Pergamon

Tetrahedron Letters, Vol. 38, No. 37, pp. 6533-6536, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01528-1

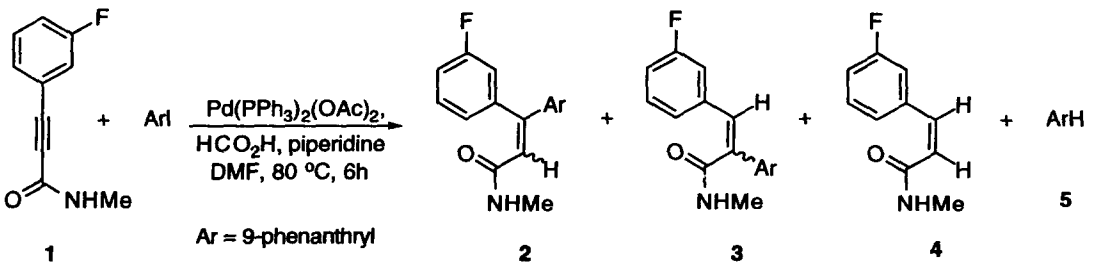
A Regio- and Stereocontrolled Method for Preparing 3,3-Diarylacrylamides

Lynne A. Hay and David Mitchell*

Chemical Process R&D, Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285-4813

Abstract: Palladium-catalyzed hydroarylation of acetylenes provides regio- and stereodefined olefins. This methodology has been extended to arylpropiolamides where 3,3-diarylacrylamides are prepared stereospecifically. In an independent fashion, both the *E*- and *Z*-isomers were prepared by judicious choice of arylpropiolamide preparation and the palladium catalyzed hydroarylation reaction. © 1997 Elsevier Science Ltd.

Hydroarylation of substituted acetylenes with aryl iodides in the presence of a palladium catalyst, formic acid, and base results in high stereo- and regioselectivity during formation of trisubstituted olefins. Among the acetylene systems that have been reported are diarylacetylenes,[1] dialkylacetylenes,[2,3] arylethynyl carbinols,[4] arylethynyl silanes,[5] alkylethynyl silanes[5] and alkyl-4-hydroxy-2-alkynoates.[6] Our interest was in preparing 3,3-diarylacrylamides through the hydroarylation of arylpropiolamides. To our knowledge, there has been no application of the methodology to this type of acetylene system. We reasoned that the amide functionality would play a key role in the regiochemical outcome due to coordination of the amide to the transient metal complex. This intramolecular amide coordination has not been studied in such systems.



Typical hydroarylation reaction conditions[4] were used initially, in which **1** was reacted with 9-iodophenanthrene in the presence of *bis*(triphenylphosphine)palladium diacetate, formic acid, piperidine and DMF as solvent. The reaction gave a mixture of all four regio- and stereoisomers (**2** & **3**), in addition to significant amounts of *cis*-olefin **4** and dehalogenated 9-iodophenanthrene **5** (Eq). After a study of the reaction parameters

(including catalyst, equivalents of aryl iodide, base, solvent, reaction time, temperature, and concentrations), a regio- and stereodefined reaction was formulated resulting in high yields of the desired 3,3-diarylacrylamide product. In our hands, the best reaction conditions consisted of ethyl acetate or THF as solvent, a phosphine-free palladium catalyst and dilute concentrations. For example, when an ethyl acetate solution of 9-iodophenanthrene, **1**, *bis*(dibenzylideneacetone)palladium, formic acid, and diethylamine was heated to reflux for 3.5 h followed by workup, only the *E*-isomer was isolated in 81% yield.

The mechanism should be similar to the palladium-catalyzed hydroarylation of acetylenes proposed by others.[1,2,7] However, a possible explanation for the high regioselectivity may be due to parameters that minimize intermolecular coordination to the transient palladium-amide complex (Figure). Phosphine present in the reaction as part of the catalyst, a highly coordinating solvent such as DMF, or a high reaction concentration would compete with the amide functionality for coordination to palladium. A decrease or removal of these parameters should allow a more effective coordination of palladium to the amide giving rise to increased selectivity.

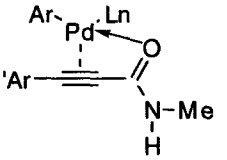
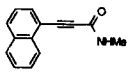
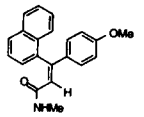
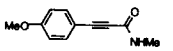
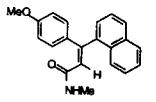
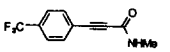
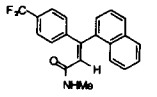
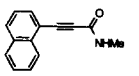
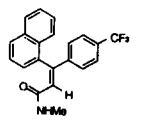
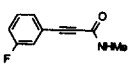
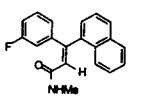
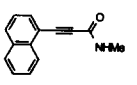
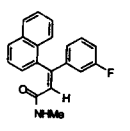
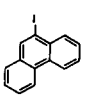
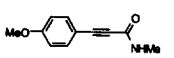
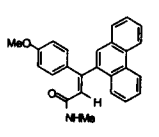
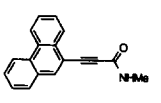
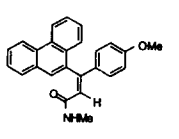


Figure. Possible Transient Palladium-Propiolamide Complex

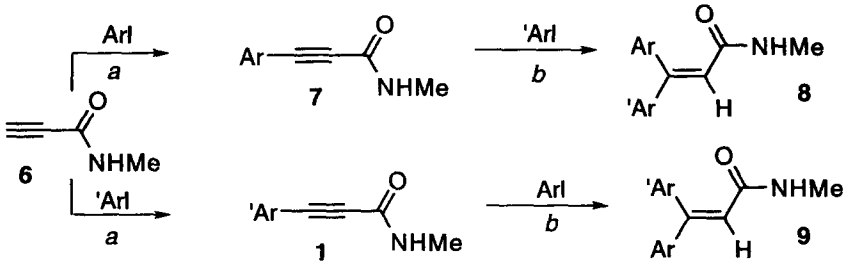
In an attempt to generalize the methodology, we focused on the *N*-methyl arylpropiolamide substrates to simplify the analysis of products by ^{1}H NMR. By judicious choice of aryl iodide in the formation of the arylpropiolamide and in the hydroarylation reaction, both the *E*- and *Z*-isomers of each substrate were prepared in an independent fashion. The concept is illustrated in Scheme 1, where **6** is coupled with 9-iodophenanthrene to provide **7**. In a hydroarylation reaction with 3-fluoroiodobenzene, the *Z*-isomer **8** was obtained in 83% yield. Conversely, **6** was coupled with 3-fluoroiodobenzene to provide **1**. Palladium-catalyzed hydroarylation with 9-iodophenanthrene provided the opposite *E*-isomer **9** in 81% yield. From the summary of examples presented (Table), the hydroarylation of propiolamides appears to be quite general. These hydroarylation conditions tolerate a variety of substituents on the aryl moiety, providing good yields and selectivity of compounds with various

Table. ***Summary of Arylpropiolamide Palladium-Catalyzed Hydroarylation*** [8]

Entry	ArI	Arylpropiolamide	Product	%Yield
1)				74
2)				71
3)				76
4)				82
5)				93
6)				72
7)				72
8)				83

steric and electronic properties. However, in a few examples where 2-substituted aryl iodides were used, we have noted reduction of the arylpropiolamide instead of hydroarylation.

Scheme 1. Independent Synthesis of *Z*- or *E*-3,3-Diarylacrylamides.



a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMSO, 25 °C. b) $Pd(dba)_2$, diethylamine, HCO_2H, EtOAc, 60 °C. Ar = phenanthryl, Ar' = 3-fluorophenyl

The palladium-catalyzed hydroarylation of arylpropiolamides represents a unique extension of the current methodology. In addition, the reaction parameters for high stereo- and regioselectivity have been investigated and are currently being applied to the synthesis of biologically interesting targets.

References and Notes

1) Cacchi, S.; Felici, M.; Pietroni, B. *Tetrahedron Lett.* **1984**, *25*, 3137.
2) Larock, R.; Yum, E.; Doty, M.; Sham, K. *J. Org. Chem.* **1995**, *60*, 3270.
3) Larock, R.; Yum, E. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
4) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1985**, *41*, 5121.
5) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1986**, *27*, 6397.
6) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481.
7) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.
8) All products gave satisfactory spectral and microanalytical data. A typical reaction procedure is as follows: Preparation of (*E*)-3-(3-fluorophenyl)-*N*-methyl-3-(9-phenanthryl)-2-propenamide (**9**). *Bis*(dibenzylideneacetone)palladium (0) (0.121 g, 0.211 mmol, 7%), **1** (0.544 g, 3.08 mmol) and 9-iodophenanthrene (0.944 g, 3.10 mmol) were dissolved in ethyl acetate (152 mL). Diethylamine (1.0 mL, 10.2 mmol) was added, followed by formic acid (0.30 mL, 7.95 mmol), and the solution was heated to reflux until reaction completion (3.5 h). The reaction was then cooled to room temperature and washed with dilute HCl, then dilute NaOH, and finally brine. The organics were dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum. Purification of the crude reaction mixture by flash column chromatography (3% $MeOH/CHCl_3$; silica) provided 890 mg (81%) of purified product as a white solid, mp 200 °C. MS (FD^+) calcd. for $C_{24}H_{18}NOF$: 355.42; found: 355.1 (M^+ 100%). Anal. Calcd for $C_{24}H_{18}NOF$: C, 81.11; H, 5.10; N, 3.94; F, 5.35. Found: C, 81.12; H, 5.02; N, 3.91; F, 5.23.

(*Received in USA* 2 *June* 1997; *accepted* 17 *July* 1997)