Copper-Free Sonogashira Cross-Coupling of Ynamides: Easy Access to Various Substituted Ynamides from Nonsubstituted Ynamides

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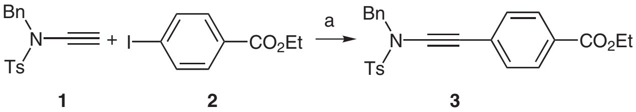
Abstract: It is demonstrated herein that palladium-catalyzed Sonogashira cross-coupling of ynamides can be accomplished with moderate to good yields of substituted ynamides in the absence of copper salt, and NaOAc plays an important role in this reaction as an additive.

Key words: carboxylate anion, copper-free, cross-coupling, palladium, ynamide

Ynamides should exhibit attractive reactivity because of their differences in π-orbital electron density compared to usual carbon–carbon triple bonds and should be useful synthons in synthetic organic chemistry.[1] Recently, several kinds of novel catalytic reactions of ynamides with transition-metal complexes have been reported.[2] We have studied the ring-closing metathesis of ynamides, which can be applied to useful synthetic methods for a wide range of heterocycles.[3] Encouraged by the success of our results, we have continued to try to develop a new transition-metal-catalyzed reaction of ynamides. Herein, we describe efficient copper-free Sonogashira cross-coupling[4,5] of ynamides, which provide substituted ynamides from nonsubstituted ones.



Scheme 1 Sonogashira cross-coupling of ynamide **1** catalyzed by palladium acetate. *Reagents and conditions*: a) $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), HCO_2NH_4 (1.5 equiv), DMF, 80 °C, 1 h, 74%.

When a reaction of ynamide **1** with aryl iodide **2** in the presence of 5 mol% of palladium acetate was carried out at 80 °C for one hour in DMF, Sonogashira cross-coupling proceeded smoothly to provide substituted ynamide **3** in 74% yield (Scheme 1).

It is well known that a dimerized product of ynamide is mainly obtained when an ynamide is exposed to a general Sonogashira cross-coupling conditions.[6] On the other hand, the Sonogashira cross-coupling of ynamides was reported by Hsung and co-workers.[7] This first Sonogashira coupling was achieved by a two-step procedure in which copper iodide was added after mixing an ynamide, aryl halide, and palladium complex in a solvent. The synthesis of 2-aminoindole derivatives, which was accomplished by the Sonogashira coupling of ynamides followed by hydroamination, was reported by Skrydstrup and coworkers[8] simultaneously with the finding of our result in Scheme 1. Unfortunately, the isolation of coupling products was not completed, although their synthesis should be achieved via a Sonogashira cross-coupling reaction. So we decided to examine the details of our coupling reaction of ynamides, because we were interested in this simple handling reaction that proceeded without a catalytic amount of copper salt to provide coupling product **3**[9] in good yield.

At first, several kinds of additives were examined and are shown in Table 1. When the reaction was carried out in the presence of ammonium acetate, a similar yield was obtained (Table 1, entry 2). An ammonium cation was not required for unimpeded coupling and excellent yield was obtained, when sodium acetate and potassium acetate were used (entry 3, 4). Although the organic base could be used for this reaction, the similar yield was obtained (entry 5). Furthermore, it is thought that the effective chemical species for this reaction is not the carbonate anion, as concluded from the lower yield observed using potassium carbonate and sodium hydrogen carbonate (entry 6, 7). It is suggested that the presence of the carboxylate anion and their basicity play the key roles from these results.

The effect of sodium acetate was examined (Table 2). When the reaction was carried out in the absence of sodium acetate, coupling product **3** was not obtained at all (entry 1). Enhancement of the yield of **3** was observed in the presence of 0.5 equivalent of the additive (entry 2), and a 60% yield of **3** was achieved by using a 1.0 equivalent of sodium acetate (entry 3). When 2.0 equivalents of sodium acetate were used, the yield resulted in a slight reduction relative to using 1.5 equivalents of the additive (entry 5).

The results of temperature effects are shown in Table 3. The yield was slightly reduced by decreasing the reaction temperature to 50 °C (entry 2). When the reaction was carried out at room temperature, the prolonged reaction time was required to provide the coupling product **3** in 76% yield (entry 3).

On the basis of these results, the optimum reaction conditions was defined as follows: Ynamide (1.0 equiv), aryl halide (1.2 equiv), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), NaOAc (1.5 equiv), DMF, 80 °C, 1 h.

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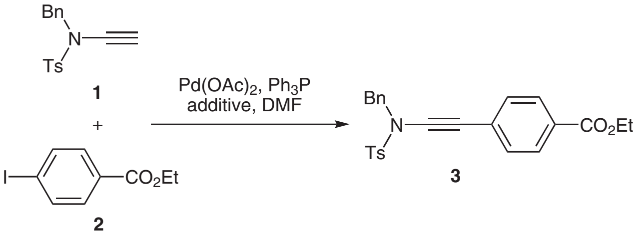
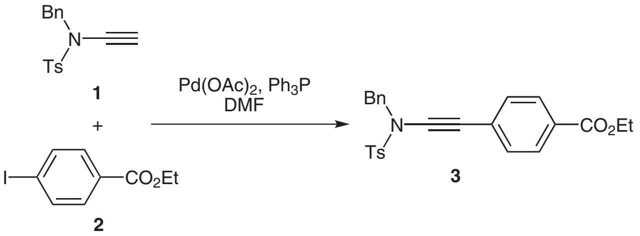
Table 1 Screening of Additives[a]



Entry	Additive (1.5 equiv)	Yield of **3** (%)[b]
1	HCO_2NH_4	74
2	NH_4OAc	74
3	NaOAc	75
4	KOAc	74
5	Et_3N	71
6	K_2CO_3	43
7	$NaHCO_3$	21

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), DMF, 80 °C, 1 h.
[b] Isolated yield.

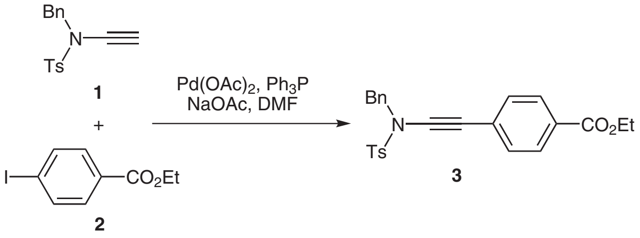
Table 2 Effect of the Amount of NaOAc[a]



Entry	NaOAc (equiv)	Yield of **3** (%)[b]
1	0	0
2	0.5	26
3	1.0	60
4	1.5	75
5	2.0	66

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), DMF, 80 °C, 1 h.
[b] Isolated yield.

Table 3 Effects of Temperature[a]

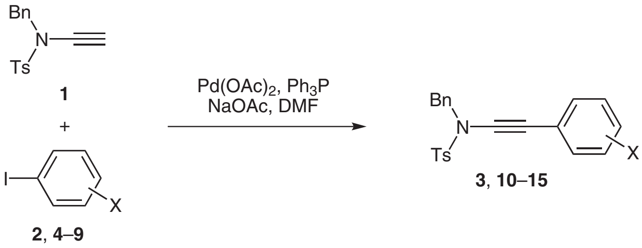


Entry	Temp (°C)	Time (h)	Yield of **3** (%)[b]
1	80	1	75
2	50	2	71
3	r.t.	5	76

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), NaOAc (1.5 equiv), DMF.
[b] Isolated yield.

The reactions of ynamide **1** with various aryl halides (**4**–**9**) were examined and are shown in Table 4. Good conversion and good product yield of **10** was obtained in the reaction of ynamide **1** with iodobenzene **4** (entry 2). The product yield decreased in the case of iodomethoxybenzene **5** which has an electron-donating group (entry 3). The reaction of **6**, having an *ortho* substituent, proceeded to provide **12** in 71% yield (entry 4), although using *ortho*-disubstituted aryl iodide **7** as a coupling partner furnished a 36% yield (entry 5). Further examinations of the effect of an electron-withdrawing group were verified, and the yields of product were satisfactory (entry 6, 7).

Table 4 Sonogashira Cross-Coupling of Ynamide **1** with Various Aryl Halides[a]

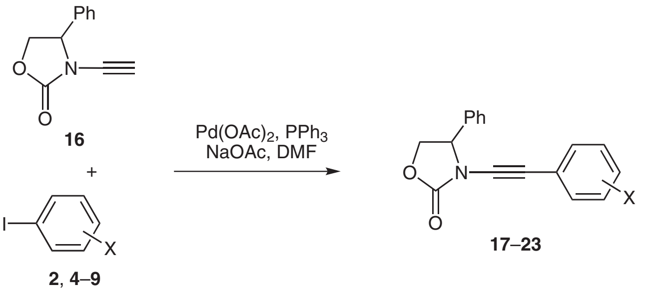


Entry	Aryl halides (X)	Products (X)	Yield (%)[b]
1	**2** (4-EtO_2C)	**3** (4-EtO_2C)	75
2	**4** (H)	**10** (H)	68
3	**5** (4-OMe)	**11** (4-MeO)	32
4	**6** (2-Me)	**12** (2-Me)	71
5	**7** (2,6-di-Me)	**13** (2,6-di-Me)	36
6	**8** (4-F_3C)	**14** (4-F_3C)	72
7	**9** (4-NC)	**15** (4-NC)	65

[a] Reaction conditions: **1** (1.0 equiv), ArX (1.2 equiv), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), NaOAc (1.5 equiv), DMF, 80 °C, 1 h.
[b] Isolated yield.

Given the success of the copper-free Sonogashira cross-coupling of ynamide **1**, we tried to use not only sulfonyl ynamide **1** as the substrate but also urethane ynamide **16** for the Sonogashira coupling. When a reaction of **16** with **2** was carried out under identical conditions, substituted ynamide **17** was afforded in 77% yield (Table 5, entry 1). A comparable yield was obtained in the reaction with iodobenzene **4** (entry 2). The electron-donating group and the *ortho* disubstituent reduced the yield of coupling products **19** and **21** (entry 3, 5). The reaction of **16** with *o*-iodotoluene **6** succeeded, and **20** was provided in 63% yield (entry 4). We had certainty about the possitive effect of electron-withdrawing group for copper-free Sonogashira coupling of ynamides, because *p*-trifluoromethyl and *p*-nitrile substituents led to good product yields (entry 6, 7).

Table 5 Sonogashira Cross-Coupling of Ynamide **16** with Aryl Halides[a]



Entry	Aryl halides (X)	Products (X)	Yield (%)[b]
1	**2** (4-EtO_2C)	**17** (4-EtO_2C)	77
2	**4** (H)	**18** (H)	62
3	**5** (4-MeO)	**19** (4-MeO)	37
4	**6** (2-Me)	**20** (2-Me)	63
5	**7** (2,6-di-Me)	**21** (2,6-di-Me)	35
6	**8** (4-F_3C)	**22** (4-F_3C)	81
7	**9** (4-NC)	**23** (4-NC)	87

[a] Reaction conditions: **16** (1.0 equiv), ArX (1.2 equiv), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), NaOAc (1.5 equiv), DMF, 80 °C, 1 h.
[b] Isolated yield.

In conclusion, we have studied the palladium-catalyzed copper-free Sonogashira cross-coupling of ynamides. The presence of a small excess of the carboxylate anion, and the absence of copper play an important role in this reaction. The dimerization of ynamide was not observed, and moderate to good yields of the coupling products were obtained. Many different kinds of syntheses of ynamides have now become possible, although it was recognized that the transformation of nonsubstituted ynamides to substituted ynamides by Sonogashira cross-coupling was limited, except for Hsung's report.[7] Further studies of this reaction and the possibility of ynamides for transition-metal-catalyzed reactions are now in progress in our laboratory.

References and Notes

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(9) **Typical Procedure for Sonogashira Cross-Coupling Reaction of Ynamide 1 Promoted by Palladium Acetate** To a solution of ynamide **1** (53.7 mg, 0.19 mmol), $Pd(OAc)_2$ (2.1 mg, 9.41 mmol, 5 mol%), Ph_3P (4.9 mg, 18.82 mmol, 10 mol%), and NaOAc (23.2 mg, 0.28 mmol, 1.5 equiv) in DMF (6 mL) was added methyl 4-iodobenzoate **2** (0.04 mL, 0.23 mmol, 1.2 equiv) at 0 °C under argon atmosphere. The reaction mixture was stirred at 80 °C for 1 h. After the consumption of starting ynamide **1** was confirmed by TLC analysis, the resulting mixture was cooled to 0 °C. H_2O (12 mL) was added to the mixture, which was extracted with Et_2O (3 × 50 mL). The organic phase was washed with brine and dried under $MgSO_4$. The volatiles were removed under reduce pressure. The residue was separated by column chromatography on silica gel (hexane–EtOAc, 10:1) to afford **3** (61.0 mg, 75%).