

A copper-, phosphorous- and solvent-free coupling of acyl halides with terminal alkynes catalyzed by palladium-Cryptand-22 complex under aerobic conditions

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Abstract:

The copper-, phosphorous- and solvent-free coupling reaction of terminal alkynes with different acyl chlorides was performed using palladium-Cryptand-22 complex as an efficient catalyst in the presence of triethylamine as base, at room temperature and under aerobic conditions. The simple, mild and green procedure, short reaction times and moderate to excellent yields make this method well-suited for ynones' synthesis.

Keywords:

Ynones; Terminal alkynes; Pd-C22; Acyl chlorides; Solvent-free reaction; Copper-free coupling.

1. Introduction

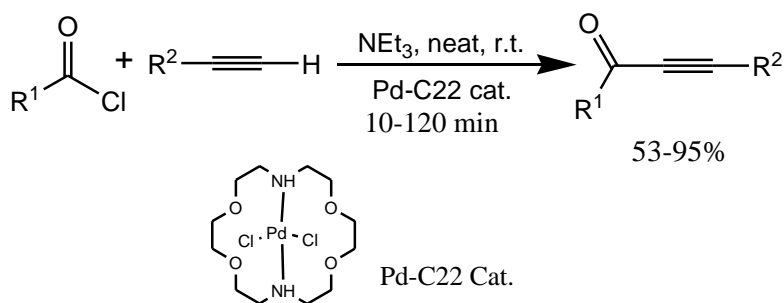
α,β -Acetylenic ketones (Ynones) are useful synthetic intermediates for the preparation of many biologically-active compounds and heterocyclic derivatives [1-3].

Various methodologies for the preparation of ynones have been reported which include: (a) oxidation of propargylic alcohols [4] which are usually obtained by nucleophilic addition of acetylides to aldehydes, (b) cross-coupling reaction of terminal alkynes with organic halides in the presence of carbon- monoxide gas [5-7], (c) oxidation of alkynes [8-10], (d) reaction of terminal alkynes with nitriles [11] and the (e) the reaction between terminal alkynes and carboxylic acid derivatives such as acid chlorides, acid anhydrides, esters, and acyl cyanides [12]. Strong bases such as *n*-BuLi [13, 14] and elements such as silver [15], zinc [16], tin [17], indium [18], gallium [19], silicon [20], lithium [21], boron [22], palladium [23] and copper [24] could be used in these reactions. However, the above synthetic protocols suffer from serious

disadvantages such as long reaction times [25], high temperatures [26, 27], use of air and moisture sensitive catalysts such as phosphorous containing catalysts [28-31], use of copper catalysts, use of hazardous organic solvents [32], use of toxic carbon-monoxide gas, need of special instruments [33] and difficult catalyst preparation methods. Taking these constraints into account, the development of new, mild, simple and efficient copper- and phosphorous-free synthetic procedures would have significant value.

2. Results and discussion

The coupling between phenyl acetylene and benzoyl chloride was chosen as a model reaction to find out the optimum reaction conditions (Scheme 1).



The best molar ratio of the reactants at ambient temperature and in the presence of NEt_3 as base was obtained to be 1:1:1.2 regarding to benzoyl chloride, phenyl acetylene and NEt_3 respectively. The highest yield of the product was obtained when the reaction was performed under solvent-free conditions. The reaction also worked in DMF and CH_3CN albeit in low yields (17 and 54 % respectively). The catalyst used in this work was Pd-Cryptand-22 which could be easily prepared according to the method described by Sun et al. [34]. The optimum amount of the catalyst was found to be 0.9 mol% (95%), as the yield of the product decreased when higher (2 mol%, 73%) or lower (0.5 mol%, 61%) amounts were used.

To examine the scope of this coupling reaction, different terminal alkynes (aliphatic and aromatic) with various acid chlorides (aliphatic, aromatic and heteroaromatic) were used (Table 1). As shown in Table 1, aromatic terminal alkynes proceeded at relatively higher rates compared with that of aliphatic ones. Both aryl and alkyl acid chlorides coupled with alkynes in a solvent-free condition in air and at

ambient temperature. The reaction was almost equally facile with both electron-donating and electron-withdrawing substituents on the aroyl chlorides. Besides, no significant steric effect was observed owing to the presence of the methyl group at the ortho position of 2-methylbenzoyl chloride. Heteroaryl acid chlorides such as 2-thiophene carbonyl chloride and 2-furane carbonyl chloride also reacted with terminal alkynes to give the products in high yields.

Table 1

C-C Coupling reaction of acyl chlorides and terminal alkynes.

Entry	R ¹	R ²	Product ^a	Time (h)	Yield (%) ^b
1	Ph	Ph	3a ³⁰	1	95
2	2-Me-C ₆ H ₄	Ph	3b ³⁰	0.75	92
3	2-Thienyl	Ph	3c ³⁰	1	93
4	2-Furyl	Ph	3d ³⁰	1	94
5	4-Cl-C ₆ H ₄	Ph	3e ³⁰	0.92	88
6	4-MeO-C ₆ H ₄	Ph	3f ³⁰	1	87
7	4-NO ₂ -C ₆ H ₄	Ph	3g ²²	0.83	89
8	<i>c</i> -C ₆ H ₁₁	Ph	3h ³⁰	0.5	86
9	4-CN-C ₆ H ₄	Ph	3i ³³	0.17	89
10	4-MeO-C ₆ H ₄	<i>n</i> -C ₄ H ₉	3j ²⁸	1.25	60
11	2-Me-C ₆ H ₄	<i>n</i> -C ₄ H ₉	3k ¹⁶	1	64
12	2-Thienyl	<i>n</i> -C ₄ H ₉	3l ¹⁶	1.5	70
13	4-MeO-C ₆ H ₄	<i>n</i> -C ₆ H ₁₃	3m ²³	1.17	53
14	<i>c</i> -C ₆ H ₁₁	<i>n</i> -C ₆ H ₁₃	3n ²⁸	2	57

^aReferences provided for known compounds. ^b Isolated yields.

3. Conclusion

In summary, we have successfully demonstrated a solvent-, copper- and phosphorous-free cross-coupling reaction of terminal alkynes with acyl halides catalyzed by Pd-C22. The simple, mild and green procedure, short reaction times and moderate to excellent yields make this method well-suited for ynone synthesis.

4. Experimental

General procedure for ynone synthesis:

A mixture of acid chloride (1.0 mmol), terminal alkyne (1.0 mmol), NEt_3 (1.2 mmol) and Pd-C22 (0.9 mol%) was stirred at room temperature (25 °C) under aerial and solvent-free conditions. The progress of the reaction was monitored by TLC. After completion, chloroform (10 mL) was added to the reaction mixture. The organic layer was washed with water (2× 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was further purified by preparative TLC (silica gel) using *n*-hexane/EtOAc (9:1) to afford the desired product. All compounds were characterized by IR, ^1H and ^{13}C NMR spectroscopy. Compound (**3c**): Brown solid (mp 55-57 °C); IR (KBr): $\nu = 2921, 2197, 1632 \text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 300 MHz): $\delta = 8.01$ (d, $J = 3.8 \text{ Hz}$, 1H), 7.73 (d, $J = 4.9 \text{ Hz}$, 1H), 7.66 (d, $J = 7.5 \text{ Hz}$, 2H), 7.39-7.51 (m, 3H), 7.19 (t, $J = 4.1 \text{ Hz}$, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 169.8, 144.9, 135.3, 135.1, 133.1, 130.9, 128.7, 128.4, 119.9, 91.8, 86.5$; (**3g**): Brown solid (mp 154-156 °C); IR (KBr): $\nu = 2929, 2197, 1646 \text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 300 MHz): $\delta = 8.38$ (s, 4H), 7.71 (d, $J = 8.1 \text{ Hz}$, 2H), 7.54 (t, $J = 6.6 \text{ Hz}$, 1H), 7.46 (t, $J = 7.5 \text{ Hz}$, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 175.9, 150.9, 141.0, 133.3, 131.5, 130.4, 128.9, 123.9, 119.4, 95.4, 86.5$; (**3j**): Yellow oil; IR (neat): $\nu = 2962, 2238, 2202, 1632 \text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 300 MHz): $\delta = 8.08$ -8.13 (m, 2H), 6.91-6.97 (m, 2H), 3.88 (s, 3H), 2.49 (t, $J = 7.1 \text{ Hz}$, 2H), 1.66 (quint, $J = 7.0 \text{ Hz}$, 2H), 1.51 (sext, $J = 7.1 \text{ Hz}$, 2H), 0.96 (t, $J = 7.3 \text{ Hz}$, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 177.1, 164.3, 131.9, 113.7, 113.6, 95.9, 79.6, 55.6, 29.9, 22.1, 18.9, 13.5$.

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