Synthesis of Cross-Conjugated Geminal Enediynes via Palladium Catalyzed Cross-Coupling Reaction of Ketene Butyltelluroacetals

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Abstract: The palladium-catalyzed cross coupling reaction of ketene butyltelluroacetals with terminal alkynes at room temperature affords cross-conjugated geminal enediynes in high yield under mild conditions.

Key words: cross-coupling, enynes, palladium, tellurium, ketene butyltellurocetals

Palladium catalyzed cross-coupling reactions have been developed into useful preparative methods during the past 20 years and are now some of the simplest and most effective methods in forming new C-C bonds.[1] Among these, facile palladium-catalyzed alkynylation of haloarenes and haloalkenes have emerged as powerful synthetic tools and have become a focus of major interest,[2,3] as well as, their possible application in the preparation of new liquid crystalline compounds.[4]

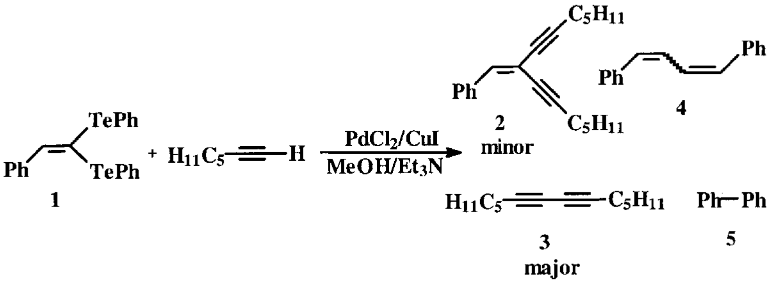
Vinylic tellurides have recently attracted considerable attention as important synthetic reagents and intermediates. One of the most useful properties of vinylic tellurides is transmetallation. Vinylic tellurides can be metallated with organolithium or higher-order cyanocuprates to give the thermodynamically more stable organometallics.[5] *Z*-Vinylic tellurides are readily accessible by means of the hydrotelluration of acetylenes.[6] One the other hand, reports on ketene telluroacetals are scarce. Their preparation is based on Wittig-Horner reactions,[7] hydroalumination[8] and hidrozirconation[9] of acetylenic chalcogenides or reaction of α-chalcogeno vinyllithium with a ditelluride.[10]

Our interest in the development of synthetic methods based on palladium catalysis[11] stimulated us to examine the reactivity of ketene telluroacetals (vinylic tellurides) with terminal alkynes to obtain conjugated and cross-conjugated enediynes via palladium catalyzed cross-coupling reactions. Herein we wish to report a mild and efficient synthesis of cross-conjugated geminal enediynes by direct coupling of ketene telluroacetals and 1-alkynes under $PdCl_2$ catalysis.

Our initial efforts were focused on the reactivity of ketene phenyltelluroacetal **1** in the cross coupling reaction with 1-alkynes. Thus, ketene phenyltelluroacetal **1** (1 equiv) was treated in methanol at room temperature with 1-heptyne (2 equiv) in the presence of $PdCl_2$ (20 mol%)–CuI (20 mol%), and Et_3N (1 equiv) as base (Scheme 1). Under these conditions, the corresponding enediyne **2** was obtained as a minor product, but **3** (major) and a small amount of homocoupling products **4** and **5** were also isolated (Scheme 1).

We tried reacting ketene phenyltelluroacetal **1** in methanol at room temperature with 1-alkynes in the presence of $PdCl_2$ as catalyst, and Et_3N as base, in the absence of CuI. Under these conditions, diyne **3** was not observed, however, the cross-coupling reaction still proceeded unsatisfactorily, providing **2** contaminated with **4** and **5**.

In view of these disappointing results, we decided to explore the reaction with the ketene butyltelluroacetals **6a**–**c**. In the course of the study we found that the cross-coupling reaction of ketene butyltelluroacetal **6a** with 1-



Scheme 1

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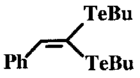
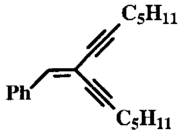
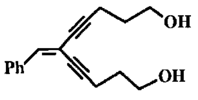
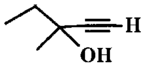
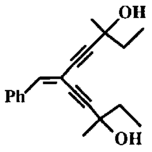
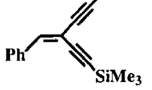
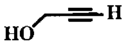
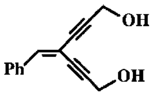
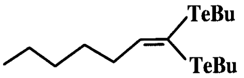
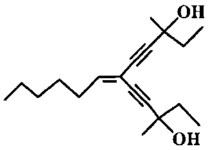
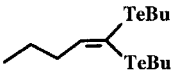
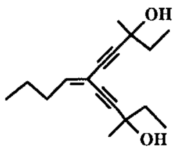
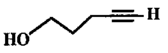
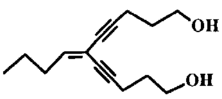
alkynes was very sensitive to the nature of the catalyst. The role of palladium(0) and palladium(II)–CuI was evidenced by the reaction with 1-heptyne in methanol and triethylamine as base. It was found that no reaction takes place without palladium(II). When palladium(0) catalyst like $Pd(PPh_3)_4$ or $Pd(PPh_3)_4$–CuI was used, no reactions were observed. However, when $PdCl_2$ was employed in the presence of a copper salt (CuI), a small amount of cross-coupling product was observed (10% isolated yield). When $PdCl_2$ was used alone, the reaction proceeded faster and with higher yields of enediynes.

The nature of the amine also proved to be very important. In the cross-coupling reaction of ketene **6a** with 1-heptyne in the presence of $PdCl_2$ (20 mol%), the best results were

Table Synthesis of Enediynes by Cross-Coupling Reaction of Ketene Butyltelluroacetals **6a**–**c** with 1-Alkynes with $PdCl_2$ in $MeOH/NEt_3$ at Room Temperature

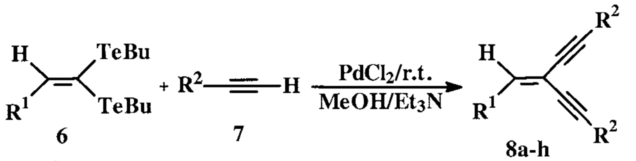
Entry	Ketene Butyltelluroacetals	Alkynes	Enediynes	Time (h)	Yield[a] (%)
1	 **6a**	$H_{11}C_5{\equiv}H$ **7a**	 **8a**	4	75
2	**6a**	 **7b**	 **8b**	4	82
3	**6a**	 **7c**	 **8c**	5	85
4	**6a**	$Me_3Si{\equiv}H$ **7d**	 **8d**	4	78
5	**6a**	 **7e**	 **8e**	5	80
6	 **6b**	**7c**	 **8f**	6	91
7	 **6c**	**7c**	 **8g**	5	75
8	**6c**	 **7b**	 **8h**	6	82

[a] Yield of isolated pure product

obtained with triethylamine (75%). Diethylamine and diisopropylamine furnished the product in lower yields (60% and 50% yields, respectively). With pyridine, pyrrolidine or piperidine, no enediyne was formed.

We also investigated the influence of the solvent in the cross-coupling reaction. THF, dichloromethane and benzene, did not give the expected enediynes. In acetonitrile and *N*,*N*-dimethylformamide only a small amount of cross-coupling product was observed. However, the use of methanol afforded enediynes in higher yields.

Thus, the optimum conditions for the coupling as described in Scheme 2 were found to be the use of $PdCl_2$ (20 mol%), MeOH (5 mL), ketene butyltelluroacetals (1 mmol), the appropriate 1-alkyne (2 mmol) and Et_3N (1 mmol) at 25 °C.[12] In a next stage, we explored the generality of our method, extending the coupling reaction to other 1-alkynes and observing that enediynes **8a–h** were obtained in good yields (Table). The reaction conditions tolerate the use of functionalities such as hydroxyl and labile acetylenic trimethyl silyl groups.



6a - R^1 = Ph
6b - R^1 = C_5H_{11}
6c - R^1 = C_3H_7

Scheme 2

In summary, we have explored the Pd(II) catalyzed cross-coupling reaction of ketene butyltelluroacetals with alkynes and established a new route to synthesize enediynes in good yields. Our approach is improved compared to described methodologies, avoiding the preparation of vinyl metals, haloalkynes or protection of hydroxyl group in propargylic alcohol. In comparison to our previously described methodology the procedure has the advantage of easy access and great stability of ketene butyltelluroacetals and we have shown that $PdCl_2$ must be used alone instead of the $PdCl_2$–CuI mixture.

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(12) Typical procedure for **8a**: To a two-necked 25 mL round-bottomed flask under argon atmosphere containing $PdCl_2$ (0.035 g, 20 mol%) and dry methanol (5 mL) was added the ketene butyltelluroacetal **6a** (0.470g, 1 mmol). After stirring the mixture for 15 minutes at room temperature, 1-heptyne (0.192 g, 2 mmol) and Et_3N (0.8 mL) were added. The reaction was stirred at room temperature for 4 h. After this time, the solids were filtered under vacuum, to the filtrate was added brine. The organics were extracted with dichloromethane (3 × 25 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash silica gel chromatography eluting with hexane; Yield 0.227 g (75%). **Selected spectral and analytical data for 8a:** ^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.86–7.82(m, 2 H), 7.33–7.30(m, 3 H), 6.89(s, 1 H), 2.42(t, 7.0 Hz, 2 H), 2.37(t, 7.0 Hz, 2 H), 1.75–1.20(m, 12 H), 0.96(t, 7.0 Hz, 3 H), 0.93(t, 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ(ppm): 140.93, 135.99, 128.52, 128.38, 128.10, 104.08, 96.99, 88.92, 80.98, 78.61, 31.28, 31.14, 28.34, 28.01, 22.47, 22.22, 19.96, 19.80, 13.95, 13.80; IR (neat, cm^{-1}): 3060, 2200, 2190, 1660, 786; LRMS (rel. int.) *m/z* 292(100), 178(80), 152(40), 91(50), 77(60).