Arch. Pharm. Res. **14**(4), 364-369 (1991)

Regio- and Stereoselective Reactions of (S)-(1-Methylpyrrolidin-2-yl)methyl Allyl Sulfide

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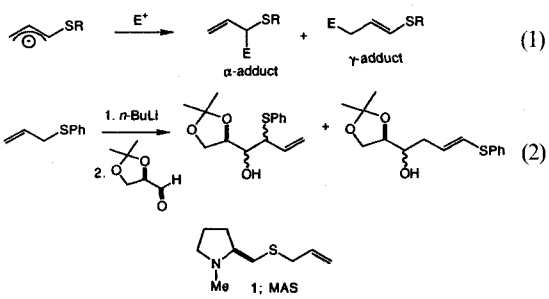
(Received December 8, 1991)

Abstract □ The synthesis and regioselective reactions of a chiral allyl sulfide, (*S*)-(+)-(1-methylpyrrolidin-2-yl)methyl allyl sulfide (MAS, **1**) are described. Remarkable α-regioselectivity was observed in the alkylation of the carbanion of MAS while 1 : 3 mixtures of α-and γ-adducts were produced in the addition of the MAS anion to aldehydes. However, a dramatic change of the regioselectivity was witnessed when Lewis acids such as Et_3Al, Et_3B, and $Ti(O^iPr)_4$ were used as additives in the addition reaction. In these cases, α-adducts were formed exclusively. A rationale for the change of regioselectivity is provided. And the stereochemical aspect of the addition reaction is also described.

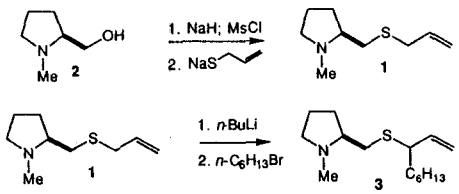
Keywords □ (*S*)-(1-Methylpyrrolidin-2-yl)methyl allyl sulfide (MAS), regioselectivity, stereoselectivity, "ate" complex, cylcic transition state.

Recently hetero-substituted allyl compounds have attracted considerable attention due to their utility in organic synthesis[1]. In particular, the reactions of anions of these compounds with electrophiles have been investigated in detail. There was a problem with the regioselectivity in these reactions, for two sites are available for the attack on electrophiles (equation 1). From the synthetic point of view, it is highly desirable to control the regiochemistry of such reactions. Consequently, a great deal of effort has been made in order to direct the attack to either α- or γ-position[2-10]. In this connection, we became interested in the utilization of thioallylic anions in organic synthesis and we have reported our preliminary results on the reaction of thioallylic anions with chiral aldehyde, (*R*)-glyceraldehyde (equation 2)[11]. High regioselectivity could be achieved by the use of some Lewis acids in the reaction. Encouraged by initial results, we set out to extend the scope of this chemistry. The present article deals with the regio- and stereochemical aspects of the reaction involving chiral allyl sulfide, (*S*)-(+)-(1-methylpyrrolidin-2-yl)methyl allyl sulfide (MAS, **1**).



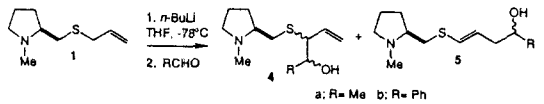
In general, the regioselectivity in the reaction of the thioallylic anions with electrophiles is influenced by a number of factors such as the nature and the size of the groups attached to the heteroatom, the metal ion, the solvent and additives, reaction temperature, and the reaction time. Evans *et al.*[5] recently have shown that the presence of chelating group is important to direct the alkylation of thioallylic anions to the α-position. Since we were interested in asymmetric induction as well as regiochemical control, we chose MAS as a suitable chiral allyl sulfide for the study.

MAS was prepared in two steps from (*S*)-1-methyl-2-pyrrolidinemethanol[12] as shown in equation 3. Lithiation of MAS can be easily performed by treating with *n*-butyllithium in THF at −78℃. Generally, a deep yellow colored solution is produced. Nucleophilic substitution reaction of *n*-hexyl bromide using this anion takes place exclusively at the α-position of the sulfur atom (equation 4). This result agrees with previous observations[5] that the pesence of chelating group controls the regio-

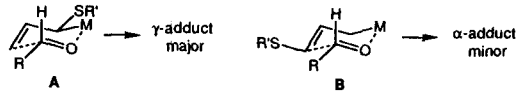


chemistry of alkyiation of thioallylic anions.

Nucleophilic addition raction of the MAS anion with aldehydes was studied under a variety of conditions. In principle, maximum of eight stereoiso-



mers can be obtained from the addition reaction; four from α-adducts and four from γ-adducts. Since our primary concern was focused on the regiocontrol of the addition reaction, the regiochemistry will be discussed first. As shown in Table I, the ratio of α- to γ- adducts was approximately 1 : 3 when any additive or Lewis acid was not used. The production of γ-adducts as major products is a general phenomenon for the addition reaction of such an allylic anion. It is suggested that the carbanion is tightly associated with the lithium cation mainly at the α-carbon because of electronic factor of the sulfur atom and the addition reaction takes place *via* a cyclic transition state[13]. Thus, γ-attack is more

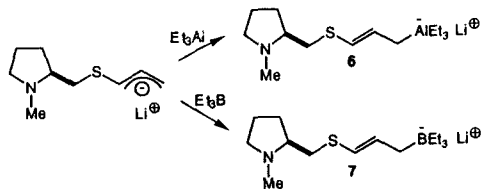


favorable. Therefore, attempts were made to improve α-regioselectivity. The results are summarized

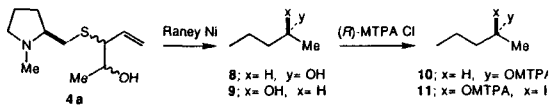
Table I. The reaction of the MAS anion with aldehydes

Entry	Additive	Electrophile	α/γ ratio	yield(%)
1	None	MeCHO	23/77	69
		PhCHO	25/75	43
2	$ZnCl_2$	MeCHO	25/75	40
3	HMPA	MeCHO	60/40	41
4	Et_3Al	MeCHO	~100/0	68
		PhCHO	~100/0	31
5	Et_3B	MeCHO	~100/0	32
		PhCHO	~100/0	49
6		**MeCHO**	~100/0	48
	$Ti(O^iPr)_4$	PhCHO	~100/0	53

in Table I. The use of $ZnCl_2$ as an additive did not affect the selectivity (entry 2). The reversed regiochemistry was observed when HMPA was used (entry 3). This result could be explained by assuming that the allylic carbanion exists as a loose ion pair in the presence of HMPA because of dissociation of the lithium ion from the carbon. Thus, the lithium cation is loosely associated with the α-carbon and the reactivity of α-carbon is enhanced. In the case of entries **4** and **5**, a dramatic change of regioselectivity was observed. When Et_3Al and Et_3B were used, α-adducts were produced exclusively for both of acetaldehyde and benzaldehyde. This result is in the same line with that of Y. Yamamoto *et al.*[14] in the reactions of allyl isopropyl sulfide with several aldehydes *via* allylic aluminum "ate" complex and allylic boron "ate" complex. The exclusive formation of γ- "ate" complexs **6** and **7** might be responsible for the dramatic improvement



of α-regioselectivity. A remarkable α-regioselectivity was also observed by the use of titanium tetra-isopropoxide (entry 6)[15]. Thus, the sterically bulky Lewis acids such as Et_3Al, Et_3B and $Ti(O^iPr)_4$ can direct the regiochemistry of the addition reaction to the α-position and this result can be applied to the synthesis of many natural products.



Scheme 1

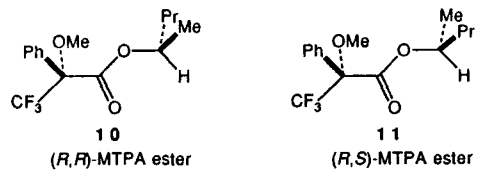


Fig. 1.Conformations or (*R*)-and (*R, S*)-MTPA esters.

Since we could control the regioselectivity for reactions of the MAS anion with electrophiles, our attention was turned to the stereochemical problem of α-adducts. For this purpose, α-adducts were desulfurized[16] with the concomitant reduction of the double bond by W-7 Raney Ni[17] to give 2-pentanols, which was then converted to their MTPA esters[18]. The absolute configuration of 2-(*R*)- and 2-(*S*)-pentanols was assigned based upon ^{1}H-NMR analysis of their MTPA esters. Methyl group of (*R, R*)-MTPA ester was expected to be different from that of (*R, S*)-diastereomer in magnetic environment due to anisotropic nature of the phenyl substituent. The ^{1}H-NMR chemical shift of the methyl group of (*R, R*)-isomer should experience the characteristic upfield shift compared to that of the corresponding group of the alternate diastereomer. Thus, the diastereomer corresponding to the methyl group appeared at 1.24 ppm was assigned (*R, R*)-MTPA ester. The methyl proton of the (*R, S*)-diastereomer resonanced at 1.31 ppm. From the ^{1}H-NMR and HPLC analysis of MTPA esters, the ratio of (*R*)- to (*S*)-alcohols, in the reaction of the MAS anion with acetaldehyde, was 1.3 : 1 and 10 : 1, with and without the use of Et_3Al, repectively. The sharp contrast in their stereoselectivities is intriguing. It is generally assumed that the addition of the allylic organometalliics to the carbonyl takes place through an allylic rearrangement of the organometallics *via* a chelate transition state as mentioned earlier. If the allylic rearrangement mechanism is accepted, α-adducts should come from γ-lithiated thioallylic anion **12b**. Howerver, such a high stereoselectivity (10 : 1) is not expected from **12b** even through a chair-like transition state since the reaction center is too far away from the pyrrolidine ring. In this case, α-adducts seemed to come also from the α-lithiated allylic anion presumably through a tricyclic transition state C. It was assumed that intramolecular chelation between the lithium cation and the nitrogen atom takes places to form the bicyclic structure **12a**. Now acetaldehyde would be coordinated to the lithium cation in a way that the steric repulsion is minimized (as shown in transition state C). The path *a* explains the production of the major α-adduct, (*R*)-alcohol. Low stereoselectivities can be predicted from the aluminum "ate" complex **6** since the reaction center is too far from the chiral inducer, the pyrrolidine ring.

EXPERIMENTAL METHODS

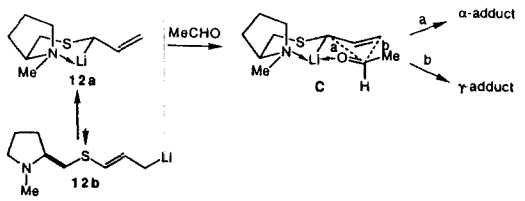
General

Tetrahydrofuran (THF) and diethylether were distilled from sodium benzophenone ketyl immediately prior to use. Other solvents were purified or dried by distillation. Silica Gel 60 (E.M. Merck, 70-230 mesh or 230-400 mesh for flash column chromatography) was used for column chromagography. TLC was performed on Merck silica gel 60 F-254 (0.25 mm, precoated on glass). HPLC was performed by Water Associates Liquid Chromatograph.

^{1}H-NMR spectra were recorded on Varian T-60A spectrometer (60 MHz), Jeol PMX spectrometer (60 MHz) or Bruker AM-200-SY spectrometer (200 MHz). Infrared spectra were recorded on Analect FX-6160 FT-IR or Perkin-Elmer Model 1310 spectrometer.

(S)-(+)-(1-Methylpyrrolidin-2-yl)methyl allyl sulfide 1

To a stirred solution of sodium alkoxide which was prepared from sodium hydride (1.2g, 50 mmonl) and N-methylprolinol **2** (4g, 34.7 mmol) in dimethylformamide (150 m*l*) was added dropwise methanesulfonyl chloride (3.08 m*l*, 40 mmol) at 0℃ and stirred further for 4 h at 0℃ under nitrogen. To the mesylate was added sodium allyl sulfide which was prepared from allyl thiol (2.47g, 40 mmol) and sodium hydride (1.2g, 50 mmol) in DMF (30 m*l*) and the mixture was stirred for 18 h at −10℃ under nitrogen. The reaction mixture was diluted with water (500 m*l*) and extracted with cyclohexane (500 m*l*). The organic layer was washed with sat. brine, dried ($MgSO_4$), and concentrated under reduced



Scheme 2

pressure to give a yellowish liquid. The residue was purified on column chromatography (chloroform: methanol=10 : 1, R_f=0.47) to give **1** (3.8g, 52%). ^{1}H-NMR ($CDCl_3$) δ 1.36-1.93 (m, 4H, -CH_2CH_2-), 1.98-3.72 (m, 5H), 2.32 (s, 3H, N-CH_3), 3.15 (d, 2H, -CH_2-CH=CH_2), 4.89-5.38 (m, 2H, =CH_2), 5.41-6.43 (m, 1H, -CH=); IR (neat) 3055, 2950, 2745, 1610, 1440, 1190, 910 cm^{-1}

(S)-(1-methylpyrrolidin-2-yl)methyl 2-(1-hexyl)-propenyl sulfide 3

To a stirred solution of MAS (235 mg, 1.37 mmol) in tetrahydrofuran (15 m*l*) was added *n*-buthyllithium (1.3 m*l*, 2.08 mmol, 1.6 M solution in *n*-hexane) at −78℃ under nitrogen. After 1 h, *n*-hexylbromide was added slowly to the above solution. After 1.5 h, the reaction mixture was quenched with sat. sodium bicarbonate solution, warmed to room temperature, and extracted with methylene chloride. The organic layer was washed with sat. brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellowish liquid, which was purified by column chromatography (chloroform: methanol=10 : 1, R_f=0.49) to give (*S*)-(1-methylpyrrolidin-2-yl)methyl-2-(1-hexyl)-propenyl sulfide **3** (179 mg, 51%). ^{1}H-NMR ($CDCl_3$) δ 0.66-1.08 (m, 3H, -CH_3), 1.09-1.56 (m, 10H, methylene protons), 1.59-1.95 (m, 4H, -CH_2 CH_2-), 2.01-3.37 (m, 6H), 2.36 (s, 3H, N-CH_3), 4.61-5.23 (m, 2H, =CH_2), 5.29-6.13 (m, 1H, -CH=).

(S)-(1-methylpyrrolidin-2-yl)methyl 1-(1-hydroxyethyl)-2-propenyl sulfide 4a and (S)-(1-methylpyrrolidin-2-yl)-methyl 1-(4-hydroxy)-pentenyl sulfide 5a

(a) Addition of MAS to acetaldehyde in the absence of any additive: *n*-Buthyllithium (1.9 m*l*, 30.4 mmol, 1.6 M solution in *n*-hexane) was added dropwise to a stirred solution of MAS (3.68g, 21.48 mmol) in tetrahydrofuran (100 m*l*) at −78℃ under nitrogen. After 1 h, excess accetaldehyde was added slowly to the above solution, and the mixture (pale yellow) was allowed to warm to 0℃. After 2 h, the mixture was quenched with sat. sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with sat. brine, dried, filtered, and concentrated *in vacuo* to give a yellowish liquid.

Column chromatograaphy of the residue (chloroform: methanol=10 : 1) gave (*S*)-(1-methylpyrrolidin-2-yl)methyl 1-(1-hydroxyethyl)-2-propenyl sulfide (α-adduct **4a**, 0.73g, R_f=0.35) and (*S*)-(1-methylpyrrolidin-2-yl)-methyl 1-(4-hydroxy)pentenyl sulfide (γ-adduct **5a**, 2.45g, R_f=0.32) (total yield 69%, **4a** : **5a**=23 : 77). **4a**: ^{1}H-NMR ($CDCl_3$) δ 1.22 (d, *J*=6.2 Hz, 3H, -CH_3), 1.39-1.99 (m, 4H, -CH_2CH_2-), 2.03-3.98 (m, 6 H), 2.37 (s, 3H, N-CH_3), 3.74 (m, 1H, -CHOH), 4.12 (s, 1H, -OH), 4.83-5.39 (m, 2H, =CH_2), 5.41-6.18 (m, 1H, -CH=); IR (neat) 3295, 3055, 2950, 2745, 1623, 1438, 1344, 1201, 1114, 1068, 909 cm^{-1}. **5a**: ^{1}H-NMR ($CDCl_3$) δ 1.19 (d, *J*=6.2 Hz, 3H, -CH_3), 1.59-1.88 (m, 4H, -CH_2CH_2-), 1.87-3.43 (m, 7H), 2.33 (s, 3H, N-CH_3), 2.69 (s, 1H, -OH), 3.87 (m, 1H, -CHOH), 5.12-6.58 (m, 2H, -CH=CH-).

(b) The addition of MAS to acetaldehyde in the presence of Lewis acids or hexamethylphosphoramide (HMPA): To a solution of MAS (213 mg, 1.24 mmol) in tetrahydrofuran (10 m*l*) (diethyl ether was used when triethylborane was added as a Lewis acid) was added slowly *n*-buthyllithium (1.24 mmol) in hexane (1.6 M) at −78℃ under nitrogen atomosphere. After 1 h, the solution was treated with one equivalent of Lewis acid ($ZnCl_2$, Et_3B, Et_3Al, or $Ti(O^iPr)_4$ or HMPA, which caused the reaction mixture to form various colors or precipitates. 10 min later, excess acetaldehyde was added dropwise, and the mixture was allowed to warm to 0℃. After stirring for 2 h at this temperature, the reaction mixture was quenched with sat. sodium bicarbonate solution (a solid formed was filtered through celite 545 before extraction), and extracted with methylene chloride. The organic layer was washed with sat. brine, dried ($MgSO_4$), filtered, and concentrated to afford a yellowish liquid. Column chromatography of the residue gave **4a** and **5a**. The yeilds and the ratio of **4a** and **5a** are reported in Table I.

(S)-(1-methyl-pyrrolidin-2-yl)methyl 1-(1-benzyl-1-hydroxymethyl)-2-propenyl sulfide (4b)

To a solution of MAS (540 mg, 3.15 mmol) in tetrahydrofuran (20 m*l*) was added *n*-buthyllithium (2.2 m*l*, 3.62 mmol, 1.6 M solution in *n*-hexane) at −78℃ under nitrogen. After 1 h, triethylalumi-

num (2 m*l*, 3.8 mmol, 1.9 M solution in toluene) was added and white solid was formed. After few minutes, excess acetaldehyde was added slowly, and the mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was cooled in an ice bath and aqueous methanolic solution was added slowly. The organic layer was separated, dried, and concentrated. The residue was purified by column chromatography (chloroform: methanol=10 : 1, R_f=0.34) to give **4b** (607 mg, 66%). ^{1}H-NMR ($CDCl_3$) δ 1.42-2.01 (m, 4H, $-CH_2CH_2-$), 2.09-3.03 (m, 8H), 2.26 (s, 3H, N-CH_3), 3.18 (s, 1H, -OH), 3.84 (m, 1H, -CHOH), 4.93-5.41 (m, 2H, $=CH_2$), 5. 46-6.23 (m, 1H, -CH=), 7.31 (s, 5H, $-C_6H_5$).

(2R)-Pentanol (8) and (2S)-Pentanol (9)

The α-adduct **4a** (2.43g, 11.3 mmol) was dissolved in 95% ethanol (40 m*l*) and heated to reflux in the presence of W-7 Raney nickel (20g) under nitrogen for an hour. After cooling and separation of the catalyst through celite 545, excess methylene chloride was added to the filtrate for the azeotropic removal of ethanol. The solution was concentrated *in vacuo*. Diethylether was added to the residue which consisted of liquid and solid, and the insoluble solid was removed. The filtrate was concentrated to give 2-pentanols **8** and **9** (429 mg, 42.6%). ^{1}H-NMR ($CDCl_3$) δ 0.91-1.04 (m, 3H, $-CH_3$), 1.24 (d, J=6.2 Hz, 3H, CH_3CHOH), 1.33-1.63 (m, 4H, methylene protons), 2.05 (s, 1H, -OH), 3.78 (m, 1H, -CHOH).

(R)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl)

A mixture of (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, 1.007g, 4.3 mmol), thionyl chloride (1.83 m*l*) and sodium chloride (13 mg) was heated to reflux for 50 h. After excess thionyl chloride was removed under reduced pressure, the residue was distilled to give MTPACl (967 mg, 89%, b.p. 54-56℃/1 mmHg).

(2R)-Pentyl (R)-α-Methoxy-α-trifluoromethylphenylacetate (10) and (2S)-Pentyl (R)-α-Methoxy-α-Methoxy-α-trifluoromethylphenylacetate (11)

A mixture of 2-pentanols **8** and **9** (424 mg, 4.81 mmol), MTPACl (1.13g, 4.47 mmol) and pyridine (1 m*l*) was stirred for 1 h. Water was added to the mixture, and the mixture was then extracted with diethyl ether. The ether extract was washed successively with 5% hydrochloric acid and 5% sodium carbonate solution, dried ($MgSO_4$) and evaporated to give a residual oil. The residue was separated by column chromatography (hexane: ethyl acetate= 30 : 1, R_f=0.21) to give a mixture of **10** and **11** (250 mg, 17.1%). ^{1}H-NMR ($CDCl_3$) δ 0.53-1.12 (m, 3H, $-CH_3$), 1.14-1.92 (m, 4H, methylene protons), 1.24 (d, 3H, J=6.2 Hz, $-C\underline{H}_3$-CHO- for **10**) and 1.31 (d, 3H, J=6.2 Hz, $-C\underline{H}_3$-CHO- for **11**), 3.59 (s, 3H, $-OCH_3$), 5.25 (m, 1H, -CHO), 7.24-7.83 (m, 5H, $-C_6H_5$).

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