

A Novel Palladium-Catalyzed Coupling of Thiol Esters with 1-Alkynes

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Abstract: A new method for synthesizing α,β -acetylenic ketones by palladium-mediated coupling of thiol esters with 1-alkynes is described. The reaction could be applied to coupling of thiol esters bearing various functional groups, such as aromatic bromides, and ketones, with functionalized terminal acetylenes.

Key words: 1-alkynyl ketones, thiol esters, Sonogashira-type coupling reaction, palladium, copper

α,β -Acetylenic ketones are useful synthetic precursors of compounds such as chiral propargyl alcohols,¹ α,β -unsaturated ketones, dienones,² allylic alcohols, as well as a variety of Michael addition products, and thus have served as crucial intermediates for the synthesis of several natural products.³ Among the synthetic methods which have been developed to date,⁴ the most reliable and widely used are reactions of metal acetylides with carboxylic acid derivatives,⁵ and palladium-catalyzed coupling of acyl halides with terminal alkynes in the presence of copper(I) and amines.^{6–8} With respect to functional group compatibility, these methods are limited in scope since the former protocol requires strong base to generate metal acetylides and the latter necessitates acidic conditions for the preparation of acid halides. In addition to these conventional methods, several unique protocols have been reported, including reaction of thiol esters and trimethylsilylacetylenes in the presence of AgBF_4 ,⁹ and Friedel–Crafts type acylations of trimethylsilyl alkynes.¹⁰ However, because of their lack of generality, none of the currently accessible protocols is suitable for the preparation of multifunctional α,β -ynones.

In the course of our investigation on the chemistry of thiol esters, we have reported a Pd-catalyzed reduction to aldehydes with triethylsilane,¹¹ and more recently, have described a ketone synthesis by Pd-catalyzed coupling with organozinc reagents.^{12,11c} These processes, which involve metal-catalyzed C–S bond scission and subsequent C–H or C–C bond formation, proceed under exceptionally mild conditions.¹³ Thus, their synthetic utility has been demonstrated by their applications to the synthesis of complex natural products.^{14,15} We now report a novel Pd-catalyzed coupling of thiol esters with 1-alkynes to furnish a range of α,β -acetylenic ketones.

Our project started with screening of the reaction conditions using 3-(4-methoxyphenyl)propionic acid ethanethiol ester (**1**) as the test substrate, which was readily prepared from the corresponding carboxylic acid by the mixed-anhydride method or with condensation reagents.¹² When **1** was subjected to the conventional Sonogashira conditions, the expected coupling product **2** was obtained, although the yield was often as low as 17% (Table 1, entry 1).⁶ We found that the yield was dramatically improved by addition of phosphine ligands, to a maximum of 64% using tri-2-furylphosphine (TFP, entry 5). Similar improvement by addition of ligand was also observed with other Pd-catalysts (entries 7–9). After extensive optimization, the desired ynone **2** was finally obtained in 93% isolated yield under the more concentrated conditions (0.5 M based on **1**) with a lower amount of reagents, [$\text{PdCl}_2(\text{dppf})$ (5 mol%), $\text{P}(2\text{-furyl})_3$ (12.5 mol%), and CuI (1.7 equiv)] (entry 10).¹⁶ In addition, the choice of solvent is also an

Table 1 Palladium-Catalyzed 1-Alkynyl Ketone Synthesis with Various Thiol Esters

Entry	Pd-catalyst	Ligand	Time (h)	Yield (%)
1	$\text{PdCl}_2(\text{PPh}_3)_2$	–	13	17
2	$\text{PdCl}_2(\text{dppf})$	–	5	34
3	$\text{PdCl}_2(\text{PPh}_3)_2$	PPh_3	7	60
4	$\text{PdCl}_2(\text{PPh}_3)_2$	BINAP ^b	7	63
5	$\text{PdCl}_2(\text{PPh}_3)_2$	TFP	6	64
6	$\text{Pd}(\text{OAc})_2$	DPPF ^b	8	48
7	$\text{Pd}(\text{OAc})_2$	TFP	6	76
8	$\text{Pd}_2(\text{dba})_3$	TFP	3	83
9	$\text{PdCl}_2(\text{dppf})$	TFP	3	87
10 ^c	$\text{PdCl}_2(\text{dppf})$	TFP	4	93

^a 0.2 M solution based on the concentration of **1** was used.

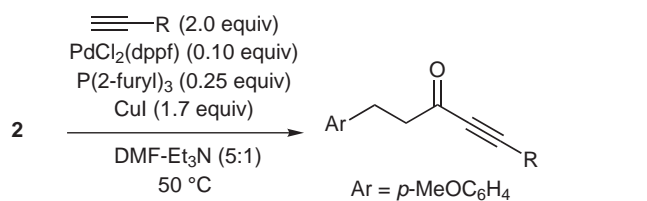
^b 0.30 Equiv of phosphines were used.

^c $\text{PdCl}_2(\text{dppf})$ (0.05 equiv), TFP (0.125 equiv), and CuI (1.7 equiv) were used in 0.5 M solution based on the concentration of **1**.

important factor. While the reaction in DMSO gave a comparable result (87%), other solvents such as acetonitrile, THF, toluene, and benzene were ineffective, providing only 25% to 46% yield of **2**.

Having established the optimal conditions, we then examined various alkynes as the coupling partner. As shown in Tables 2, 1-hexyne as well as an *O*-protected propargyl alcohol, an acetone adduct of acetylene, phenylacetylene, and trialkylsilylacetylenes¹⁷ smoothly reacted to afford the corresponding ynones in high yields (entries 2–6). It should be noted that even the highly functionalized acetylene, prepared¹⁸ from the Garner aldehyde,¹⁹ is compatible with the reaction conditions (entry 7).

Table 2 Palladium-Catalyzed 1-Alkynyl Ketone Synthesis with Various Thiol Esters



Entry	≡-R	Time (h)	Yield (%)
1		2	94
2		1	68
3		2	93
4		4	83
5		1	95
6		2	77
7 ^a		1	85

^a 1.2 Equiv of alkyne was used.

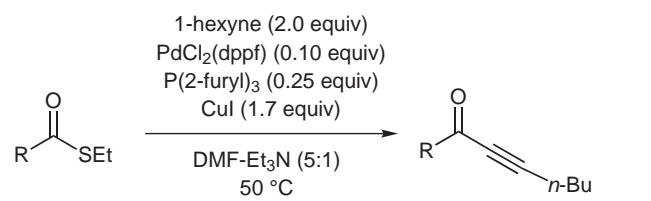
The generality of our method has been demonstrated using thiol esters bearing various functionalities (Table 3). In addition to the substrates derived from aliphatic carboxylic acids (entries 1–3), α,β -unsaturated and aryl²⁰ substrates could also be used under these reaction conditions (entries 4–7). It is noteworthy that several functional groups such as ketones, aromatic bromides, and chlorides are compatible with this protocol.

Although the mechanistic detail of this reaction is not clearly understood, the process would probably involve transmetalation between an acylpalladium species and the cuprous acetylides. Several experimental observations support this process. First, the reaction in the absence of

the Pd-catalyst gave only 3% of the coupling product **2** with recovery of **1** (90%) even after 24 hours at 50 °C. Second, it is crucial to use excess CuI, and the reaction with 0.5 equivalents of CuI afforded only 25% of **2**.²¹ These facts indicate that the copper(I) probably traps the thiolate anion after transmetalation, thereby preventing poisoning of the Pd-catalyst.

In summary, we have developed a mild and general method for the synthesis of α,β -alkynyl ketones from thiol esters. Because of the unusually high chemoselectivity, this protocol should provide a powerful alternative to the preparation of functionalized ynones and may find widespread use in organic synthesis.

Table 3 Palladium-Catalyzed 1-Alkynyl Ketone Synthesis with Various Thiol Esters



Entry	Substrate	Time (h)	Yield (%)
1		2	94
2		3	80
3		1	80
4		2	64
5		4	64
6		2	71 ^a
7		1	74 ^a

^a Ca. 15% of the starting compound was recovered. Prolonged reaction time gave the byproduct resulting from conjugate addition of ethanethiol to the product.

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- Typical Procedure:** To a solution of thiol ester **1** (1.00 g, 4.48 mmol), PdCl₂(dppf) (365 mg, 0.448 mmol), CuI (1.45 g, 7.61 mmol), and tri-2-furylphosphine (260 mg, 1.12 mmol) in a mixture of DMF (7.5 mL) and Et₃N (1.5 mL) was added 1-hexyne (1.02 mL, 892 mmol) at r.t. After stirring for 3 h at 50 °C, Celite was added to the mixture and the resulting suspension was stirred for 5 min. The mixture was diluted with Et₂O (50 mL) and the reaction was quenched by addition of H₂O (50 mL). The mixture was filtered through a pad of Celite and separated. The aqueous layer was extracted with Et₂O (20 mL × 2). The combined organic extracts were washed with brine (20 mL), dried over anhyd MgSO₄ and concentrated in vacuo. Purification by flash column chromatography on silica gel (40 g, 5–8% Et₂O/hexanes) gave 1.03 g (4.21 mmol, 94%) of α,β-alkynyl ketone **2** as a brown oil. Compound **2**: IR(film): 2958, 2871, 2214, 1671, 1513, 1247, 1178, 1036, 825 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.11 (d, *J* = 8.3 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 3.78 (s, 3 H), 2.92 (t, *J* = 6.8 Hz, 2 H), 2.83 (t, *J* = 7.1 Hz, 2 H), 2.37 (t, *J* = 6.8 Hz, 2 H), 1.58–1.52 (m, 2 H), 1.46–1.40 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 187.1, 158.0, 132.4, 129.2, 113.9, 94.8, 80.8, 55.2, 47.3, 29.7, 29.1, 21.9, 18.6, 13.5. HRMS (FAB): *m/z* calcd for C₁₆H₂₀O₂: 244.1463. Found: 244.1458.
- The reaction using trimethylsilylacetylene gave only recovered starting material **1**.
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- Since the aryl alkynyl ketone products are relatively active Michael-acceptors, the ethyl thiolate adducts were obtained as byproducts. For this reason, the reactions using those substrates were quenched while some starting material remained (Figure 1).

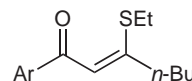


Figure 1

- The yield of **2** increased as the amount of CuI increased. The yields of **2** with no CuI, 0.5, 1.0, 1.5, 2.0, and 2.5 equiv are 11%, 25%, 33%, 62%, 65%, and 87%, respectively. However, addition of more than 3.0 equiv of CuI did not improve the yield.