# A Facile Synthesis of Novel Cyclic Esters of γ-Keto Acid Derivatives by Heck Coupling Reaction

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 $\gamma$ -Keto acids and esters are highly useful compounds in organic synthesis, because a number of five-membered carbocycles and various other heterocycles can be readily obtained from them. A number of  $\gamma$ -keto acids derivatives have been synthesized with high yield by Heck coupling reaction with different alkenes using Pd(OAc)<sub>2</sub> as catalyst in dioxane solvent. The obtained products were characterized by elemental analysis, IR, proton NMR, and mass spectral studies.

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## **INTRODUCTION**

Among the class of oxygen heterocycles, benzoannelated butyrolactones (phthalides) are of considerable interest, because of their natural occurrence and wide range of biological activity [1–13]. They are active human CCR5 receptor antagonist, an important anti-HIV-1 target, which interferes with HIV entry into cells (fuscinarin) [2]. Some members of this group are cytotoxic [7-12] or antibacterial [13,14]. The 3-butylphthalide is a constituent in the Chinese folk medicine extracted from celery seed oil [15], reduces brain damage in mice [16], has been used for seasoning and flavoring purposes, shows anticonvulsant action [17], increases the duration of anesthesia [18], and exhibits cerebral anti-ischemic action [19-24]. The biological activity is strongly dependent on their configuration; hence, the synthesis of the asymmetric compounds of biological interest is highly desirable. The  $\gamma$ -keto acids and esters are highly useful compounds in organic synthesis, because a number of five-membered carbocycles such as cyclopentane-1,3-diones and cyclopentenones and various other heterocycles such as  $\gamma$ -lactones, butenolides,  $\gamma$ -lactams, and thiophenes were readily obtained from them. However, by this method, levulinic acid derivatives bearing substituents on their  $\alpha$ -position,  $\beta$ -position, and/ or  $\gamma$ -position were not easily convertible because of their methodological limitations.

Majority of the reported work on  $\gamma$ -keto acids were concerned to only the kinetic studies such as esterification of  $\gamma$ -keto acids and hydrolysis of the esters. In contrast, we have synthesized the new derivatives by introducing  $\gamma$ -keto acid halides by the Heck coupling reactions wherein the lability of halides are found to be useful to obtain the novel derivatives.

Over the past three decades, the Heck reaction has become one of the most fundamental metal-catalyzed C–C bond forming processes for the synthesis of complex molecules [25–35]. It has had a huge impact on organic synthesis despite the disadvantages that the overall coupling of the two fragments requires two discrete activation steps: (1) the formation of an aryl or vinyl halide and (2) the union of two reactants with Pd(0) catalyst.

#### **RESULTS AND DISCUSSION**

The starting materials 3-bromophthalide (**7a**) and *o*-benzoylbenzoic acid (**4**) required for the synthesis of the derivatives of  $\gamma$ -keto acids were prepared by the literature methods [36,37]. The 3-bromophthalide was found to be a suitable reagent, and its feasibility for the Heck reaction was studied. After obtaining good results, *o*-benzoylbenzoic acid (**4**) was cyclized using SOCl<sub>2</sub>, which produced 3-chloro-3-phenyl-2benzofuran-1(3*H*)-one (**6**) (Scheme 1).

The obtained pseudocyclic ester chloride was further coupled with alkenes using Pd(OAc)<sub>2</sub> catalyst in the presence of tri-*o*-tolylphosphine as ligand and TEA in dioxane solvent (Scheme 2). The yield of the products was low when the reaction was carried out in acetonitrile and DMF solvents, whereas in dioxane medium, it was increased to about 70% (Table 1). The obtained products were purified by column chromatography.

The IR spectra of the compounds were taken as KBr pellet, which exhibit absorption band in the ranges of

Scheme 1. Preparation of  $\gamma$ -keto acid chlorides.



1800–1780 cm<sup>-1</sup> and 1230–1220 cm<sup>-1</sup> due to C=O and C–O stretching, respectively. The appearance of a new absorption band at 1665 cm<sup>-1</sup> spectrum of the products is due to C=C str, and a band at 944 cm<sup>-1</sup> is due to –HC= str.

In the spectrum of the products, a band at  $643 \text{ cm}^{-1}$  is not obtained, which confirms the formation product with the elimination of halogen. The <sup>1</sup>H NMR spectra of the compounds were taken in DMSO- $d_6$  or CDCl<sub>3</sub>. The spectral data are compiled in Table 2. The <sup>1</sup>H NMR spectra of the compounds 9a-c showed a doublet in the range of  $\delta$  6–6.8 for the rigid proton attached to the lactone ring. The spectra of compounds 9d-f showed two doublets in the range of  $\delta$  5.70–6.55 due to the proton of Ar-HC=C- and Ar-C=CH-, respectively. All the aromatic protons appeared as multiplet between  $\delta$  7.3 and 8.1. Trans coupling of the alkenes has been confirmed by J coupling values. The mass spectra were analyzed in LC-MS, and the compounds showed [M+1] molecular ion peak that is in agreement with the mass of the product. The data are compiled in Table 2.

### CONCLUSION

The Heck reaction of phthalide derivatives has been studied for substituting alkene group by using Pd(OAc)<sub>2</sub> in dioxane and characterized by the elemental analysis, IR, <sup>1</sup>H NMR, and mass spectral studies. The obtained product can be used as effective intermediates by transformation to obtain substituted heterocyclic compounds.

Where

 Table 1

 Percentage yield and purity of 9a in different solvents.

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Solvent	% Yield	Purity*	
DMF Acetonitrile Dioxane	42 39 75	95.6 99.7 98.5	

\*HPLC purity after column purification

Hence, the recent study helps in obtaining new good intermediates.

#### EXPERIMENTAL

All the reagents and solvents were used as received from commercial suppliers, unless otherwise stated. All chemicals used for the synthesis were of analytical grade or laboratory grade and procured from HiMedia Laboratories Pvt. Ltd., India, Sigma Chemical Co., USA, E. Merck, Germany, and Sarabhai Merck Company, India, and specialty chemicals are procured as samples from the commercial suppliers (SD fine Chemicals, Mumbai, IN). All equipment was inspected visually for cleanliness and integrity before use. Mass spectra of the synthesized compounds were recorded on an Agilent 6320 Ion Trap mass spectrometer. IR spectra were recorded on a Shimadzu IR-470 spectrometer. <sup>1</sup>H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 MHz.

Analytical HPLC was performed on an Agilent 1200 system with UV detection at a wavelength of 230 nm using Inertsil 3V ODS  $5 \mu$ , 4.6 mm × 250 mm column, and eluting with the 0.1% *o*-phosphoric acid solution/acetonitrile (7:3). Melting point was determined using a Buchi melting point B-540 model and are uncorrected.

**Conversion of o-benzoylbenzoic acid (4) to acid chloride** (6). *o*-Benzoylbenzoic acid (4, 0.01 mol) was dissolved in dichloromethane (MDC) (20 mL) in a three-necked round bottom flask fitted withreflux condenser and CaCl<sub>2</sub> guard tube. About 5 mL of thionyl chloride was added and refluxed for 3 h. The reaction was monitored by TLC. After the completion of reaction, the excess thionyl chloride and the solvent were



Scheme 2. Heck coupling reaction of  $\gamma$ -keto acid halides.

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 Table 2

 Elemental analysis, <sup>1</sup>H NMR, and mass spectral data of synthesized compounds.

		Elemental analysis				
Sl. no.	Product	С	Н	<sup>1</sup> H NMR	m/z	mp (°C)
9a		81.08 (81.34)	5.23 (5.12)	δ 4.38 (t, 1H, –CH=C–Ar, <i>J</i> = 11.52), δ 5.98 (d, 1H, –C=CH–Ar), δ 7.2 (d, 1H, rigid H), δ 7.2–7.5 (m, 9H, Ar–H)	236.3	96–98
9b		66.01 (66.05)	4.65 (4.62)	δ 3.78 (s, 3H, –CH <sub>3</sub> ), δ 6.83 (m, 2H, –CH <b>=</b> CH–, <i>J</i> =11.68), δ 6.86 (d, 1H, rigid H), δ 7.2–7.8 (m, 4H, Ar–H)	218.2	83-85
9c	of of of o	67.21 (67.23)	5.18 (5.21)	δ 2.58 (s, 3H, –CH <sub>3</sub> ), δ 4.40 (d, 2H, –CH <sub>2</sub> –), δ 6.3–6.4 (m, 2H, – CH=CH–, <i>J</i> = 11.6), δ 6.58 (d, 1H, rigid H), δ 7.8–7.9 (m, 2H, Ar– H), δ 8.0–8.1 (d, 2H, Ar–H)	232.2	76–78
9d		84.53 (84.59)	5.21 (5.16)	δ 5.65 (d, 1H, -C=CH-Ar, <i>J</i> = 12.56), δ 6.58 (d, 1H, -CH=C-Ar), δ 7.2–8.2 (m, 14H, Ar-H)	312.4	119–121
9e		73.45 (73.46)	4.72 (4.79)	δ 2.47 (s, 3H, –CH <sub>3</sub> ), δ 6.45(s, 1H, –CH=C–COOMe, <i>J</i> = 12.68), δ 7.27 (d, 1H, –C=CH–COOMe), δ 7.3–8.0 (m, 9H, Ar–H)	294.3	105–107
9f		73.96 (74.01)	5.27 (5.23)	δ2.45 (s, 3H, -CH <sub>3</sub> ), δ4.52 (d, 2H, -CH <sub>2</sub> ), δ5.79 (d, 1H, - C=CH-CH <sub>2</sub> , <i>J</i> = 12.43), δ 7.26 (s, 1H, -CH=C-CH <sub>2</sub> ), δ 7.3- 8.1 (m, 9H, Ar-H	308.3	98–100

removed by distillation under reduced pressure. Yield 87%, mp 52–55  $^{\circ}\mathrm{C}$  [26,36].

General procedure for the Heck coupling reaction 9a–f. A mixture of alkenes 8a–c (10 mmol), pseudocyclic ester halides 7a, b (10 mmol), palladium acetate (0.09 g), tri-*o*-tolylphosphine (1.86 g), and TEA (9 mL) in dioxane (30 mL) was heated to 85 °C under nitrogen for 18 h. The reaction mixture was cooled to ambient temperature and filtered, and the filter cake was washed with dioxane (5 mL). The combined washings and filtrate were concentrated in vacuum to obtain a semisolid substance. The material was purified by column chromatography by eluting with ethyl acetate/hexane.

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