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One pot direct synthesis of β-ketoesters via carbonylation of aryl halides

using cobalt carbonyl

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Abstract

A direct method for the synthesis of β -ketoesters from aryl halides (iodide, bromide) has been described by using cobalt carbonyl as carbon monoxide source in microwave irradiation. Using this protocol, a wide variety of substituted aryl halides has been successfully converted to corresponding β -ketoesters.

Key words: Aryl halides, Carbonylation, β-ketoesters, Imidazole, Co₂(CO)₈

Over the years, transition metal catalyzed cross-coupling reactions have emerged as a valuable method for making carbon-carbon bonds. In these reactions, palladium mediated carbonylative cross coupling of aryl halides with a variety of nucleophiles offered compounds which are important building blocks in the field of pharmaceutical and natural products. Ever since, Heck reported the first successful carbonylative method in 1974, many synthetic protocols using carbon monoxide gas in such reactions are known in literature.¹ Later, metal carbonyls have also been reported as an alternate source for $CO_{(g)}$.² During the past decade, apart from esters and amides, a variety of carbon nucleophiles have also been employed in carbonylative cross-coupling reactions of aryl halides such as Heck,³ Sonagashira,⁴ C-H activation,⁵ Suzuki,⁶ Stille⁷ and Negishi⁸ type coupling reactions.

In organic synthesis, reagents containing variety of functionalities play very important role as they can be used as versatile and effective source for the preparation of complex structures from relatively simple starting materials. In particular, β -ketoesters are used as significant building blocks in natural product chemistry for making a variety of complex structures and biologically active heterocyclic molecules. To synthesize β ketoesters, a number of approaches have been documented, through the formation of either one of the following different bonds in Figure 1.

1



Figure 1. General formula of β -ketoesters

Frequently, they were synthesized by the formation of C_1 - C_2 and C_2 - C_3 bonds by using aliphatic /aromatic acid derivatives and unsymmetrical ketones, respectively.⁹ Methods involving C-alkylation at C_2 have also been reported.¹⁰ A three-component alkoxycarbonylation (C₂-C₃-O₃) of α -halo ketones with CO_(g) and alcohol nucleophiles have been found to afford β -ketoesters.¹¹ However, synthesis of β -ketoesters by making R¹-C₁bond is relatively difficult and less studied.

Review of literature revealed that in 1986 Tanaka and Kobayashi have documented for the synthesis of β -ketoesters directly from aryl iodides by intermolecular carbonylative arylation method in the presence of large excess of carbon monoxide gas (20 atm).¹² However, the yields of the reactions are not stabilized and it covered only four substrates. Torii and co-workers have reported the preparation of cyclic β -ketoesters through intramolecular carbonylative Heck coupling using large excess of CO gas.¹³ Very recently, Korsager *et al.* have developed a method for the synthesis of β -ketoesters from aryl halides using *ex situ* CO_(g) and acids (acetic acid or formic acid).¹⁴ However, special reaction set-ups and a palladium source are required to generate CO gas for the reaction. All these reported methodologies involve the use of external CO source. Herein, we report an effective method for the synthesis of β -ketoesters by using cobalt carbonyl as an *in situ* CO source in microwave irradiation.

In the present work, we have demonstrated an effective reaction protocol for the synthesis of β -ketoesters directly from aryl halides (bromides and iodides) using Co₂(CO)₈ as the carbonyl source under microwave irradiation. To the best of our knowledge this is the first systematic attempt to synthesize β -ketoesters directly from aryl halides in good yields in the absence of external CO gas. The carbonylation of aryl halides-, to yield β -ketoesters-, has been carried out using potassium monoethylmalonate as carbon nucleophile in the presence of Pd(OAc)₂/xantphos and Co₂(CO)₈ (0.3 eqv.) under microwave irradiation. To optimize the reaction conditions, carbonylation of 4-bromotoluene has been carried out in the presence of different bases and solvents, Pd(OAc)₂/Xantphos, and the chosen cobalt carbonyl. Of all the bases tried, MgCl₂ (2 eqv.)/TEA system showed the formation of the desired product (Entry 1, Table 1). The reaction performed with different

solvents (Entry 2-5) showed that THF was the best solvent for the reaction. Further change in any of the other parameters gave no improvement in yields.

Table 1. Screening reaction conditions



All the reaction were executed with 0.5 mmol of 4-bromotoluene, 5 mol% of Pd(OAc)₂, 5 mol% of xantphos (4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene) and 0.15 mmol $Co_2(CO)_8$; 90 °C under microwave irradiation for 30 min. Bt = Benzotriazole, W. amine = N,O-Dimethylhydroxylaminehydrochloride, Map amine = Methyl-pyridin-2-yl-amine. ^a Isolated yields; ^b Reaction performed without the addition of cobalt carbonyl.

Recently, Buchwald *et al.* have established that the less reactive aryl chlorides can effectively be converted to corresponding amides through aminocarbonylation by adding sodium phenoxide as an additive.¹⁵ In line with the above in the present study the carbonylation has also been carried out in the presence of different additives (Entry 6-10). The results indicated that addition of sodium phenoxide, Weinreb amine and Map amine yielded corresponding acyl derivatives (**1a**) as major product. To our delight, in the presence of imidazole (Entry 9, Table 1), a moderate yield of the desired β -ketoester was obtained. Also, the results indicated that in the absence of either MgCl₂/TEA or Co₂(CO)₈ there is no product formation (Entry 11-12). After fine tuning the reaction conditions, we observed that an excellent yield of the desired product was obtained in the presence of 2 equivalents of imidazole (Entry 13). Hence, this has been employed as the optimum condition for further study.



Table 2. Screening of different palladium catalytic systems

All the reaction were executed with 0.5 mmol of bromobenzene, 0.75 mmol of MgCl₂, 1.5 mmol of Et₃N, 0.22 mmol of $Co_2(CO)_8$, 1 mmol of imidazole in THF at 90 °C under microwave irradiation for 30 min. ^a Isolated yields.

The optimization of the catalytic system employed in the study has been carried out with different Pd sources and ligands and the results obtained are shown in Table 2. The results indicated that the Pd(OAc)₂/xantphos catalytic system was found to be the most successful system in the conversion of bromo benzene to the corresponding β -ketoester (Table 2, Entry 1). Once the optimized reaction conditions were identified, the title reaction has been carried out with different aryl halides (bromides and iodides). The products obtained with isolated yields are shown in Scheme 1. The results indicated that both aryl bromides and aryl iodides gave good to excellent yields (55-92%) of the products (**3a-3w**). When compared to the substrates with electron withdrawing substituents, those with electron releasing substituents gave relatively better yields. Chemo selectivity was observed in the case of substrates with fluoro (**1d**), fluoro/chloro (**1k**). In the case of 4-chloro-1-iodobenzene (**3e**), the chloro was also coupled to monoethyl potassium malonate to some extent. Hetro aryl halides (**3s-w**) also gave good yields.

	Ar-X	$\begin{array}{c} \text{KO} \\ O \\ O \\ O \\ Pd(OAc)_2, \text{ Xant} \end{array}$	phos		
Ai	1(a - w) X = Br, I x = aryl, hetero	Imidazole, MgCl ₂ /Et ₃ N Co ₂ (CO) ₈ , M/W, 90 °C, ryl 30 min		Ar \sim Of $3(\mathbf{a} \cdot \mathbf{w})$	
	Entry	Ar	Х	Yield (%) ^a 3 (3a - w)	
	1	$4-MeC_6H_4$	Br/I	89/77	
	2	C ₆ H ₅	Br/I	85/82	
	3	4-OMeC ₆ H ₄	Br/I	92/89	
	4	$4-FC_6H_4$	Br/I	70/62	
	5	4-ClC ₆ H ₄	Br	74	
	6	$4 - tBuC_6H_4$	Br/I	90/87	
	7	4-CF ₃ C ₆ H ₄	Br	84	
	8	3-OMeC ₆ H ₄	Br/I	70/82	
	9	4-PhC ₆ H ₄	Br/I	90/88	
	10	3-MeC ₆ H ₄	Br/I	66/73	
	11	3-Cl-5-FC ₆ H ₃	Br	81	
	12	3,5-di-OMeC ₆ H ₃	Br	56	
	13	3,5-di-FC ₆ H ₃	Br	68	
	14	3-CNC ₆ H ₄	Br	60	
	15	3,5-di-MeC ₆ H ₃	Br	77	
	16	3-COPhC ₆ H ₄	Br	70	
O	17	4-COOEtC ₆ H ₄	Br/I	55/74	
	18	3,5-di-CF ₃ C ₆ H ₃	Br	89	
	19	Pyridine-3-yl	Br	71	
7	20	Thiophen-3-yl	Br	86	
	21	6-F-Pyridin-3-yl	Br	66	
	22	2-dibenzothiophene	Br	75	
	23	2-dibenzofuran	Br	69	

Scheme 1. The synthesis of β -ketoesters from different substituted aryl and heteroaryl halides (I, Br).

^a Isolated yield(s) of product from corresponding Br/I aryl and heteroaryl halides.

With an aim to examine the CO source used in the carbonylation of aryl halides the reaction has been carried out by varying the available metal carbonyl compounds. The results obtained are collected in Table 3 (Entry 1-6). It is evident from the results that $Co_2(CO)_8$ was observed to be the effective carbonyl source in the reaction with an observed yield of 85% of the desired β -ketoester (Table 3, Entry 1). The 57% yield was observed, when the reaction is carried out with external CO(g) at 1 atm pressure in autoclave reactor (Table 3, Entry 5). Also, the reaction was found to yield significant amount of the desired product when carried out under traditional thermal heating condition (Table 3, Entry 6).

6

5

Table 3. Experiments on other CO sources



Entry	Carbonyl	Temp	Yield(%) ^a
	source	(°C)	
1	Co ₂ (CO) ₈ ^b	90	85
2	Cr(CO) ₆ ^c	90	20
3	Mo(CO)6 ^c	90	44
4	W(CO) ₆ ^c	90	-
5	$\mathrm{CO_g}^{\mathrm{d}}$	80	57
6 ^e	$Co_2(CO)_8^{\ b}$	90	64

^a Isolated yield, ^b0.3 eqv. of cobalt carbonyl per eqv. of aryl halide, ^c0.5 eqv. of Cr, Mo, W- metal carbonyls per eqv. of aryl halide, ^d The reaction was executed in autoclave equipment at 1 atm pressure for 14 h. ^eReaction executed in traditional thermal heating condition.

Based on the foregoing results and discussion the following mechanism has been tentatively proposed for the carbonylation of aryl halides (Figure 2). The transformation of **I** to **IV** is well established and documented in literature.¹⁶ The conversion of **IV** to **V** is supported by the observation that the added imidazole significantly increased the yield of the product. This is further supported by the fact that, the reaction of **VII** with **V** to yield the corresponding β -ketoester is known in literature.¹⁷

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Figure 2. Plausible reaction mechanism

In summary, we have demonstrated the synthesis of β -ketoesters directly from aryl and heteroaryl halides using cobalt carbonyl as an *in situ* carbon monoxide source.¹⁸ This reaction is mainly useful for laboratory scale synthesis of β -ketoesters as we did not observe high pressure (<1 bar observed) formation during the course of microwave irradiation, hence safe. Further, the proposed methodology was found to work well with both arylbromide and aryl iodides possessing electron releasing and withdrawing substituents without the use of external CO gas.

Supporting Information Supplementary data (synthesized compounds) associated with this article can be found, in the online version, at http://

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18. General procedure for the synthesis of β -ketoesters of aryl halides (I, Br). To a stirred mixture of aryl or heteroaryl halide (Br, I) (0.5 mmol), potassium mono ethyl malonate (0.75 mmol) in THF (10 mL) taken in a 30 mL microwave vial, was added Pd(OAc)₂ (5 mol%), xantphos (5 mol%), MgCl₂ (0.75), Et₃N (0.75 mmol), imidazole (1 mmol) followed by Co₂(CO)₈ (0.15 mmol). The vial was sealed immediately and microwave irradiated at 90 °C for 30 min. The reaction mixture was concentrated and diluted with ethyl acetate and water. The ethyl acetate layer was separated, dried over sodium sulphate and concentrated. The crude product obtained was purified by column chromatography (60-120 mesh silica gel; 0-25% v/v ethyl acetate in hexane) to get the pure compound.

All the compounds (**3a-w**) in Scheme 1 were prepared by adopting the same procedure using the corresponding aryl halides (**Br**, **1**). The products were characterized using ¹H and ¹³C NMR spectral techniques (see supporting information) and LCMS or UPLC mass spectrometry. The spectra results of ¹H NMR & ¹³C NMR studies indicated the existence of most of the products in keto-enol tatuomeric form wherein keto form is present in excess.

Highlights

- * Direct one pot synthesis of β-ketoesters from wide variety of aryl halides.
- * Cobalt carbonyl as an in situ CO source in microwave irradiation without CO gas.
- * This is one of very few methods of making β -ketoesters in good yields.

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Graphical Abstract

One pot direct synthesis of β -ketoesters via carbonylation of aryl halides using Cobalt carbonyl Poongavanam Baburajan and Kuppanagounder P. Elango* KO **OEt** Ô OEt Pd(OAc)₂, Xantphos R Imidazole, MgCl₂/Et₃N Co₂(CO)₈, M/W, 90 °C, 30 min 1(a - r) 3(a - w) X= Br, I