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Controllable and efficient oxidation of thioether by 2-iodoxybenzoic acid (IBX) in water: semisynthesis of sophocarpine

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ABSTRACT

A metal-free, environment friendly, easy-to-operate, and efficient method for the semisynthesis of sophocarpine from matrine has been developed in an overall yield of 91%. The route features a controllable and efficient oxidation of thioether to sulfoxide by 2-iodoxybenzoic acid (IBX) in water.

Introduction

Matrine-type alkaloids widely exist in the *sophora flavescens*, *sophora alopecuroides*, and *sophora subprostrara* and attract considerable attentions[1–4] because of their broad biological activities, such as analgesic, anti-arrhythmic, antiviral, anti-inflammatory, anti-tumor, diuresis, detumescence, immunosuppression, antibacterial, and insecticidal.[5–13] Matrine, oxymatrine, and sophocarpine[14] (Fig. 1) are the representative natural matrine-type alkaloids.

Matrine has a high content in total alkaloid of sophora species (for example, the content of matrine in total alkaloid of *sophora alopercuroides* L. is 32%[15]) and can be easily purified. In China, matrine suppository is clinically used to treat colpitis and chronic cervicitis while matrine injection is used to cure hepatitis. It is also reported to have moderate anti-tumor activities.[16] Oxymatrine also exists in the total alkaloid of *sophora alopercuroides* L., and it probably derives from matrine, because matrine can be easily oxidized to oxymatrine.[17] In contrast, sophocarpine only accounts for 6% of total alkaloid of *sophora alopercuroides* L.[15] The low abundance and the difficulty in purification limited its further application.

Structure modification of matrine-type alkaloids and evaluating their biological activities have become the focus of the scientists from all over the world.[1–4] Sophocarpine is convenient for derivatization because of its conjugated double bond, therefore, it is of great significance to develop a practical method to synthesize sophocarpine from easily available matrine.

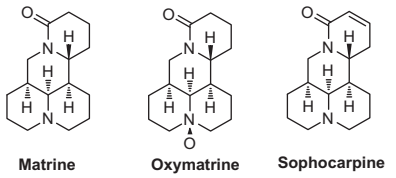
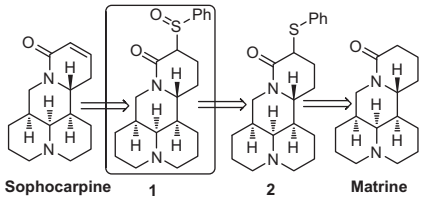


Figure 1. Structure of matrine, oxymatrine, and sophocarpine.



Scheme 1. Retrosynthetic analysis of sophocarpine.

Matrine and sophocarpine belong to lactam and α,β-unsaturated lactam, respectively. Commonly used transformation methods from amide to α,β-unsaturated amide including: (1) preparation of α-phenylselenide, followed by elimination of the corresponding oxyselenide, in which highly toxic and expensive selenium reagents such as PhSeCl[18], PhSeBr,[19] or PhSeSePh[20] are inevitable; (2) elimination of phenylsulfinyl from α-phenylsulfinyl

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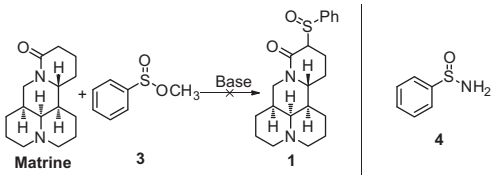
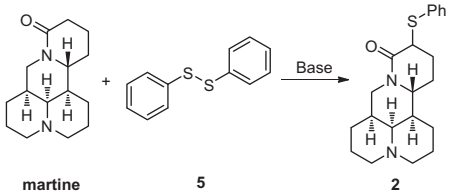


Scheme 2. Reaction of matrine and methyl phenylsulfinate.

Table 1
Preparation of 14-thiophenylmatrine **2**



Entry	Base	Ratio matrine:base	Temperature	Isolated yield
1	NaH	1:3	0–25 °C or reflux	0[a]
2	*t*-BuOK	1:3	0–25 °C or reflux	0[a]
3	LDA	1:2.2	−78–25 °C	96%[b]

[a] Reaction conditions: Matrine (0.5 mmol) and NaH/*t*-BuOK (4.5 mmol) were refluxed in THF (50 mL) for 60 min, then **5** (1.8 mmol) was added slowly, and the reaction mixture was refluxed for another 4 h. TLC showed this reaction did not work.
[b] Reaction conditions Ref. 31.

amide, which is directly prepared from amide and methyl phenylsulfinate[21] or by oxidation of α-phenylsulfide amide[22–25]; (3) dehydrogenation to the corresponding α,β-unsaturated lactams in one-pot manner at −78 °C just by treating their lithium enolates with *N*-*tert*-butylbenzenesulfinimidoyl chloride[26], but the reagent needs to be prepared in advance. All of the above methods seem to be able to be applied to the semisynthesis of sophocarpine, but up till now no exact transformation has been accomplished, which suggests that the transformation may not be as easy as we think.

In this Letter, we would like to first report a metal-free, environment friendly, and efficient method for the semisynthesis of sophocarpine via the intermediate 14-phenylsulfinylmatrine **1**, with controllable and efficient oxidation of thioether to sulfoxide by 2-iodoxybenzoic acid (IBX) in water as the key step (Scheme 1).

Results and discussion

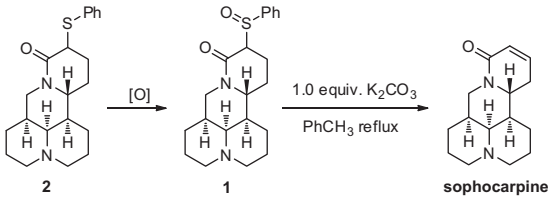
At the beginning, we attempted to oxidize matrine to sophocarpine by IBX directly as some ketones could be oxidized to α,β-unsaturated ketones.[27] Unfortunately, we recovered all the matrine after refluxing with IBX in acidic aqueous solution for more than 20 h.

Next, we attempted the direct sulfinylation through condensation reaction of matrine and methyl phenylsulfinate **3**[21] (Scheme 2). However, several kinds of bases or solvents such as NaH/THF, NaH/$PhCH_3$, LDA/THF, and LiHMDS/THF were used, but little or no desired product was obtained. Byproduct **4** was separated as the main product when LiHMDS was used as the base, which was also mentioned in the reported literature.[28]

Then, we envisioned preparing 14-thiophenylmatrine (**2**) by deprotonation of matrine followed by reacting with diphenyl disulfide (**5**). NaH and *t*-BuOK showed no effect (Table 1, entry 1,2). LDA was proved to be efficient deprotonating reagent, and **2** was obtained in excellent isolated yield (96%, Table 1, entry 3). The product was identified by ^{1}H NMR, ^{13}C NMR, and TLC to be a pair of diasteroisomers. Subsequent experiments showed that the two isomers have similar reactivities, so they are unnecessary to be separated with each other.

With **2** in hand, we then focused our attention to the oxidation of **2** to sulfoxide **1**. Several kinds of commonly used oxidant were tried, such as N-bromosuccinimide[22], $NaIO_4$[23], oxone[24], and *m*-chloroperoxybenzoic acid[25], but no acceptable result was obtained because the thiophenyl of **2** was found to be over-oxidized to sulfone and the tertiary amine was also apt to be oxidized to N-oxide

Table 2
Oxidization and desulfuration of 14-thiophenylmatrine **2**[a]



Entry	Oxidant	Ratio **2**:oxidant	Solvent and additives	Temperature	Time (h)	Yield[b]
1	NBS	1:1.1	CH_3OH:CH_2Cl_2 = 1:1	25 °C	6	0
2	$NaIO_4$	1:2	CH_3OH:H_2O = 1:1	25 °C	6	—[c]
3	Oxone	1:1.2	CH_3OH	25 °C	6	—[c]
4	*m*-CPBA	1:1.2	CH_2Cl_2	25 °C	6	—[c]
5	IBX	1:2	$CHCl_3$:H_2O = 1:1 TBAB[d]	Reflux	3	0
6	IBX	1:2	DMSO	Reflux	3	0
7	IBX	1:2	H_2O TsOH(1.5 equiv)	Reflux	3	45
8	IBX	1:3	H_2O TsOH(1.5 equiv)	Reflux	2	66
9	IBX	1:3	H_2O TsOH(1.5 equiv)	70 °C[e]	4	83
10	IBX	1:3	H_2O HCl(1.5 equiv)	70 °C[e]	3	95
11[f]	IBX	1:3	H_2O HCl(1.5 equiv)	70 °C[e]	3	94

[a] Oxidation reaction conditions: **2** (2.0–3.0 mmol), solvent (40 mL).
[b] Isolated yield of sophocarpine.
[c] TLC shows that several byproducts are generated at the first step, and compound **1** is difficult to be purified.
[d] Catalytic amount.
[e] Internal temperature.
[f] **2** (11.0 mmol), solvent (240 mL).