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Copper-, ligand- and solvent-free synthesis of ynones by coupling acid chlorides with terminal alkynes

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Abstract—A general and efficient copper-, ligand- and solvent-free synthesis of ynones by coupling of a wide range of acid chlorides with terminal alkynes catalyzed by palladium(II) acetate at room temperature is reported.

Ynones are of considerable synthetic interest because of their widespread occurrence among natural products and their physiological properties.[1] They are extremely versatile intermediates for the synthesis of important biologically active heterocycles.[2] The synthesis of ynones via the palladium catalyzed coupling of acid chlorides and terminal alkynes has been widely employed due to the versatile nature of this protocol, increased functional group tolerance and improved yields. As a part of our continuing interest in palladium catalyzed carbon–carbon cross-coupling reactions, we recently reported ligand- and copper-free Sonogashira reactions at ambient temperature under ultrasonic irradiation.[3] We have now extended our studies to the synthesis of ynones by coupling acid chlorides with terminal alkynes.

Hagihara and co-workers, reported the synthesis of 1-alkynyl ketones by coupling terminal alkynes with acid chlorides catalyzed by $PdCl_2(PPh_3)_2$/CuI in Et_3N, but the reactions were limited by unwanted side reactions between the acid chlorides and the Et_3N solvent, reducing the yields.[4] Recently, Najera and co-workers, reported a similar reaction catalyzed by an oxime derived palladacycle under phosphine and copper free conditions at high temperature in toluene using 3 equiv of Et_3N as the base.[5] In their study, they also reported the coupling of acid chlorides with terminal alkynes employing $Pd(OAc)_2$ as the catalyst, but requiring much longer reaction times (23 h) with lowered yields. Chen and Li, reported the synthesis of ynones, catalyzed by $PdCl_2(PPh_3)_2$/CuI with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base in water.[6] However, their methodology involved the use of 5 mol % CuI and the reactions were carried out at 65 °C for 4 h. More recently, Cox et al. reported the room temperature palladium catalyzed coupling of acyl chlorides with terminal alkynes.[7] Their

Table 1. Comparison of the reaction conditions and the results of coupling of benzoyl chloride with phenyl acetylene at room temperature

Entry	Author	Pd complex (mol %)	CuI (mol %)	Solvent	Time	Yield (%)	Reference
1	Hagihara and co-workers	$PdCl_2(PPh_3)_2$ (0.1)	0.5	Et_3N	15 h	96	4
2	Najera and co-workers	$Pd(OAc)_2$ (0.5)	None	Toluene	23 h	99[a]	5
3	Chen and Li	$PdCl_2(PPh_3)_2$ (2)	5	Water	4 h[b]	98	6
4	Cox et al.	$PdCl_2(PPh_3)_2$ (0.9)	3	THF	10 min	96	7
5	Present report	$Pd(OAc)_2$ (0.2)	None	None	10 min	93	

[a] GC yield.
[b] Reaction was carried at 65 °C.

Keywords: Ynones; Ligandless; Neat.
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Table 2. Effect of solvent on the coupling of benzoyl chloride with phenyl acetylene

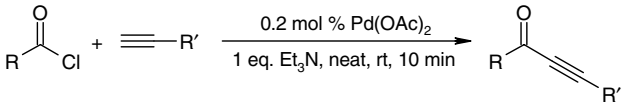
Entry	Solvent	Yield[a] (%)
1	Et_3N	60
2	Toluene	87
3	CH_2Cl_2	85
4	THF	51
5	DMF	46
6	Acetonitrile	30
7	Neat	93[b]

[a] Isolated yield.
[b] Reaction time 10 min.

protocol also involves the use of CuI and $PdCl_2(PPh_3)_2$ in THF.

A comparative study of the reaction conditions and results for the palladium catalyzed cross-coupling of benzoyl chloride with phenyl acetylene using the methods described above and that reported in the present letter is recorded in Table 1 which clearly demonstrates the advantages of the present methodology. It should also be noted that almost all the methods reported so far make use of an excess of the acid chloride (1.5–2 mol per mole of phenyl acetylene) and Et_3N

Table 3. Synthesis of ynones by coupling of acid chlorides with terminal alkynes[a]



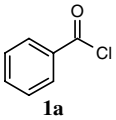
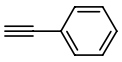
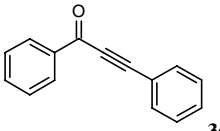
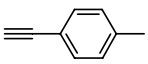
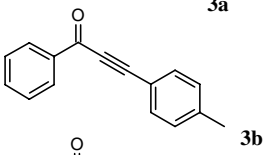
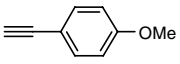
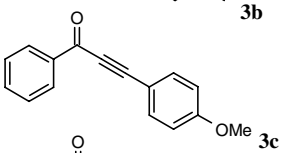
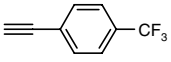
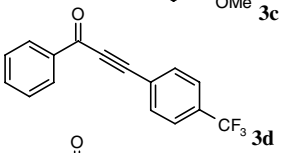
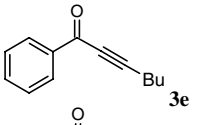
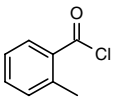
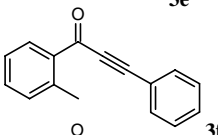
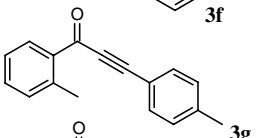
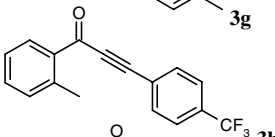
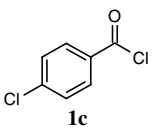
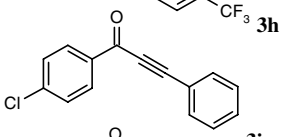
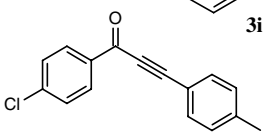
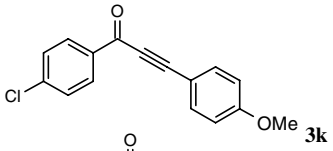
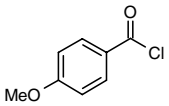
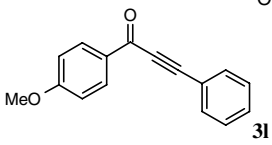
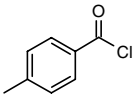
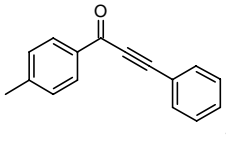
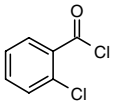
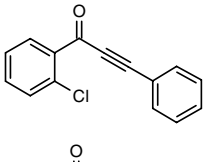
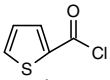
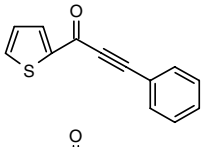
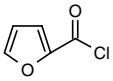
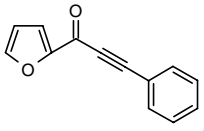
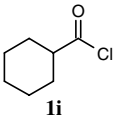
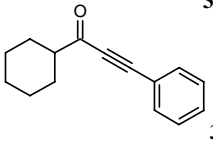
Entry	Alkyne **1**	Acetylene **2**	Product **3**	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	93
2	**1a**	 **2b**	 **3b**	84
3	**1a**	 **2c**	 **3c**	82
4	**1a**	 **2d**	 **3d**	65
5	**1a**	 **2e**	 **3e**	40[c]
6	 **1b**	**2a**	 **3f**	98
7	**1b**	**2b**	 **3g**	75
8	**1b**	**2d**	 **3h**	93
9	 **1c**	**2a**	 **3i**	86
10	**1c**	**2b**	 **3j**	93

Table 3 (*continued*)

Entry	Alkyne **1**	Acetylene **2**	Product **3**	Yield[b] (%)
11	**1c**	**2c**	 **3k**	84
12	 **1d**	**2a**	 **3l**	93
13	 **1e**	**2a**	 **3m**	95
14	 **1f**	**2a**	 **3n**	95
15	 **1g**	**2a**	 **3o**	91
16	 **1h**	**2a**	 **3p**	85
17	 **1i**	**2a**	 **3q**	89

[a] Reaction conditions: acid chloride (1 mmol), 1-alkyne (1 mmol), $Pd(OAc)_2$ (0.2 mol %) and Et_3N (1 mmol).
[b] Isolated yields.
[c] Reaction time was 3 h.

(2–3 equiv). In the present letter, we report a simple and efficient ligandless, copper- and solvent-free room temperature palladium catalyzed synthesis of ynones by coupling acyl chlorides with terminal alkynes which makes use of only 1 equiv of acid chloride and 1 equiv of Et_3N, respectively, and a relatively low amount of catalyst loading (0.2 mol %). The reaction tolerates a wide range of functional groups giving isolated purified products in high yields.

In the present study, we first tested the role of solvent for the coupling of benzoyl chloride with phenyl acetylene. The results are reported in Table 2. It was noted that toluene and dichloromethane were good solvents for this coupling reaction. However, dipolar aprotic solvents, such as THF, DMF and acetonitrile, gave inferior results with the formation of the corresponding anhydride as a side product. To our surprise, when the reaction was performed without a solvent the highest yield of product was obtained. Consequently, all further reactions were performed neat under anhydrous conditions and the results are recorded in Table 3.

Table 3 shows that the reaction is equally facile with both electron donating and electron withdrawing substituents present on the aryl ring of both the aroyl chloride and the terminal alkyne resulting in excellent isolated yields of ynones. Hetero-aryl acid chlorides, such as 2-thiophene carbonyl chloride (Table 3, entry 15) and furoyl chloride (Table 3, entry 16), reacted smoothly with phenyl acetylene to give the isolated products in 91% and 85% yields, respectively. Cyclohexane acid chloride also afforded the desired product in 89% isolated yield. The reaction was sluggish in the case of the aliphatic alkyne, 1-hexyne (Table 3, entry 5), giving a relatively lower yield after a much longer time (3 h).

In conclusion, we have developed a simple, efficient and rapid copper-, ligand- and solvent-free synthesis of ynones at room temperature by the coupling of a variety of acid chlorides with terminal alkynes, catalyzed by $Pd(OAc)_2$ using Et_3N as the base.[8] The rapid reaction time, high selectivity and excellent isolated yields make the method well suited to generate a combinatorial library of a diverse array of ynones.

Acknowledgements

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8. *General procedure for ynone synthesis*: A mixture of acid chloride (1 mmol), terminal alkyne (1 mmol), Et_3N (1 mmol) and $Pd(OAc)_2$ (0.2 mol%) was stirred at room temperature for 10 min under an atmosphere of argon. Completion of the reaction was monitored by TLC. After completion, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water to dissolve the amine hydrochloride formed. The organic layer was then separated, dried over magnesium sulfate, filtered and concentrated under vacuum to obtain the crude product. The crude product was further purified by column chromatography using ethyl acetate/petroleum ether as eluent to afford the desired product.

Analytical data for some representative compounds.

1-Phenyl-3-p-tolylprop-2-yn-1-one **3b**. Colourless solid; mp 60–61 °C; IR (film, cm^{-1}) 3018, 2196, 1637, 1215, 700; ^1H NMR (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.23 (d, 2H, $J = 8.08$ Hz), 7.47–7.67 (m, 5H), 8.23 (dt, 2H, $J = 6.96$ Hz, 1.64 Hz); ^{13}C NMR (50 Hz, $CDCl_3$): δ 21.7, 86.7, 93.7, 116.9, 128.5, 129.4, 133.0, 133.9, 136.9, 141.5, 177.9. Anal. Calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.15; H, 5.43.

3-(4-(Trifluoromethyl)phenyl)-1-o-tolylprop-2-yn-1-one **3h**. Colourless solid; mp 72 °C; IR (film, cm^{-1}) 2926, 2160, 1650, 1303, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 2.68 (s, 3H), 7.26–7.54 (m, 3H), 7.67 (d, 2H, $J = 8.48$ Hz), 7.77 (d, 2H, $J = 8.21$ Hz), 8.29 (d, 1H, $J = 7.50$ Hz); ^{13}C NMR (50 Hz, $CDCl_3$): δ 21.9, 89.2, 89.5, 120.7, 124.2, 125.6, 125.9, 131.7, 132.3, 132.9, 133.2, 135.3, 140.7, 179.2. Anal. Calcd for $C_{17}H_{11}F_3O$: C, 70.83; H, 3.85. Found: C, 70.81; H, 3.71.

1-(4-Chlorophenyl)-3-p-tolylprop-2-yn-1-one **3j**. Colourless solid; mp 117–119 °C; IR (film, cm^{-1}) 3019, 2196, 1636, 1215, 668; ^1H NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.23 (d, 2H, $J = 8.09$ Hz), 7.48 (d, 2H, $J = 8.65$ Hz), 7.57 (d, 2H, $J = 8.07$ Hz) 8.15 (d, 2H, $J = 8.71$ Hz); ^{13}C NMR (50 Hz, $CDCl_3$): δ 21.7, 86.4, 94.3, 116.7, 128.9, 129.5, 130.7, 133.1, 135.3, 140.5, 141.7, 176.6. Anal. Calcd for $C_{16}H_{11}ClO$: C, 75.45; H, 4.35. Found: C, 75.78; H, 4.31.

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one **3k**. Colourless solid; mp 116–117 °C; IR (film, cm^{-1}) 3019, 2192, 1635, 1215, 758; ^1H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.86 (dt, 2H, $J = 9.07$, 1.94 Hz), 7.41 (dt, 2H, $J = 8.75$, 1.89 Hz), 7.56 (dt, 2H, $J = 8.91$, 2.11 Hz), 8.07 (dt, 2H, $J = 8.75$, 2.05 Hz); ^{13}C NMR (50 Hz, $CDCl_3$): δ 55.3, 86.5, 94.8, 111.5, 114.4, 128.8, 130.7, 135.1, 135.3, 140.3, 161.8, 176.5. Anal. Calcd for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.10. Found: C, 70.84; H, 4.42.

3-Phenyl-1-(thiophen-2-yl)prop-2-yn-1-one **3o**. Colourless solid; mp 53–54 °C; IR (film, cm^{-1}) 3016, 2200, 1618, 1411, 756; ^1H NMR (200 MHz, $CDCl_3$): δ 7.17–7.21 (m, 1H), 7.37–7.53 (m, 3H), 7.64–7.74 (m, 3H), 8.01 (dd, 1H, $J = 2.96$, 1.31 Hz); ^{13}C NMR (50 Hz, $CDCl_3$): δ 86.4, 91.6, 119.7, 128.3, 128.6, 130.7, 132.8, 135.2, 144.8, 169.6. Anal. Calcd for $C_{13}H_8OS$: C, 73.56; H, 3.80. Found: C, 73.48; H, 4.16.