Tetrahedron Letters 50 (2009) 6993-6997

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed cyclization/cyclopropanation reaction for the synthesis of fused N-containing heterocycles

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ARTICLE INFO

Article history: Received 16 July 2009 Revised 23 September 2009 Accepted 26 September 2009 Available online 1 October 2009

Keywords: Heterocycles Tetrahydropyridine Cyclopropanation Intramolecular Heck reaction

ABSTRACT

Palladium-catalyzed cyclization/cyclopropanation can be used to convert a range of substituted cyclic N-aryl allyl/methallyl amines efficiently and selectively to the corresponding fused tetrahydropyridine/ cyclopropane-fused isoquinoline derivatives via β -hydrogen elimination or a domino sequence. © 2009 Elsevier Ltd. All rights reserved.

Among numerous approaches towards the synthesis of heterocycles as well as carbocycles, the palladium-catalyzed cyclization/ cyclopropanation has proven to be a novel and versatile method.^{1–3} Since several reactions take place in a sequential fashion, cyclopropanation can be used for the synthesis of polycyclic organic molecules. Fused cyclopropane moiety is a basic unit of biologically active natural products such as CC-1065 and duocarmycin.⁴ The construction of substituted pyridine frameworks has also been used by numerous groups in the total synthesis of alkaloids and other nitrogen containing natural products such as decumbenine B,⁵ carnegine,⁶ antidesma⁷ and krukovine.⁸ Lamellarin D, which is one of the most potent lead candidates for anticancer chemotherapy and is an inhibitor of topoisomerase I, can also be synthesized using the Heck reaction.⁹

Based on these reports we have developed a methodology for the synthesis of fused tetrahydropyridine derivatives via a palladium-catalyzed intramolecular Heck reaction¹⁰ of substituted cyclic derivatives of *N*-aryl allyl amine (**5a–5j**) and cyclopropanefused isoquinoline derivatives via palladium-catalyzed cyclopropanation^{11–14} of *N*-aryl methallyl amines (**6a–6f**).

The starting materials for this palladium-catalyzed reaction were prepared by alkylation of bromomethylvinyl bromides **3** with monoallylated aniline derivatives **4**. At first the bromovinyl aldehydes **1** were reduced to get bromomethylvinyl alcohols **2** with NaBH₄ in CH₃CN at room temperature (25–30 °C). Then these bromomethylvinyl alcohols **2** were brominated using PBr₃ in CCl₄ to

* Corresponding author. E-mail address: jkray@chem.iitkgp.ernet.in (J.K. Ray). get bromomethylvinyl bromides **3**. On the other hand monoallylation of aniline derivatives was achieved from 4-substituted anilines and allyl bromides by using KF-Celite in CH₃CN at reflux temperature. After this, bromomethylvinyl bromides **3** were alkylated with monoallylated aniline derivatives **4** in the presence of Et₃N in DMF at 60 °C to get the precursors **5** and **6** for the Heck reaction (Scheme 1).

The precursors **5a–5j** on reaction with $Pd(OAc)_2$ (10 mol %), PPh₃ (0.25 equiv) and Cs_2CO_3 (1.2 equiv) in DMF (6 mL) at 90–100 °C yielded the fused tetrahydropyridine derivatives **7a–7j** (Table 1) in excellent yield¹⁵ via 6-*exo-trig* cyclization (Scheme 2).

But when N-methallylated derivatives **6a–6f** were subjected to the Heck reaction under the same reaction conditions¹⁵ they gave cyclopropa[*d*]fused isoquinoline derivatives **8a–8f** (Scheme 3, Table 2).

A plausible rationale for the formation of the products (**8a–8f**) is shown in Scheme 4. At first an alkenyl palladium intermediate is formed by oxidative addition of Pd(0) to the sp² C–Br bond which undergoes addition to the unactivated double bond to produce an alkylpalladium which is again added to the unactivated double bond followed by β -H elimination to afford the cyclopropane-fused compounds^{16–18} (Scheme 4).

Both electron-donating and electron-withdrawing substituents are compatible with this reaction except the nitro group. These reactions can also be performed with acetonitrile as a solvent and Et_3N as a base. A reaction temperature of 100 °C and a time of 5–6 h were found to be optimum. Lower temperatures and shorter reaction times lead to incomplete conversion of the starting materials to the products.



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Scheme 1. Alkylation of bromomethylvinyl bromides with monoallylated aniline derivatives.

Table 1 Pd(0)-catalyzed intramolecular reaction of N-aryl allyl derivative 5



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Table 1 (continued)





Scheme 2. Pd(0)-catalyzed intramolecular cyclization of N-aryl allyl derivative 5.

In conclusion, we have developed a general methodology for the synthesis of fused tetrahydropyridine derivatives and cyclopropane-fused compounds by a palladium-catalyzed domino reaction. This methodology can also be used for the synthesis of various types of nitrogen containing natural products and other heterocyclic compounds.



Scheme 3. Pd(0)-catalyzed intramolecular cyclization of *N*-aryl methallyl derivative 6. Reagents and conditions: 5a-5j (1 equiv), Pd(OAc)₂ (10 mol %), PPh₃ (0.25 equiv), Cs₂CO₃ (1.2 equiv), DMF, 90–100 °C.

Table 2

Pd(0)-catalyzed intramolecular reaction of N-aryl methallyl derivative 6





Scheme 4. A plausible rationale for the Pd(0)-catalyzed cyclopropanation reaction. Reagents and conditions: 6a-6f (1 equiv), Pd(OAc)₂ (10 mol %), PPh₃ (0.25 equiv), Cs₂CO₃ (1.2 equiv), DMF, 90–100 °C.

Acknowledgements

Financial support from CSIR is gratefully acknowledged. D.S.T. is also thanked for providing funds for the project and creating 400 MHz NMR facility under the IRPHA programme.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.156.

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- 15. Typical experimental procedure for the Heck reaction: Compounds **5** or **6** (1 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv) and DMF (6 mL) were placed in a two-neck round-bottomed flask. After degassing with N₂, the mixture was heated at 90–100 °C for 5 h. After cooling, the reaction mixture was diluted with cold water and extracted with ether (30 mL × 3) and the combined organic layers were dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by preparative thin layer chromatography.

Spectral data of representative compounds: 2-(4-Chloro-phenyl)-4-methylene-1,2,3,4,5,6-hexahydro-benzo[h]isoquinoline (**7**): Yellow liquid, ¹H NMR (CDCl₃, 200 MHz) δ : 2.50 (t, 2H, J = 8.4 Hz), 2.84 (t, 2H, J = 8.2 Hz), 4.01 (s, 2H), 4.23 (s, 2H), 5.05 (s, 1H), 5.25 (s, 1H), 6.97 (dd, 2H, J₁ = 2.0 Hz, J₂ = 8.8 Hz), 7.18–7.25 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ : CH₂ at 22.25, 27.77, 50.04, 53.36, 109.05, CH at 117.65 (2C), 121.84, 126.50, 127.27, 127.50, 128.94 (2C), qC at 128.91, 129.01, 130.46, 133.78, 136.12, 139.74, 149.05; Anal. Calcd for C₂₀H₁₈CIN: C, 78.04; H, 5.89; N, 4.55. Found: C, 78.20; H, 6.0; N, 4.41; HRMS calcd for C₂₀H₁₉CIN [M*+H]: 308.1206, found: 308.1104.

3-(4-Chloro-phenyl)-1a-methyl-1,1a,2,3,4,6,7,8-octahydro-3-aza-cyclopropa[d]naphthalene (**8a**): Yellow liquid, ¹H NMR (CDCl₃, 200 MHz) δ : 0.29 (d, 1H, J = 4.6 Hz), 1.16 (d, 1H, J = 4.6 Hz), 1.19 (s, 3H), 1.68–1.78 (m, 4H), 2.09 (br s, 2H), 3.07 (d, 1H, J = 12 Hz), 3.51 (t, 2H, J = 11.6 Hz), 3.82–3.92 (m, 1H), 5.59–5.63 (m, 1H), 6.63 (dd, 2H, J₁ = 2.0 Hz, J₂ = 7 Hz), 7.15 (dd, 2H, J₁ = 2.2 Hz, J₂ = 6.8 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ : CH₃ at 17.28, CH₂ at 21.84, 22.20, 25.27, 28.96, 51.0, 51.96, CH at 113.97 (2C), 121.36, 128.72 (2C), qC at 23.90, 25.40, 121.53, 134.24, 148.48; Anal. Calcd for C₁₇H₂₀ClN: C, 74.57; H, 7.36; N, 5.12. Found: C, 74.69; H, 7.49; N, 4.99; HRMS calcd for C₁₇H₂₁ClN [M⁺+H]: 274.1363, found: 274.1355.

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