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Chiral Acetylenic Sulfoxides in Organic Synthesis: Secondary Amine Cyclization and Total Synthesis of (S)-(-)-Carnegine

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Abstract. Michael addition of secondary amines **1b-1g** onto chiral acetylenic sulfoxides **2** followed by acid induced cyclization afforded structures of tetrahydroisoquinoline skeleton in high to moderate diastereoselectivity. Optical pure (S)-(-)-carnegine has been synthesized.

The use of sulfoxide functionality as a chiral synthon to control diastereoselectivity and enantioselectivity in organic synthesis is a matter of continuous interest.[1] Recently, we have reported the use of chiral acetylenic sulfoxide in the enantioselective synthesis of tetrahydroquinoline and tetrahydro-β-carboline alkaloids. [2,3] In our approach, the crucial 2-step sequence involved the Michael addition of a primary amine **1a** onto chiral acetylenic sulfoxide followed by the highly stereoselective cyclization of the resultant vinyl sulfoxide **3a** in acidic medium to give **5a** as the only isolated product (Scheme 1).

We now reported the extension of this reaction viability to include secondary amines (i.e. **1b-1g**) in the initial Michael addition reaction. In contrast to primary amine, not only a more convergent way of constructing tetrahydroquinoline alkaloids has realized, but also a reversed diastereoselectivity bias in the crucial cyclization reaction were observed. Thus (S)-(-)-carnegine together with many other chiral intermediates can be prepared in facile via this approach.

A series of secondary amines (**1b-1g**) was synthesized in good yield by reductive amination of 2-(3,4-dimethoxyphenyl)ethylamine with the corresponding aldehydes. Each of the secondary amines prepared plus the commercially available N-methyl-2-(3,4-dimethoxyphenyl)ethyl amine was subjected to the two-step sequence as illustrated in Scheme 1. Michael addition of the amine onto (R)-(+)-ethynyl *o*-nitrophenyl sulfoxide (**2**) was achieved at room temperature for a period of several hours. Without isolation of the addition intermediate, a crucial carbon-carbon bond was then assembled by acid induced cyclization of the electron-rich aromatic moiety to the β-carbon of the chiral sulfoxide. In principle, in addition to the sulfoxide chirality, a new chiral centre was created at the benzyl methine carbon. For a wide variety of secondary amines, a good control of diastereoselectivity was observed in this one-pot addition-cyclization sequence (Table 1). The stereochemistry of the cyclized products was established by chemical correlation or proton NMR splitting pattern of the benzylic protons (see below). For instance, N-(2,3-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)ethylamine (**1c**), obtained in 72% yield by reductive amination between 2-(3,4-dimethoxybenzyl-2(3,4-dimethoxyphenyl)ethylamine and 2,3-dimethoxybenzaldehyde in the presence of excess sodium cyanoborohydride, was added onto (R)-(+)-ethynyl *o*-nitrophenyl sulfoxide **2** in chloroform at room temperature. The crude adduct was treated with 40 equivalent trifluroacetic acid (TFA) in dichloromethane

Scheme 1

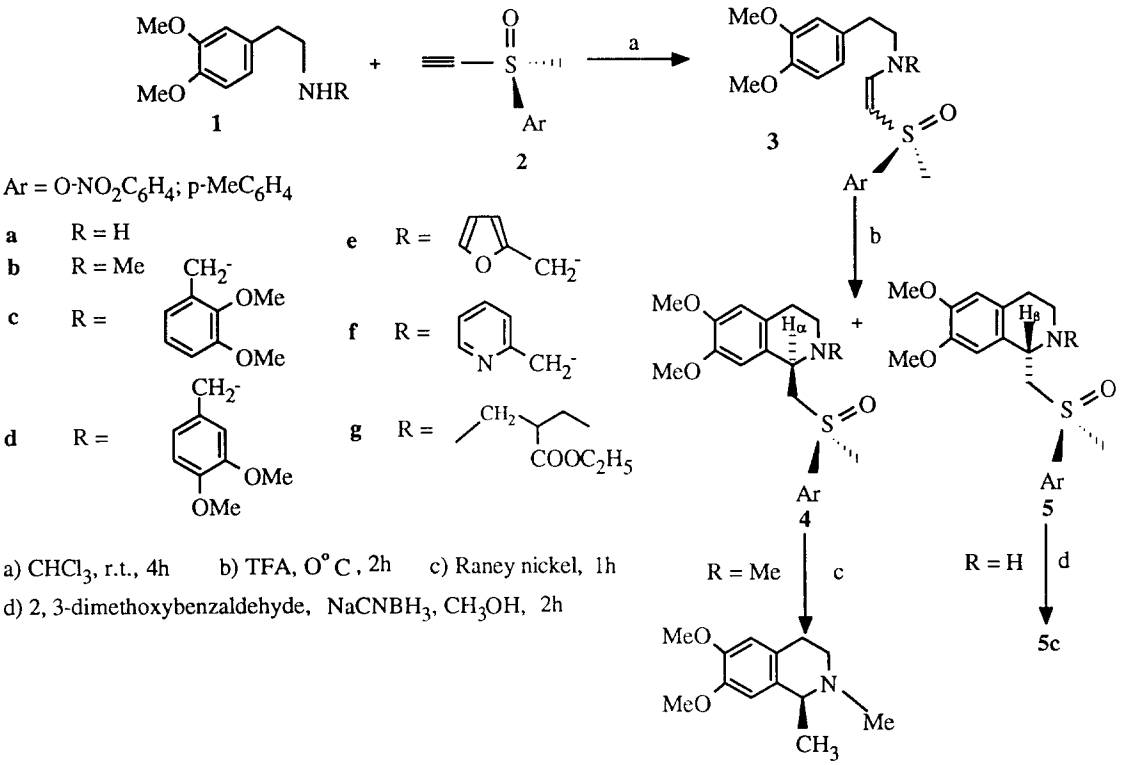

Table 1 Diastereoselectivity on Cyclization of 3b-3g

Entry	Ar	Vinyl sulfoxide	T/°C[a]	Diastereoisomeric ratio **4 : 5**	Yield (%)	Method of stereochemistry assignment[b]
1	*o*-$NO_2C_6H_4$	**3b**	0°	1.8 : 1	88	A & B
2	*o*-$NO_2C_6H_4$	**3c**	-30°	no reaction		
3	*o*-$NO_2C_6H_4$	**3c**	-15°	6 : 1	64	A
4	*o*-$NO_2C_6H_4$	**3c**	25°	2.7 : 1	-	A
5	*o*-$NO_2C_6H_4$	**3d**	0°	4.7 : 1	82	B
6	*o*-$NO_2C_6H_4$	**3e**	0°	5.4 : 1	72	B
7	*o*-$NO_2C_6H_4$	**3f**	0°	1 : 4.3	87	A & B
8	*o*-$NO_2C_6H_4$	**3g**	reflux	**4g** exclusively	68	A & B

[a] cyclization induced by TFA [b] A: chemical correlation; B: ^{1}H NMR splitting pattern method

at -15°C, resulted the formation of a diastereoisomeric mixture **4c** and **5c** in a ratio of 6:1 with a total yield of 64% (Table 1, entry 3). These diastereoisomers could be separated by column chromatography on silica gel (7:3 in ethyl acetate and petroleum ether).[4,5]

The stereochemistry of the products was established by chemical correlation with compound **5a** in which the absolute configuration of the benzyl methine carbon is known.[2] Thus reductive amination of 2,3-dimethoxybenzaldehyde with chiral **5a** gave product which is identical in NMR spectroscopic properties with that of the product of secondary amine cyclization **5c**. As a result, the stereochemistry of **4c** and **5c** can be established unambiguously. Lowered the reaction temperature did not cause any significant improvement of the diastereoselectivity and the reaction stop at -30°C. In this regard, the present secondary amine series is less reactive in the cyclization step as compared to the primary amine series. However, poor selectivity was resulted if the reaction was carried out at 25°C (Table 1, entry 4). On the other hand, *p*-toluenesulfonic acid was not effective in facilitating the cyclization reaction, only a complex mixture was resulted. Agreed with our previous finding, the *o*-nitrophenyl sulfinyl group which exhibits a stronger electron withdrawing power played an important role in this cyclization. Replacing it with *p*-tolyl sulfinyl group forbidded the cyclization reaction to take place. Other secondary amines (i.e. **3d-3e**) followed the same reaction sequence with moderate diastereoselectivity in reasonable good yield (72-87% over two steps). Exceptional good diastereoselectivity was observed for the cyclization of **3g** (Table 1, entry 8). Presumably, only the thermodynamically stable diastereoisomer was formed at elevated temperature. For unknown reason, in comparison with the cyclization of other secondary amines, **3f** gave a mixture with reversed diastereoisomeric bias.

Close examination of the ^{1}H NMR spectra of the diastereoisomers formed in each of the cyclization reaction revealed that the coupling pattern of their benzyl methine protons are highly characteristic and distinguishable. The α-methine hydrogen (H_α) of diastereoisomer **4c** appears as a partially overlapped doublet of doublet whereas the β-methine hydrogen (H_β) of **5c** as a distinct doublet of doublet. The validity of using this NMR characteristic to assign structures was substantiated in several cases (i.e. Table 1, entries 1, 7 and 8) by the unambiguous chemical correlation as mentioned above. Interestingly, compounds **4b-4g** are also consistently less polar in tlc than their corresponding diastereoisomers **5b-5g**.

For most of the cases, in contrast to primary amine cyclization (**3a→5a**), diastereoisomer **4** came out as the major product. Therefore, this new route works complementary with our previous one and allow the expeditious preparation of the previously inaccessible diastereoisomer **4**. In this regard, (S)-(-)-carnegine can be synthesized effective as followed. Michael addition of commercially available N-methyl-2-(3,4-dimethoxyphenyl)ethylamine onto acetylenic sulfoxide followed by TFA treatment gave a mixture of **4b** and **5b** in a ratio of 1.8 to 1 of a total yield of 88%. The mixture was separated by column chromatography on silica gel to yield pure **4b**.[6] Desulfurization of **4b** with excess Raney nickel gave (S)-(-)-carnegine [$[\alpha]_D^{28}$ = -21.5°(C 0.83, ethanol); literature value for its enantiomer[7] $[\alpha]_D^{18}$ = +23.4° (C 0.15, ethanol)].

In summary, the scope and limitation of using secondary amines in the 2-step diastereoselective cyclization with chiral acetylenic sulfoxides have been explored. Further elaboration of the cyclization intermediates to other tetrahydroisoquinoline and emetine alkaloids are in progress.

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4. **4c**: mp = 135-136°; $[\alpha]_D^{28}$ = +194.9 (c = 1.04, $CHCl_3$); IR: 1520, 1340; ^{1}H NMR (270 MHz, $CDCl_3$, δ = 0, TMS, J = Hz): 8.39-8.29 (m, 2H, ArH), 7.93-7.87 (m, 1H, ArH), 7.68-7.62 (m, 1H, ArH), 7.17-7.02 (m, 2H, ArH), 6.85-6.81 (m, 1H, ArH), 6.61 (s, 2H, ArH), 4.45 (dd, 1H, J 5.67 and 9.18, SOC*H*), 4.05-3.80 (m, 2H, NCH_2), 3.88 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.75 (s, 3H, OMe),3.54-3.44 (m, 2H, ArCH_2), 3.27-3.19 (m, 1H, NC*H*), 3.16-2.91 (m, 1H, NC*H*), 2.47-2.41 (m, 1H, NC*H*). ^{13}C NMR (67.8 MHz, $CDCl_3$): 152.5, 148.0, 147.4, 147.5, 145.4, 144.4, 135.2, 132.5, 130.9, 127.4, 127.1, 126.4, 125.1, 123.8, 122.3, 111.8, 110.9, 110.4, 66.2, 60.8, 58.0, 56.0, 55.8, 55.6, 50.7, 41.8, 22.8; HRMS: (M-*o*-$NO_2C_6H_4SOH)^+$ calcd for $C_{21}H_{25}O_4N$: 355.1783, Obsd: 355.1773; Analyse: $C_{27}H_{30}O_7N_2S$, Calcd%: C = 61.58, H = 5.74, N = 5.32, found: C = 61.40, H = 5.78, N = 5.29.
5. **5c**: ^{1}H NMR (270 MHz, $CDCl_3$): 8.43-8.40 (m, 1H, ArH), 8.29-8.25 (m 1H, ArH), 7.97-7.91 (m, 1H, ArH), 7.68-7.62 (m, 1H, ArH), 7.39-7.36 (m, 1H, ArH), 7.26-7.08 (m, 1H, ArH), 6.87-6.84 (m, 1H, ArH), 6.61 (s, 1H, ArH), 6.54 (s, 1H, ArH), 4.42 (dd, 1H, J 4.05 and 12.69, SOCH_2), 4.20 (d, 1H, J 13.5), 3.88 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.50-3.36 (m, 1H, NC*H*), 3.20-3.09 (m, 2H, NCH_2), 2.81 (dd, 1H, J = 4.32 and 13.5, SOC*H*), 2.42-2.35 (m, 1H, NC*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$): 152.5, 148.0, 147.5, 145.5, 144.7, 135.5, 132.7, 130.9, 126.9, 126.7, 126.4, 125.0, 124.0, 122.8, 112.1, 110.9, 110.1, 63.8, 61.0, 56.3, 56.0, 55.9, 55.7, 50.5, 40.5, 21.6; HRMS: (M-*o*-$NO_2C_6H_4SOH)^+$ Calcd for $C_{21}H_{25}O_4N$:, 355.1783, Obsd: 355.1778.
6. **4b**: $[\alpha]_D^{28}$ = +341.9 (C = 1.01, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 8.41-8.30 (m, 2H, ArH), 7.97-7.91 (m, 1H, ArH), 7.71-7.65 (m, 1H, ArH), 6.61 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.11 (dd, 1H, J 5.75 and 7.02), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.36-3.34 (m, 2H, NCH_2), 3.12-3.07 (m, 1H, NC*H*), 2.93-2.85 (m, 1H, NC*H*), 2.73-2.66 (dd, 1H, J 7.02 and 13.50, SOC*H*), 2.44-2.37 (dd, 1H, J 5.75 and 13.50), 2.24 (s, 3H, NMe); ^{13}C NMR (67.8 MHz, $CDCl_3$): 147.9, 147.6, 144.7, 144.2, 134.9, 130.8, 127.3, 127.0, 126.0, 124.8, 111.5, 110.3, 63.0, 57.5, 56.0, 55.8, 44.4, 41.0, 22.3; HRMS: (M-*o*-$NO_2C_6H_4SOH)^+$ Calcd for $C_{13}H_{17}O_2N$: 219.1259, Obsd: 219.1256.
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