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)

by **Pravin R. Likhar***, **M. S. Subhas**, **Moumita Roy**, **Sarabindu Roy**, and **M. Lakshmi Kantam**

Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad, 500007, India
(fax: +91-40-27160921; e-mail: plikhar@iict.res.in)

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])
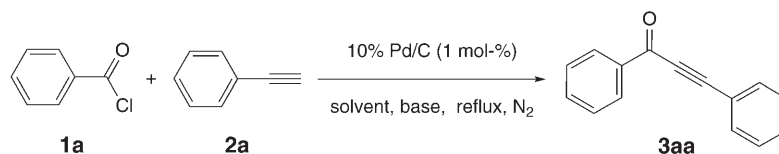
Entry	Solvent	Base	Time [h]	Temperature [°]	Yield[b]) [%]
1	dry toluene	Et$_3$N	2	110	96
2	dry toluene	NaOAc	5	110	20
3	dry toluene	^{i}Pr$_2$EtN	2	110	80
4	dry toluene	Pyridine	3	110	30
5	dry toluene	DABCO[c])	2	110	68
6	dry THF	Et$_3$N	4	80	70
7	dry DMF	Et$_3$N	5	100	53
8	MeCN	Et$_3$N	5	90	42
9	dry toluene	Et$_3$N	8	r.t.	48
10	dry toluene	Et$_3$N	5	110	78[d])
11	dry toluene	Et$_3$N	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 α,β-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-diarylchrome-nones. 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-iodo-chromenones 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$_6$H$_4$	**2a**	**3ba**	2	90
3	**1c**; R = Ph−CH=CH	**2a**	**3ca**	2.5	91
4	**1d**; R = 4-NO$_2$−C$_6$H$_4$	**2a**	**3da**	4	65
5	**1e**; R = 4-Cl−C$_6$H$_4$	**2a**	**3ea**	3	95
6	**1f**; R = 4-MeO−C$_6$H$_4$	**2a**	**3fa**	2	89
7	**1g**; R = 2-MeO−C$_6$H$_4$	**2a**	**3ga**	3	90
8	**1h**; R = 4-^{t}Bu−C$_6$H$_4$	**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$_6$H$_4$	**3ab**	2	90
12	**1a**	**2c**; R′ = hexyl	**3ac**	3.5	72
13	**1a**	**2d**; R′ = 4-MeO−C$_6$H$_4$	**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$_3$N (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$_3$N (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**
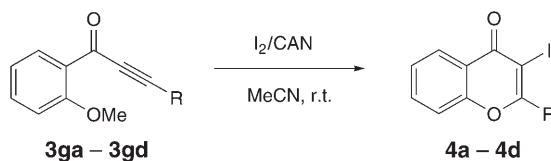
Entry	R	Alkynone	Time [min]	Product[b])	Yield[c]) [%]
1	Ph	**3ga**	15	**4a**	97
2	4-Me–C$_6$H$_4$	**3gb**	15	**4b**	95
3	hexyl	**3gc**	30	**4c**	91
4	4-MeO–C$_6$H$_4$	**3gd**	15	**4d**	98

[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.

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; $\tilde{v}$ in cm^{-1}. NMR Spectra: *Bruker Avance-300* and *Varian Gemini-200* spectrometers; chemical shifts δ 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$_3$N (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$_2$O (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$_2$S$_2$O$_3$ 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-4H-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)-4H-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-4H-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)-4H-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).

REFERENCES

[1] K. Utimoto, H. Miwa, H. Nozaki, *Tetrahedron Lett.* **1981**, *22*, 4277; A. V. Kelin, A. W. Sromek, V. Gevorgyan, *J. Am. Chem. Soc.* **2001**, *123*, 2074.

[2] A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Muller, *Chem. Commun.* **2005**, 2581; A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Muller, *Eur. J. Org. Chem.* **2006**, *13*, 2991.

[3] H. Arzoumanian, M. Jean, D. Nuel, A. Cabrera, J. L. G. Gutierrez, N. Rosas, *Organometallics* **1995**, *14*, 5438; B. G. Van den Hoven, B. El Ali, H. Alper, *J. Org. Chem.* **2000**, *65*, 4131; V. Lellek, H.-J. Hansen, *Helv. Chim. Acta* **2001**, *84*, 3548.

[4] D. B. Grotjahn, S. Van, D. Combs, D. A. Lev, C. Schneider, M. Rideout, C. Meyer, G. Hernandez, L. Mejorado, *J. Org. Chem.* **2002**, *67*, 9200; G. Cabarrocas, M. Ventura, M. Maestro, J. Mahia, J. M. Villalgordo, *Tetrahedron: Asymmetry* **2000**, *11*, 2483; X. Wang, J. Tan, L. Zhang, *Org. Lett.* **2000**, *2*, 3107.

[5] J. P. Waldo, R. C. Larock, *Org. Lett.* **2005**, *7*, 5203.

[6] A. S. Karpov, T. J. J. Muller, *Org. Lett.* **2003**, *5*, 3451; M. C. Bagley, D. D. Hughes, P. H. Taylor, *Synlett* **2003**, 259.

[7] M. C. Bagley, D. D. Hughes, R. Lloyd, V. E. C. Powers, *Tetrahedron Lett.* **2001**, *42*, 6585; A. Arcadi, F. Marinelli, E. Rossi, *Tetrahedron* **1999**, *55*, 13233.

[8] C. Zhou, A. V. Dubrovsky, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 1626.

[9] a) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874, and refs. cited therein; b) L. Chen, C. J. Li, *Org. Lett.* **2003**, *5*, 3451; c) D. A. Alonso, C. Najera, M. C. Pacheco, *J. Org. Chem.* **2004**, *69*, 1615.

[10] M. Seki, *Synthesis* **2006**, 2975; L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133.

[11] A. Eisenstadt, European Patent EP0461322, 1990.

[12] Y. H. Joo, J. K. Kim, S. H. Kang, M. S. Noh, J. Y. Ha, J. K. Choi, K. M. Lim, C. H. Lee, S. Chung, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413; E. S. C. Wu, T. E. Cole, T. A. Davidson, J. C. Blosser, A. R. Borrelli, C. R. Kinsolving, T. E. Milgate, R. B. Parker, *J. Med. Chem.* **1987**, *30*, 788; E. S. C. Wu, T. E. Cole, T. A. Davidson, M. A. Dailey, K. G. Doring, M. Fedorchuk, J. T. Loch III, T. L. Thomas, J. C. Blosser, A. R. Borrelli, C. R. Kinsolving, R. B. Parker, *J. Med. Chem.* **1989**, *32*, 183; E. S. C. Wu, J. T. Loch III, B. H. Toder, A. R. Borrelli, D. Gawlak, L. A. Radov, N. P. Gensmante, *J. Med. Chem.* **1992**, *35*, 3519.
[13] N. Ahmed, C. Dubuc, J. Rousseau, F. Bénard, J. Lier, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3212.
[14] V. Nair, A. Deepthi, *Chem. Rev.* **2007**, *107*, 1862; F. J. Zhang, Y. L. Li, *Synthesis* **1993**, 565.