Pergamon

Tetrahedron Letters 43 (2002) 1951–1953

TETRAHEDRON LETTERS

The Heck reaction with unprotected allylic amidines and guanidines

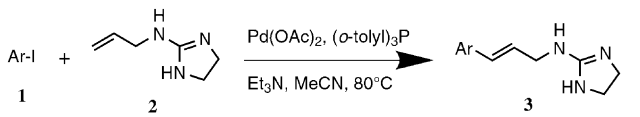
Edward C. Lawson,* William A. Kinney, Diane K. Luci, Stephen C. Yabut, David Wisnoski and Bruce E. Maryanoff

Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA 19477-0776, USA

Received 17 January 2001; accepted 25 January 2002

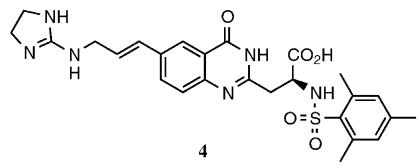
Abstract—The applicability of Heck methodology to the introduction of unprotected amidines and guanidines was investigated. Unprotected guanidine-substituted olefins were coupled to various simple aryl iodides, and this methodology was then applied to a highly functionalized 6-iodoquinazolinone substrate, providing an efficient synthesis of a new class of vitronectin receptor ($\alpha_V\beta_3$ integrin) antagonists.

A number of important biologically active molecules incorporate amidine or guanidine moieties,[1] with examples in diverse areas, such as histamine H2 receptor antagonists,[2] antithrombotic agents,[3] and antidiabetic agents.[4] Usually, syntheses of building blocks containing an amidine or guanidine moiety have been accomplished with *N*-protecting groups installed. Although the Heck reaction has proven to be a versatile method for carbon–carbon bond formation in the presence of a variety of functional groups,[5] including protected allylic amines,[6–8] there are just limited reports relating to unprotected allylic amine derivatives.[9] We describe herein an exploratory study of Heck coupling with unprotected amidine- and guanidine-containing substrates.



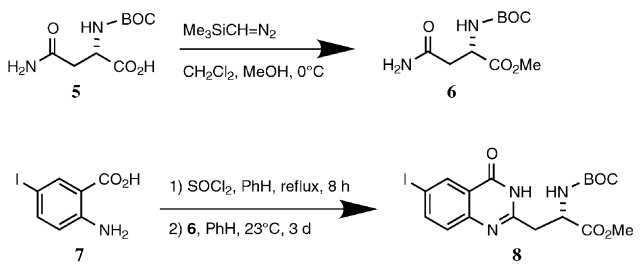
1 2 3 (1)

We initially studied the coupling between allylaminoimidazoline and substituted iodobenzenes for the construction of guanidine-containing building blocks. Fortunately, typical Heck reaction conditions worked very well for this coupling by using a palladium catalyst that was formed in situ (Eq. (1); Table 1). This reaction required the use of 4.5 mol equiv. of the allylaminoimidazoline relative to the iodobenzene.[10] ^{1}H NMR spectra of the crude products indicated only the presence of the *trans* isomer and only coupling at the less substituted carbon of the allyl fragment.



4

We applied this method to the synthesis of a novel series of vitronectin receptor ($\alpha_V\beta_3$) antagonists based on a quinazolinone peptidomimetic scaffold, as represented by target compound **4**, and further extended it by utilizing different allylic amidines and guanidines. The requisite 6-iodoquinazolinone (**8**) was synthesized by using a procedure by Kametani, as shown in Eq. (2).[11,12] Commercially available *N*-α-*t*-butoxycarbonyl-L-asparagine **5** was esterified with trimethylsilyldiazomethane to give **6** (96% yield), which was condensed with activated 4-iodoanthranilic acid (oil) to give **8** as a light yellow solid (52% yield).[13] Compound **8** was then employed as a substrate in a series of Heck coupling reactions.

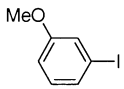
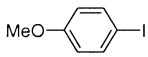
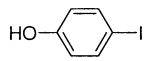


5 6 7 8 (2)

* Corresponding author.

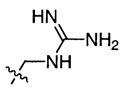
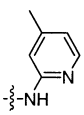
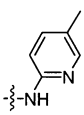
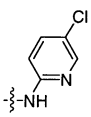
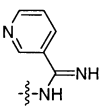
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00182-X

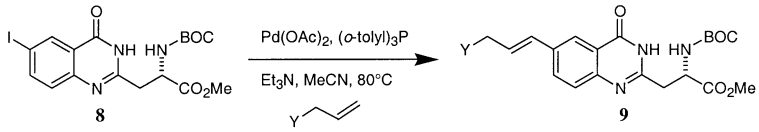
Table 1. Heck reaction of allylaminoimidazoline and aryl iodides

Cmpd	Ar-I	Yield (%)
3a	Ph—I	82
3b		85
3c		83
3d		81
3e		83

A key step in the synthesis of quinazolinone-based vitronectin receptor antagonists is the Heck reaction shown in Eq. (3).[14] Coupling of iodoquinazolinone **8** with different allylic amidines and guanidines provided quinazolinones **9** in moderate to good isolated yields (Table 2). The use of acetonitrile as solvent was critical for good results, as neither benzene nor toluene afforded any **9**. As for the catalyst, palladium acetate and tri-(*o*-tolyl)phosphine gave higher yields than palladium tetrakis(triphenylphosphine). Compound **9a**, containing an allylic aminoimidazoline, and **9b**, containing an *N*-methylimidazole, were obtained in good yield. The butenyl guanidine and allyl aminopyridine compounds were also compatible substrates, affording **9c** and **9d** efficiently. Some of the allyl amidines suffered from slightly lower yields (**9e**–**h**).

Table 2. Heck reaction of 6-iodoquinazolinone and allylic amidines/guanidines

Compd	Y	Yield (%)
9a		77
9b		79
9c		78
9d		81
9e		58
9f		62
9g		54
9h		66



(3)

In summary, we have executed an effective Heck reaction between a highly functionalized iodoquinazolinone and an assortment of unprotected allyl amidines and guanidines. This methodology represents a straightforward approach for the synthesis of aryl allylic amidines and guanidines. As an application of this chemistry, we conveniently assembled quinazolinones **9**, which were further elaborated into biologically interesting quinazolinones **4**.[15]

References

1. Greenhill, J. V.; Lue, P. *Progr. Med. Chem.* **1993**, *30*, 203.
2. Mills, J. G.; Koch, K. M.; Webster, C.; Sirgo, M. A.; Fitzgerald, K.; Wood, J. R. *Aliment. Pharmacol. Ther.* **1997**, *11*, 129.
3. Hirsh, J. *Am. Heart J.* **2001**, *142*, S3–S8.
4. Hitoshi, I. *Farumashia* **2001**, *37*, 818.
5. (a) Heck, R. F. *Org. React. (NY)* **1982**, *27*, 345; (b) Brase, S.; de Meijere, A. *Met.-Catal. Cross-Coupling React.*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 3, pp. 99–166.
6. Crisp, G. T.; Glink, P. T. *Tetrahedron* **1992**, *48*, 3541.
7. Dong, Y.; Busacca, C. A. *J. Org. Chem.* **1997**, *62*, 6464.
8. Itaya, T.; Hozumi, Y. *Chem. Pharm. Bull. (Tokyo)* **1998**, *46*, 1094.
9. Katritzky, A. R.; Ferwananh, A.; Denisenko, S. *Heterocycles* **1999**, *50*, 767.
10. As little as 2 equivalents of the allylic amine substrate can be used in the Heck reaction. However, using less than 4.5 equivalents of the allylic amine slightly decreased yields and increased reaction times. The unused allylic amine can also be recovered upon chromatography.
11. Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186.
12. Kametani, T.; Higa, T.; Van Loc, C.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306.
13. Iodoquinazolinone **8** was synthesized from **5** as follows. A mixture of **5** (6.45 g, 28.0 mmol), CH_2Cl_2 (170 mL), and MeOH (30 mL) in a three-neck flask fitted with an addition funnel was cooled to 0°C. A 2.0 M solution of $TMSCHN_2$ (42 mL, 83.0 mmol) in hexanes was added to this mixture via an addition funnel over 30 min. The reaction was stirred for 30 min at 0°C and concentrated in vacuo. Diethyl ether (3×100 mL) was added and the solution was concentrated in vacuo to give a white solid, **2** (6.8 g, 27.0 mmol). Compound **7** (8.8 g, 33.0 mmol), $SOCl_2$ (22 mL, 302 mmol), and benzene (335 mL) were refluxed for 8 h, cooled to rt, and concentrated in vacuo to give an oil. Compound **6** (6.8 g, 27.0 mmol) was dissolved in benzene (250 mL) and cannulated into the crude oil. The resulting mixture was kept at room temperature for 3 days. The solid was filtered off and washed with benzene to give iodoquinazolinone **8** (6.6 g, 14 mmol, 52%). ^{1}H NMR (CD_3OD) δ 8.5 (s, 1H), 8.2 (d, 1H), 7.4 (d, 1H), 4.7 (m, 1H), 3.7 (s, 3H), 3.4 (dd, 1H), 3.1 (dd, 1H), 1.2 (s, 9H); ES/MS m/z 474 (MH^+).
14. For the Heck reaction of iodoquinazolinone **8** to give quinazolinone **10a**, $Pd(OAc)_2$ (0.058 g, 0.26 mmol) and tri-(*o*-tolyl)phosphine (0.20 g, 0.66 mmol) were dissolved in MeCN (15 mL). The mixture was stirred at room temperature for 10 min. Iodoquinazolinone **8** (1.1 g, 2.0 mmol) was then added to the mixture. Allylaminoimidazoline (1.13 g, 9.0 mmol) was dissolved in MeCN (10 mL) and added to the mixture. Et_3N (0.56 mL, 4.0 mmol) was added and the mixture was refluxed for 5 h and concentrated in vacuo. The residue was purified by silica gel flash-column chromatography by using a gradient solvent system (CH_2Cl_2/MeOH/NH_4OH; 95/4/1 to 50/49/1) to give a white solid (0.84 g, 2.0 mmol, 77%). ^{1}H NMR (CD_3OD) δ 8.2 (s, 1H), 8.0 (d, 1H), 7.6 (m, 1H), 6.8 (d, 1H), 6.4 (m, 1H), 4.8 (m, 1H), 4.0 (d, 2H), 3.8 (s, 3H), 3.7 (s, 4H), 3.4 (m, 1H), 3.1 (m, 1H); ES/MS m/z 471 (MH^+).
15. The biological results will be reported separately. This work was presented in part at the 222nd National Meeting of the American Chemical Society, Chicago, Illinois, August 2001; MEDI-78.