Synthesis of Oxathiocine Derivatives by Palladium-Catalyzed Intramolecular Heck Reaction

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Abstracts: A novel approach towards the synthesis of hitherto unreported oxathiocine derivatives has been described by utilizing palladium-catalyzed intramolecular Heck reaction starting from deactivated allylic compounds.

Keywords: Heck reaction, sulfur heterocycles, 2-bromobenzene sulfonyl chloride, palladium catalyst, oxathiocine, 8-*exo*-trig.

During the last decades palladium-catalyzed Heck reaction became an extremely powerful tool to synthetic organic chemists for the synthesis of a number of target molecules including different interesting heterocyclic compounds [1,2]. This is because of its functional group tolerance and high regioselectivity. Formation of the medium-sized ring [3-5] is an ongoing challenge to the organic chemists as these types of fragments are frequently found in a number of naturally occurring compounds [6,7]. Different protocols are available in literature for constructing medium-sized rings [8-15], among which transition-metal catalyzed cyclization is well known. Recently, we have reported some interesting medium-sized oxa-heterocycles utilizing palladium-catalyzed intramolecular Heck reaction [16-18]. Sulfones and sultones are two important classes of organosulfur compounds that are used as important intermediates in modern organic syntheses [19]. A number of cyclic sulfones are the key subunit for the construction of biologically active molecules e.g., proteases and β-lactamase inhibitors [20-22]. Medium ring cyclic sulfones are frequently used for the construction of cyclic olefines [23-25]. On the other hand sultones have some toxicological [26] and antiviral properties [27]. There are fewer examples of palladium-catalyzed Heck reactions of sulfur compounds [28,29] in literature and to the best of our knowledge synthesis of medium-sized heterocycles containing sulfur atom at the appropriate position has been rare. Probably there is only one example to construct eight-membered sultones by Heck reaction conditions starting from highly activated vinylic system [30]. But, there is no such example available in literature for the synthesis of sulfone or sultone derivatives from the unactivated allylic systems. This is why the synthesis of medium sized sulfur heterocycles by the Pd-catalyzed cyclization is a challenge to the organic chemists. Recently we have reported interesting oxathiocine derivatives starting from unactivated vinylic systems with the help of palladium-catalyzed intramolecular Heck reaction [31]. So in continuation of our effort to synthesize medium sized heterocyclic compounds, we decided to enrich the scope of Heck reaction of different unactivated allylic systems containing sulfur atom at the key position.

The compounds **1**(**a-d**) were prepared by refluxing α- and β-naphthols with different allyl bromides in acetone in the presence of anhydrous potassium carbonate and followed by Claisen rearrangement. The Heck precursors **3**(**a-d**) for our present investigation were prepared by the process outlined in (Scheme **1**). Reaction of compound **1a** with 2-bromobenzenesulfonyl chloride **2** in dry dichloromethane in the presence of triethylamine and a catalytic amount of DMAP at 0 ^{o}C for 2 h afforded the compound **3a** in 81% yield. Similarly, compounds **3**(**b-d**) were prepared from compounds **1**(**b-d**) in 74-84% yields. The compound **3a**, when subjected to the intramolecular Heck reaction in the presence of 10 mol% $Pd(OAc)_2$ as catalyst, KOAc as base, TBAB as promoter in dry DMF at 100 ^{o}C for 3 h using the Jeffery's two-phase protocol [32] the *exo*- cyclized 8-membered oxathiocene derivative **4a** was obtained regioselectively, in 97% yield (Scheme **2**). Generally, in this type of reaction, there is always a chance to yield mixture of regioisomeric products [18]. But, in this case, we obtained the *exo*-Heck product **4a**, as the sole product. Increasing the reaction temperature to 150-160 ^{o}C did not improve the yield of the cyclized product and on further increasing the temperature considerable decomposition of the product was observed. The use of $Pd(PPh_3)_2Cl_2$ as catalyst was also found to be effective but the yield of the cyclized product **4a** was reduced to some extent whereas the catalyst $Pd(PPh_3)_4$ showed very poor catalytic activity. Here it is important to note that in the absence of the base the reaction did not occur at all. Optimization of the reaction was achieved through a series of experiments and it was observed that the base Cs_2CO_3 or NaOAc showed lower activity compared to that of KOAc. It is interesting to note that the phosphine ligands, such as triphenyl phosphine or tri-*o*-tolylphosphine did not show any effect upon the yield of the reaction. Therefore, it is clear that our developed protocol is quite simple because it is known that the ligand free approach does not work well for the aryl bromides and this is obviously due to the fact that in almost all the cases a palladium black is precipitated and the reaction is stopped before the completion of the reaction. To test the generality of the reaction, compounds **3**(**b-d**) were subjected to the Heck reaction at optimized

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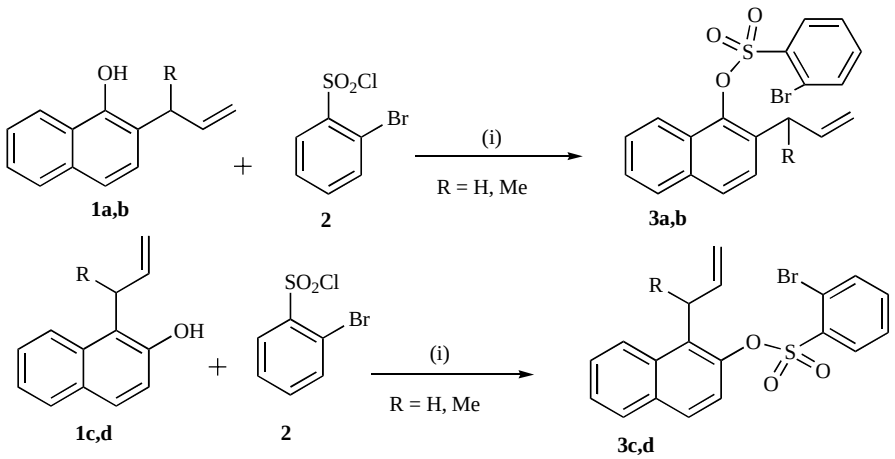
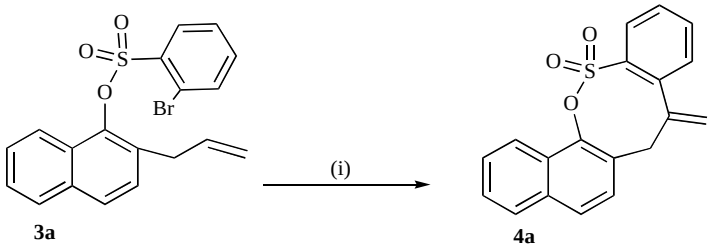
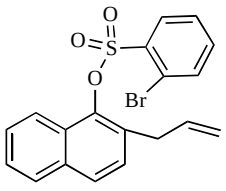
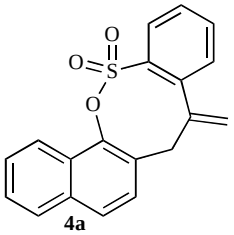
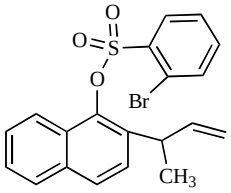
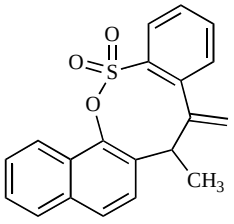
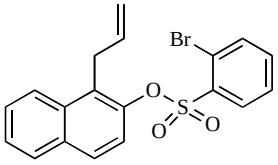
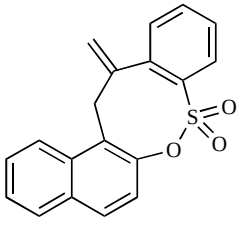


Scheme 1. Reagents and conditions: (i) Dry DCM, Et_3N, DMAP, 0 °C.

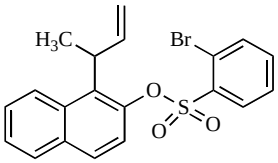
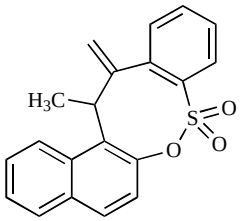


Scheme 2. Reagents and conditions: (i) $Pd(OAc)_2$, KOAc, TBAB, DMF, 100 °C.

Table 1. Summarized Results of the Heck Reaction

Entry	Precursors	Time(h)	Products	Yield(%)
1	 **3a**	3	 **4a**	97
2	 **3b**	3.5	 **4b**	91
3	 **3c**	3.2	 **4c**	95

(Table 1). Contd…..

Entry	Precursors	Time(h)	Products	Yield(%)
4	 **3d**	3.4	 **4d**	84

conditions to afford the cyclized products **4**(**b-d**) in 84-95% yields. The results are summarized in (Table **1**). The exclusive formation of benzoxathiocine derivatives **4a-d** [33] *via* 8-*exo* mode of cyclization is quite unusual. Because, Beletskaya and Cheprakov reported [34] that the *exo*-Heck cyclization can occur only in case of the substrate which generates small to common ring system; otherwise mixture of products of *exo*-cyclization and *endo*-cyclization is formed. However, in the present instance, exclusively the eight-membered oxathiocine derivatives *via* 8-*exo* trig mode of cyclization are obtained.

In conclusion, we have developed an efficacious regioselective method for the construction of eight-membered oxathiocine derivatives *via* an 8-*exo* trig cyclization using a Claisen rearrangement followed by intramolecular Heck cyclization as the key steps. The method represents a simple synthetic protocol for the formation of fused oxathiocine derivatives.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

REFERENCES AND NOTES

[1] Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York and London, **1972**; Vol. *II*.
[2] Faulkner, D. J. *Nat. Prod. Rep.*, **1984**, *1*, 251, 551; **1986**, *3*, 1; **1987**, *4*, 539; **1989**, *5*, 613.
[3] Denieul, M. P.; Skrydstrup, T. *Tetrahedron Lett.*, **1999**, *40*, 4901.
[4] Kricka, L. J.; Ledwith, A. *Chem. Rev.*, **1974**, *74*, 101.
[5] Hoberg, J. O. *Tetrahedron*, **1998**, *54*, 12631.
[6] Oishi, T.; Ohtsuka, Y. *Studies in Natural Products Chemistry;* Rahaman, A.; Ed.; Elsevier: Amsterdam, **1989**, p. 73.
[7] Moody, C. J. *Studies in Natural Products Chemistry*, Rahaman, A.; Ed.; Elsevier: Amsterdam, **1992**, p. 201.
[8] Petasis, N. A.; Patane, M. A. *Tetrahedron*, **1992**, *48*, 5757.
[9] Mehta, G.; Singh, V. *Chem. Rev.*, **1999**, *99*, 881.
[10] Roxburg, C. J. *Tetrahedron*, **1993**, *49*, 10749.
[11] Rousseau, G. *Tetrahedron*, **1995**, *51*, 2777.
[12] Evans, P. A.; Holmes, A. B. *Tetrahedron*, **1991**, *47*, 9131.
[13] Yet, L. *Tetrahedron*, **1999**, *55*, 9349.
[14] Hoberg, J. O. *Tetrahedron*, **1998**, *54*, 12631.
[15] Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron*, **2007**, *63*, 3919.
[16] Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tertahedron Lett.*, **2007**, *48*, 7633.
[17] Majumdar, K. C. Chattopadhyay, B.; Sinha, B. *Tetrahedron Lett.*, **2008**, *49*, 1319.
[18] Majumdar, K. C.; Chattopadhyay, B. *Synlett*, **2008**, 979.
[19] Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: Oxford, **1993**.
[20] Kim, C. U.; McGee, L. R.; Krawczyk, S. H.; Harwood, E.; Harada, Y.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Cherrington, J. M.; Xiong, S. F.; Griffin, L.; Cundy, K. C.; Lee, A.; Yu, B.; Gulnik, S.; Erickson, J. W. *J. Med. Chem.*, **1996**, *39*, 3431.
[21] Richter, H. G.; Angehrn, P.; Hubschwerlen, C.; Kania, M.; Page, M. G.; Specklin, J.-L.; Winkler, F. K. *J. Med. Chem.*, **1996**, *39*, 3712.
[22] Buynak, J. D.; Vogeti, L.; Chen, H. *Org. Lett*., **2001**, *3*, 2953.
[23] MaGee, D. I.; Beck, E. J. *J. Org. Chem.*, **2000**, *65*, 8367.
[24] Vedejs, E.; Singer, S. P. *J. Org. Chem.*, **1978**, *43*, 4884.
[25] McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.*, **2001**, *42*, 1197.
[26] Roberts, D. W.; Williams, D. L. *Tetrahedron*, **1987**, *43*, 1027.
[27] Pérez-Pérez, M.-J.; Balzarini, J.; Hosoya, M.; Clercq, E. D.; Camarasa, M. *J. Bioorg. Med. Chem. Lett.*, **1992**, *2*, 647.
[28] Jin, Z.; Fuchs, P. L. *Tetrahedron Lett.*, **1993**, *34*, 5205.
[29] Fu, C.; Ma, S. *Org. Lett*., **2005**, *7*, 1605.
[30] Arnold, L. A.; Luo, W.; Guy, R. K. *Org. Lett*., **2004**, *6*, 3005.
[31] Majumdar, K. C.; Chattopadhyay, B.; Sinha, B. *Synthesis*, **2008**, 3857.
[32] Jeffery, T. *J. Chem. Soc., Chem. Commun*., **1987**, 1288.
[33] **Compound 4a:** Yield: 97%; yellow solid; mp 130-131 ^{0}C; IR (KBr, cm^{-1}): 1188, 1369; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 3.91 (s, 2H, =CHC**H$_2$**), 5.34 (s, 2H, =CH$_2$), 7.28 (d, 1H, *J* = 8.2 Hz, Ar**H**), 7.36 (d, 1H, *J* = 7.6 Hz, Ar**H**), 7.42 (t, 1H, *J* = 7.4 Hz, Ar**H**), 7.48 (dt, 1H, *J* = 7.8 Hz, *J* = 1.0 Hz, Ar**H**), 7.57-7.63 (m, 2H, Ar**H**), 7.70 (d, 1H, *J* = 8.4 Hz, Ar**H**), 7.80 (d, 1H, *J* = 8.2 Hz, Ar**H**), 8.06 (d, 1H, *J* = 2.3 Hz, Ar**H**). 8.36 (d, 1H, *J* = 8.6 Hz, Ar**H**). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 40.1, 119.8, 120.3, 122.7, 126.8, 127.5, 127.8, 127.9, 128.0, 128.4, 129.6, 130.8, 134.2, 134.5, 145.2, 145.6. HRMS: Calculated for $C_{19}H_{14}O_3S$: 345.0561 (M+Na)$^+$. Found: 345.0561 (M+Na)$^+$. Anal. Calcd. for $C_{19}H_{14}O_3S$: C, 70.79; H, 4.38%. Found: C, 70.98; H, 4.09%.
[34] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*., **2000**, *100*, 3009.