

Facile Synthesis of Alkyl 1-Oxo-3-phenyl-1*H*-indene-2-carboxylate through Palladium-catalyzed Carboalkoxylation from 2-Bromo-3-phenylinden-1-ones

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Palladium-catalyzed carboalkoxylation of 2-bromo-3-phenylindenones in various alcoholic solvents afforded diverse alkyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylates in high yields.

Palladium-catalyzed carbonylation reaction of aryl or vinyl halides is considered a valuable method for the synthesis of carboxylic acid derivatives,¹ and has been applied to the preparation of several biologically active substances.² In the course of our medicinal chemistry program, the alkyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate (**1**) (Figure 1) and their *N*-oxide derivatives were identified as an agonist of peroxisome proliferator-activated receptor γ (PPAR γ), which is a promising target for treatment of diabetes.³

Furthermore, indenone moieties have been shown to be useful starting materials toward preparing biologically active molecules such as C-nor-D-homosteroids,⁴ estrogen-binding receptors,⁵ angiotensin II receptor antagonists,⁶ etc.⁷ Due to the structural interests, many synthetic methods of indenone have been developed using Friedel–Crafts,⁸ Grignard,⁹ super-acid,¹⁰ and organometallic¹¹ reaction conditions. We tried to synthesize indenone compounds **1** by a known method,¹² however encountered problems in terms of decomposition of β -keto-ester intermediate under acidic conditions. Therefore, we examined palladium-catalyzed carboalkoxylation with 2-bromoindenone derivatives. To the best of our knowledge, no organometallic carboalkoxylation of indenones has been reported in the literature. Now, we wish to report a facile synthetic method for obtaining alkyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate from 2-bromo-3-phenylinden-1-one through palladium-catalyzed carboalkoxylation.

As a model, we investigated a catalytic carboalkoxylation of 2-bromo-6-methoxy-3-phenylinden-1-one¹³ in ethyl alcohol under 10 atmospheres of CO in the presence of Pd^{II} and base. The results are summarized in Table 1. We used Pd^{II} catalysts such as PdCl₂, PdCl₂(PPh₃)₂, Pd(dppf), and Pd(OAc)₂, which could be converted to Pd⁰ species in the reaction medium. In the presence of PdCl₂(PPh₃)₂ catalyst, using Et₃N or Na₂CO₃ as a base, the desired product was produced in low yields of 43% (Entries 1 and 2) along with significant amount of by-

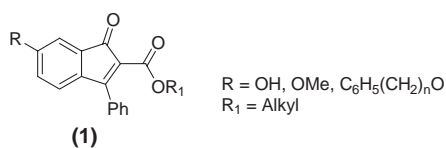


Figure 1.

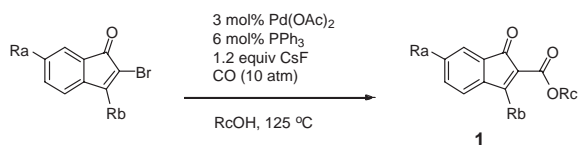
Table 1. Carboalkoxylation of 2-bromo-3-phenylinden-1-one under diverse reaction conditions

Entry ^a	Pd ^{II}	Ligand	Base	Isolated yield (%)
1	PdCl ₂ (PPh ₃) ₂	—	Et ₃ N	43
2	PdCl ₂ (PPh ₃) ₂	—	Na ₂ CO ₃	43
3	PdCl ₂ (PPh ₃) ₂	—	CsF	85
4	PdCl ₂ (dppf)	—	CsF	85
5	PdCl ₂ (dppf)	dppf	CsF	85
6	PdCl ₂ (dppf)	dppf	KF	70 ^b
7	PdCl ₂	dppf	CsF	84
8	PdCl ₂	Ph ₃ P	CsF	89
9	PdCl ₂	—	CsF	<5
10	Pd(OAc) ₂	Ph ₃ P	CsF	92
11	Pd(OAc) ₂	—	CsF	<5

^aAll reactions were examined with 1 mmol scale. ^bStarting material was recovered (20%).

product (i.e., debrominated indenone). When CsF was used as a base, yield was improved to 85% (Entry 3). Introduction of PdCl₂(dppf) as a catalyst exhibited similar yield of 85% with PdCl₂(PPh₃)₂ (Entries 4 and 5).

The reaction using KF¹⁴ as a base gave 70% yield of ethyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate with 20% remaining starting material (Entry 6). Finally, we examined several reactions using PdCl₂ and Pd(OAc)₂ catalyst. The reactions provided high yields of ethyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate with PPh₃ ligand (84–92%, Entries 7–11). From the results, we assumed that the palladium(II) species did not have significant influence on carboalkoxylation of indenones, but the yield of product was significantly influenced by use of base and phosphine ligand. The optimum conditions for the carboalkoxylation were found to be of 3 mol % of Pd^{II}, 6 mol % of phosphine ligand, 1.2 equiv of CsF respectively and with a specific alcoholic solvent. Palladium-catalyzed carboalkoxylation using 6-substituted 2-bromo-3-phenylindenone was examined with several alcoholic solvents under the optimum reaction conditions. The results are summarized in Table 2. The reactions using ethyl alcohol as a solvent gave the corresponding ethyl esters in high yield of 85% (Entries 1 and 2). Similarly reaction using isopropyl alcohol also provided the desired product in 87% (Entry 3). Furthermore, the reaction using sterically hindered *t*-butyl

Table 2. Synthesis of alkyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate via palladium-catalyzed carboalkoxylation

Entry	R _a	R _b	R _c	Time/h	Yield/%
1	BnO	Ph	Et	6	85 (1b)
2	Ph(CH ₂) ₃ O	Ph	Et	6	85 (1c)
3	MeO	Ph	<i>i</i> -Pr	6	87 (1d)
4	MeO	Ph	<i>t</i> -Bu	4	84 (1e)
5	H	Ph	Et	4	84 (1f)
6	H	Ph-4-F	Et	4	86 (1g)
7	H	Ph-4-OMe	Et	4	94 (1h)
8	OH	Ph	Me	4	92 (1i)
9	OH	Ph	Et	4	86 (1j)

alcohol resulted in good yield of *t*-butyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate (84%, Entry 4). Meanwhile, 2-bromo-3-phenylindene-1-one (R_a = H, Entry 5) provided the coupling product in similar yield (84%) with 6-substituted derivatives. We tried to evaluate substituent effect at the R_b position. 4-Fluoro and 4-methoxy substituents (Entries 6 and 7) showed better yields than that of unsubstituted. In order to introduce a variety of alkoxy groups at the 6-position of indenone, reaction was carried out using 6-hydroxy-3-phenylindene-1-one substrate and obtained carboalkoxylated products in high yields (86–92%, Entries 8 and 9). Finally, we examined possible preparation of ethyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylate in multigram scale (up to 5 gram) and found it to give reproducible results.¹⁵

In summary, the palladium-catalyzed carboalkoxylation of 2-brom-3-phenylindene-1-one in the presence CsF provided the corresponding alkyl 1-oxo-3-phenyl-1*H*-indene-2-carboxylates in high yields. The procedure could employ various alkyl alcohols without any steric or electronic effects under palladium(II) species with phosphine ligand.

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