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Novel synthesis of oxocine derivatives by Wittig olefination and intramolecular Heck reaction via 8-*endo trig* cyclization

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Abstract

A concise and efficient method for the preparation of oxocine derivatives is described via sequential Wittig and intramolecular Heck reactions. The method is highly regioselective and affords high yields of the products.

Keywords: Pd-catalyst; Heck reaction; Wittig reaction; 8-*endo trig*; Oxocine

The Heck reaction has become a useful synthetic tool due to its excellent functional group tolerance and high stereoselectivity. The Heck reaction was introduced to organic chemists in the late 1960s,[1] but only in the past decade or so it has witnessed rapid development and wide applications in carbon–carbon bond-forming reactions.[2] Generally, many natural products such as rhazinilam[3] and its congener rhazinal,[4] and naphthoxepin[5] that contain medium-sized heterocyclic rings fused to aryl rings have attracted the attention of both biologists and synthetic organic chemists.[6] Oxepin is an important structural subunit present in numerous biologically active molecules and has received considerable attention over the last 20 years. For example, naphthoxepin derivatives such as **1**[7] have been used as antipsychotic drugs (Fig. 1).

In continuation of our interest in the Pd-catalyzed synthesis of heterocycles, we have devised an approach for construction of the oxepin ring employing a Wittig reaction followed by a highly regioselective intramolecular Heck reaction. We envisioned that this route would not only lead to the naphthoxepin derivatives, but also to a variety of new analogs possessing modification around the aryl ring.

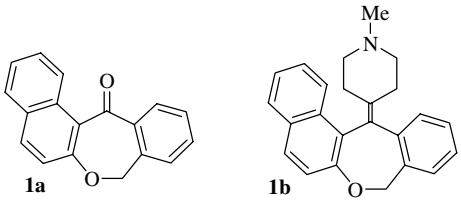

Fig. 1.

The synthesis of heterocyclic compounds utilizing organometallic compounds such as ruthenium or palladium-complexes has been studied recently in our laboratory.[8–15] The palladium-catalyzed intramolecular cyclizations seemed to be particularly fascinating, since a number of different nucleophiles are known to react with olefinic compounds to afford useful natural and unnatural heterocyclic compounds.

The intramolecular Heck reaction has two possible modes of ring closing, that is, *exo*- and *endo*-cyclization. Small to medium size (5–8) ring formation is usually favored by *exo*-cyclization[16–18] since the corresponding *endo*-cyclization is sterically very demanding; *endo*-cyclization requires that the olefinic bond moves into the loop of the substrate generating an energetically favorable substituted alkene product. Thus large size ring (~20) formation with a flexible tether generally favors *endo*-cyclization.[19–22]

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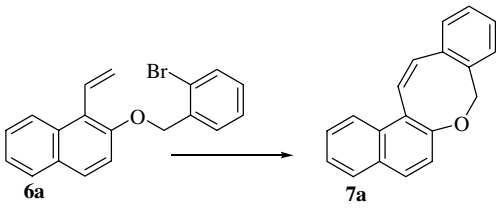
To the best of our knowledge, only a limited number of examples of *endo*-cyclization for the formation of medium-sized rings have appeared in the literature.[23,24]

The required Heck precursors **6a–h** were synthesized in 89–93% yields by the Wittig reaction of substrates **5a–h**. The Wittig reagent was prepared from PPh_3MeI in dry THF in the presence of ^{n}BuLi at 0 °C–rt for about 1 h. Substrates **5a–h** were in turn prepared in almost quantitative yields by the reaction of hydroxy-aldehydes **3a–d** with either 2-bromobenzyl bromide **4a** or 2-bromo-5-methoxybenzyl bromide **4b** in dry acetone in the presence of anhydrous potassium carbonate and a small amount of sodium iodide[25] (Scheme 1). Compounds **3a–d** were prepared by the Reimer–Tiemann reaction.

When the intramolecular Heck reaction was performed with precursor **6a**[26] in the presence of $Pd(OAc)_2$ as a catalyst, KOAc as a base, and tetrabutylammonium bromide (TBAB) as an additive in dry DMF as solvent for 2 h under a nitrogen atmosphere, the eight-membered naphthoxocine compound **7a**[27,28] was obtained in excellent yield (86%). Only the *Z*-isomer was formed as indicated by ^{1}H NMR analysis ($J_{Ha-Hb} = 13.8$ Hz). Molecular models also show that the compound can be considered as a bridged *cis*-stilbene. The optimum conditions for the cyclization were found through a series of experiments where various changes were made to the catalyst, base, additive, and solvent (Table 1).

During the course of the optimization of the *exo*-Heck reaction, we found that the catalyst, base, additive, and solvent had a profound effect on the reaction yield. The catalyst $Pd(PPh_3)_2Cl_2$, which is used mostly in this type of Heck cyclization,[23] provided a 21% yield of the product, whereas $Pd(PPh_3)_4$ provided **7a** in 43% yield. Therefore, we examined the results of the reaction taking $Pd(OAc)_2$ as a catalyst and succeeded in obtaining excellent yields in the intramolecular Heck cyclization. The reaction did not proceed under the reaction conditions described in Table 1, entries 4, 5, 9–11. The catalyst $PdCl_2$ was also found to be effective but the yield of the reaction was only 36%. Here, it is important to note that the additive plays an important role in the Heck cyclization. We performed the reaction in the presence of TBAB, Table 1 (entries 1, 2, 6–9). In the absence of TBAB, the reactions (entries 1, 2, and 6–9) did not occur.

Table 1
Optimization of the palladium-catalyzed cyclization[a] of **7a** from **6a**



6a **7a**

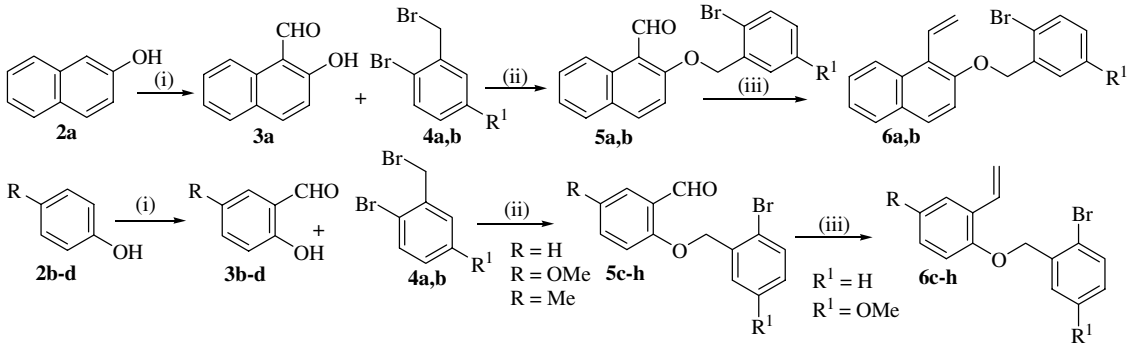
Entry	Catalyst	Base	Solvent	Yield (%)
1[b]	$Pd(OAc)_2$	KOAc	DMF	86
2[b]	$Pd(OAc)_2$	Et_3N	DMF	<5
3	$Pd(OAc)_2$	K_2CO_3	DMF	63
4	$Pd(OAc)_2$	Ag_2CO_3	DMF	NR
5	$Pd(OAc)_2$	Cs_2CO_3	DMF	NR
6[b]	$Pd(PPh_3)_4$	KOAc	DMF	43
7[b]	$Pd(PPh_3)_2Cl_2$	KOAc	DMF	21
8[b]	$PdCl_2$	KOAc	DMF	36
9[b]	$Pd(OAc)_2$	KOAc	DMF	NR
10	$Pd(OAc)_2$	Et_3N	Et_3N	NR
11	$Pd(OAc)_2$	Et_3N	MeCN	NR
12	$Pd(OAc)_2$	Et_3N	Dioxane	<5
13	$Pd(OAc)_2$	KOAc	Dioxane	<5

[a] All reactions were carried out at 100 °C and the amount of catalyst used in the reaction was 10 mol %.
[b] TBAB was used as an additive. NR indicates no reaction.

The effect of base on the reaction was also investigated. The use of the organic base Et_3N dramatically reduced the rate of reaction (entries 2 and 12) and no reaction was observed in the case of entries 10 and 11. Replacement of the organic base with inorganic KOAc was found to be highly effective and excellent yields of products were obtained. Other inorganic bases, for example, K_2CO_3, Ag_2CO_3, and Cs_2CO_3 were explored, and K_2CO_3 was found to be effective (entry 3); however, the use of Ag_2CO_3 and Cs_2CO_3 led to no reaction.

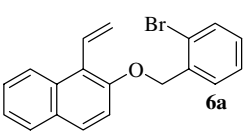
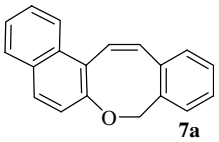
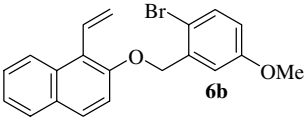
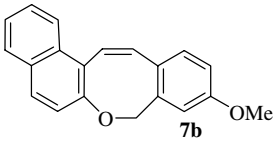
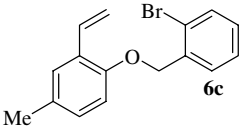
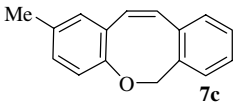
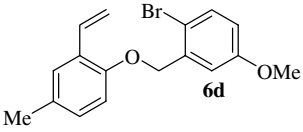
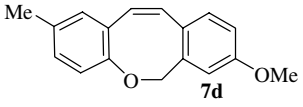
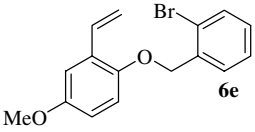
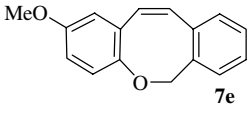
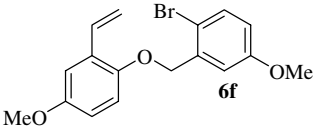
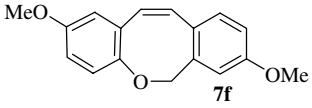
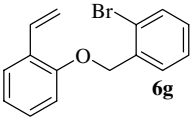
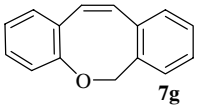
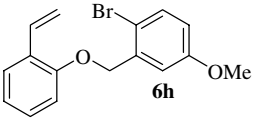
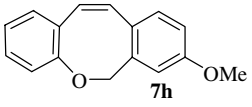
A study of the influence of various solvents (DMF, CH_3CN, Et_3N, and dioxane) suggested that DMF was the best choice.

Substrates **6b–h** when treated under optimized reaction conditions [$Pd(OAc)_2$/TBAB/KOAc/DMF/100 °C] affor-



Scheme 1. Reagents and conditions: (i) aq NaOH, $CHCl_3$, reflux, 4 h; (ii) acetone, K_2CO_3, NaI, 3–4 h; (iii) PPh_3MeI, ^{n}BuLi, THF, 0 °C–rt. Yields: **6a**, 88%; **6b**, 91%; **6c**, 94%; **6d**, 87%; **6e**, 90%; **6f**, 95%; **6g**, 88%; **6h**, 89%.

Table 2
Results of the Heck reactions[a]

Entry	Heck precursor	Product	Time (h)	Yield[b](%)
1	 **6a**	 **7a**	2	86
2	 **6b**	 **7b**	3.5	67
3	 **6c**	 **7c**	4	76
4	 **6d**	 **7d**	5	70
5	 **6e**	 **7e**	5	69
6	 **6f**	 **7f**	3.5	66
7	 **6g**	 **7g**	4	71
8	 **6h**	 **7h**	5	68

[a] All the reactions were carried out using the optimized reaction conditions.
[b] Isolated yields.

ded the corresponding eight-membered cyclized oxocine derivatives **7b–h**. Only the *Z*-isomer was formed as indicated by ^{1}H NMR analysis ($J_{Ha–Hb} = 13.8$ Hz). The results are summarized in Table 2.

The mechanistic rationalization for the regioselective formation of the oxocine derivatives by the 8-*endo trig* cyclization is unusual. Denieul and Skrydstrup[23] recently showed that during intramolecular Heck cyclization, the 7-*exo trig* mode of cyclization of a compound having a vinyl group attached to an aromatic ring was favored over the 8-*endo trig* mode. In the present instance, we obtained exclusively the eight-membered heterocyclic compounds, that is, the oxocine derivatives via 8-*endo trig* cyclization.

In conclusion, we have developed an efficient and regioselective method for the synthesis of eight-membered heterocyclic compounds via 8-*endo trig* cyclization using a Wittig reaction followed by intramolecular Heck cyclization as the key steps. This method constitutes a simple synthetic protocol for the formation of fused oxocine derivatives in high yields.

Acknowledgments

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References and notes

1. Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.
2. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
3. Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, 909.
4. Kam, T.-S.; Tee, Y.-M.; Subramaniam, G. *Nat. Prod. Lett.* **1998**, *12*, 307.
5. Kotha, S.; Mandak, K. *Tetrahedron Lett.* **2004**, *45*, 1391.
6. Baudoin, O.; Guenard, D.; Gueritte, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 333.
7. Carl, K.; Joseph, L. U.S. Patent 4,073,912, 1972; *Chem. Abstr.* **1978**, *89*, 24156.
8. Majumdar, K. C.; Islam, R.; Rahaman, H.; Roy, B. *Org. Biomol. Chem.* **2006**, *4*, 2393.
9. Majumdar, K. C.; Muhuri, S.; Rahaman, H.; Islam, R.; Roy, B. *Chem. Lett.* **2006**, *35*, 1430.
10. Majumdar, K. C.; Rahaman, H.; Muhuri, S.; Roy, B. *Synlett* **2006**, 466.
11. Majumdar, K. C.; Rahaman, H.; Islam, R.; Roy, B. *Tetrahedron Lett.* **2006**, *47*, 2111.
12. Majumdar, K. C.; Mondal, S. *Tetrahedron Lett.* **2007**, *48*, 6951.
13. Majumdar, K. C.; Pal, A.; Taher, A.; Debnath, P. *Synthesis* **2007**, 1707.
14. Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tetrahedron Lett.* **2007**, *48*, 7633.
15. Majumdar, K. C.; Chattopadhyay, B.; Taher, A. *Synthesis* **2007**, 3647.
16. Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.
17. Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.
18. Negishi, E.; Coperet, C.; Ma, S. M.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.
19. Denieul, M. P.; Laursen, B.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 6052.
20. Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.
21. Ma, S.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 6345.
22. Stocks, M. J.; Harrison, R. P.; Teague, S. J. *Tetrahedron Lett.* **1995**, *36*, 6555.
23. Denieul, M.-P.; Skrydstrup, T. *Tetrahedron Lett.* **1999**, *40*, 4901.
24. Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447.
25. Gazith, M.; Noys, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 6091.
26. *Compound* **6a**: Yield 88%; solid; mp 44–45 °C; IR (KBr): $\nu_{max} = 2850,\ 2921\ cm^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 5.27$ (s, 2H, OCH_2), 5.75 (dd, 1H, $J = 11.2$ Hz, $J = 2.0$ Hz, $=CH_aH_b$), 5.80 (dd, 1H, $J = 17.7$ Hz, $J = 2.0$ Hz, $=CH_aH_b$), 7.13 (m, 2H, $CH_2=CH$ and Ar**H** overlapped), 7.27 (d, 1H, $J = 9.0$ Hz, Ar**H**), 7.31 (t, 1H, $J = 7.5$ Hz, Ar**H**), 7.36 (t, 1H, $J = 7.2$ Hz, Ar**H**), 7.46 (t, 1H, $J = 7.0$ Hz, Ar**H**), 7.59 (m, 2H, Ar**H**), 7.74 (d, 1H, $J = 9.0$ Hz, Ar**H**), 7.77 (d, 1H, $J = 8.1$ Hz, Ar**H**), 8.20 (d, 1H, $J = 8.6$ Hz, Ar**H**). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 70.6, 114.7, 121.0, 121.9, 122.2, 123.7, 124.4, 126.4, 127.5, 128.2, 128.7, 128.8, 129.1, 129.5, 130.3, 132.4, 132.5, 136.6, 152.9$. HRMS: calcd for $C_{19}H_{15}BrO$: 339.0379 [M+H]; 341.0361 [MH+2]. Found: 339.0391 [M+H]; 341.0391 [MH+2]. Anal. Calcd for $C_{19}H_{15}BrO$: C, 67.27; H, 4.46. Found: C, 67.39; H, 4.54.
27. *Compound* **7a**: Yield 86%; solid, mp 115–116 °C; IR (KBr): $\nu_{max} = 2851,\ 2922\ cm^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 5.47$ (s, 2H, OCH_2), 6.97 (d, 1H, $J = 13.8$ Hz, $=CH_aH_b$), 7.04 (d, 1H, $J = 13.8$ Hz, $=CH_aH_b$), 7.13–7.21 (m, 4H, Ar**H**), 7.29–7.35 (m, 2H, Ar**H**), 7.44 (t, 1H, $J = 7.3$ Hz, Ar**H**), 7.61 (d, 1H, $J = 8.9$ Hz, Ar**H**), 7.69 (d, 1H, $J = 8.0$ Hz, Ar**H**), 7.89 (d, 1H, $J = 8.5$ Hz, Ar**H**). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 73.9, 120.4, 121.8, 123.8, 124.0, 126.2, 127.1, 127.3, 127.8, 128.1, 129.1, 129.2, 129.3, 129.6, 131.3, 133.2, 134.8, 138.5, 152.8$. HRMS: calcd for $C_{19}H_{14}O$: 258.1045 [M^+]. Found: 258.1045 [M^+]. Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.41; H, 5.61.
28. Compound **7g** was earlier synthesized by Wittig reaction. See: Begasse, B.; Corre, M. L. *Synthesis* **1981**, 197.