.26–53.79. The ^{1}H and ^{13}C NMR of **6** are similar to those of **5** except for the absence of phenolic —OH group proton and the decrease of carbon signals number for it.

CONCLUSIONS

In conclusion, dimethoxy curcumin is a nontoxic, highly promising natural antioxidant compound having a wide spectrum of biological functions. However, few studies on its mechanism of action and chemical reactions have been carried out yet. So, we provide an acceptable method for the synthesis of stable heterocyclic product with variable functionalities from curcumin and acetylenedicarboxylates or alkyl propiolates in the presence of triphenylphosphine without any activation or modification. According to these reactions, the phenolic group is more reactive than the other sites of curcumin and the enol functionality of it only reacts with the less hindered substrate. On the other hand, the one-pot nature of the present procedure allows straightforward access to curcumin derivatives.

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