HETEROCYCLES, Vol. 61, 2003, pp. 65 - 68
Received, 26th June, 2003, Accepted, 5th September, 2003, Published online, 2nd October, 2003

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

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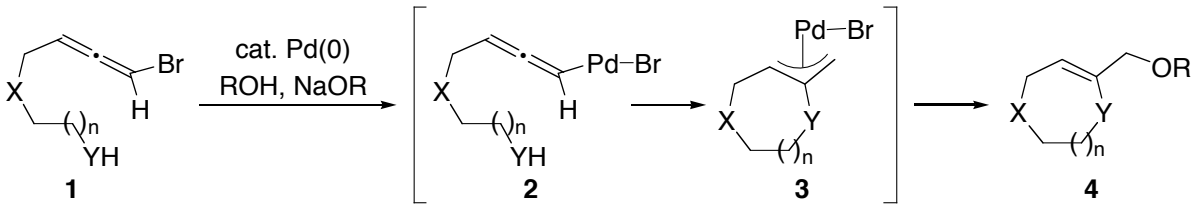
Abstract – Novel and efficient synthesis of medium-sized heterocycles such as azepine, oxepine, and benzo[*d*]azocine derivatives is described. Treatment of bromoallenes having a nucleophilic moiety with sodium alkoxide and a palladium(0) catalyst in the presence of an alcohol leads to regioselective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

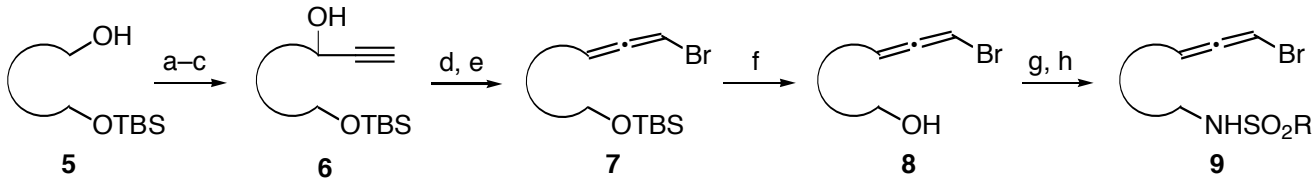
Recently, we found that bromoallenes can act as allyl dication equivalents that are extremely useful for the synthesis of medium-sized heterocycles bearing two heteroatoms (Scheme 1, X = NR', Y = NR'' or O).[4] Thus, reaction of bromoallene (**1**) with sodium alkoxide in the presence of a palladium(0) 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

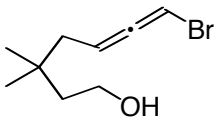
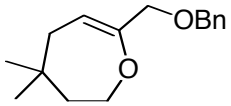
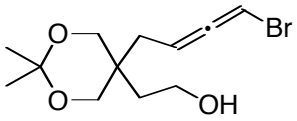
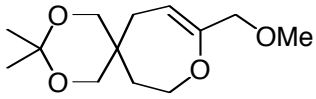
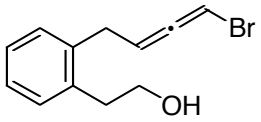
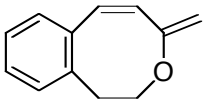
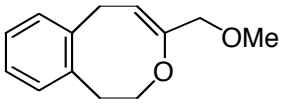
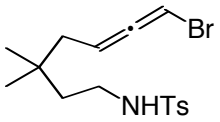
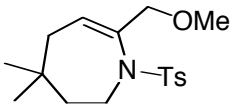
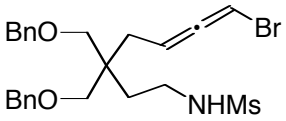
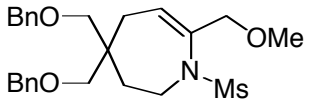
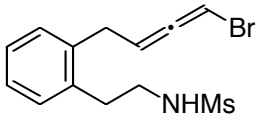
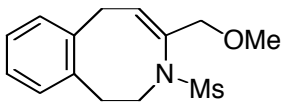
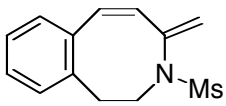
The requisite bromoallenes were readily prepared starting from mono-protected diols or related compounds. Typically, as shown in Scheme 2, Swern oxidation of **5** and subsequent ethynylation of the resulting aldehydes afforded a propargyl alcohol (**6**), which was converted into a bromoallene (**7**) 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).

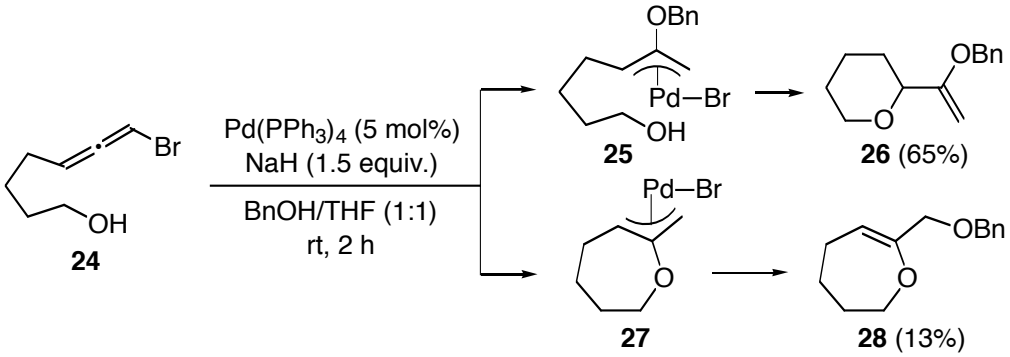
Table 1. Palladium-catalyzed medium-ring formation from bromoallenes[a]

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 □-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

This work was supported by a Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Culture, Sports, Science and Technology of Japan. H.H. is grateful to Research Fellowships of the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

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