ORGANIC LETTERS

2002
Vol. 4, No. 2
193−196

Synthesis of 3-Substituted 4-Aroylisoquinolines via Pd-Catalyzed Carbonylative Cyclization of *o*-(1-Alkynyl)benzaldimines

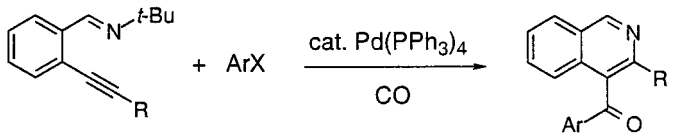
Guangxiu Dai and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

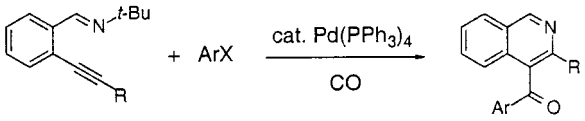
Received October 12, 2001

ABSTRACT



***o*-(1-Alkynyl)benzaldimines react with aryl iodides and 1 atm of CO in the presence of tri-*n*-butylamine and a Pd(PPh$_3$)$_4$ catalyst to afford good yields of 3-substituted 4-aroylisoquinolines by acylpalladation of the carbon–carbon triple bond and cyclization.**

The palladium-catalyzed carbonylative cyclization of alkynes bearing proximate nucleophilic centers using unsaturated organic halides/triflates in the presence of carbon monoxide is a versatile and convenient process for the preparation of ketone-containing indoles[1] and benzofurans.[2] Although we have recently reported convenient methods for the preparation of 3-monosubstituted[3] and 3,4-disubstituted[4,5] isoquinolines using organopalladium methodology, there is presently no simple approach to the corresponding 3-substituted 4-aroylisoquinolines. In a previous Letter,[5] we described a convenient approach to the synthesis of 3-substituted 4-aryl, allylic, and alkynyl isoquinolines from *N*-*tert*-butyl-*o*-(1-alkynyl)benzaldimines and a wide variety of organic halides (or esters). We report here a successful synthesis of 3-substituted 4-aroylisoquinolines by the palladium-catalyzed carbonylative cyclization of *N*-*tert*-butyl-*o*-(1-alkynyl)benzaldimines using aryl iodides and CO in the presence of a palladium catalyst (eq 1).



(1)

We started out our investigation of the reaction conditions by using *N*-*tert*-butyl-*o*-(phenylethynyl)benzaldimine (**1,** 0.25 mmol), 5 equiv of 4-iodoanisole, 5 mol % of Pd(PPh$_3$)$_4$ as the catalyst, and 5 equiv of a base in 5 mL of DMF as the solvent under 1 atm of pressure of carbon monoxide. Besides the desired product, 4-(4-methoxybenzoyl)-3-phenylisoquinoline (**2**), two other isoquinoline products were also observed, which were 4-(4-methoxyphenyl)-3-phenylisoquinoline (**3**) formed without incorporation of CO and 3-phenylisoquinoline (**4**) generated by thermal or Pd(II)-catalyzed cyclization of the imine starting material.[3]

The yield of 4-(4-methoxybenzoyl)-3-phenylisoquinoline (**2**) was strongly dependent on the base employed. The presence of inorganic bases, such as K_2CO_3 and KOAc, drastically reduced the yield of the 4-aroylisoquinoline **2**, and the distribution of the three isoquinoline products **2**, **3**,

(1) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem.* **1999**, *64*, 1137. (b) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, *5*, 620. (c) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437.

(2) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

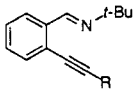
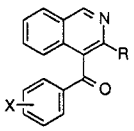
(3) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.

(4) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

(5) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, **3**, 4035.

10.1021/ol010230y CCC: $22.00
Published on Web 12/20/2001

Table 1. Synthesis of 3-Substituted 4-Aroylisoquinolines by the Pd-Catalyzed Carbonylative Cyclization of *N-tert*-Butyl-*o*-(1-alkynyl)benzaldimines and Aryl Halides (eq 1)[a]

entry		ArX /ArCOCl	time (h)		% isolated yield[b]
1	R = C_6H_5 (**1**)	*p*-$MeOC_6H_4I$	12	X = *p*-MeO (**2**)	74 (0, 5)
2	**1**	*p*-$MeOC_6H_4Br$	24	X = *p*-MeO (**2**)	0 (0, 20)
3	**1**	*m*-$MeOC_6H_4I$	48	X = *m*-MeO (**5**)	76 (0, 5)
4	**1**	*o*-$MeOC_6H_4I$	48	X = *o*-MeO (**6**)	50 (9, 6)
5	**1**	C_6H_5I	24	X = H (**7**)	84 (9, 4)
6	**1**	*m*-$EtO_2CC_6H_4I$	48	X = *m*-EtO_2C (**8**)	68 (0, 7)
7	**1**	*p*-$F_3CC_6H_4I$	24	X = *p*-F_3C (**9**)	52 (0, 11)
8	**1**	*p*-$O_2NC_6H_4I$	12	X = *p*-O_2N (**10**)	31 (37, 7)
9[c]	**1**	*p*-$O_2NC_6H_4I$	12	X = *p*-O_2N (**10**)	56 (11, 4)
10[d]	**1**	*p*-$O_2NC_6H_4I$	48	X = *p*-O_2N (**10**)	52 (10, 5)
11[e]	**1**	*p*-$O_2NC_6H_4I$	24	X = *p*-O_2N (**10**)	66 (7, 0)
12	R = 1-cyclohexenyl (**12**)	*m*-$EtO_2CC_6H_4I$	24	X = *m*-EtO_2C (**13**)	55 (0, 0)
13	R = *n*-Bu (**14**)	*m*-$EtO_2CC_6H_4I$	24	X = *m*-EtO_2C (**15**)	64 (0, 0)
14	**1**	PhCOCl	48	X = H (**7**)	62 (0, 13)
15[f]	**1**	PhCOCl	48	X = H (**7**)	42 (0, 20)

[a] See the text for the procedure used. [b] The numbers in parentheses are the isolated yields of the corresponding 3-substituted 4-arylisoquinolines and 3-monosubstituted isoquinolines, respectively. [c] The reaction was run under 3.5 atm of CO. [d] The reaction was run at 80 °C. [e] The reaction was run under 3.5 atm of CO at 80 °C. [f] The reaction was run with no CO present. A 12% yield of *o*-(phenylethynyl)benzaldehyde was also isolated.

and **4** was not satisfactory. On the other hand, organic amine bases, such as triethylamine and tri-*n*-butylamine, afforded high yields of **2**, very little of **4**, and none of **3**. The more hindered amine base *N*,*N*-diisopropylethylamine, the aromatic amine *N*,*N*-dimethylaniline, and pyridine all gave lower yields of 4-aroylisoquinoline **2**, and none of the side product **3** was observed.

We also explored the effect on the yield of the reaction of the temperature and the amounts of the base and the aryl iodide used. The combination of *N-tert*-butyl-*o*-(phenylethynyl)benzaldimine (**1**, 0.25 mmol), 5 equiv of aryl iodide, 5 mol % of $Pd(PPh_3)_4$, and 5 equiv of tri-*n*-butylamine[6] in 5 mL of DMF at 100 °C under 1 atm of pressure of CO gave the best results. This procedure provided the three isoquinolines **2**, **3**, and **4** in 74%, 0%, and 5% yields, respectively (Table 1, entry 1).

We subsequently turned our attention to evaluating the effect on the yield of varying the electronic nature of the substituents present on the aryl iodide under these standard reaction conditions. As indicated in Table 1, entries 1−7, the reactions tolerate both electron-donating and electron-withdrawing substituents on the aryl iodides, although there is a slight decrease in the yields with electron-withdrawing substituents (Table 1, entries 6 and 7). Unlike aryl iodides, the electron rich aryl bromide 4-bromoanisole gave none of the desired ketone (entry 2). Steric hindrance does not appear to be a major problem since 2-iodoanisole affords the corresponding 4-aroylisoquinoline **6** in a 50% yield (Table 1, entry 4).

4-Iodonitrobenzene performed differently from the other aryl iodides (entry 8) using the standard procedure, generating 4-(4-nitrobenzoyl)-3-phenylisoquinoline (**10**) and 4-(4-ni-

(6) Tri-*n*-butylamine and triethylamine afforded the same yields of **2**, **3**, and **4**. Tri-*n*-butylamine was chosen over triethylamine because tri-*n*-butylamine has a higher boiling point than triethylamine and is less easily lost during the reaction.

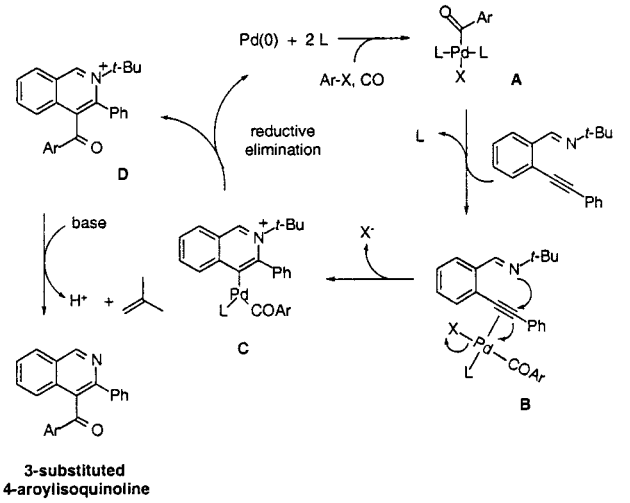
trophenyl)-3-phenylisoquinoline (**11**) in comparable yields, indicating very poor selectivity for this reaction. Considering that 4-iodonitrobenzene gave the best result of any aryl iodide in the palladium-catalyzed cross-coupling of *N*-*tert*-butyl-*o*-(phenylethynyl)-benzaldimine (**1**) without CO to form 4-(4-nitrophenyl)-3-phenylisoquinoline (**11**),[5] the low yield of **10** and the poor selectivity between **10** and **11** apparently result from the very similar reactivities of the ArPdI and ArCOPdI intermediates with the alkynyl imine, both of which promote cyclization to the isoquinolines. In an attempt to improve the selectivity of the reaction and the yield of the desired ketone, we have carried out three further experiments in which we have increased the CO pressure[1c] and decreased the reaction temperature (entries 9−11).[7] We were pleased to observe that these experiments provided higher yields of the desired product **10** and better selectivity between the two 3,4-disubstituted isoquinolines **10** and **11**. Using both a lower temperature and higher CO pressure improved the yield of the ketone product **10** and the **10**/**11**/**4** ratio significantly (entry 11).

We also investigated the reactions of ethyl 3-iodobenzoate with imino alkynes containing different R groups at the end of the triple bond. Imino alkyne **12** bearing a 1-cyclohexenyl group afforded the corresponding 4-aroylisoquinoline **13** in a good yield, 55% (entry 12). Imine **14** containing an *n*-butyl group afforded the desired product **15** in a 64% yield (entry 13). However, *N*-*tert*-butyl-2-phenylethynyl-3-pyridinealdimine did not afford any of the desired ketone product.

Acyl halides readily undergo oxidative addition to Pd(0) to form acylpalladium intermediates RCOPdX, which subsequently undergo a wide range of useful transformations.[8] We have, therefore, studied the utility of benzoyl chloride in our chemistry. Under 1 atm of CO (Table 1, entry 14) and with no CO present (entry 15), neither reaction afforded 3,4-diphenylisoquinoline (**15**) at all, indicating that the initially formed acylpalladium intermediate does not undergo decarbonylation to the corresponding arylpalladium species very easily.[9] However, whether there is external CO or not does make a difference in the yields of the product **7** and the reaction rates. The reaction was complete after 48 h under 1 atm of CO and was not complete after the same amount of time without CO. Better results were obtained using 1 atm of CO, in which case a 62% yield of ketone **7** was obtained (entry 14).

The mechanism shown in Scheme 1 is proposed for this process. It consists of the following key steps: (1) oxidative addition of the organic halide to the Pd(0) catalyst, followed by CO insertion, (2) the resulting acylpalladium intermediate **A** coordinates to the alkyne triple bond to form complex **B**, which activates the triple bond toward nucleophilic attack,

Scheme 1



(3) intramolecular nucleophilic attack of the nitrogen atom of the imine on the activated carbon−carbon triple bond to afford intermediate **C**, (4) reductive elimination to form the carbon−carbon bond between the carbonyl group and the isoquinoline ring in **D** and simultaneous regeneration of the Pd(0) catalyst, (5) cleavage of the *tert*-butyl group from the nitrogen to release the strain between the *tert*-butyl group and the 3-phenyl group with simultaneous generation of the 3-substituted 4-aroylisoquinoline. Two competing processes are (1) cyclization of the starting material by a thermal or Pd(II)-catalyzed process to afford the 3-monosubstituted product[3] and (2) cyclization of the imine starting material promoted by an arylpalladium intermediate to afford a 3-substituted 4-arylisoquinoline.[5]

The yields of ketones obtained by this process are relatively independent of the nature of the substituents on the aryl iodide, while the yields of 4-arylisoquinolines obtained from arylation of these same imines[5] are highly dependent on the nature of the substituents present in the aryl iodide. This is easily understood when one considers that the key step in the present synthesis apparently involves attack of an electron-deficient acylpalladium species on the carbon−carbon triple bond. The nature of the substituents present in the aroylpalladium intermediate is not going to change their electronics as profoundly as they would the electronics of the corresponding arylpalladium species. The presence of steric hindrance in the aryl iodide is also less likely to affect the yield in the carbonylative cyclization, because of the presence of the carbonyl group in the aroylpalladium intermediates.

In summary, we have developed an efficient synthetic approach for the carbonylative cyclization of *N*-*tert*-butyl-*o*-(1-alkynyl)benzaldimines to the corresponding 3-substituted 4-aroylisoquinolines. A systematic and extensive study of the scope and limitations of this process is currently under investigation in our laboratory and will be reported in due course.

(7) During our optimization work, we found out that the reactions of substrate **1** and 4-iodoanisole at 80 and 100 °C gave the same yields of products **2**, **3**, and **4**, although the reaction at 80 °C took a much longer time to complete.

(8) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1999; p 253.

(9) (a) Tsuji, J.; Ohno, K. *J. Am. Chem. Soc*. **1968**, *90*, 94. (b) Blaser, J. U.; Spencer, A. *J. Organomet. Chem*. **1982**, *233*, 267. (c) Spencer, A. *J. Organomet. Chem*. **1982**, *240*, 209. (d) Spencer, A. *J. Organomet. Chem*. **1984**, *265*, 323.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and Kawaken Fine Chemicals Co., Ltd. and Johnson Matthey Inc. for donation of the palladium catalysts.

Supporting Information Available: Experimental procedures and characterization data for all compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010230Y