

Ring Closure Selectivity of the Intramolecular Heck Reaction

Hyun-Joon Ha*, Young-Gil Ahn, and Jun-Sik Woo

Department of Chemistry, Hankuk University of Foreign Studies, Yongin, Kyunggi-Do 449-791, Korea

Received April 29, 1998

The Heck reaction, π -allyl palladium catalyzed C-C bond forming method, has been applied to build several valuable organic molecules.¹ Its application for the cyclization was also proceeded for the synthesis of noble carbocycles.^{2,3} However no systematic study was performed to find out the preference of the Heck type ring closure reaction among several possible pathways. Here we would like to report the ring closure selectivity of the intramolecular Heck reaction with σ -iodoanilines bearing *N*-allyl, *N*-homoallyl and *N*-pent-4-enyl as pendants. Substrates were synthesized from *N*-alkylation of either *N*-methyl- σ -iodoaniline or *N*-allyl- σ -iodoaniline in good yields.⁴

The reactions of *N*-methyl- σ -iodoaniline with one of the pendants among *N*-allyl, *N*-homoallyl and *N*-pent-4-enyl yielded only *exo* cyclized products without *endo* cyclization under the standard reaction condition with Pd(OAc)₂/PPh₃, Et₃N in CH₃CN (entries 1-3). Indole ring formation in the entries 1 and 4 from *N*-allyl pendant came from the rearrangement of 5-*exo* cyclized product that considered as *exo* preference.⁵ The same *exo* preference was observed from the reaction under Jeffery's condition (Pd(OAc)₂, *n*-Bu₄NCl, KOAc in DMF) that sometimes change the reaction in different way.⁶ Significant amount of *endo* cyclized product

were obtained from the aqueous reaction⁷ of PdCl₂/TPPTS (triphenylphosphinetrisulfonated sodium salt), diisopropylethylamine in H₂O and CH₃CN. However the ratio of those products stayed as minors. It seems that this *exo* preference is an intrinsic characteristics of the reaction with all tested substrates. Between five and six membered ring cyclization from *N*-allyl-*N*-homoallyl- σ -iodoanilines the smaller ring formation was preferred (entry 4). This may arise from the shorter distance of *N*-allyl pendant rather than *N*-homoallyl being reacted with arylpalladium(II) complex. All four possible products were observed under the aqueous Heck reaction. Among all isolated products 25% of the *endo*-cyclized six and seven membered ring and 32% of the six membered *exo*-cyclized products were observed including the expected indole ring as a major of 43%. Under the standard reaction condition *exo* cyclized six membered ring formation was preferred to seven membered ring (entry 5).

In conclusion we have found that the regiochemical outcome of the Heck cyclization reaction favors *exo* pathways in order of 5-*exo*, 6-*exo* and 7-*exo*-trig over any possible *endo*-trig closure. Formation of *exo* cyclized products were always dominant in the reaction with Pd(OAc)₂/PPh₃ in CH₃CN while *endo* cyclized compounds could be obtained to the certain extent from the reaction in the aqueous media using water-soluble PdCl₂/TPPTS catalyst.

Acknowledgment. This work was supported by Ministry of Education (BSRI 97-3437), HUFs grant, and KOSEF (No. 97-0501-02-01-3). We are also grateful to professor Jean-Pierre Genêt of CNRS for providing TPPTS.

References

- For a comprehensive review see, (a) Heck, R. F. *Org. React.* **1982**, 27, 345. (b) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 4, pp. 844-863. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2379. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, 28, 2. (e) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: New York, U. S. A., 1995. (f) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, 53, 7371.
- For a comprehensive review see, Thebtraranonth, C.; Thebtraranonth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, U. S. A., 1994, pp 255-330.
- Ring closure selectivities in certain cases were studies. (a) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, 20, 1133. (b) Mori, M.; Oda, I.; Ban, Y. *Tetrahedron Lett.* **1982**, 23, 5315. (c) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073. (d) O'Connor, B.; Zhang, Y.; Negishi, E.-i. *Tetrahedron Lett.* **1988**, 29, 3903. (e) Hegedus, L. S.; Sestrick, M. R.; Michaelson, E.

Table 1. Intramolecular Heck reactions under the conditions of either (a) Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), Et₃N (2 equiv.) in CH₃CN under reflux, or (b) PdCl₂ (10 mol%), TPPTS (20 mol%), diisopropylethylamine (1.2 equiv.) in H₂O and CH₃CN under reflux

Entry	Substrate	Yield ^a (%)	Products (Ratio)
1		(a) 92 (b) 83	
2		(a) 94 (b) 85	
3		(a) 96 (b) 77	
4		(a) 79 (b) ^b 64	
5		(a) 81	

^a Isolated pure yields. ^b determined by HPLC.

T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141. (f) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687. (g) Gaudin, J.-M. *Tetrahedron Lett.* **1991**, *32*, 6113. (h) Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thornton-Pett, M.; Worakun, T. *Tetrahedron* **1991**, *47*, 9703. (i) Black, D. St. C.; Keller, P. A.; Kunmar, N. *Tetrahedron* **1992**, *48*, 7601. (j) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312.

4. (a) Ha, H.-J.; Ahn, Y.-G. *Synth. Commun.* **1997**, *27*, 1543. (b) Ha, H.-J.; Ahn, Y.-G.; Chon, J.-K. *J. Chem. Soc., Perkin Trans. I.* **1995**, 2631.
5. Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709.
6. Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834.
7. Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genet, J.-P. *Tetrahedron Lett.* **1996**, *37*, 2003.

A New HPLC Chiral Stationary Phase for the Direct Resolution of Racemic Quinolone Antibacterials Containing a Primary Amino Group

Myung Ho Hyun*, Jong Sung Jin, and Wonjae Lee*†

Department of Chemistry and Chemistry Institute for Functional Materials, Pusan National University, Pusan 609-735, Korea

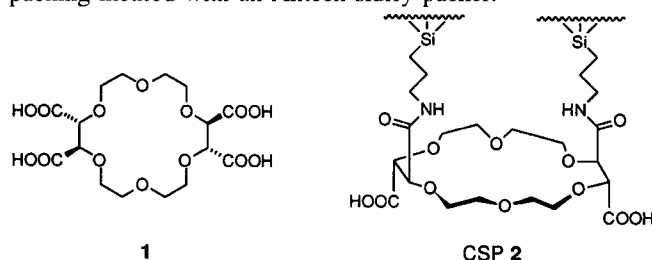
†LG Chemical Ltd., P.O. Box 61, Yu-Sung, Taejeon 305-380, Korea

Received June 2, 1998

Since norfloxacin was reported to show potent antibacterial activity,¹ a number of new quinolone antibacterials such as ofloxacin, enoxacin, ciprofloxacin, lomefloxacin and fleroxacin have been developed. Among others, ofloxacin is chiral and it is quite interesting to note that the (–)-S-enantiomer is more active than the (+)-R-enantiomer or the racemic form.² The effort to develop more potent quinolone antibacterials is still going on and various quinolones have been prepared.³ Some of them are also chiral. Consequently, during the process of developing new quinolone antibacterial agents, the establishment of analytical techniques that distinguish between two enantiomers is essential in order to meet the government regulations such as US FDA's guide lines for the development of new stereoisomeric drugs.⁴ In this aspect, liquid chromatographic direct separation of enantiomers on chiral stationary phases (CSPs) might be the choice because this technique has been known as one of the most convenient and accurate means of determining the enantiomeric composition of chiral compounds.⁵ In this study, we wish to report that a new HPLC chiral stationary phase (CSP) derived from (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid **1** can be successfully employed in resolving various investigational racemic quinolones containing a primary amino group. Previously compound **1** has been utilized in resolving primary amino compounds by capillary zone electrophoresis.⁶ However, to the best of our knowledge, the use of compound **1** bonded to silica gel as an HPLC CSP has not been reported.

A new CSP (CSP **2**) used in this study was prepared by bonding (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid **1** (available from Aldrich) to amino propyl silica gel via simple two step procedure. (+)-(18-Crown-6)-2,3,11,12-tetracarboxylic acid **1** was first converted into its dianhydride by treating with acetyl chloride via the known procedure.⁷ And then, the dianhydride compound was treated in dry methylene chloride at 0 °C under an argon atmosphere for 2 days

with triethylamine and aminopropyl silica gel (particle size: 5 µm, available from Rainin) which was dried in advance by azeotropic removal of water in refluxing benzene. The modified silica gel (CSP **2**) was washed with methanol, water, 1 N HCl solution, water, methanol, dichloromethane and hexane and then dried under high vacuum.⁸ The structure of CSP **2** is believed to be *syn*-diamide form based on the previous study concerning the stereoselective *syn*-opening of the dianhydride by primary amino compound in the presence of triethylamine.⁹ CSP **2** thus prepared was slurried in methanol and then packed into a 150 mm × 4.6 mm I.D. stainless-steel HPLC column using a conventional slurry packing method with an Alltech slurry packer.



CSP **2** was successfully employed in resolving various investigational racemic quinolones **3** containing a primary amino group.¹⁰ The representative chromatograms are shown in Figure 1 and the resolution results are summarized in Table 1. As shown in Table 1, eight quinolones (**3a-h**) based on 4(1H)-quinolinone-3-carboxylic acid and four quinolones (**3i-l**) based on 4-oxo-1,8-naphthyridine-3-carboxylic acid are resolved with reasonable separation factors. Elution orders were determined only for two configurationally known quinolones (**3e** and **j**), the (R)-enantiomer being retained longer. For the quinolone (**3l**) containing two chiral centers, all of the four stereoisomers are separated as shown in Figure 1b and in Table 1. However, at the present stage, we were not able to assign which peak corresponds to which isomer be-