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A Remarkably Efficient Coupling of Acid Chlorides with Alkynes in Water

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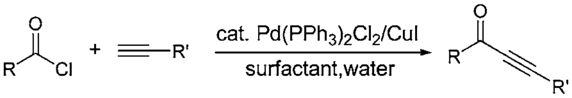
ABSTRACT



A highly effective direct coupling of acid chloride with terminal alkynes catalyzed by $PdCl_2(PPh_3)_2$/CuI together with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base provided ynones in high yields in water.

The utilization of ynones is a common strategy in the synthesis of many biologically important compounds.[1] Traditionally, ynones are generally synthesized via the coupling of carboxylic acid chlorides and lithium acetylides.[2] However, such a reaction is quite drastic and lacks chemical selectivity in the presence of other electrophiles. Functional groups such as hydroxyls, acids, amines, aldehydes, ketones, etc. also have to be protected prior to the reaction. More recently, an alternative coupling of carboxylic acid halides with terminal alkynes has been developed by using palladium[3] and copper catalysts,[4] which can proceed at mild conditions and enhanced chemoselectivities. However, anhydrous conditions, protected acidic functional groups (such as hydroxyl), and an organic base are essential for such reactions.

There has been considerable recent attention toward the development of carbon−carbon bond formation reactions in water.[5] An underlining implication of such reactions is their tolerance to various functional groups, and thus the protection−deprotection processes for certain acidic-hydrogen-containing functional groups can be avoided, which contributes to the overall synthetic efficiency.[6] Additionally, water-soluble compounds, such as carbohydrates, can be directly

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Table 1. Direct Coupling of Phenylacetylene and Benzoyl Chloride in Water[a]

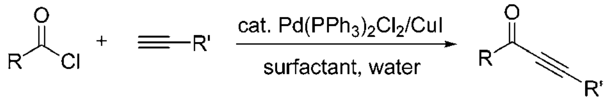
entry	catalyst	additive/base	yield (%)
1	5% CuI	sodium laurylsulfate/K_2CO_3	<5[b]
2	5% $Pd(OAc)_2$	sodium laurylsulfate/K_2CO_3	nr
3	5% $Pd(OAc)_2$/10%TDMPP[c]	sodium laurylsulfate/K_2CO_3	nr
4	2% $PdCl_2(PPh_3)_2$	sodium laurylsulfate/K_2CO_3	nr
5	5% $Pd(OAc)_2$/5% CuI	sodium laurylsulfate/K_2CO_3	nr
6	5% $Pd(OAc)_2$/10% tricyclohexylphosphine/5% CuI	sodium laurylsulfate/K_2CO_3	nr
7	5% $Pd(OAc)_2$/10% TDMPP[c]/5% CuI	sodium laurylsulfate/K_2CO_3	29
8	5% $Pd(OAc)_2$/10% $P(OMe)_3$	sodium laurylsulfate/K_2CO_3	83
9	**2% $PdCl_2(PPh_3)2$/5% CuI**	**sodium laurylsulfate/K_2CO_3**	**98**
10	2% $PdCl_2(PPh_3)2$/5% CuBr	sodium laurylsulfate/K_2CO_3	92
11	2% $PdCl_2(PPh_3)2$/5% CuCl	sodium laurylsulfate/K_2CO_3	11
12	2% $PdCl_2(PPh_3)2$/5% CuCN	sodium laurylsulfate/K_2CO_3	50
13	2% $PdCl_2(PPh_3)_2$/5% AgI	sodium laurylsulfate/K_2CO_3	<5[b]
14	2% $PdCl_2(PPh_3)_2$/5% CuI	cetyltrimethylammonium bromide/K_2CO_3	33
15	2% $PdCl_2(PPh_3)_2$/5% CuI	triethylbenzylammonium bromide/K_2CO_3	27
16	2% $PdCl_2(PPh_3)_2$/5% CuI	none/K_2CO_3	9
17	2% $PdCl_2(PPh_3)_2$/5% CuI	sodium laurylsulfate/NaOH	46
18	2% $PdCl_2(PPh_3)_2$/5% CuI	sodium laurylsulfate/$NaHCO_3$	16

[a] Conditions: 1 mmol of phenylacetylene, 2 mmol of benzoyl chloride, 20 mg of additives, and 3 mmol of base were used in 1 mL of water at 65 °C for 4 h. [b] Determined by ^1H NMR. [c] Tris(2,6-dimethoxylphenyl)phosphine.

reacted without the need for derivatization and water-soluble catalysts provide a way for product isolation and catalyst recycling.[7] Among the many carbon−carbon bond formation reactions, recently various Barbier−Grignard reactions have been successful in water.[8]

In light of the current interest in developing new fundamental reactions that could lead to high synthetic efficiency, it is highly desirable to develop a direct coupling of carboxylic acid chlorides with terminal alkynes in water. However, as it is common knowledge that carboxylic acid halides are quite water-sensitive (leading to rapid hydrolysis), such an aspiration seems virtually impossible. On the other hand, the well-known Schotten−Baumann method utilizes strong nucleophiles, such as alcohols or amines, to attack acid chloride in aqueous media.[9] Nevertheless, herein we wish to report for the first time a remarkably efficient coupling of carboxylic acid chlorides with terminal alkynes that has a relatively weak nucleophilicity in water (Scheme 1).

Scheme 1



There are two competitive reactions related to carboxylic acid chlorides in water: (1) hydrolysis by water and (2) coupling reaction with terminal alkynes in the presence of a catalyst. Furthermore, the solvent water molecule has a stronger nucleophilicity (compared to that of the terminal alkynes) toward the carboxylic acid chlorides. To overcome the thermodynamically unfavorable reactivity of carboxylic acid chlorides with alkynes in the presence of water, we hypothesized that the use of a surfactant would decrease the kinetics of hydrolysis by preventing and/or diminishing the acid chlorides from encountering the water molecules.[10] In addition, water can dissolve the HCl generated from the coupling reaction, which will further drive the reaction toward the formation of the desired product. The coupling of phenylacetylene with benzoyl chloride was used to optimize the reaction conditions, and the results are summarized in Table 1.

At first, we tested the stability of carboxylic acid chlorides in water. It showed benzoyl chloride was converted into benzoic acid completely (recovery of benzoic acid >99%) at 65 °C for 4 h. The use of $PdCl_2(PPh_3)_2$/CuI as cocatalysts together with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base provided the desired

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(6) For examples, see: Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 6674. Chan, T. H.; Li, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 747. Chappell, M. D.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2003. Warwel, M.; Fessner, W. D. *Synlett* **2000**, 865. Canac, Y.; Levoirier, E.; Lubineau, A. *J. Org. Chem.* **2001**, *66*, 3206.

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Table 2. Ynones via the Coupling of Terminal Alkynes with Acid Chlorides in Water[a]

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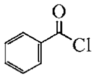
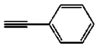
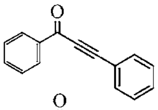
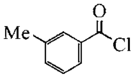
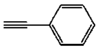
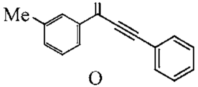
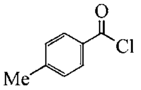
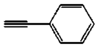
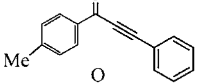
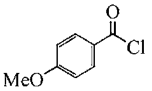
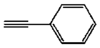
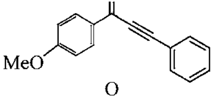
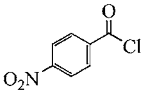
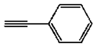
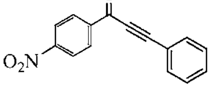
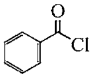
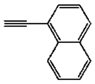
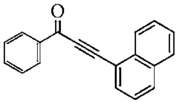
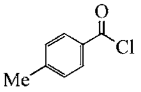
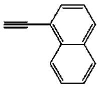
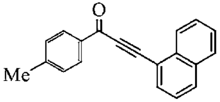
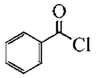
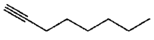
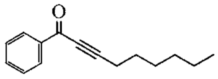
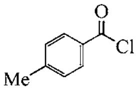
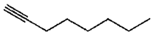
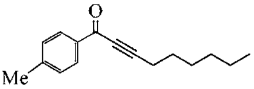
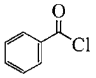
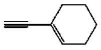
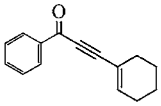
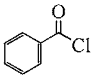
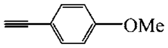
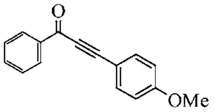
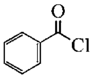
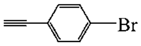
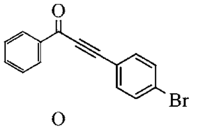
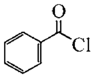
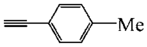
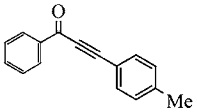
1				98
2				99
3				98
4				82
5				51[b]
6				80
7				97
8				66
9				77
10				83
11				99
12				88
13				92

[a] Reactions were carried out using 1 mmol of terminal alkynes, 2 mmol of acid chlorides, 20 mg of sodium lauryl sulfate (7 mol%), 14 mg of $PdCl_2(PPh_3)_2$(2 mol%), 10 mg of CuI (5 mol%), and 414 mg of K_2CO_3 (3 mmol) in 1 mL of water at 65 °C for 4 h. [b] 4-Nitrobenzoyl chloride was dissolved in 200 mg of toluene before adding as a starting material.

product in 98% isolated yield (entry 9). No reaction was observed when either Cu(I) alone or Pd(II) alone was used as the catalyst (entries 1−4). The use of surfactant is also critical for the success of the reaction; without a surfactant/ phase-transfer reagent the yield dropped from 98% to 9% (compare entries 9 and 16). Sodium lauryl sulfate is the most effective surfactant/ phase-transfer agent (compare entries 9, 14, 15) for the current coupling under the same reaction conditions. The strength of the base also played a role in the reaction: the use of either stronger base NaOH or weaker base $NaHCO_3$ decreased the yield of the reaction (entries 17 and 18).

Subsequently, various acid chlorides were coupled with terminal alkynes under the optimized conditions (Table 2). Both aliphatic and aromatic alkynes are effective for the current reaction. Nearly quantitative yields were obtained in almost all cases when both aromatic acid chlorides and aromatic alkynes were used, with an exception of *p*-nitrobenzoyl chloride, which can be attributed to the solid nature of the compound. The use of aliphatic alkynes decreased the yields slightly. It is interesting to note that the aryl bromide functionality remained unaffected during the reaction (entry 12).

In summary, a highly effective direct coupling of acid chlorides with terminal alkynes catalyzed by $PdCl_2(PPh_3)_2$/CuI together with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base provided ynones in high yields in water. The scope, mechanism, and synthetic applications of this reaction are currently under investigation.

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Supporting Information Available: Representative experimental procedure and the full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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