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NOVEL SYNTHESIS OF AZOCINE, AZEPINE, OXOCINE, AND OXEPINE DERIVATIVES BY PALLADIUM-CATALYZED MEDIUM-RING FORMATION FROM BROMOALLENES

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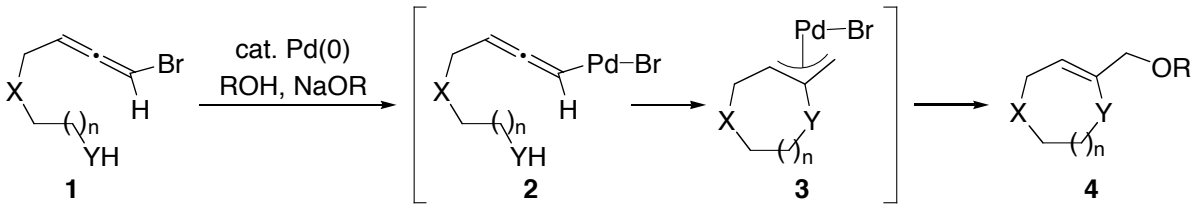
Abstract – Novel and efficient synthesis of medium-sized heterocycles such as azepine, oxepine, and benzo[*d*]azocine derivatives is described. Treatment of bromoallenes having a nucleophilic moiety with sodium alkoxide and a palladium(0) catalyst in the presence of an alcohol leads to regioselective formation of medium-sized rings at the central position of the allenic carbon.

INTRODUCTION

The importance of medium-sized heterocycles such as azocines, azepines, oxocines and oxepines is apparent by a number of seven- and eight-membered heterocycles with interesting pharmacological properties.[1,2] Today, the most powerful methodology for the synthesis of medium-sized rings is the ring-closing metathesis (RCM),[3] that is not always an ideal process: in many cases, the RCM requires high dilution conditions and involves generation of by-products such as ethylene.

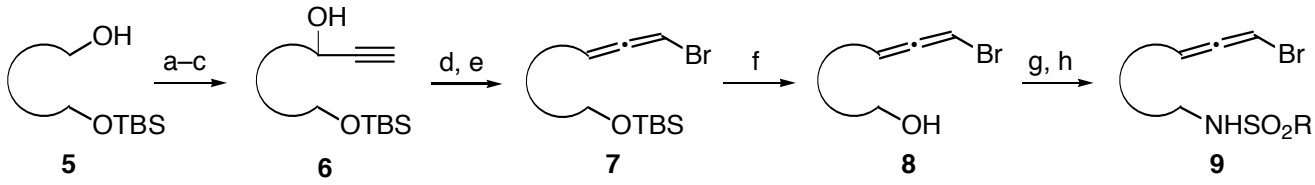
Recently, we found that bromoallenes can act as allyl dication equivalents that are extremely useful for the synthesis of medium-sized heterocycles bearing two heteroatoms (Scheme 1, X = NR', Y = NR'' or O).[4] Thus, reaction of bromoallene (**1**) with sodium alkoxide in the presence of a palladium(0) catalyst and alcohol affords π-allylpalladium(II) intermediate (**3**) by intramolecular nucleophilic reaction. The second nucleophilic substitution of **3** with alkoxide provides **4** in good to high yields. Although similar types of reaction are often observed in propargylic carbonates,[5,6] the reaction of allenic substrates and the synthesis of eight-membered rings were unprecedented. In this communication, a novel synthesis of seven- and eight-membered heterocycles possessing one heteroatom (X = CH_2, Scheme 1), such as hexahydroazocines, tetrahydroazepines, tetrahydrooxocine, and tetrahydrooxepine, is reported.



Scheme 1. Palladium(0)-catalyzed medium-ring formation from bromoallenes

RESULTS AND DISCUSSION

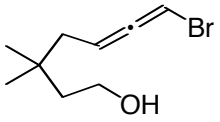
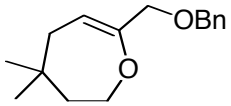
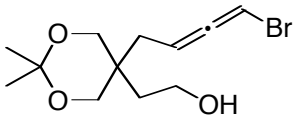
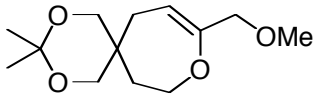
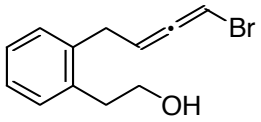
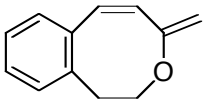
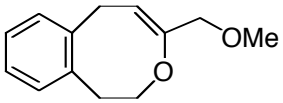
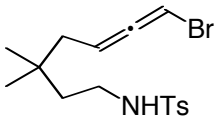
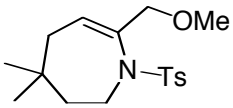
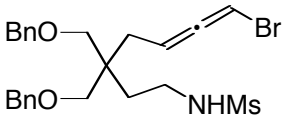
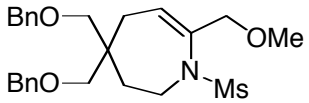
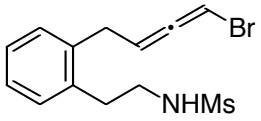
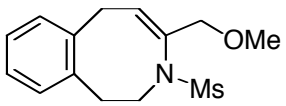
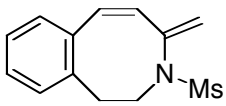
The requisite bromoallenes were readily prepared starting from mono-protected diols or related compounds. Typically, as shown in Scheme 2, Swern oxidation of **5** and subsequent ethynylation of the resulting aldehydes afforded a propargyl alcohol (**6**), which was converted into a bromoallene (**7**) by treatment of the corresponding mesylate with CuBr·SMe_2/LiBr.[7] Desilylation of **7** gave **8** having an oxygen nucleophilic moiety, which was then converted into the corresponding azacycle precursor (**9**) by Mitsunobu condensation followed by deprotection with dilute HCl.



Scheme 2. *Reagents*: a) $(COCl)_2$, DMSO, then $(i\text{-Pr})_2NEt$; b) trimethylsilylacetylene, *n*-BuLi; (c) NaOMe, MeOH; (d) MsCl, Et_3N; (e) CuBr·SMe_2, LiBr; (f) 1% HCl, EtOH; (g) RSO_2NHBoc, PPh_3, diethyl azodicarboxylate; (h) 3N HCl, EtOAc.

We next investigated the palladium-catalyzed medium-ring formation of bromoallenes. As we expected, treatment of the bromoallene (**10**) with a stirred mixture of NaH, BnOH, and THF in the presence of $Pd(PPh_3)_4$ gave the tetrahydrooxepine derivative (**16**) in 72% yield (entry 1) by the first intramolecular nucleophilic addition to form a □-allylpalladium intermediate followed by the second nucleophilic attack by methoxide. Similarly, the allene (**11**) having a protected diol moiety was converted into **17** (entry 2). In contrast, exposure of **12** to the identical cyclization conditions afforded eight-membered ring (**18**) as a major product (entry 3), which was formed by □-hydride elimination of the □-allylpalladium(II) intermediate of the type (**3**) (Scheme 1). This is presumably due to the relatively highly-acidic nature of the □-hydride at the benzylic position.[8] Medium-sized nitrogen heterocycles (**20**–**23**) were also synthesized starting from the bromoallenes (**13**–**15**) bearing a protected amino group (entries 4–6). Interestingly, when the amino allene (**15**) was used (entry 6), a methoxylated benzo[*d*]azocine derivative (**22**) was obtained as a major product (60% yield) along with a small amount of □-elimination product (**23**) (5% yield).

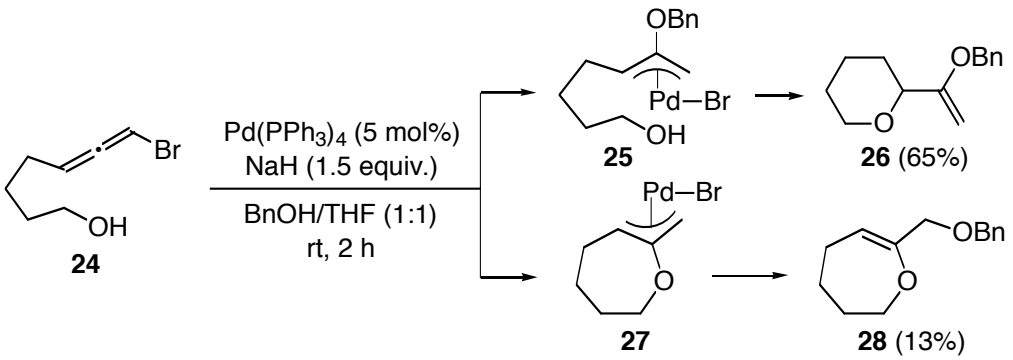
Table 1. Palladium-catalyzed medium-ring formation from bromoallenes[a]

entry	bromoallene	conditions	product (yield[b])
1	 **10**	BnOH/THF (1:3) rt, 5 h	 **16** (72%)
2	 **11**	MeOH 55 °C, 2 h	 **17** (72%)
3	 **12**	MeOH/THF (1:1) rt, 4 h	 **18** (70%)  **19** (13%)
4	 **13**	MeOH 55 °C, 5 h	 **20** (76%)
5	 **14**	MeOH 55 °C, 2 h	 **21** (76%)
6	 **15**	MeOH/THF (1:1) rt, 4 h	 **22** (60%)  **23** (5%)

a) All reactions were carried out using $Pd(PPh_3)_4$ (5 mol%) and NaH (1.5 equiv). b) Isolated yields.

It should be clearly noted that, in contrast to the seven- and eight-membered ring formation possessing two heteroatoms,[4] bromoallene (**24**) having an unsubstituted carbon tether afforded six-membered ring (**26**) in 65% yield (Scheme 3), as a result of the first intermolecular nucleophilic attack by benzyloxide to form π-allylpalladium (**25**), followed by the intramolecular nucleophilic reaction. From these results, it is apparent that the substituents on the tether assist the formation of the intermediate of the type **27**.

In conclusion, we have developed a novel synthetic method of seven- and eight-membered heterocycles such as azocine, azepine, oxocine, and oxepine derivatives through the cyclization of bromoallenes that bear an oxygen or nitrogen functionality in the presence of a palladium(0) catalyst and an alcohol. The present synthetic method for medium-sized rings would provide a wide variety of heterocycles including those having an enamine or enol moiety, that are not easily accessible by other means.



Scheme 3. Reaction of bromoallene **24** having an unsubstituted carbon tether.

ACKNOWLEDGEMENTS

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8. Exposure of the minor product (**19**) to the cyclization conditions led to complete recovery of **19**.