Copper-Catalyzed, Palladium-Free Carbonylative Sonogashira Coupling Reaction of Aliphatic and Aromatic Alkynes with Iodoaryls

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Abstract: Copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate) catalyzed carbonylative Sonogashira coupling reactions of aliphatic/aromatic alkynes with iodoaryls are reported for the first time. The protocol eliminates the use of a toxic, air-sensitive, and expensive Pd–phosphine-based catalytic system, and provides high yields of desired products.

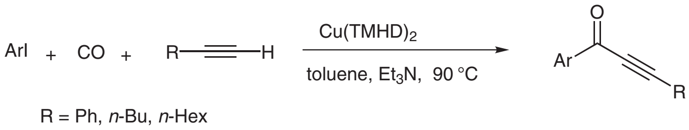
Key words: Sonogashira, carbonylation, iodoaryls, alkynes, copper

Alkynyl ketones have attracted considerable biological interest due to their utility as synthetic intermediates, particularly for the synthesis of heterocyclic systems.[1] One of the routes to prepare these compounds involves the reaction of alkynyl organometallic reagents such as sodium,[2] lithium,[3] cadmium,[4] zinc,[5] copper,[6] and tin[7] with acid chlorides. However, these methods require use of dry solvents in an inert atmosphere. Alternatively, alkynyl ketones can be synthesized using transition-metal-catalyzed coupling of terminal alkynes with organic halides in the presence of carbon monoxide (carbonylative Sonogashira coupling). Sonogashira coupling is a well-known reaction catalyzed by palladium–ligand-based[8] catalytic systems. More recently, the use of copper instead of palladium was found to be an effective catalyst for this transformation.[9] However, the carbonylative Songashira coupling reaction has been explored only with Pd-based catalysts such as $Pd(OAc)_2/CuI$,[10] $PdCl_2$ [1,1′-bis(diphenylphosphino)ferrocene],[11] $[(PPh_3)Pd(Ph)(\mu\text{-}OH_2)]_2$,[12] $PdCl_2(PPh_3)_2$/aq NH_3,[13] or $PdCl_2/PPh_3$ in water.[14] Recently, Ryu et al. have reported a Pd/N-heterocyclic carbene (NHC)-catalyzed carbonylative Sonogashira coupling reaction using a multiphase microflow system.[15] In spite of significant advances in this area, all the above reports involve use of a palladium source along with toxic, air-sensitive, and expensive phosphine-based ligands, and the use of stoichiometric amounts of copper salt additives. However, palladium-free, copper-catalyzed carbonylative Sonogashira coupling reaction has not yet been explored. Thus there is a need to develop a chemically well-defined, stable transition-metal complex, which could overcome the above disadvantages and could directly catalyze carbonylative Sonogashira couplings of both aliphatic and aromatic alkynes. This paper reports the first example of the use of a copper-based catalytic system for the carbonylative Sonogashira coupling reaction under milder conditions.

Previously, we had reported metal/TMHD (2,2,6,6,-tetramethyl-3,5-heptanedionate)-based catalytic systems for various transformations.[16] Herein, we report a facile carbonylative Sonogashira coupling reaction of aliphatic and aromatic alkynes with iodoaryls using a preformed $Cu(TMHD)_2$ complex (Scheme 1). The ease of preparation of this complex,[17] its high solubility in organic solvents, indefinite shelf life, and stability towards air makes it an ideal complex for the carbonylative Sonogashira coupling reaction.

Initially, the effects of various catalysts, solvents, and bases were investigated for the carbonylative Sonogashira coupling reaction of phenyl acetylene with iodobenzene at 90 °C under 20 atm of carbon monoxide (Table 1). Copper salts, such as $Cu(OAc)_2$, $CuCl_2$, CuI, were found to be less effective due to their poor solubility in organic solvents. The N- or P-containing ligands, such as EDA and PPh_3, and metal complexes, such as copper bis(2,2,6,6,-tetramethyl-3,5-heptanedionate) [$Cu(TMHD)_2$], copper bis(acetylacetonate) [$Cu(acac)_2$], and copper bis(ethyl acetoacetonate) [$Cu(eaa)_2$], were also tested, and among them $Cu(TMHD)_2$ was found to be the most effective catalyst providing an excellent yield of 80%.

The reactivity trend could result from the fact that a better balance exists between the electronic and steric effects in the $Cu(TMHD)_2$ complex. The effect of various solvents on the reaction system was investigated. It was observed



Scheme 1

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that the reaction was more favorable in nonpolar solvents such as toluene, as compared to polar solvents such as water, DMF, or THF. The probable reason may be due to the high solubility and stability of the catalyst in nonpolar solvents providing higher yield. In order to evaluate the effect of base, various organic and inorganic bases, such as K_2CO_3, Cs_2CO_3, KO*t*-B, and Et_3N, were studied. Out of them, Et_3N was found to be the most effective, providing an 80% yield of the desired product at three equivalents loading relative to the aryl iodide.

Table 1 Effect of Catalyst, Solvent, and Base for the Carbonylative Sonogashira Coupling Reaction of Phenyl Acetylene with Iodobenzene[a]

Entry	Catalyst	Solvent	Base	Yield (%)
Effect of catalyst				
1	$Cu(OAc)_2$	toluene	Et_3N	38
2	$CuCl_2$	toluene	Et_3N	44
3	CuI	toluene	Et_3N	35
4	$Cu(TMHD)_2$	toluene	Et_3N	80
5	$Cu(acac)_2$	toluene	Et_3N	62
6	$Cu(eaa)_2$	toluene	Et_3N	58
7	$Cu(OAc)_2/PPh_3$	toluene	Et_3N	68
8	$Cu(OAc)_2$/EDA	toluene	Et_3N	08
Effect of solvent				
9	$Cu(TMHD)_2$	H_2O	Et_3N	05
10	$Cu(TMHD)_2$	DMF	Et_3N	08
11	$Cu(TMHD)_2$	THF	Et_3N	24
12	$Cu(TMHD)_2$	none	Et_3N	10
Effect of base				
13	$Cu(TMHD)_2$	toluene	K_2CO_3	08
14	$Cu(TMHD)_2$	toluene	Cs_2CO_3	10
15	$Cu(TMHD)_2$	toluene	KO*t*-Bu	35
16[b]	$Cu(TMHD)_2$	toluene	Et_3N	70

[a] Reaction conditions: iodobenzene (2.0 mmol), phenylacetylene (3.0 mmol), catalyst (5 mol%), base (6.0 mmol), solvent (10 mL), CO (20 atm), 14 h, 90 °C.
[b] Base (3.0 mmol).

Thus, using $Cu(TMHD)_2$ as the preferred catalyst, toluene as solvent, and Et_3N as base, the carbonylative Sonogashira coupling of phenyl acetylene with various electron-donating and electron-withdrawing iodoaryls was studied (Table 2).[18] Electron-donating substituents such as Me and OMe on the iodoarene were well tolerated (entries 2 and 3). No significant steric electronic effect was observed for *ortho* or *para* substituents. The reaction of deactivated substrates such as 4-iodonitrobenzene also proceeded smoothly under the present conditions giving 68% yield (entry 5). The reaction also works well with a heterocyclic iodoaryl such as 2-iodothiophene, providing a moderate yield of 67% (entry 6).

Table 2 Carbonylative Sonogashira Coupling of Phenyl Acetylene with Aryl Iodides[a]

Entry	Ar	R	Yield (%)[b]
1	Ph	Ph	80[15]
2	$4-MeC_6H_4$	Ph	78[14]
3	$4-MeOC_6H_4$	Ph	76[13]
4	$2-MeC_6H_4$	Ph	73[15]
5[c]	$4-O_2NC_6H_4$	Ph	68[11]
6	thien-2-yl	Ph	67[11]

[a] Reaction conditions: aryl iodide (2.0 mmol), phenylacetylene (3.0 mmol), $Cu(TMHD)_2$ (5 mol%), Et_3N (6.0 mmol), toluene (10 mL), CO (20 atm), 14 h, 90 °C.
[b] Yields of isolated product.
[c] Reaction time: 18 h.

To check the generality of the process, the catalytic system was extended for the carbonylative coupling reaction of aliphatic alkynes with aryl iodides (Table 3).[18] Aliphatic alkynes, such as 1-hexyne, were found to react smoothly with iodobenzene under the present conditions, providing a 74% yield of the desired product (entry 1). Electron-donating substituents at the *ortho*- or *para*-positions of the iodobenzene were tolerated. However, the reaction of 2-iodothiophene was found to be sluggish providing a 52% yield of coupled product. 1-Octyne was also found to react efficiently with iodoaryls providing good to excellent yields (70–77%) of the desired product.

Table 3 Carbonylative Sonogashira Coupling of Alkynes with Aryl Iodides[a]

Entry	Ar	R	Yield (%)[b]
1[c]	Ph	*n*-Bu	74[14]
2[c]	$4-MeC_6H_4$	*n*-Bu	72[14]
3[c]	$4-MeOC_6H_4$	*n*-Bu	68[14]
4[c]	$2-MeC_6H_4$	*n*-Bu	63[14]
5[c]	thien-2-yl	*n*-Bu	52[14]
6[d]	Ph	*n*-Hex	77[14]
7[d]	$4-MeC_6H_4$	*n*-Hex	73[13]
8[d]	$4-MeOC_6H_4$	*n*-Hex	70[13]

[a] Reaction conditions: aryl iodide (2.0 mmol), alkyne (3.0 mmol), $Cu(TMHD)_2$ (5 mol%), Et_3N (6.0 mmol), toluene (10 ml), CO (20 atm), 14 h, 90 °C.
[b] Yields of isolated product.
[c] Alkyne = 1-hexyne.
[d] Alkyne = 1-octyne.

In summary, several important features are demonstrated in this study. The Cu(TMHD)$_2$ complex was found to be an excellent alternative to the toxic, air-sensitive, and expensive palladium–phosphine catalyst systems; the ease of preparation of this complex, its high solubility in organic solvents, indefinite shelf life, and stability towards air make it an ideal complex for the carbonylative Sonogashira coupling reaction; the system works well with a wide variety of iodoaryls with different steric and electronic properties.

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(17) **Typical Procedure for the Preparation of Cu(TMHD)$_2$**
NaOH (22 mmol) was dissolved in MeOH (20 mL) with stirring and the resulting solution was cooled to r.t., followed by addition of TMHD (20 mmol). To the mixture, a solution obtained by dissolving Cu(NO$_3$)$_2$·6H$_2$O (10 mmol) in MeOH (20 mL) was added over a period of 30 min. The reaction mixture was stirred for 6 h and the resulting precipitate was filtered and dried. Yield 93%, mp 196–198 °C.

(18) **General Procedure**
To an 100 mL autoclave, phenylacetylene (3.0 mmol), iodobenzene (2.0 mmol), Cu(TMHD)$_2$ (0.1 mmol), toluene (10 mL) and Et$_3$N (6.0 mmol) were added. The mixture was first stirred for 10 min, then the vessel pressures 8–20 atm of CO and the reaction mixture was heated at 90 °C for 14 h. After the reaction was complete, the mixture was extracted with EtOAc (3×10 mL), the combined organic extracts were dried over Na$_2$SO$_4$, and the solvent was removed under vacuum. The residue obtained was purified by column chromatography (silica gel, 60–120 mesh) using PE (60:80)–EtOAc as eluent to afford the pure products. All the compounds are known and were characterized by GC–MS (Shimadzu) and NMR (Varian 300 MHz).
Spectroscopic Data of Representative Compounds
Table 2, Entry 1: GC-MS: *m/z* (%) = 206 [M$^+$], 178, 129 (100). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.49–7.54 (m, 5 H), 7.61–7.63 (m, 1 H), 7.68–7.70 (m, 2 H), 8.23 (ddd, *J* = 8.4, 2.1, 1.2, 2 H) ppm. ^{13}C NMR (70 MHz, CDCl$_3$, 25 °C): δ = 87.0, 93.2, 120.2, 128.8, 128.8, 129.2, 130.9, 133.2, 134.3, 137.0, 178.1 ppm.
Table 2, Entry 2: GC-MS: *m/z* (%) = 220 [M$^+$], 192 (100), 165, 129. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.44 (s, 3 H), 7.29–7.44 (m, 5 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 8.11 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (70 MHz, CDCl$_3$, 25 °C): δ = 21.9, 87.0, 92.7, 120.3, 128.8, 129.4, 129.9, 130.8, 133.1, 134.7, 145.3, 177.8 ppm.
Table 3, Entry 1: GC-MS: *m/z* (%) = 186 [M$^+$], 105 (100), 77. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 0.98 (t, *J* = 2.8, 4.8, 7.2, 3 H), 1.26–1.33 (m, 2 H), 1.63–1.69 (m, 2 H), 2.51 (t, *J* = 7.2, 6.8, 2 H), 7.460–7.59 (m, 3 H), 8.12–8.15 (m, 2 H) ppm. ^{13}C NMR (70 MHz, CDCl$_3$, 25 °C): δ = 13.7, 19.1, 22.7, 29.9, 80.0, 97.0, 128.6, 129.7, 131.8, 134.0, 178.1 ppm.