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Novel synthesis of medium-sized oxa-heterocycles by palladium-catalyzed intramolecular Heck reaction

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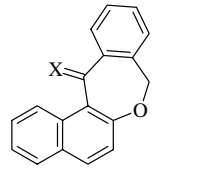
Abstract—An efficient and high yielding method for the synthesis of eight-membered heterocyclic skeletons has been developed via palladium-catalyzed intramolecular Heck reaction.

Over the past decade, palladium-catalyzed cyclization processes have proven to be an extremely powerful and useful tool for the construction of carbon–carbon, as well as carbon–heteroatom bonds.[1–3] Furthermore, palladium is typically used in catalytic amounts and tolerates a wide variety of functional groups, thus neatly avoiding protection group chemistry. Generally, many natural products, drugs and preclinical leads contain medium-sized heterocycles fused to aryl rings, for example, naphthoxepin derivatives such as **A** and **B** which are used as antipsychotic drugs[4] (Fig. 1).

However, a general synthesis of this type of medium-sized heterocyclic compound is lacking. The synthesis of medium-sized ring compounds, mainly seven- and eight-membered, was reported[5] based on ring closing metathesis reactions. Herein, we report a simple approach to the synthesis of eight-membered heterocyclic compounds from readily available α- and β-naphthol and resorcinol based on the thermal Claisen rearrangement, followed by phosphine-free,[6] palladium-catalyzed intramolecular Heck reaction.[7]

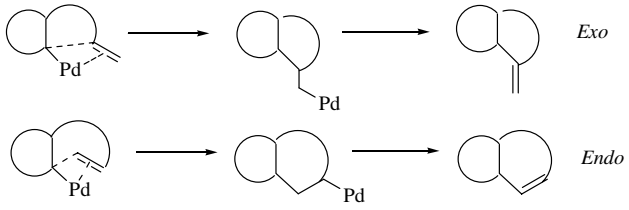


A, X = O
B, X = *N*-methylcyclohexane

Figure 1. Naphthoxepin derivatives used as antipsychotic drugs.

Entropy[8] plays an important role in intramolecular Heck reactions for the formation of cyclized products. In the majority of cases, the reaction proceeds in the *exo*-trig mode which is far less sterically demanding. The *endo*-trig mode of cyclization requires the olefinic bond to be positioned inside the intermediate π-complex. This requires a flexible tether between the olefinic bond and the aromatic ring for it to be able to bend into the proper conformation (Scheme 1) and is highly improbable due to geometric reasons.[9]

The Heck precursors **5a**–**d** required for our present study were synthesized in 70–80% yields by refluxing α- and β-naphthols **3a**,**b** with either 2-bromobenzyl bromide **4a** or 2-bromo-3-methoxybenzyl bromide **4b** in dry acetone in the presence of anhydrous potassium carbonate and a small amount of sodium iodide[10] (Scheme 2). Naphthols **3a**,**b** in turn were prepared in good to excellent yields by the reaction of α- and β-naphthols **1a**,**b**



Scheme 1. *exo* and *endo* mode of cyclization.

Keywords: Palladium catalyst; Medium-sized ring; Claisen rearrangement; 8-*exo*-Trig; 9-*endo*-Trig; Intramolecular Heck reaction.
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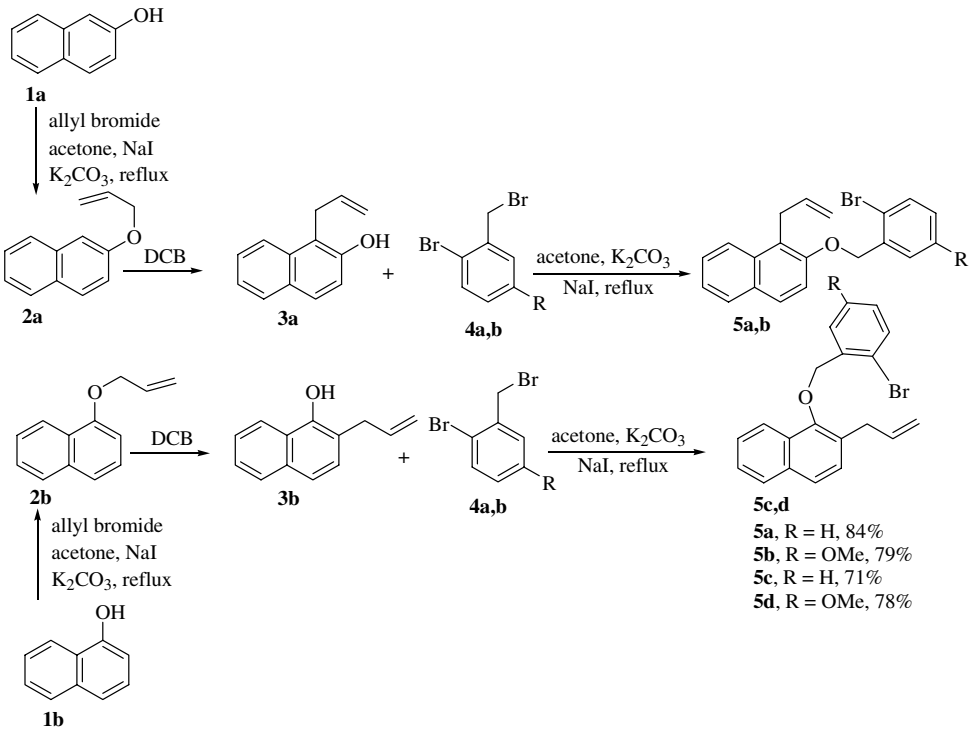


Scheme 2.

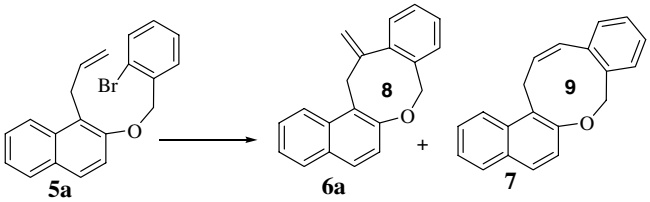
with allyl bromide followed by a Claisen rearrangement in refluxing dichlorobenzene (DCB) for about 8–9 h.

When the intramolecular Heck reaction was carried out with **5a** in the presence of 10 mol % of $Pd(OAc)_2$ as a catalyst and KOAc (2.75 equiv) as a base and tetrabutylammonium bromide as a promoter[11] in DMF at 120 °C for 4–6 h, the 8-*exo* cyclized product **6a**[12] was obtained as the major product in 78% yield, along with the 9-*endo* cyclized **7** as a minor product in 20% yield. The use of $Pd(PPh_3)_2Cl_2$ as a catalyst was also found to be effective but the nine-membered *endo*-Heck product was completely absent and the yield of the eight-membered *exo*-Heck product was low (49%). We have examined the effects of various bases, and experimentally, it was found that Et_3N (4 equiv) and K_2CO_3 (2 equiv) were also effective but the yield of the 8-*exo* cyclized products were lower than for the above-mentioned catalytic systems. The effect of temperature plays an important role in this reaction. When the reaction was performed with the low-boiling solvent acetonitrile the reaction did not proceed at all, probably due to the unactivated allylic system. Continuing the reaction for a long time at elevated temperature rapidly decreased the yield due to decomposition of the cyclized product. Other catalytic systems such as $PdCl_2$ yielded a number of unidentified products along with unreacted starting material. The results are summarized in Table 1.

Substrates **5b–d** were reacted under the conditions described in entry 1, Table 1, to afford the eight-membered *exo*-cyclic ring products. The 9-*endo* Heck products were not obtained, probably in these cases due to the instability of the *endo*-Heck product; the results are summarized in Table 2. We then extended the reaction to the readily available, inexpensive starting material resorcinol.

Resorcinol **1c** on reaction with allyl bromide in the presence of acetone, K_2CO_3 and NaI gave the O,O-dialkylated product **2c**. The dialkylated product on refluxing in *o*-DCB for 20–25 h afforded the rearranged product **3c**, which on treatment with 2-bromobenzyl bromide

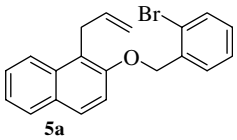
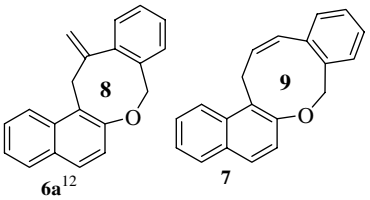
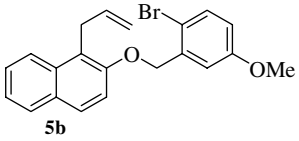
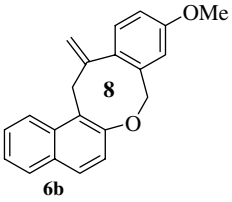
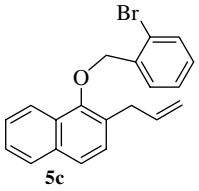
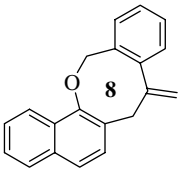
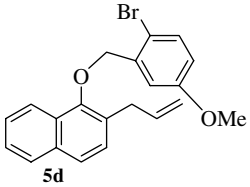
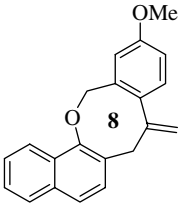
Table 1. Cyclization[a] of compound **5a** to **6a** and **7**



Entry	Catalyst[b]	Base[c]	Solvent	Yield of **6a**:**7** (%)
1	$Pd(OAc)_2$	KOAc	DMF	78:20
2	$Pd(OAc)_2$	K_2CO_3	DMF	58:0
3	$Pd(OAc)_2$	Et_3N	DMF	NR
4	$Pd(OAc)_2$	Et_3N	DMF	NR
5	$Pd(OAc)_2$	Et_3N	DMF	40:0
6	$Pd(OAc)_2$	KOAc	MeCN	NR
7	$PdCl_2$	KOAc	DMF	NR
8	$PdCl_2$	Et_3N	MeCN	NR
9	$Pd(PPh_3)_2Cl_2$	—	DMF	49:0
10	$Pd(PPh_3)_2Cl_2$	Et_3N	DMF	NR

[a] Tetrabutylammonium bromide (TBAB) was used as a promoter. All the reactions were performed at 120 °C for 4–6 h.
[b] 10 mol % of catalyst was used.
[c] 2.75 equiv of base was used. NR = No reaction.

Table 2. Summarized results of the Heck reaction with **5a–d**

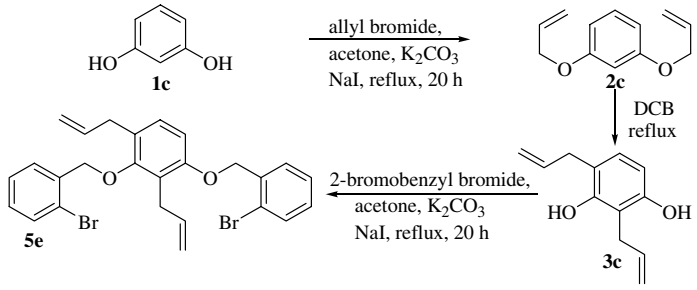
Entry	Substrate	Product	Yield (%) of **6**
1	 **5a**	 **6a**[12] **7**	78
2	 **5b**	 **6b**	72
3	 **5c**	 **6c**	81
4	 **5d**	 **6d**	77

afforded the corresponding Heck precursor **5e** (Scheme 3).

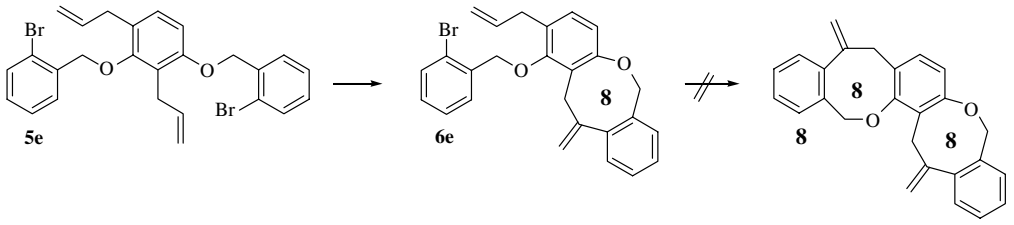
When the reaction of **5e** was performed using the conditions described in entry 1, Table 1, for 4 h at 120 °C, the 8-*exo* cyclized product (69%) and starting material (21%) were isolated. Increasing the reaction time caused considerable decomposition of the cyclized product. At elevated temperature (>160 °C) extensive decomposition also occurred. When the reaction was carried out using the conditions described in entries 2, 5 and 10, Table 1, the same product was obtained as under the conditions described in entry 1, Table 1, but the yields were lower (44%, 41% and 29%, respectively). There was no reaction under the conditions described in entries 3, 4 and 6–9, Table 1. Only one of the allylic groups underwent cyclization to form the eight-membered heterocyclic compound **6e**. We also failed to cyclize preformed **6e** to the doubly cyclized Heck product **8** (Scheme 4).

The formation of the 8-*exo* trig product[13] is quite reasonable due to the less sterically demanding environment. Formation of product **7**, that is, the nine-membered ring by the 9-*endo*-trig mode of cyclization, is quite interesting and follows a pathway that is not common in cyclization chemistry.[14]

In summary, we have developed an efficient method for the synthesis of eight-membered heterocyclic ring compounds. This method may be applicable to other hetero-



Scheme 3.



Scheme 4.

cyclic systems and compounds that contain unactivated allylic double bonds. Implementation of this strategy to the synthesis of a heterocyclic library is underway and will be reported in due course.

Acknowledgement

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12. Compound **6a**: Yield 78%, solid, mp 109–111 °C, IR (KBr): 2850, 2921 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 4.27$ (s, 2H, =C–C**H**$_2$), 5.26 (d, 1H, $J = 6.9$ Hz, =C**H**$_a$H$_b$), 5.38 (s, 2H, OC**H**$_2$), 5.46 (d, 1H, $J = 6.9$ Hz, =CH$_a$**H**$_b$), 7.09–7.15 (m, 5H, Ar**H**), 7.30–7.34 (m, 1H, Ar**H**), 7.45 (dt, 1H, $J = 1.2$ Hz, $J = 8.4$ Hz, Ar**H**), 7.55 (d, 1H, $J = 8.8$ Hz, Ar**H**), 7.69 (d, 1H, $J = 8.0$ Hz, Ar**H**), 7.93 (d, 1H, $J = 8.5$ Hz, Ar**H**). HRMS: calcd: 273.1274 (M+H). Found: 273.1250 (M+H). ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta_C = 36.4$, 75.8, 88.6, 112.5, 112.6, 114.5, 122.4, 122.6, 123.1, 124.4, 125.0, 126.6, 128.1, 128.5, 128.8, 128.9, 129.1, 129.7, 147.6, 154.9. Anal. Calcd for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.29; H, 6.01.
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