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Ytterbium-mediated synthesis of 2,4-diarylpyrroles from α-bromo oxime ethers†

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A novel and efficient ytterbium promoted reductive cyclisation dimerization of α-bromo-oxime ethers affording 2,4-diarylpyrroles with high regioselectivity has been developed. Compared with the reported synthesis methods, the method has the following advantages: readily available and safe starting material, one-pot single step operation and mild and neutral reaction conditions.

Pyrroles are one of the most versatile and important classes of heterocycles as well as building blocks, being present in many natural products,[1] synthetic medicinal agents[2] and functionalized materials.[3] As a consequence, various synthetic methods have been developed for the preparation of pyrroles.[4] However, most of the existing methods lead to pyrroles with functional groups at various positions and therefore further synthetic operation is required to afford simple alkyl or aryl substituted pyrroles. Particularly, synthetic approaches to simple 2,4-diaryl substituted pyrroles are even more limited.[5–8] Common limitations in the synthesis of 2,4-diaryl substituted pyrroles are: explosive substrates,[5] multiple synthetic steps,[6] harsh reaction conditions with high pressure[7] and limited substrate scope.[8] Therefore, the establishment of a simple and convenient synthetic method for preparation of 2,4-diaryl substituted pyrroles continues to be actively pursued.

The rapid development of lanthanides, especially Samarium reagents, in organic synthesis has been recently achieved.[9,10c] Ytterbium is one of the most important rare earth metals, due to its role as a reducing agent[11] and its reactivity towards various electrophilic organic compounds.[12] In addition, the reaction of an ytterbium-type Grignard reagent with electrophiles is another important application of ytterbium.[13,14]

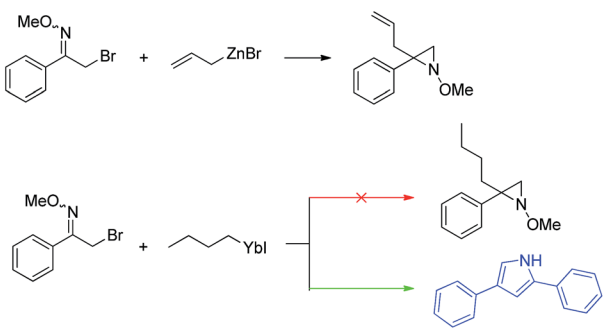
In the course of other studies in progress in this laboratory, we found that Barbier reaction of α-bromo-oxime ethers with butyl bromide promoted by ytterbium afforded unexpected product – 2,4-diarylpyrrole instead of aziridine (Scheme 1).[15]

Rational analysis of the result reveals that is a reductive cyclisation dimerization reaction of α-bromo-oxime promoted with ytterbium. In view of the importance of this class of compound and the limitation of previous synthesis methods, we believe it is necessary to further investigate and develop this method to afford 2,4-diarylpyrroles. Herein, we report a convenient one-pot protocol for the synthesis of 2,4-diarylpyrroles by the reductive cyclisation dimerization reaction of α-bromo-oxime promoted with ytterbium.

Our exploration of this transformation began with 2-bromo-1-phenylethanone *O*-methyl oxime (*E*/*Z* mixture) **1a** (Table 1) as substrate. It was found that when **1a** was treated with 1.5 equiv. of Yb, catalytic amount I_2 in THF, 2-bromo-1-phenylethanone *O*-methyl oxime had been completely consumed and a new product had been formed, it was interesting to notice the formation of 2,4-diphenylpyrrole in 58% yield instead of the proposed products shown in Scheme 1.

Then other reductants were employed in the controlled experiments to select the suitable reductant. The results in Table 1 shown that 2,4-diphenyl-1*H*-pyrrole was obtained in 33%, 35% and 38% yields when butyl ytterbium(II) iodide, YbI_2 and SmI_2 were successively used as the reductants in dry THF at room temperature (Table 1, entries 2–4). Some other metals except of zinc and indium, such as samarium, neodymium, dysprosium and magnesium can also promote the reaction to get product **2a** in different yields (Table 1, entry 5–10). As we can see, ytterbium is the most suitable reductant.

In order to investigate the effect of the configuration of substrates on yield, the reaction of (*Z*)-2-bromo-1-phenylethanone



Scheme 1 Reactions of α-bromo oxime ether with allyl zinc bromide and butyl ytterbium(II) iodide.

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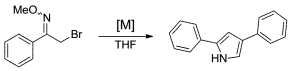
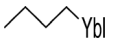
Table 1 Optimization of reductant[a]



Entry	Reductant (yield)[b]	Entry	Reductant (yield)[b]
1	Yb (51[c]/58[d]/48[e]/56[f]/37[g])	6	Nd (48)
2	 (33)	7	Dy (44)
3	YbI_2 (35)	8	Mg (28)
4	SmI_2 (38)	9	Zn (0)
5	Sm (54)	10	In (0)

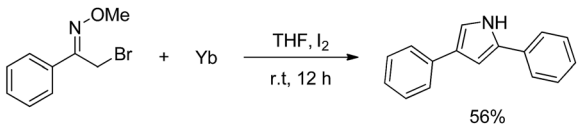
[a] Unless noted, the reaction was take under a nitrogen atmosphere at room temperature. [b] Isolated yield. [c] 12 h α-bromo oxime/Yb = 1/1. [d] 12 h α-bromo oxime/Yb = 1/1.5. [e] 12 h α-bromo oxime/Yb = 1/2. [f] 0 °C, 12 h, α-bromo oxime/Yb (1/1.5). [g] 65 °C, 12 h, α-bromo oxime/Yb (1/1.5).

O-methyl oxime **1aa** with ytterbium was performed, the yield did not change obviously compared with **1a** (Scheme 2).

The scope of the above reductive process was further investigated by extending the substrate to other α-halo oxime ethers. As summarized in Table 2, an array of α-halo oxime ethers was suitable for this pyrrole formation process.

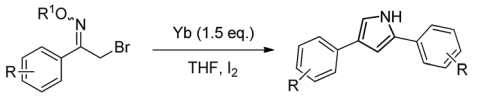
As shown in Table 2, moderate yields were obtained with α-bromo oxime ethers bearing electron-donating groups on the aryl ring, such as *p*-methyl (**1b**), *m*-methyl (**1c**), *o*-methyl (**1d**), *p*-pentyl (**1e**) (Table 2, entries 2–5). With α-bromo oxime ethers bearing electron-withdrawing groups on the aryl ring, such as 4-chloro (**1f**), 4-fluoro (**1g**), 3,4-dichloro (**1h**) and 2,4-dichloro (**1i**), the products were obtained in lower yields than electron-donating groups (Table 2, entries 6–9). However, other functional groups on the aryl ring **1j–l** failed to afford the corresponding pyrrole products (Table 2, entries 10–12). Electron-withdrawing groups at *meta*- and *ortho*-position on the aryl ring (**1m** and **1n**) were more reactive and provided the products 2,4-diarylpyrroles in higher yields than **1f–i**. Fused ring compound such as 2-bromo-1-(naphthalen-2-yl)ethanone *O*-methyl oxime (**1o**) in this reaction leads to a complex mixtures and only few amounts of product was detected by LC-MS. Moreover, a heterocyclic substrate such as 2-bromo-1-(thiophen-2-yl) ethanone *O*-methyl oxime (**1p**) is unreactive and no corresponding pyrrole was achieved. Then, 2-bromo-1-phenylethanone *O*-benzyl oxime (**1q**) was used as the substrate to investigate the reaction, the corresponding 2,4-diphenylpyrrole **2a** was afforded in 42% yield under the aforementioned conditions.

To further determine the reactivity of alkyl α-bromo oxime ethers, 1-bromopropan-2-one *O*-methyl oxime (**1r**) as substrate



Scheme 2 Reaction of **1aa** with ytterbium.

Table 2 Ytterbium-mediated synthesis of 2,4-diarylpyrroles from α-bromo oxime ethers[a]



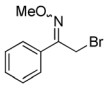
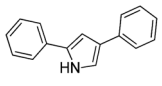
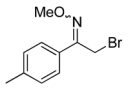
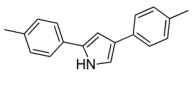
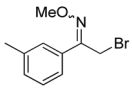
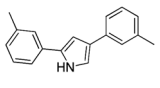
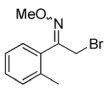
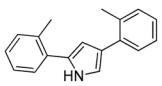
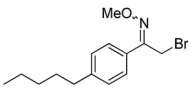
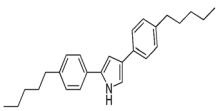
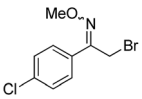
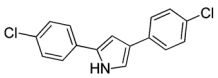
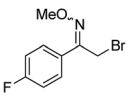
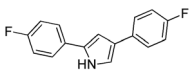
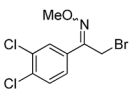
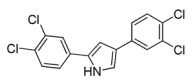
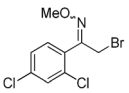
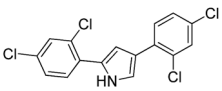
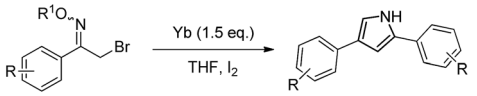
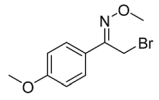
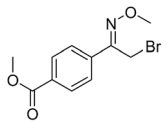
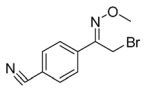
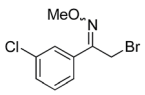
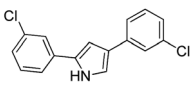
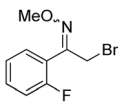
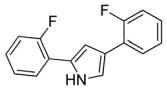
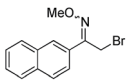
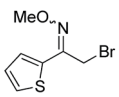
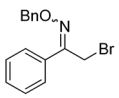
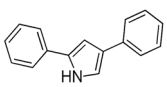
Entry	Substract	Product (yield%)[b]
1	 **1a**	 **2a (58)**
2	 **1b**	 **2b (52)**
3	 **1c**	 **2c (55)**
4	 **1d**	 **2d (51)**
5	 **1e**	 **2e (50)**
6	 **1f**	 **2f (43)**
7	 **1g**	 **2g (45)**
8	 **1h**	 **2h (45)**
9	 **1i**	 **2i (41)**

Table 2 (*Contd.*)



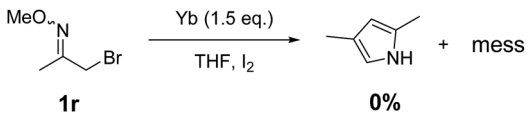
Entry	Substract	Product (yield%)[b]
10	 **1j**	—
11	 **1k**	—
12	 **1l**	—
13	 **1m**	 **2j (57)**
14	 **1n**	 **2k (56)**
15	 **1o**	—
16	 **1p**	—
17	 **1q**	 **2a (42)**

[a] Reaction conditions: α-bromo oxime (0.5 mmol), ytterbium powder (0.75 mmol), catalytic amount I_2 and THF (4 mL) at r. t. under nitrogen for 12 h. [b] Isolated yield based on **1**.

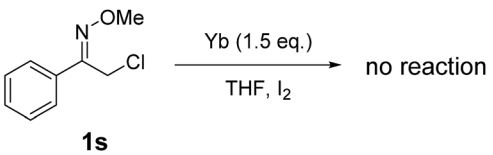
was used under the standard reaction conditions. Also, the reaction leads to a complex mixtures and no expected pyrrole was obtained (Scheme 3).

Finally, we investigated the reaction of (*Z*)-2-chloro-1-phenylethanone *O*-methyl oxime (**1s**) with ytterbium to examine the reactivity of α-chloro oxime ethers. Unfortunately, ytterbium cannot promote the reaction to generate 2,4-diphenylpyrrole (Scheme 4).

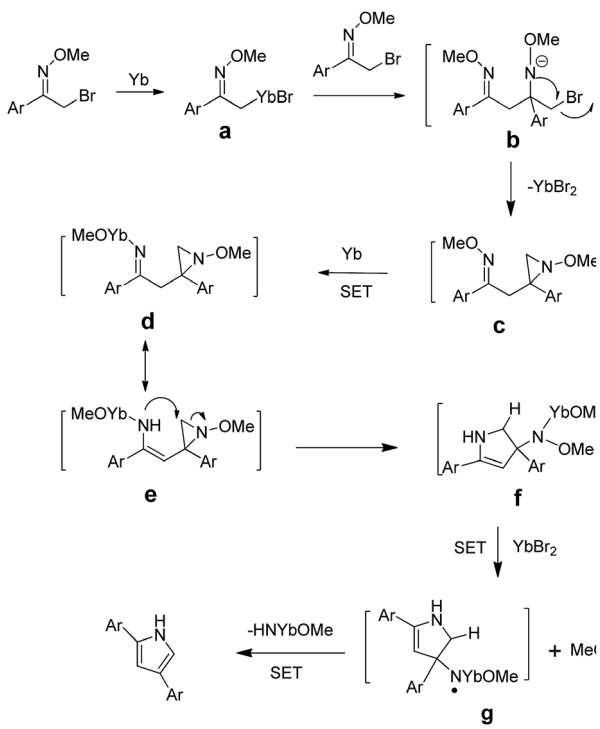
Although the detailed mechanism of the above reaction has not been clarified, a plausible mechanism is proposed in Scheme 5. The cleavage of the C–Br bond could be achieved through two single electron transfer (SET) process, in which Yb would donate two electrons to afford intermediate **a**. Another α-bromo oxime ether would then react with **a** through nucleophilic addition to afford **b**. Then intermediate **c** could be formed



Scheme 3 The reactivity of alkyl α-halo oxime ethers **1r**.



Scheme 4 The reactivity of α-chlor oxime ethers **1s**.



Scheme 5 The plausible mechanism.

from **b** through intramolecular substitution. The cleavage of the O–N bond could be achieved through two single electron transfer (SET) process, in which Yb would donate two electrons to afford intermediate **d**, and whose tautomer **e**. Then intermediate **f** could be formed from **e** through intramolecular substitution. The one single electron transfer (SET) process takes place in which $YbBr_2$ would donate one electron to afford intermediate **g**. After the intramolecular SET process, intermediate **g** could afford the final product.

Conclusions

In conclusion, a novel, one-pot method for the preparation of 2,4-diarylpyrroles from α-bromo oxime ethers has been developed, which is mediated by ytterbium. In this reaction, the starting materials are readily available and the reaction conditions are mild and neutral. This work may provide a useful method for the preparation of 2,4-diarylpyrroles. Researches to explore the mechanism of this process and to develop other new uses of rare earth metals are under investigation in our group.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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