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Scope of the radical addition–cyclization–elimination reaction of oxime ether towards the synthesis of tricyclic lactam derivatives

Habibur Rahaman, Atsushi Shirai, Okiko Miyata, Takeaki Naito *

Kobe Pharmaceutical University, 4-19-1, Motoyamakita, Higashinada, Kobe 658-8558, Japan

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ABSTRACT

The synthesis of tricyclic lactam building blocks by the radical addition–cyclization–elimination (RACE) reaction is presented. A range of oxime ethers carrying unsaturated ester part have been tested for the radical reaction. A variety of substituents were incorporated around the aromatic backbones and their effect on the RACE reaction has been examined. In addition, the power of RACE reaction is demonstrated by preparation of a key intermediate for the synthesis of constrained analogue of methoctramine.

1. Introduction

Fused pyrrolidine rings are common structural motif of many natural alkaloids.[1] Compounds of the ring type **1** (Fig. 1: X = NH) are found in naturally occurring martinelline or martinellic acid alkaloids, and they possess antibacterial activity and act as a bradykinin receptor antagonist.[2] On the other hand, naturally occurring chromene or chromane derivatives exhibit remarkable physiological properties and some pyrrolidine annulated benzopyran compounds are known as selective dopamine D_3 receptor antagonist.[3] Over the past few years, most research laboratories have utilized the [3+2] cycloaddition reactions of azomethine ylides to construct the substituted pyrrolidine ring system **2**.[4] Recently, the synthesis of chromeno [4,3-*b*] pyrroles by intramolecular 1,3-dipolar cycloaddition reaction under ultrasonic irradiation has been performed.[5] And we also published a few reports on the pyrroloquinoline compounds **1** produced by utilizing the RACE reaction.[6] However, to the best of our knowledge, there is no report on the synthesis of substituted pyrrolidine derivatives (like compound **2**) by RACE reaction. In this Letter, we wish to report the stannyl radical mediated synthesis of chromeno [4,3-*b*] pyrrole derivatives by radical addition–cyclization–elimination reaction.

Accordingly, we initiated a study on intramolecular radical reaction of oxime ether carrying an unsaturated ester part. The requisite substrate **5a** for this reaction was prepared via straightforward alkylation of compound **4a** with ethyl 4-bromocrotonate in the presence of K_2CO_3 at room temperature. The product **5a** was isolated in 83% yield along with an isomerized product **6a** in 12% yield (Scheme 1). In the literature, a similar kind of base-catalyzed isomerization–cyclization reaction is reported.[7]

With a collection of substituted oxime ether **5a** in hand, its radical reaction was next investigated. Thus, the reaction of the oxime ether substrate **5a** connected to the aromatic nucleus bearing an ethoxycarbonyl group in oxygen tether with Bu_3SnH and AIBN in refluxing benzene furnished the tricylic lactams **7a** and **8a** along with a cleaved product **4a** (Scheme 2). The yields of the tricyclic compounds **7a**, **8a** are higher and reaction time is shorter than those of our previously reported nitrogen analogues.[6b] In our earlier report on the nitrogen congeners, we have obtained the bicyclic amino ester derivatives along with pyrroloquinoline

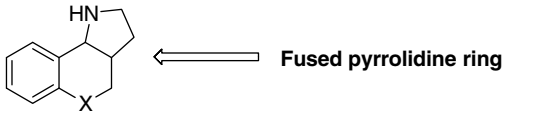
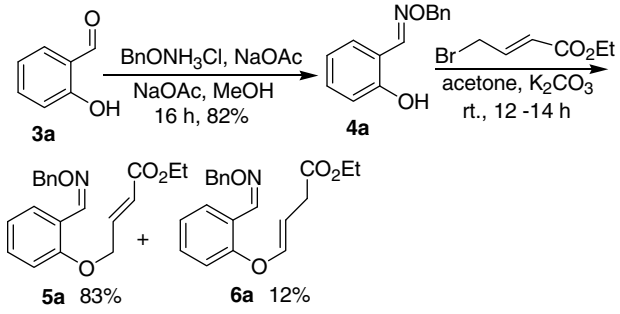


Figure 1.



Scheme 1.

* Corresponding author. Tel.: +81 78 441 7554; fax: +81 78 441 7556.
E-mail address: taknaito@kobepharma-u.ac.jp (T. Naito).

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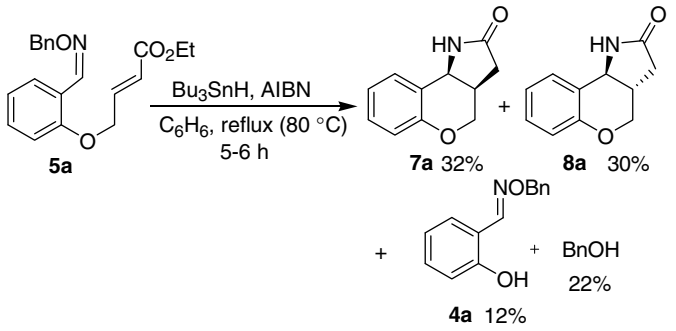
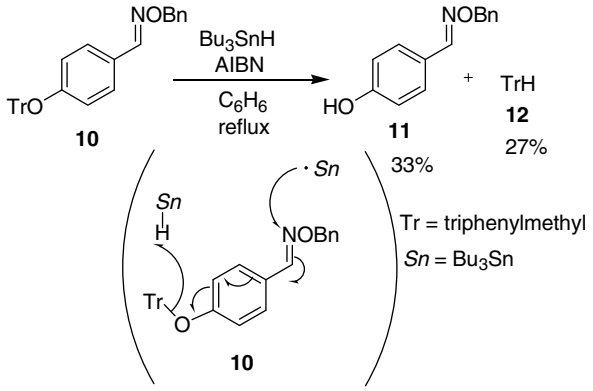


Scheme 2.



Scheme 4.

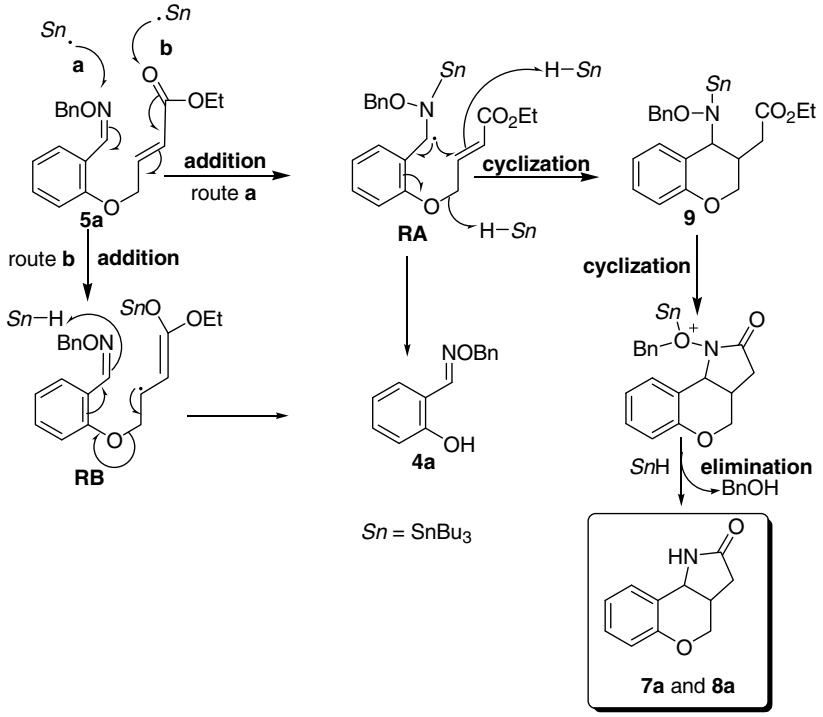
compounds, but interestingly, in our present study no bicyclic amino ester derivative was found.

Compounds **7a** and **8a** were characterized from their spectral analyses[8] and the absence of benzyloxy group in the ^{1}H NMR spectra suggests that this group on oxime ether moiety was eliminated during the transformation process.

According to the proposed mechanism given for RACE reaction of nitrogen derivatives,[6b] a plausible reaction pathway for the oxygen heterocycle is depicted in Scheme 3. Tributyl stannyl radical generated from Bu_3SnH and AIBN would add mainly to oxime part of **5a** to give the intermediate radical **RA**, which upon cyclization will produce the amino stannane **9** (route **a**). The more nucleophilic amino stannane **9** undergoes intramolecular cyclization to the ester, transfer of the stannyl group on nitrogen to oxygen and cleavage of the benzyloxy group to form tricyclic NH–lactams **7a** and **8a**. We propose two possible pathways for the formation of phenol **4a**: one is via the radical intermediate **RA**, which upon bond cleavage between oxygen and carbon will produce compound **4a** and ethyl crotonate. Another possibility is that the stannyl radical would attack the ester part to generate the unstable intermediate radical **RB** which would be readily subjected to bond cleavage between carbon and oxygen to afford the phenol **4a** (route **b**).

A possible attack of the stannyl radical on the oxime ether group was firmly established by the reaction of simple oxime ether **10** with Bu_3SnH and AIBN, which yielded the compounds **11** and **12** in 33% and 27% yields, respectively. The formation of these compounds explains that the tributyl stannyl radical first attacked the oxime part of the compound **10** to generate the more stable triphenylmethyl radical, which subsequently produced the triphenylmethane **12** and the phenolic compound **11** in moderate yields (Scheme 4). This reaction could also be an indirect evidence for the formation of **4a** from the intermediate radical **RA** (in Scheme 3). More detail mechanistic investigation of the RACE reaction on the oxygen heterocycle is in progress in our laboratory.

In order to investigate the effects of tether atom on the intramolecular RACE reaction, we also attempted the RACE reaction of sulfur derivatives **13** and **14**,[9] which, however, gave only unidentified products (Fig. 2). Therefore, both oxygen and nitrogen atoms are found to be better tether than sulfur in our RACE reaction.



Scheme 3.

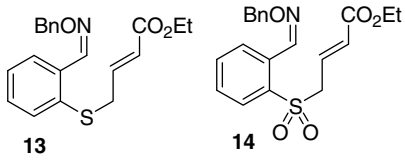


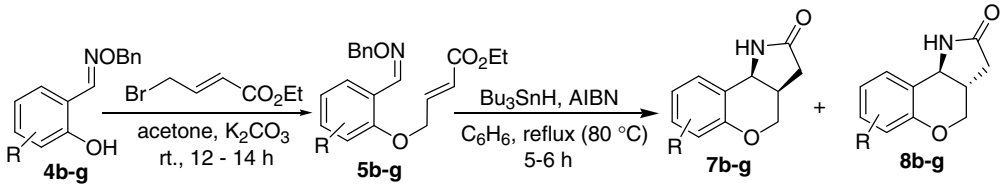
Figure 2.

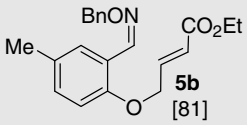
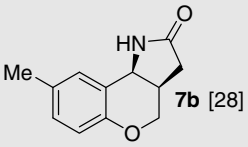
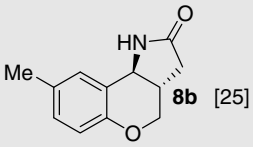
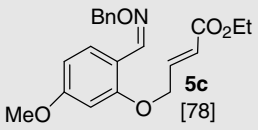
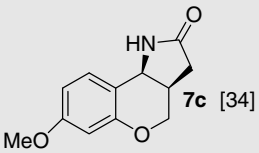
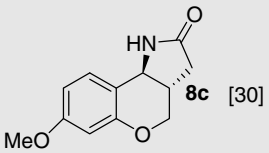
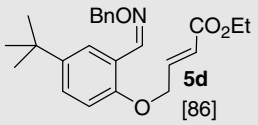
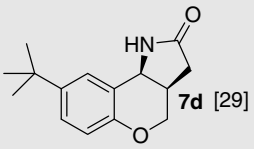
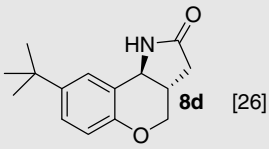
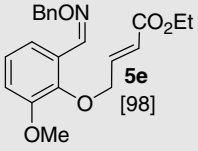
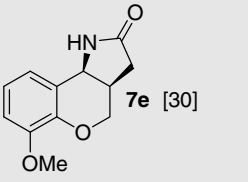
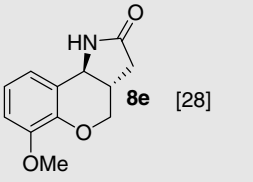
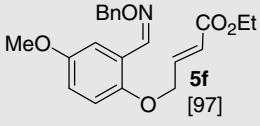
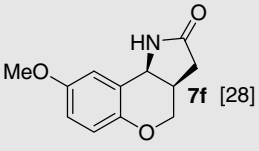
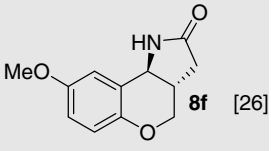
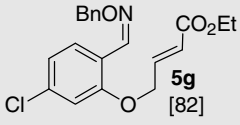
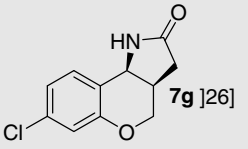
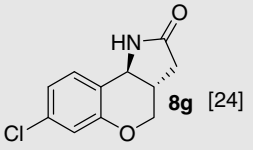
2. Substituent effect of the aromatic ring of the oxime ether

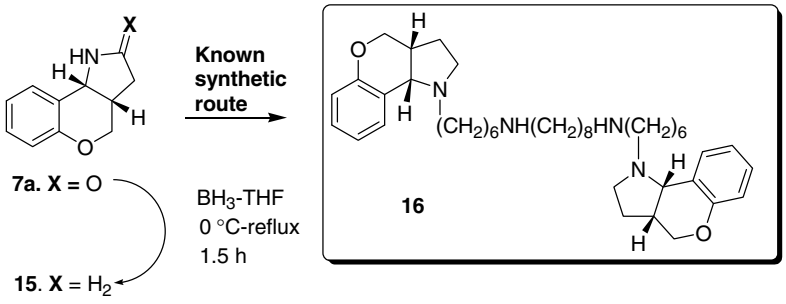
In our previous work, we observed that the substituent of aromatic ring of the oxime ether plays an important role on the intermolecular radical addition reaction.[10] We then decided to introduce electron-donating and electron-withdrawing substituents around the aromatic backbone of the oxime ether to understand their effects on reactivity and selectivity of the RACE reaction. The RACE precursors **5b–g** were prepared in good to excellent yields (see Table 1 for the isolated yields of **5b–g** starting from the compounds **4b–g**) according to the procedure described in Scheme 1. In the RACE reaction, introduction of methyl, *tert*-butyl and methoxy group at para position to the aromatic ether provided almost similar stereoselectivity and comparable yield (Table 1, entries 1, 3 and 5). High yield was obtained with the substrate bearing an electron-donating group at the four position of the aromatic ring (Table 1, entry 2). We were pleased to isolate the chloro-substituted derivatives **7g** and **8g** in moderate yields (Table 1, entry 6).[11]

The examples given in Table 1 demonstrate the power of RACE reaction in constructing the polycyclic lactam backbones, which are useful building blocks of many natural and unnatural products. One of the important applications of our strategy would be the construction of constrained analogue of methoctramine derivative **16**.[12]

Table 1
Preparation and intramolecular radical addition–cyclization–elimination reaction of **5b–g**



Entry	**5b–g**; yield in (%)	**7b–g**; yield in (%)	**8b–g**; yield in (%)
1	 **5b** [81]	 **7b** [28]	 **8b** [25]
2	 **5c** [78]	 **7c** [34]	 **8c** [30]
3	 **5d** [86]	 **7d** [29]	 **8d** [26]
4	 **5e** [98]	 **7e** [30]	 **8e** [28]
5	 **5f** [97]	 **7f** [28]	 **8f** [26]
6	 **5g** [82]	 **7g**]26]	 **8g** [24]



Scheme 5.

Methoctramine is the prototype polyethylene tetraamine for antagonism of muscarinic acetylcholine receptor (mAChR).[13] Compound **16** is a weaker antagonist than its free analogue at both nAChR and M_2 mAChR, but similarly potent at M_3 mAChR. Borane reduction of the lactam **7a** produced the viable synthetic intermediate **15** in 70% yield.

One can easily prepare the constrained analogue of methoctramine derivative **16** from the compound **15** by known synthetic way (Scheme 5).[12]

In conclusion, the scope of the radical addition–cyclization–elimination has been described. The reaction proceeds with a variety of substrates including the electron-donating and electron-withdrawing groups. Keeping moderate yield in mind, this methodology will allow the preparation of highly substituted aromatic and heteroaromatic subunits that could be well set during the natural product synthesis. Currently, we are elaborating the reaction sequences not only for the construction of tricyclic lactams, but also towards the total synthesis of pyrrolidine fused natural alkaloids.

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7. For similar type of base-catalyzed cyclization reaction see: Ciganek, E. *Synthesis* **1995**, 1311–1314.
8. *Typical procedure for the RACE reaction of oxime ether* **5a**: To a boiling solution of **5a** (270 mg, 0.79 mmol) in benzene (20 ml) was added a solution of Bu_3SnH (0.4 ml, 1.5 mmol) and AIBN (30 mg, 0.18 mmol) in benzene (10 ml) by syringe pump under a N_2 atmosphere. After being stirred at reflux for 5 h, the reaction mixture was extracted with hexane/MeCN. The MeCN phase was concentrated at reduced pressure and the residue was purified by flash chromatography (hexane/AcOEt) to afford **7a** (32%), **8a** (30%), **4a** (12%) and benzyl alcohol (22%).
Compound **7a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.19 (1H, dd, J = 17, 3.5 Hz). 2.66 (1H, dd, J = 17, 8.5 Hz), 2.92 (1H, m), 3.86 (1H, dd, J = 11.5, 9 Hz), 4.12 (1H, dd, J = 11.5, 4.5 Hz), 4.76 (1H, d, J = 6.5 Hz), 6.54 (1H, br s), 6.90 (1H, dd, J = 8.5, 1.5 Hz), 6.97 (1H, td, J = 7.5, 1.5 Hz), 7.20 (2H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 32.8, 33.0, 50.7, 65.7, 117.7, 121.4, 121.8, 129.4, 129.6, 154.8, 176.1; HRMS (ESI$^+$): m/z calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0789.
Compound **8a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.29 (1H, m), 2.54 (2H, m), 4.29 (1H, dd, J = 12, 10 Hz), 4.42 (1H, d, J = 10 Hz), 4.53 (1H, dd, J = 10, 4.5 Hz), 6.85 (1H, d, J = 9 Hz), 6.91 (1H, td, J = 7.5, 1 Hz), 7.01 (1H, br d, J = 7.5 Hz), 7.18 (2H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.5, 40.1, 56.0, 69.1, 116.7, 120.3, 122.9, 123.8, 128.8, 152.5, 178.2; HRMS (ESI$^+$): m/z calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0780.
9. The sulfur containing compound **13** was prepared from 2-mercaptobenzaldoxime ether according to the procedure described in Scheme 1. The two-step yield of the compound **13** was 77% and the m-CPBA oxidation of **13** provided the compound **14** in 68% yield.
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11. 4-Chlorosalicylaldehyde **3g** was prepared according to the published procedure, see; Leonard, K.; Marugan, J. J.; Roboisson, P.; Calvo, R.; Gushue, J. M.; Koblish, H. K.; Lattanze, J.; Zhao, S.; Cummings, M. D.; Player, M. R.; Maroney, A. C.; Lu, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3463–3468.
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