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Tetrahedron Letters 46 (2005) 763-765

Tetrahedron Letters

Synthesis of conjugated enediynes via palladium catalyzed cross-coupling reactions of potassium alkynyltrifluoroborates

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Accepted 6 December 2004 Available online 21 December 2004

Abstract—An efficient synthesis of cross-conjugated enediynes has been developed utilizing the palladium catalyzed cross-coupling reactions of 1,1-dibromo-1-alkenes with potassium alkynyltrifluoroborates under mild conditions. © 2004 Elsevier Ltd. All rights reserved.

Cross-conjugated enediynes have recently received considerable attention due to their extensive applications in non-linear optics (NLO),¹ macrocyclic ligands,² optical switches,³ and the synthesis of polycyclic aromatic hydrocarbons (PAHs).⁴ Preparative methods for enediynes are limited. The Sonogashira reaction can be utilized⁵ as well as the palladium catalyzed coupling reaction of ketene butyltelluroacetals with alkynes.⁶ The Sonogashira reaction normally produces a mixture of bromoenyne, enediyne, and recovered starting dibromoalkene.^{5e,7} In some cases the yields are low.^{5c,d} The butyltelluroacetal method involves the use of vinylic telluride compounds that are toxic and often difficult to prepare. Thus, the development of a simple and efficient approach to cross-conjugated enediynes is of great interest.

During the past 20 years, Suzuki-Miyaura cross-coupling reactions have provided preparative methods for effectively creating carbon–carbon bonds. The coupling reactions of aryl-, alkyl-, and alkenylboron compounds (including boronate esters, boranes, and boronic acids) have been investigated extensively.⁸ However, the coupling of alkynylboron compounds has been limited to B-alkynyl-9-BBN borate complexes,⁹ alkynyltrialkoxyborate complexes,¹⁰ and lithium 1-alkynyl(triisopropoxy)borates.¹¹ Because alkynylboronic esters are stronger Lewis acids than aryl- and alkenylboronate esters and are easily hydrolyzed,¹² their use in organic reactions can be problematic. Recently the use of potassium alkynyltrifluoroborates in carbon–carbon bond forming reactions has attracted significant attention due to their stability and accessibility.¹³ In connection with our ongoing studies of cross-coupling reactions using potassium organotrifluoroborates,¹⁴ we developed an efficient synthesis of cross-conjugated mono-enediynes using the cross-coupling of potassium alkynyltrifluoroborates with 1,1-dibromo-1-alkenes. Herein, we wish to disclose the results of this study.

Various palladium catalysts, solvents, and reaction conditions were examined using (2,2-dibromovinyl)-benzene, 1, and potassium (p-tolylethynyl)trifluoroborate, 2, as model substrates (Table 1). 1 (1 equiv) was treated with 2 (2 equiv) in the presence of 5 mol % of Pd(dppf)Cl₂/Cs₂CO₃ (3 equiv) at 50 °C in methanol (Table 1, entry 1). Under these conditions, the reaction was sluggish. Fifty-two percent of the starting material, 1, was recovered after 12 h. The corresponding enediyne 3 was obtained in 10% yield, and 1,3-diyne 4 was isolated as the major product in 36% yield. The homocoupling product of 1,1-dibromo-1-alkene and monosubstituted bromoenyne were not detected although they are commonly reported as byproducts in Sonogashira reactions.^{5,6} Using DMF and toluene as solvents, the isolated yields of enedivne 3 were 21% and 18%, respectively (Table 1, entries 2 and 3). When THF was used as solvent, the yield of 3 increased to 43% and only 26% of starting material 1 was recovered (Table 2, entry 4). The addition of a small amount of water increased the yield of 3 to 52% as well as decreased the reaction time to 4 h (Table 1, entry 5).¹⁵ As the reaction proceeds, the mixture becomes black. Gas chromatographic analysis of the black reaction mixture (presumably due to metallic

Keywords: Enediynes; Trifluoroborate; Cross-coupling; Palladium catalyzed.

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Entry	Conditions ^b	Yield % ^c		
		3	4	1 (recovered)
1	Pd(dppf)Cl ₂ , MeOH, 12 h	10	36	52
2	Pd(dppf)Cl ₂ , DMF, 16 h	21	20	56
3	Pd(dppf)Cl ₂ , Toluene, 12 h	18	12	64
4	Pd(dppf)Cl ₂ , THF, 6 h	43	19	26
5	Pd(dppf)Cl ₂ , THF/H ₂ O (20:1), 4 h	52	16	14
6	Pd(dppf)Cl ₂ 10 mol %, THF/H ₂ O (20:1), 2 h	76	8	0
7	Pd(OAc) ₂ 10 mol %, THF/H ₂ O (20:1), 16 h	23	26	45
8	Pd(PPh ₃) ₄ 10 mol %, THF/H ₂ O (20:1), 12 h	21	22	54
9 ^d	Pd(dppf)Cl ₂ , THF/H ₂ O (20:1), 16 h	30	18	50

^a The ratio of **1** to **2** was 1:2.

 b Reaction carried out at 50 °C in the presence of 5 mol % of catalyst and 3 equiv of Cs_2CO_3.

^c Isolated yield.

^d 3 equiv of (*i*-Pr)₂NEt were used in place of Cs₂CO₃.

Table 2. Cross-coupling of 1,1-dibromo-1-alkenes with potassium alkynyltrifluoroborates^a

Br		Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ , 10 mol% Cs ₂ CO ₃ , 3 equiv	R
R Br	+ R' BF ₃ K -	THF/H ₂ O (20:1) 50 °C, 2h	R

Entry	R	R′	Yield (%) ^b
1	Phenyl	<i>n</i> -Butyl	85
2	Phenyl	3-Chloropropyl	82
3	Phenyl	Isopropenyl	74
4	Phenyl	Phenyl	73
5	Phenyl	<i>p</i> -Tolyl	76
6	<i>p</i> -Chlorophenyl	Phenyl	81
7	<i>p</i> -Chlorophenyl	3-Chloropropyl	73
8	<i>p</i> -Tolyl	3-Chloropropyl	76
9	o-Tolyl	3-Chloropropyl	66
10	1-Naphthyl	3-Chloropropyl	82
11	<i>p</i> -Nitrophenyl	3-Chloropropyl	64
12	Octyl	Phenyl	75

^a Reactions carried out using 10 mol % of Pd(dppf)Cl₂ with 3 equiv of Cs₂CO₃ in THF/H₂O (20:1) at 50 °C for 2 h. ^b Isolated yield.

palladium) indicated formation of the desired product. Increasing the amount of catalyst to 10 mol % generated 3 in 76% yield (Table 1, entry 6). Other palladium catalysts, such as Pd(OAc)₂ and Pd(PPh₃)₄, were less effective (Table 1, entries 7 and 8). Cs₂CO₃ gave higher yields of enediyne than diisopropylethylamine (Table 1, entry 9). Optimum conditions for the reaction were found to be 10 mol% of Pd(dppf)Cl₂ and 3 equiv of Cs_2CO_3 in THF/H₂O (20:1) at 50 °C for 2 h.

To enhance the utility of the reaction, we prepared a variety of potassium alkynyltrifluoroborates via depro-

tonation of 1-alkynes, followed sequentially by transmetallation with boronic esters and treatment in situ with KHF₂. 1,1-Dibromo-1-alkenes were prepared by literature methods.¹⁶ Under the optimized conditions, reactions of various potassium alkynyltrifluoroborates with different 1,1-dibromo-1-alkenes were evaluated¹⁷ and the results are summarized in Table 2. The reaction resulted in good isolated yields. No significant differences in reactivity with respect to the electronic and steric effects of the substituents were observed. 1-(2,2-Dibromovinyl)-4-nitrobenzene also gave a good yield, 54%.

In summary, we have developed a convenient method for preparing cross-conjugated geminal enediynes from readily accessible 1,1-dibromo-1-alkenes and stable potassium alkynyltrifluoroborates. The reaction conditions are very straightforward and enediynes are obtained in high yield.

Acknowledgements

We thank the U.S. Department of Energy, The National Institutes of Health, and the Robert H. Cole Foundation for support of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet. 2004.12.021.

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- Typical experimental procedure: (2,2-dibromovinyl)benzene, 1, (0.2 mmol) was placed in an oven-dried round-bottomed flask under a nitrogen atmosphere. THF (2.0 mL) and H₂O (0.1 mL) were added and the resultant solution stirred. Potassium (*p*-tolylethynyl)trifluoroborate, 2, (0.4 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), and Pd(dppf)Cl₂ (10 mol %) were then added. The mixture was stirred at 50 °C for 2 h. The mixture was extracted with ethyl ether (4×5 mL). The organic layer was separated, dried over anhydrous MgSO₄, and filtered. The solvent was removed under reduced pressure and the product purified by silica gel chromatography (ethyl acetate–hexane).