Pergamon

Tetrahedron Letters 43 (2002) 6673–6676

TETRAHEDRON LETTERS

# A copper-free palladium catalyzed cross coupling reaction of vinyl tosylates with terminal acetylenes

Xiaoyong Fu,* Shuyi Zhang, Jianguo Yin and Doris P. Schumacher

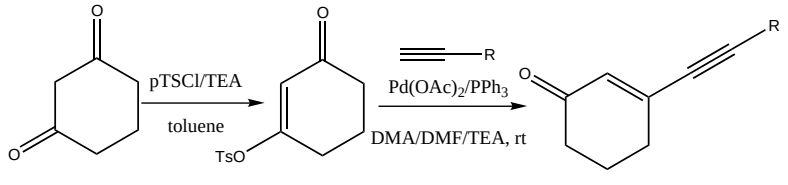
*Synthetic Chemistry Department, Schering Plough Research Institute, 1011 Morris Avenue, Union, NJ 07083, USA*

Received 7 June 2002; revised 26 June 2002; accepted 28 June 2002

**Abstract**—A copper-free palladium-catalyzed cross coupling of vinyl tosylate (**2**) and terminal acetylenes was investigated, affording a convenient and efficient method for construction of an $sp$–$sp^2$ carbon–carbon bond. The tosylate (**2**) derived from 1,3-cyclohexanedione was reacted with terminal acetylene under the copper-free conditions at ambient temperature, in the presence of palladium acetate and triphenylphosphine, to provide the conjugated en-yn-one products in excellent overall yields while leaving other functional groups intact. This reaction protocol was extended to coumarin tosylate (**12**). 

The palladium-catalyzed cross coupling reaction of aryl and alkenyl halides with terminal alkynes in the presence of a cocatalyst of cuprous iodide (Sonogashira[1] reaction) is a useful methodology[2] for the construction of conjugated arylalkyne or enyne systems which are valuable intermediates in the synthesis of natural products,[3] pharmaceuticals,[4] and in the preparation of liquid crystalline materials and conducting polymers.[5] As in the other palladium-catalyzed cross coupling reactions, aryl and vinyl triflates are useful alternatives to halides in the Sonogashira reaction.[6] On the other hand, vinyl tosylates are generally considered inactive in this reaction.[7] Wu et al. recently reported successful palladium-catalyzed cross couplings of tosylcoumarins with terminal acetylenes in the presence of cuprous iodide.[8] Recent multi-kilogram scale production of Schering pharmaceutical intermediate 3-(3-oxo-1-cyclohexene-1-yl)-2-propenoic acid methyl ester employed an unprecedented utilization of vinyl tosylate in palladium-catalyzed Heck reaction to provide a robust process in manufacturing the dienone product.[9] The scope of this work was further expanded to include terminal acetylenes, with the anticipated trend of reactivity to be observed for enyne formations. We wish to report a direct couplings of tosylate with terminal acetylenes as a more cost effective and the simplest route for the construction of en-yn-one compounds.

A one-pot, two-step synthesis (Scheme 1) was devised using the Heck reaction conditions employed in our previous study. Tosylate **2** was prepared by reacting 1,3-cyclohexanedione **1** with *p*-toluenesulfonyl chloride in the presence of triethylamine with the TEA–HCl salt filtered upon the completion of the reaction. The solvent was replaced with DMA/DMF/TEA and the intermediate **2** was coupled with phenylacetylene to form 3-(phenylethynyl)-2-cyclohexen-1-one (**4**) in the presence of 1.5% palladium acetate and triphenylphosphine. Like the findings in our previous study, the acetylenic coupling did not proceed in the absence of




1 2 3

**Scheme 1.**

*Keywords*: vinyl tosylate; copper-free Sonogashira reaction.

* Corresponding author. Tel.: 908-820-6165; fax: 908-820-6620; e-mail: xiaoyong.fu@spcorp.com

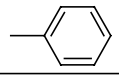
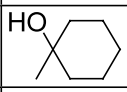
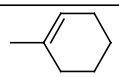
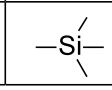
0040-4039/02/$ - see front matter 
PII: S0040-4039(02)01447-8

the catalyst or the ligand. Although the 1:1 ratio of the catalyst to the ligand was proved to provide the most active catalytical system in the related Heck reaction,[9,10] the system with other ratios of palladium to phosphine such as 1:2 also gave an efficient catalysis for this Sonogashira reaction. The mixture was filtered once the reaction was complete, the filtrate was washed with water/brine, and concentrated to afford the crude material. The pure product was isolated via flash column chromatography. The yields of this reaction are generally excellent with all the terminal acetylenes studied (Table 1).

Some of the compounds in Table 1 such as 3-(phenylethynyl)-2-cyclohexen-1-one (**4**) and 3-[(trimethylsilyl)ethynyl]-2-cyclohexen-1-one (**10**) were prepared by different methods reported in the literature. Nucleophilic 1,2-additions of lithium acetylide or its Grignard counterpart to a vinyl ketone,[11] vinylic selenide,[12] ether[13] or ester resin[14] followed by acid hydrolysis or oxidation were employed to construct such en-yn-one compounds with high yields. In addition, acyl anion equivalents such as vinyl cuprate and vinyl zinc were documented to transform 1-haloalkynes to the desired products.[15] However, all these are multistep, temperature dependent reactions. The Sonogashira reaction of the tosylate **2** with terminal acetylenes clearly offers the simplest and most cost effective preparation for the en-yn-one compounds.

It should be emphasized that this efficient procedure does not require cuprous iodide as a cocatalyst previously deemed necessary for the Sonogashira reaction. A copper-free procedure was recently reported for the Sonogashira reaction of aryl bromides with terminal alkynes catalyzed $Pd_2(dba)_3$ and $P(tBu)_3$.[17] A copper-free procedure simplifies the reaction protocol and is especially useful for the optimization of reaction parameters. This has triggered our interest in extending our procedures to other electron deficient tosylates. The cross coupling of coumarin tosylate with terminal alkynes[8] was reexamined under our reaction conditions. It is interesting to note that the coupling reaction took place smoothly at room temperature without addition of copper iodide (Scheme 2). The results are summarized in Table 2. Excellent conversions were observed for all substrates studied with good overall yields.

**Table 1.** Reaction profile of tosylate **2** with terminal acetylenes

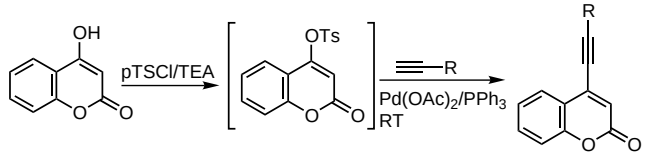
| Entry | -R | Prod | Time | Conv. | Yield |
|---|---|---|---|---|---|
| 1 |  | **4**[16] | 3.5 hours | 99 % | 91 % |
| 2 |  | **5**[16] | 1 hour | 99 % | 94 % |
| 3 |  | **6**[16] | 3 hours | 98 % | 91 % |
| 4 |  | **7**[16] | 16 hours | 100 % | 77 % |
| 5 |  | **8**[16] | 2 hours | 99 % | 93 % |
| 6 |  | **9**[16] | 1.5 hours | 100 % | 91 % |
| 7 |  | **10**[16] | 16 hours | 100 % | 88 % |

Note: % conversion denotes the ratio of product over the sum of product and tosylate **2** by HPLC area. Product yield is the total yield from starting material **1**.

The tosylate **2** and coumarin tosylate **12** are prepared from 1,3-dione and β-ketoester, respectively, within a six-membered ring. Both tosylates contain a conjugated enone structural moiety with a double bond being substituted by a tosyl group. This substitution enhances the electrophilicity of the double bond carbon. These unique structural features might be the key elements that differentiate these two tosylates from other tosylates with respect to their reactivities in coupling with terminal alkynes. The mechanism of this reaction is not clear to us and further mechanistic studies are needed.

**General reaction procedure**:

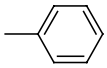
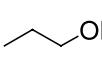
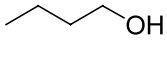
To a 1 L three-necked round bottom flask equipped with a thermometer, a mechanical stirrer and nitrogen inlet, 1,3-cyclohexanedione **1** (30.0 g, 267.6 mmol), *p*-toluenesulfonyl chloride (51.0 g, 1 equiv.) and toluene (300 mL) were mixed and slurried at room temperature.




**11** **12** **13**

**Scheme 2.**

**Table 2.** Reaction profile of tosylate **12** with terminal acetylenes

| Entry | -R | Prod | Time | Conv. | Yield |
|---|---|---|---|---|---|
| 1 |  | **14** | 16 hours | 96 % | 65 % |
| 2 |  | **15**[16] | 3.5 hours | 97 % | 72 % |
| 3 |  | **16** | 7 hours | 97 % | 59 % |
| 4 |  | **17** | 16 hours | 93 % | 75 % |

Note: % conversion was calculated from HPLC and % yield reflects overall yield from the coumarin starting material. A similar amount of catalyst load was used, 0.1 mol equivalence, as reported in Wu's paper.[8] $Pd(Ph_3)_2Cl_2$ without CuI used in Wu's system was also tested and gave similar results. The NMR spectroscopic data for compounds **14**–**17** are in agreement with those published.

Triethylamine (49 mL, 1.3 equiv.) was slowly introduced via addition funnel while maintaining the reaction temperature to between 20 and 30°C. The mixture was further agitated at 20–25°C and filtered upon the completion of the reaction (<1% **1**) as followed by HPLC (Waters HPLC with PDA module, isocratic mobile phase composed of 1:1 water and acetonitrile, μ-Bondpak C-18 column; UV 254 nm). The filtrate was concentrated under reduced pressure, followed by solvent replacement with *N*,*N*-dimethylacetamide to a volume of about 120 mL.

With triphenylphosphine (1.05 g, 0.015 equiv.), palladium(II) acetate (0.90 g, 0.015 equiv.), *N*,*N*-dimethylformamide (60 mL), triethylamine (60 mL), *N*,*N*-dimethylacetamide (30 mL) and phenylacetylene (44.1 mL, 1.5 equiv.) added, the mixture was stirred at ambient temperature for 3.5 h. Following the completion of the reaction that was monitored by HPLC, the mixture was diluted with 300 mL of toluene, filtered through a Celite pad and washed with water to afford a fairly clean product solution with a yield of 91.3%. After evaporation of the solvent, the analytically pure product was obtained by flash chromatography (1:2 ethyl acetate and *n*-heptane) as a yellow oil.

In summary, a synthetically useful palladium-catalyzed cross coupling of vinyl tosylates and acetylenes has been discovered as an efficient and cost effective method for this type of chemical transformations. The extremely mild reaction conditions, simple procedure and high isolated yield also make it a superior method over other existing processes.

## Acknowledgements

The authors thank Professor Li Deng for helpful discussions and Mr. Danny Angeles for experimental assistant.

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16. $^{1}H$ and $^{13}C$ NMR spectral data for compounds **4**–**10**, **15**.
Compound **4**: $^{1}H$ NMR ($CDCl_3$): 7.51 (m, 2H, $J=8.5$), 7.40 (m, 3H), 6.31 (t, 1H, $J=1.6$ Hz), 2.57 (m, 2H), 2.46 (t, 3H, $J=6.3$ Hz), 2.08 (m, 2H).$^{13}C$ NMR ($CDCl_3$): 199.1, 143.3, 132.8, 132.3, 129.9, 128.9, 122.4, 100.1, 88.8, 37.7, 30.9, 23.0
Compound **5**: $^{1}H$ NMR ($CDCl_3$): 6.17 (t, 1H, $J=1.4$ Hz), 3.13 (s, 1H), 2.41 (m, 4H), 2.01–1.91 (m, 4H), 1.69–1.45 (m, 7H), 1.25 (m, 1H).$^{13}C$ NMR ($CDCl_3$): 199.6, 144.2, 132.7, 104.7, 83.7, 69.3, 40.0, 37.6, 31.0, 25.5, 23.6, 22.9
Compound **6**: $^{1}H$ NMR ($CDCl_3$): 6.27 (m, 1H, $J=1.9$ Hz), 6.17 (d, 1H, $J=1.4$ Hz), 2.47–2.39 (m, 4H), 2.16 (m, 4H), 2.03 (m, 2H), 1.62 (m, 4H).$^{13}C$ NMR ($CDCl_3$): 199.1, 144.4, 138.7, 131.9, 128.8, 120.6, 102.5, 86.7, 37.6, 31.0, 29.1, 26.3, 23.1, 21.7
Compound **7**: $^{1}H$ NMR ($CDCl_3$): 6.14 (s, 1H), 4.68 (q, 1H, $J=6.6$ Hz), 3.67 (broad s, 1H), 2.38 (m, 4H), 1.97 (m, 2H), 1.46 (d, 3H, $J=6.7$ Hz).$^{13}C$ NMR ($CDCl_3$): 199.9, 144.3, 132.7, 103.0, 83.0, 58.7, 37.6, 30.8, 24.3, 22.8
Compound **8**: $^{1}H$ NMR ($CDCl_3$): 6.10 (s, 1H), 3.73 (t, 2H, $J=6.5$ Hz), 3.21 (broad s, 1H), 2.63 (t, 2H, $J=6.5$ Hz), 2.37 (m, 4H), 1.96 (m, 2H) $^{13}C$ NMR ($CDCl_3$): 199.9, 145.1, 132.4, 99.5, 81.8, 60.9, 37.6, 31.1, 24.4, 22.9

Compound **9**: $^{1}$H NMR ($CDCl_3$): 6.14 (s, 1H), 3.65 (t, 2H, $J=6.3$ Hz), 2.61 (t, 2H, $J=6.8$ Hz), 2.40 (q, 4H, $J=7.3$ Hz), 2.02 (m, 4H)$^{13}$C NMR ($CDCl_3$): 199.1, 144.4, 132.5, 100.1, 81.5, 43.9, 37.6, 31.3, 31.1, 22.9, 17.6

Compound **10**: $^{1}$H NMR ($CDCl_3$): 6.22 (t, 1H, $J=1.7$ Hz), 2.44 (m, 4H), 2.03 (m, 2H), 0.23 (m, 9H)$^{13}$C NMR ($CDCl_3$): 199.1, 143.4, 133.4, 106.4, 103.8, 37.7, 30.7, 22.9, 0.0

Compound **15**: $^{1}$H NMR ($CDCl_3$): 7.82 (dd, 1H, $J1=7.8$ Hz, $J2=1.5$ Hz), 7.50 (m, 1H), 7.27 (m, 2H), 6.47 (s, 1H), 3.94 (t, 2H, $J=6.3$ Hz), 2.85 (t, 3H, $J=6.3$ Hz) $^{13}$C NMR ($CDCl_2$): 161.0, 153.7, 138.2, 132.6, 127.1, 124.9, 118.9, 118.8, 117.2, 102.2, 76.2, 60.9, 24.5.

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