

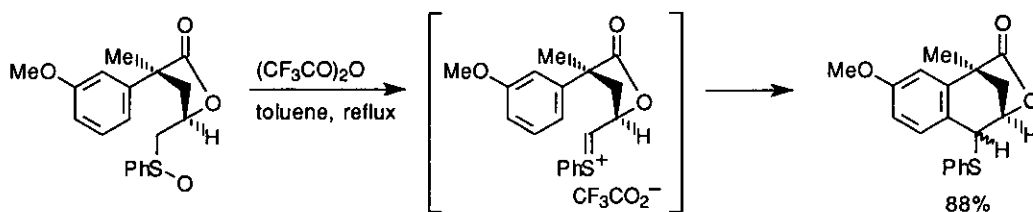
A FACILE ROUTE TO TETRAHYDROISOQUINOLINE ALKALOIDS VIA SULFOXIDE MEDIATED CYCLIZATION

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Abstract — A facile route to 1,2,3,4-tetrahydroisoquinoline framework has been developed by employing the sulfoxide mediated cyclization reaction. Utilizing the reaction developed some naturally occurring isoquinoline alkaloids have been synthesized.

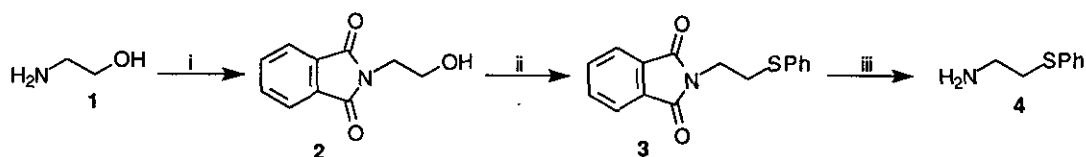
Although it has been well-recognized that activated sulfoxides such as β -keto sulfoxides can participate in cyclization reactions forming carbocycles and heterocycles under acidic conditions *via* generation of highly activated β -keto sulfenium intermediate,^{1,2} only a small number of examples where simple sulfoxides involved in the cyclization reaction were so far reported.^{3,4} In relation to the simple sulfoxide-mediated hydronaphthalene formation reaction which we developed recently (Scheme 1),⁴ we now examined the construction of isoquinoline framework as an extension.



Scheme 1

We first prepared 2-aminoethyl phenyl sulfide⁵ (4) from ethanolamine (1) in three steps. Thus, condensation of ethanolamine with phthalic anhydride followed by treating the resulting imide (2) with diphenyl disulfide

in the presence of tri-*n*-butylphosphine⁶ yielded the phenyl sulfide (3) which was exposed to hydrazine hydrate to give the amino sulfide (4) in 60% overall yield (Scheme 2).

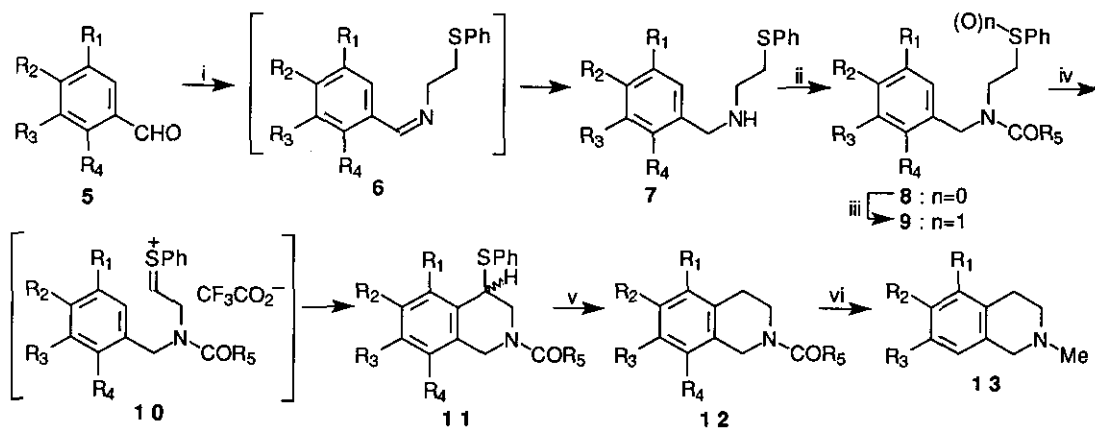


Scheme 2

Reagents and conditions: i) phthalic anhydride (1.0 equiv.), toluene, reflux, 3 h; ii) (PhS)₂ (1.5 equiv.), *n*-Bu₃P (1.5 equiv.), pyridine, 60 °C, 4 h; iii) H₂NNH₂·H₂O (3 equiv.), EtOH, reflux, 1 h.

Condensation of the amine (4) with aromatic aldehydes (5a~f), followed by reduction of the resulting Schiff bases (6a~f) with sodium borohydride afforded the secondary amines (7a~f) without difficulty in satisfactory overall yields. On sequential acylation and oxidation with *m*-chloroperbenzoic acid, the amines (7a~f) afforded the substrate sulfoxides (9a~g) in good overall yields *via* the sulfides (8a~g), respectively.

Upon exposure to 1,3 equiv. of trifluoroacetic anhydride in refluxing toluene,⁴ the sulfoxides (9a~g) reacted within a minute to give the unstable cyclization products (11a~g) which were immediately treated with Raney



Scheme 3

Reagents and conditions: i) 4 (1.0 equiv.), *p*-TsOH (cat.), benzene, reflux, overnight, then NaBH₄ (4.0 equiv.), MeOH, room temperature, 2 h; ii) methyl chlorocarbonate (1.2 equiv.) for a~f, or acetyl chloride for g, pyridine (1.2 equiv.), CH₂Cl₂, 0 °C, 2 h; iii) *m*-chloroperbenzoic acid (*m*-CPBA) (1.1 equiv.), NaHCO₃ (3.0 equiv.), CH₂Cl₂, -30 °C, 2.5 h; iv) trifluoroacetic anhydride (TFAA) (3.0 equiv.), toluene, reflux, 0.5 min; v) Raney Ni, EtOH, reflux, 3 h; vi) LiAlH₄ (9.0 equiv.), THF, reflux, 3 h.

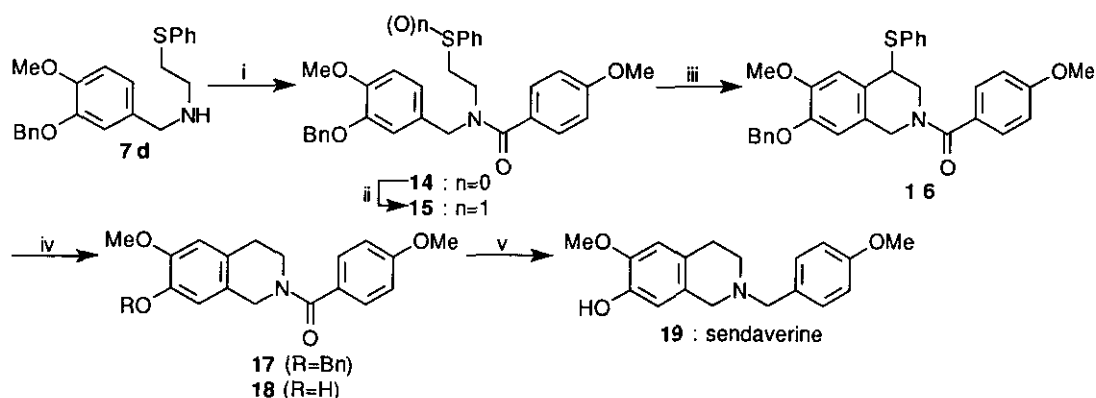
Table 1: Formation of the tetrahydroisoquinolines (12) from the Sulfoxides (9) via 11

Sulfoxide (9)	R ₁	R ₂	R ₃	R ₄	R ₅	Isoquinoline (12)	R ₁	R ₂	R ₃	R ₄	R ₅	Yield (%)
(a)	H	-OCH ₂ O-	H	OMe		(a)	H	-OCH ₂ O-	H	OMe		38
(b)	H	MeO	MeO	H	OMe	(b)	H	MeO	MeO	H	OMe	36
(c)	MeO	MeO	MeO	H	OMe	(c)	MeO	MeO	MeO	H	OMe	44
(d)	H	MeO	BnO	H	OMe	(d)*	H	MeO	HO	H	OMe	62
(e)	H	H	MeO	MeO	OMe	(e)	H	H	MeO	MeO	OMe	30
(f)	H	H	MeO	BnO	OMe	(f)*	H	H	MeO	HO	OMe	46
(g)	H	MeO	MeO	H	Me	(g)	H	MeO	MeO	H	Me	53

* Concomitant debenzoylation occurred under the desulfurization conditions.

nickel in ethanol to furnish the *N*-acyl-1,2,3,4-tetrahydroisoquinolines (12a-g) in moderate overall yields (Table 1). Among these products, reduction of the carbamates (12a-d) with lithium aluminum hydride in refluxing tetrahydrofuran furnished the naturally occurring alkaloids, hydrohydrastinine⁷ (13a), methylcorypalline⁸ (13b), tehaunine⁹ (13c), and corypalline¹⁰ (13d), respectively (Scheme 3).

On the other hand, the amine (7d) was transformed into the *p*-methoxybenzamide (14) which then was oxidized to the sulfoxide (15). Upon the same treatments above 15 furnished the *N*-*p*-methoxybenzoyltetrahydroisoquinoline (18) via 16 and 17 in 33% overall yield with spontaneous debenzoylation. The resulting

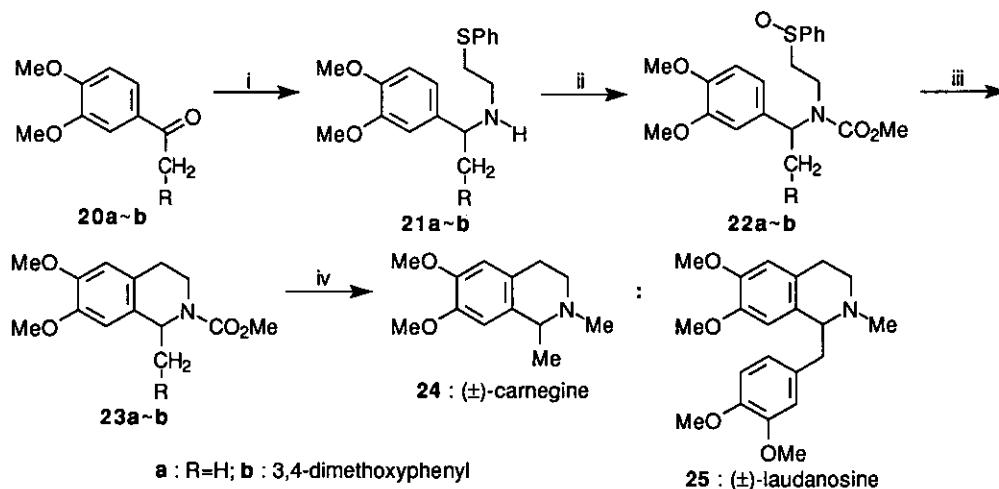
**Scheme 4**

Reagents and conditions: i) *p*-methoxybenzoyl chloride (1.2 equiv.), Et₃N (1.2 equiv.), CH₂Cl₂, room temperature, 1.5 h; ii) *m*-CPBA (1.2 equiv.), NaHCO₃ (3.0 equiv.), CH₂Cl₂, -30 °C, 2 h; iii) TFAA (3.0 equiv.), toluene, reflux, 0.5 min; iv) Raney Ni, EtOH, reflux, overnight; v) LiAlH₄ (9.0 equiv.), THF, reflux, 3 h.

amide (**18**) was reduced with lithium aluminum hydride to afford another naturally occurring alkaloid, sendaverine¹¹ (**19**), in 67% yield (Scheme 4).

To obtain 1-substituted isoquinoline alkaloids, we next carried out the reaction starting from the aryl ketones (**20a~b**). On reductive condensation with the sulfide amine (**4**), these gave the corresponding secondary amines (**21a~b**) which were sequentially carbamoylated and oxidized to furnish the corresponding sulfoxides (**22a~b**), respectively, in satisfactory yields *via* the sulfide (**21a~b**).

Upon exposure to 1.3 equivalent of trifluoroacetic anhydride in refluxing toluene followed by desulfurization with Raney nickel in refluxing ethanol as above, both of the sulfoxides (**22a~b**) afforded the corresponding 1-substituted tetrahydroisoquinolines (**23a~b**) in yields of 82 and 81%, respectively. The resulting carbamates (**23a~b**) were then reduced with lithium aluminum hydride to give ($\pm$)-carnegine¹² (**24**) and ($\pm$)-laudanoline¹³ (**25**) in 79 and 80% yields, respectively (Scheme 5).



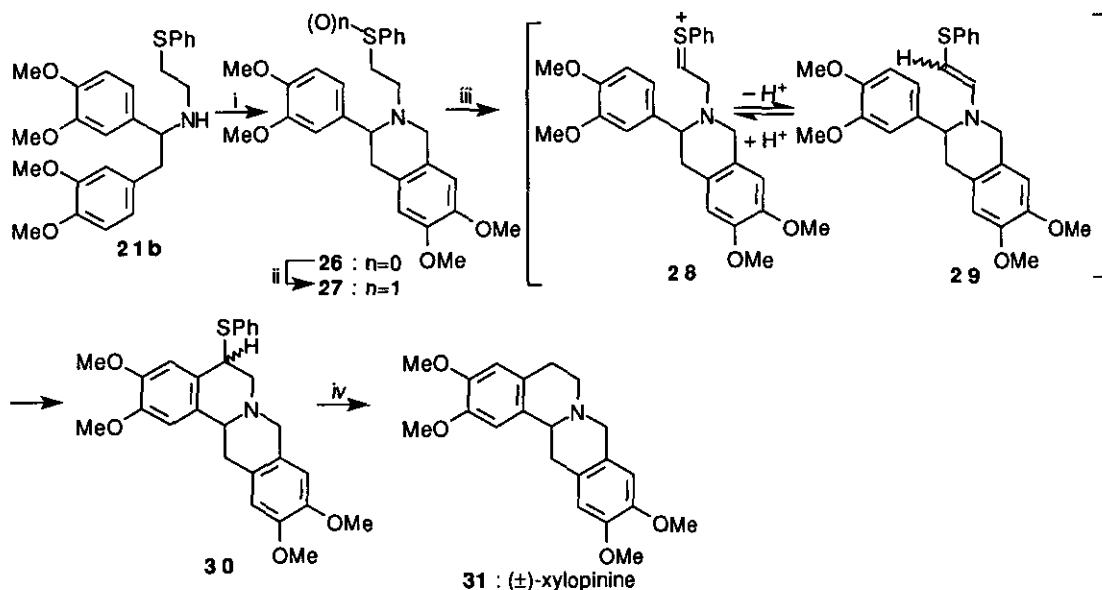
Scheme 5

Reagents and conditions: i) **4** (1.0 equiv.), *p*-TsOH (cat.), benzene, reflux, overnight, then NaBH₄ (4.0 equiv.), MeOH, room temperature, 5 h; ii) methyl chlorocarbonate (1.2 equiv.), pyridine (1.2 equiv.), CH₂Cl₂, 0 °C, 8 h, then *m*-CPBA (1.1 equiv.), NaHCO₃ (3.0 equiv.), CH₂Cl₂, -30 °C, 2 h; iii) TFAA (5.0 equiv.), toluene, reflux, 0.5 min then Raney Ni, EtOH, room temperature, overnight; iv) LiAlH₄ (9.0 equiv.), THF, room temperature, 3.5 h.

The secondary amine (**21b**), on the other hand, was treated with 30% formalin in refluxing methanol containing hydrochloric acid to give the 2,3-disubstituted tetrahydroisoquinoline (**26**) in 78% yield. Treatment of the resulting tertiary amine (**26**) with one equivalent of *m*-chloroperbenzoic acid in

dichloromethane at -30°C in the presence of sodium hydrogen carbonate allowed chemoselective oxidation to give the sulfoxide (27) in 60% yield.

Upon the same cyclization conditions above, the sulfoxide (27) did not furnish the expected tetracyclic amine (30), but the unstable vinyl sulfide (29) as a stereoisomeric mixture which, presumably, was generated from the sulfenium intermediate (28) preceding to the cyclization. We, therefore, added trifluoroacetic acid to the reaction medium to maintain the sulfenium structure (28) with expectation to give rise to the cyclization product (30) rather than the vinyl sulfide (29). As expected when the sulfoxide (27) was treated with three equivalents of trifluoroacetic anhydride in refluxing toluene containing three equivalents of trifluoroacetic acid, the cyclization occurred to give the tetracyclic sulfide (30) as a mixture of diastereomers which afforded ($\pm$)-xylopinine¹⁴ (31) in 42% overall yield on desulfurization with Raney nickel in refluxing ethanol (Scheme 6).



Scheme 6

Reagents and conditions: i) 30% formalin (1.2 equiv.), aq. HCl (cat.), MeOH, reflux, overnight; ii) *m*-CPBA (1.0 equiv.), NaHCO₃ (5 equiv.), CH₂Cl₂, -30°C , 3.5 h; iii) trifluoroacetic anhydride (3.0 equiv.), trifluoroacetic acid (3.0 equiv.), toluene, reflux, 0.5 min; iv) Raney Ni, EtOH, reflux, overnight.

In conclusion the present method may be generally applicable for the construction of a variety of the isoquinoline alkaloids having 1,2,3,4-tetrahydroisoquinoline framework as a complement to the conventional Pomeranz-Fritsch reaction¹⁵ and the related isoquinoline formation reactions.

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