# Copper-Free *Sonogashira* Coupling of Acid Chlorides with Terminal Alkynes in the Presence of a Reusable Palladium Catalyst: An Improved Synthesis of 3-Iodochromenones (= 3-Iodo-4*H*-1-benzopyran-4-ones)

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Pd/C is used as an efficient catalyst for the copper-free *Sonogashira* coupling of acid chlorides and terminal alkynes to afford ynones in high yields (*Tables 1* and *3*). Cyclization of (2-methoxyaryl)-substituted ynones induced by $I_2$/ammonium cerium(IV) nitrate (CAN) at room temperature gave 3-iodochromenones (= 3-iodo-4*H*-1-benzopyran-4-ones) in excellent yield (*Table 4*).

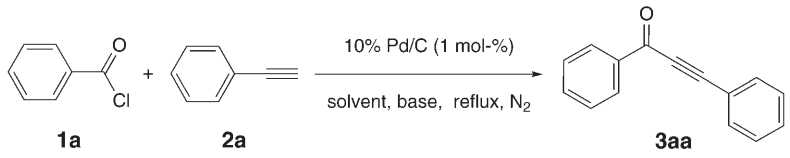
**Introduction.** – Ynones are important synthetic targets for the preparation of heterocyclic derivatives such as pyrroles [1], furans [2], furanones [3], pyrazoles [4], isoxazoles [5], pyrimidines [6], quinolines [7], and iodochromones [8], *etc.* Ynones are generally synthesized *via* coupling of carboxylic acid chlorides and alkynes by using palladium and copper catalysts under homogeneous conditions [9]. Despite the synthetic elegance, all of these homogeneous catalytic protocols suffer from the loss of the precious palladium catalyst at the end of the reaction. Further, the use of a copper co-catalyst facilitates the homocoupling of alkynes, which in turn makes the separation of the products more tedious. So it is highly desirable to develop a copper-free reusable catalytic system for the coupling of acid chlorides with alkynes.

Recently Pd/C has received considerable attention in organic synthesis for its availability, low cost, heterogeneous nature, and ease of handling [10]. It was effectively used in numerous C–C bond forming reactions. Buoyed with the literature reports [10], we wish to examine the catalytic activity of Pd/C in the coupling of alkynes with acid chlorides.

**Results and Discussion.** – Initially we studied the coupling of benzoyl chloride (**1a**) and ethynylbenzene (**2a**) in the presence of 1 mol-% of Pd/C catalyst under different conditions (*Table 1*). It was evident from *Table 1* that the maximum formation of product **3aa** was observed when dry toluene was used as solvent in the presence of triethylamine as base. By lowering the catalyst amount from 1 mol-% to 0.1 mol-%, good to moderate yields were obtained after a longer reaction time (*Table 1*, *Entries 10* and *11*). Even at room temperature, Pd/C afforded 48% of **3aa** within 8 h (*Table 1*, *Entry 9*). To widen the scope of this catalytic protocol, several other alkynes and acid chlorides were allowed to react under the optimized conditions. The results are summarized in *Table 2*.

From *Table* 2, it can be observed that aromatic acid chlorides with electron-withdrawing groups reacted more sluggishly than the aromatic acid chlorides with

Table 1. *Optimization of Reaction Conditions for the Coupling of Ethynylbenzene and Benzoyl Chloride*[a])




**1a** **2a** **3aa**

| *Entry* | Solvent | Base | Time [h] | Temperature [°] | Yield[b]) [%] |
|---|---|---|---|---|---|
| *1* | dry toluene | $Et_3N$ | 2 | 110 | 96 |
| *2* | dry toluene | NaOAc | 5 | 110 | 20 |
| *3* | dry toluene | $^{i}Pr_2EtN$ | 2 | 110 | 80 |
| *4* | dry toluene | Pyridine | 3 | 110 | 30 |
| *5* | dry toluene | DABCO[c]) | 2 | 110 | 68 |
| *6* | dry THF | $Et_3N$ | 4 | 80 | 70 |
| *7* | dry DMF | $Et_3N$ | 5 | 100 | 53 |
| *8* | MeCN | $Et_3N$ | 5 | 90 | 42 |
| *9* | dry toluene | $Et_3N$ | 8 | r.t. | 48 |
| *10* | dry toluene | $Et_3N$ | 5 | 110 | 78[d]) |
| *11* | dry toluene | $Et_3N$ | 8 | 110 | 57[e]) |

[a]) Reaction conditions: Alkyne (1 mmol), acid chloride (1.2 mmol), Pd/C (1 mol-%) (10 wt-% Pd/charcoal), base (2 mmol), $N_2$ atmosphere. [b]) GC Yield, with tridecane as internal standard. [c]) DABCO = 1,4-Diazabicyclo[2.2.2]octane. [d]) Pd/C (0.5 mol-%). [e]) Pd/C (0.1 mol-%).

electron-donating groups (*Table 2*, *Entry 4*). Also an $\alpha,\beta$-unsaturated acid chloride or cyclic aliphatic acid chloride reacted smoothly to afford the respective ynone in high yield (*Table 2*, *Entries 3* and *10*). In case of a heterocyclic acid chloride, the coupling product was obtained in good yield (*Table 2*, *Entry 9*). The reaction of aliphatic alkynes provided relatively lower yields than that of aromatic alkynes (*Table 2*, *Entries 12* and *15*).

For any heterogeneous catalyst, it is important to know its ease of separation and possible reusability. In this coupling reaction, the Pd/C catalyst was separated by a simple filtration, washed with a copious amount of toluene and water, followed by acetone, and then air-dried. The recovered catalyst was charged in the next cycle. The yield of product decreased from 96 to 67% after the 6th cycle (*Table 3*). When the Pd-content of the catalyst after the 6th cycle was analyzed by atomic absorption spectroscopy (AAS), an almost 15% decrease in Pd-content was noticed. This nonreversible leaching phenomenon was already observed in case of Pd/C [11].

The 2,3-diarylchromenones (=2,3-diaryl-4*H*-1-benzopyran-4-ones) are known to be antihypertensive and anti-inflammatory agents as well as COX-2 inhibitors [12]. The 3-iodochromenones can be used as a precursor for the synthesis of 2,3-diarylchromenones. Iodochromenones are potential intermediates in the synthesis of bioactive molecules [13]. Recently, *Larock* and co-workers have shown that iodine monochloride (ICl) induced cyclization of heteroatom-substituted alkynones into various 3-iodochromenones and analogues [8]. ICl is highly moisture- and light-sensitive. To develop an easy and alternative methodology, it is necessary to have stable and safe reagent systems. When molecular iodine ($I_2$) was used in place of ICl for the cyclization of a (2-

Table 2. *Coupling of Acid Chlorides with Alkynes in the Presence of Pd/C Catalyst*[a])

| *Entry* | Acid chloride RC(=O)Cl | Alkyne R′−C≡C−H | Product RC(=O)−C≡C−R′[b]) | Time [h] | Yield[c]) [%] |
|---|---|---|---|---|---|
| *1* | **1a**; R = Ph | **2a**; R′ = Ph | **3aa** | 2 | 92 |
| *2* | **1b**; R = 4-Me−$C_6H_4$ | **2a** | **3ba** | 2 | 90 |
| *3* | **1c**; R = Ph−CH=CH | **2a** | **3ca** | 2.5 | 91 |
| *4* | **1d**; R = 4-$NO_2$−$C_6H_4$ | **2a** | **3da** | 4 | 65 |
| *5* | **1e**; R = 4-Cl−$C_6H_4$ | **2a** | **3ea** | 3 | 95 |
| *6* | **1f**; R = 4-MeO−$C_6H_4$ | **2a** | **3fa** | 2 | 89 |
| *7* | **1g**; R = 2-MeO−$C_6H_4$ | **2a** | **3ga** | 3 | 90 |
| *8* | **1h**; R = 4-$^t$Bu−$C_6H_4$ | **2a** | **3ha** | 2 | 82 |
| *9* | **1i**; R = furan-2-yl | **2a** | **3ia** | 2.5 | 78 |
| *10* | **1j**; R = cyclohexyl | **2a** | **3ja** | 2.5 | 83 |
| *11* | **1a** | **2b**; R′ = 4-Me−$C_6H_4$ | **3ab** | 2 | 90 |
| *12* | **1a** | **2c**; R′ = hexyl | **3ac** | 3.5 | 72 |
| *13* | **1a** | **2d**; R′ = 4-MeO−$C_6H_4$ | **3ad** | 3 | 90 |
| *14* | **1g** | **2b** | **3gb** | 2.5 | 85 |
| *15* | **1g** | **2c** | **3gc** | 3 | 60 |
| *16* | **1g** | **2d** | **3gd** | 2 | 89 |

[a]) Reaction conditions: Terminal alkyne (1 mmol), acid chloride (1.2 mmol), $Et_3N$ (2 mmol), dry toluene (2 ml), Pd/C (1 mol-%) (10 wt-% Pd/charcoal), 110°, $N_2$. [b]) All the products were characterized by $^1$H-NMR and mass spectrometry. [c]) Yield of isolated pure product.

Table 3. *Reusability of the Pd/Catalyst in the Coupling of Ethynylbenzene* (**2a**) *and Benzoyl Chloride* (**1a**)[a])

| | 1st cycle | 2nd cycle | 3rd cycle | 4th cycle | 5th cycle | 6th cycle |
|---|---|---|---|---|---|---|
| Time [h] | 2 | 2 | 2.5 | 3 | 4 | 6 |
| Yield[b]) [%] | 96 | 90 | 83 | 78 | 72 | 67 |

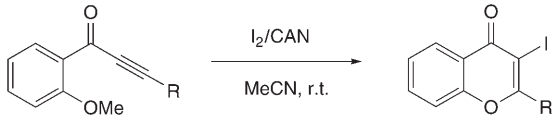
[a]) Reaction conditions: Ethynylbenzene (**2a**; 3 mmol), benzoyl chloride (**1a**; 3.6 mmol), $Et_3N$ (6 mmol), dry toluene (6 ml), 110°, $N_2$. [b]) GC Yield, with tridecane internal standard.

methoxyaryl)-substituted alkynone, no iodochromenone product formation was observed [8]. It is believed that for the facile formation of 3-iodochromenone, it is essential to generate the iodine cation on the C≡C bond of the ynone (iodonium intermediate) *via* activation of $I_2$. A literature search on the activation of $I_2$ revealed ammonium cerium(IV) nitrate (CAN) as an efficient and convenient activator for $I_2$ in the iodination of ketones, aromatic compounds, uracil derivatives, enones, and flavones [14].

When **3ga** was treated with $I_2$/CAN, we obtained 97% of **4a** (*Table 4*, *Entry 1*). Consequently, several other substituted alkynones were treated with $I_2$/CAN, and the results are summarized in *Table 4*. It was observed that aliphatic substituted ynones needed a longer reaction time than aromatic substituted ynones (*Table 4*, *Entry 3*).

In conclusion, we have developed a heterogeneous protocol for the coupling of acid chlorides and alkynes. The catalyst can be easily separated and reused for several cycles

Table 4. *Synthesis of 3-Iodochromenones* **4** *with the $I_2$/CAN System*[a])




**3ga – 3gd** **4a – 4d**

| *Entry* | R | Alkynone | Time [min] | Product[b]) | Yield[c]) [%] |
|---|---|---|---|---|---|
| *1* | Ph | **3ga** | 15 | **4a** | 97 |
| *2* | 4-Me–$C_6H_4$ | **3gb** | 15 | **4b** | 95 |
| *3* | hexyl | **3gc** | 30 | **4c** | 91 |
| *4* | 4-MeO–$C_6H_4$ | **3gd** | 15 | **4d** | 98 |

[a]) Reaction conditions: Ynone (0.3 mmol), $I_2$ (0.36 mmol), CAN (0.33 mmol), MeCN (3 ml), at r.t. [b]) All the products were characterized by $^1$H-NMR and mass spectrometry. [c]) Yield after isolation.

of reactions. We have also developed a mild and highly efficient $I_2$/CAN system for the iodocyclization of (2-methoxyaryl)-substituted ynones.

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## Experimental Part

1. *General.* The 10% Pd/C was purchased from *SRL*, India. All other reactants were commercially available and used without purification. Toluene was distilled over sodium benzophenone. GC: *Shimadzu GC 2010*, *ZB-5* capillary column. IR Spectra: *Perkin-Elmer FT* spectrophotometer; $\tilde{\nu}$ in $cm^{-1}$. NMR Spectra: *Bruker Avance-300* and *Varian Gemini-200* spectrometers; chemical shifts $\delta$ in ppm rel. to $SiMe_4$ as internal standard, coupling constants $J$ in Hz.

2. *Ynones: General Procedure.* In an oven-dried vessel, a mixture of alkyne (1 mmol), $Et_3N$ (2 mmol), 10% Pd/C (1 mol-%, 10 mg), and dry toluene (1 ml) was stirred for 10 min under $N_2$. Next, the acid chloride (1.2 mmol) in dry toluene (1 ml) was added dropwise to the mixture within 2 min. The mixture was stirred at 110° under $N_2$, and the progress of the reaction was monitored by GC. After completion, the catalyst was separated by filtration, and to the filtrate, $H_2O$ (20 ml) was added. The mixture was extracted with AcOEt (3 × 20 ml), the combined org. phase dried ($MgSO_4$), and the solvent evaporated. The crude product was purified by column chromatography (CC) (silica gel, hexane/AcOEt 9 :1): pure ynone. The ynones were characterized by $^1$H-NMR and MS and compared with literature data. The spectral data of some representative products are given below.

*1,3-Diphenylprop-2-yn-1-one* (**3aa**) [9c]: $^1$H-NMR (200 MHz, $CDCl_3$): 7.35 – 7.72 (*m*, 8 H); 8.15 – 8.24 (*m*, 2 H). EI-MS: 206 (82, $M^+$), 178 (100), 129 (76).

*1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-one* (**3da**) [9c]: $^1$H-NMR (300 MHz, $CDCl_3$): 7.42 – 7.56 (*m*, 3 H); 7.68 – 7.72 (*m*, 2 H); 8.37 (*s*, 4 H). EI-MS: 251 (20, $M^+$), 223 (8), 129 (100).

*1-(Furan-2-yl)-3-phenylprop-2-yn-1-one* (**3ia**) [9c]: $^1$H-NMR (300 MHz, $CDCl_3$): 6.55 – 6.60 (*m*, 1 H); 7.34 – 7.49 (*m*, 4 H); 7.60 – 7.69 (*m*, 3 H). EI-MS: 196 (65, $M^+$), 168 (68), 139 (88), 129 (100), 101 (10), 74 (50).

*1-Cyclohexyl-3-phenylprop-2-yn-1-one* (**3ja**) [9c]: $^1$H-NMR (300 MHz, $CDCl_3$): 1.14 – 2.13 (*m*, 10 H); 2.38 – 2.54 (*m*, 1 H); 7.31 – 7.46 (*m*, 3 H); 7.52 – 7.62 (*m*, 2 H). EI-MS: 212(2, $M^+$), 130 (8), 129 (100), 102 (20), 75 (18), 55 (70).

*3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one* (**3ad**) [9b]: $^1$H-NMR (300 MHz, $CDCl_3$): 3.85 (*s*, 3 H); 6.90 (*d*, $J$ = 9.0, 2 H); 7.49 (*t*, $J$ = 7.6, 2 H); 7.55 – 7.65 (*m*, 3 H); 8.18 (*d*, $J$ = 8.3, 2 H). EI-MS: 236 (57, $M^+$), 208 (32), 165 (20), 159 (100), 144 (12).

*1-(2-Methoxyphenyl)non-2-yn-1-one* (**3gc**): IR (neat): 2928, 2856, 2210, 1647, 1627, 1596, 1485, 1462, 1298, 1240, 1022, 755. $^1$H-NMR (200 MHz, $CDCl_3$): 0.91 (*t*, *J* = 6.8, 3 H); 1.29–1.37 (*m*, 4 H); 1.41–1.52 (*m*, 2 H); 1.59–1.69 (*m*, 2 H); 2.44 (*t*, *J* = 6.8, 2 H); 3.91 (*s*, 3 H); 6.92–7.01 (*m*, 2 H); 7.42–7.49 (*m*, 1 H); 7.95 (*dd*, *J* = 7.5, 1.5, 1 H). $^{13}$C-NMR ($CDCl_3$, 75 MHz): 13.97; 19.22; 22.50; 27.90; 28.58; 31.22; 55.78; 81.80; 95.29; 112.15; 120.09; 126.90; 132.78; 134.59; 159.65; 177.09. EI-MS: 244 (25, $M^+$), 187 (80), 174 (100), 173 (67), 135 (84), 121 (71), 115 (34), 91 (22), 77 (47). Anal. calc. for $C_{16}H_{20}O_2$ (244.33): C 78.65, H 8.25; found: C 78.79, H 8.15.

3. *3-Iodochromenones: General Procedure.* In an oven-dried reaction tube, a mixture of ynone (0.3 mmol), $I_2$ (0.36 mmol), CAN (0.33 mmol), and MeCN (3 ml) was stirred at r.t., and the progress of reaction was monitored by TLC. To the mixture, sat. aq. $Na_2S_2O_3$ soln. (3 ml) and then sat. NaCl soln. (20 ml) was added. The mixture was extracted with AcOEt (3 × 10 ml), the combined org. layer dried ($MgSO_4$), and the solvent evaporated. The residue was purified by CC (silica gel, hexane/AcOEt 9:1): pure iodochromenone. All the reported iodochromenones were identified by comparison with their published spectral data.

*3-Iodo-2-phenyl-4*H*-1-benzopyran-4-one* (**4a**) [8]: $^1$H-NMR (200 MHz, $CDCl_3$): 7.39–7.58 (*m*, 5 H); 7.64–7.82 (*m*, 3 H); 8.23–8.33 (*m*, 1 H). EI-MS: 348 (100, $M^+$), 221 (65), 165 (67), 121 (35).

*3-Iodo-2-(4-methylphenyl)-4*H*-1-benzopyran-4-one* (**4b**): $^1$H-NMR (200 MHz, $CDCl_3$): 2.48 (*s*, 3 H); 7.23–7.35 (*m*, 2 H); 7.37–7.50 (*m*, 2 H); 7.62–7.75 (*m*, 3 H); 8.27 (*d*, *J* = 7.8, 1 H). EI-MS: 362 (100, $M^+$), 235 (36).

*2-Hexyl-3-iodo-4*H*-1-benzopyran-4-one* (**4c**): IR (neat): 2954, 2927, 2857, 1650, 1611, 1559, 1353, 1112, 758. $^1$H-NMR (300 MHz, $CDCl_3$): 0.92 (*t*, *J* = 6.8, 3 H); 1.29–1.53 (*m*, 6 H); 1.74–1.85 (*m*, 2 H); 3.03 (*t*, *J* = 7.6, 2 H); 7.36–7.43 (*m*, 2 H); 7.61–7.68 (*m*, 1 H); 8.20 (*dd*, *J* = 8.3, 2.3, 1 H). $^{13}$C-NMR ($CDCl_3$, 75 MHz): 14.05; 22.43; 26.97; 28.68; 31.48; 38.63; 88.35; 117.39; 120.06; 125.39; 126.43; 133.77; 155.44; 169.11; 173.85. EI-MS: 356 (15, $M^+$), 229 (18), 159 (26), 131 (88), 121 (100), 95 (32), 69 (20). Anal. calc. for $C_{15}H_{17}IO_2$ (356.20): C 50.58, H 4.81; found: C 50.60, H 4.74.

*3-Iodo-2-(4-methoxyphenyl)-4*H*-1-benzopyran-4-one* (**4d**): $^1$H-NMR (200 MHz, $CDCl_3$): 3.90 (*s*, 3 H); 6.95–7.04 (*m*, 2 H); 7.37–7.50 (*m*, 2 H); 7.63–7.82 (*m*, 3 H); 8.22–8.30 (*m*, 1 H). EI-MS: 378 (100, $M^+$), 251 (24).

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