REGIOSELECTIVE SYNTHESIS OF SEVERAL HETEROCYCLIC FUSED AZEPINES USING DIISOBUTYLALUMINUM HYDRIDE

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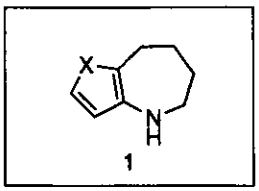
Abstract--5,6,7,8-Tetrahydrothieno[3,2-*b*]azepine,5,6,7,8-tetrahydro-1*H*-furo[3,-2-*b*]azepine, and 1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine were synthesized by the ring expansion reaction of heterocyclic fused cyclohexanone oximes with diisobutylaluminum hydride (DIBAH). The mechanism of the reaction was different from that of Beckmann rearrangement.

From the viewpoint of both synthetic chemistry and medicinal chemistry, it is an interesting problem to construct regioselectively the fundamental unsubstituted skeleton of 5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (1a), 5,6,7,8-tetrahydrofuro[3,2-*b*]azepine (1b), and 1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine (1c). A survey of the literature revealed no previous papers on regioselective construction of these unsubstituted skeleton. Some papers have described synthetic procedures for compounds (IIa) and/or (IIb) by Beckmann rearrangement[1] of oxime or oxime sulfonate (I) and preparation of compound (III) by Dieckmann condensation,[2] and one patent[3] showed the three-step synthesis of tetrahydrothieno[3,2-*b*]azepine (1a) from oxime (3a) *via* oxime tosylate (6a) and lactam (9a). (See Scheme 2) In the present paper, we report a more efficient and direct one-step procedure for synthesizing tetrahydrothieno[3,2-*b*]azepine (1a) from oxime (3a) *(E/Z)*. (See Schemes 1 and 2)

In order to obtain the desired compound (1a), we first studied Beckmann rearrangement of oxime (3a) with PCl_5-ether (0 °C-rt, 1 h)[1a] or P_2O_5-methanesulfonic acid (100 °C, 5 h) and found the ratio of the product (9a) /(10a)[4] was 4/1 (40 % yield) in the case of PCl_5 and 1/2 (90 % yield) with P_2O_5-methanesulfonic acid. When oxime sulfonate (8a) was treated with 3 eq of sodium acetate-aqueous ethanol (reflux, 12 h), lactam (9a) was obtained in an 82 % yield. Compound (1a) could be obtained by reduction of 9a with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene (60 °C, 1 h). On the other hand, Dieckmann condensation of methyl 3-[(4-methoxy-1, 4-dioxobutyl) amino]thiophene-2-carboxylate with potassium hydride in toluene was reexamined from the literature[2] to give a 4*H*-thieno[3,2-*b*]azepine derivative, which was decarboxyled with aqueous DMSO (150 °C) to give compound (11a) in a 48 % yield. Reduction of compound (11a) with 1.8 mol eq of $LiAlH_4$-THF (reflux, 3 h) afforded a yellow solid, which was identical with compound (1a) synthesized by the procedure mentioned above. However, the three-step procedure was inconvenient to obtain compound (1a) from oxime (3a). More conveniently, we developed a

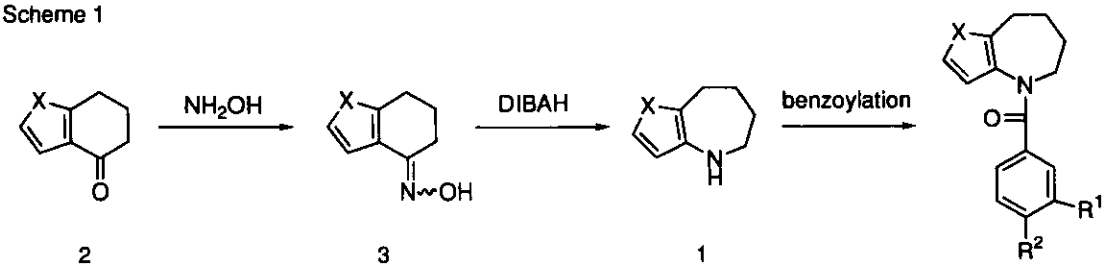
Figure 1



1

a X=S
b X=O
c X=NH
d X=NMe

Scheme 1



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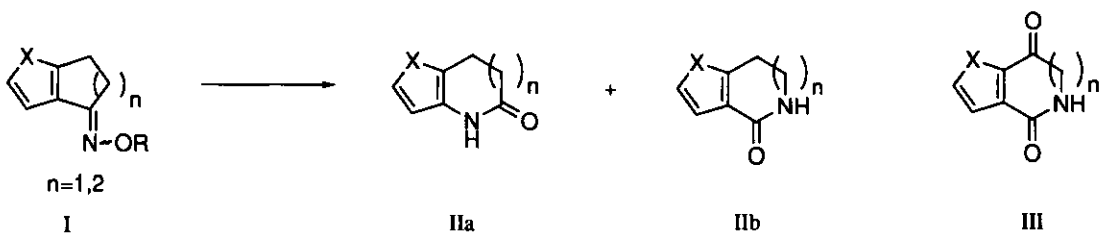
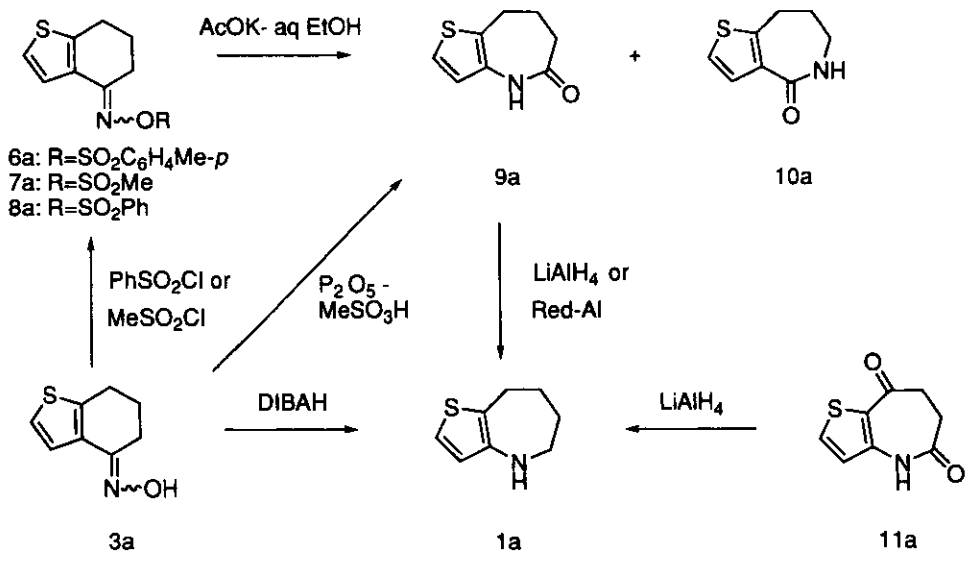




Scheme 3

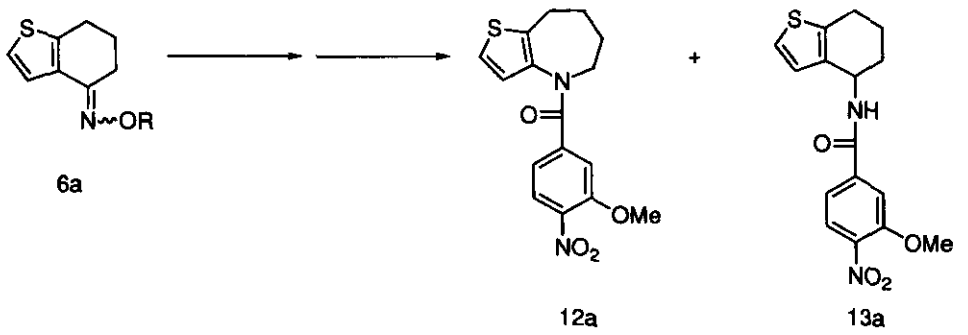
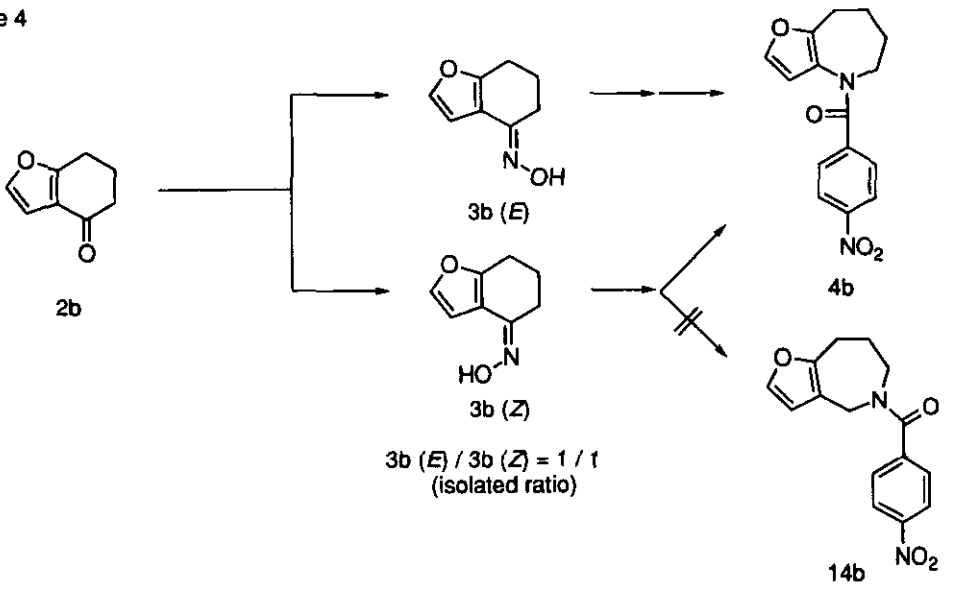


Table The ratio of compound (12a) and (13a) was measured by the signal intencity of protons of methoxy group in NMR spectra.

#	R	Reaction Conditions	Compound (12a)	Compound (13a)
6a	H	4.5 eq. DIBAH, toluene, 0-25 ℃	91.5	8.5
6a	H	4.5 eq. DIBAH, toluene, 0-14 ℃	97.9	2.1
6a	H	2.2 eq. $LiAlH_4$, THF, reflux	50	50
7a	SO_2Me	4.5 eq. DIBAH, toluene, 0-25 ℃	28.3	71.7
8a	SO_2Ph	4.5 eq. DIBAH, toluene, 0-25 ℃	54.9	45.1

Scheme 4



Scheme 5 Reaction mechanism

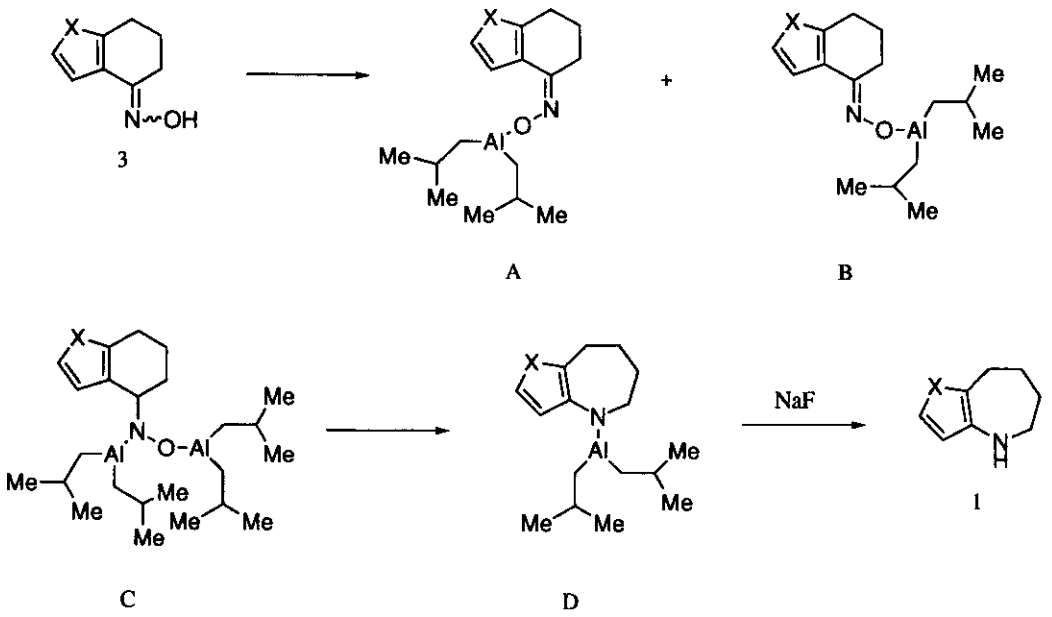
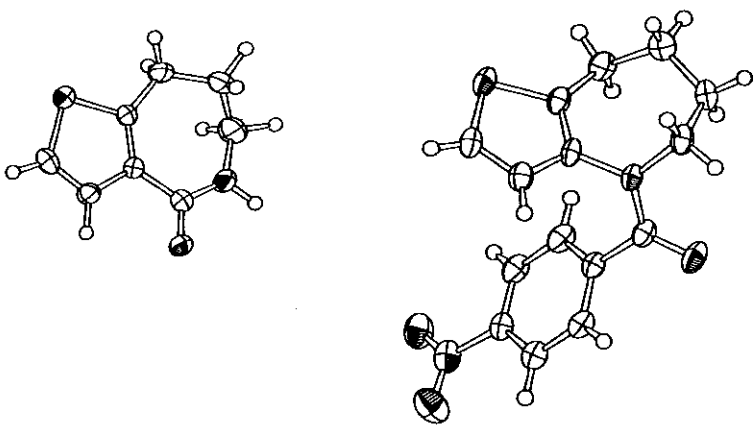


Figure 2 ORTEP drawings of compound (10a) (left) and compound (4a) (right).



new direct method to obtain several heterocyclic fused azepines (1) by ring expansion of oxime (3) with diisobutylaluminum hydride (DIBAH).[5]

Initially, we examined the conditions for reaction of oxime (3a)[6] with DIBAH or $LiAlH_4$. (See Table) In case of $LiAlH_4$, the double bond of oxime was fairly reduced. However, thienoazepine (1a) was mainly obtained with 4.5 eq of DIBAH in methylene chloride or toluene. The reaction temperature should be kept below 14 °C to suppress the production of 4-amino-4,5,6,7-tetrahydrothianaphthene. Interestingly, a regioisomer of compound (1) was not detected with the thienoazepine synthesis. Generally, in Beckmann rearrangement, migration of the group *anti* to the departing hydroxy group occurs to give a regioselective lactam. Therefore, we must separate the *E/Z* isomers of an oxime to obtain a regioselective lactam. In contrast to Beckmann rearrangement, reductive ring expansion of the mixture of *E/Z* isomers (9/1) with DIBAH gave only azepine (1a) in an 83 % yield. Unsubstituted 5,6,7,8-tetrahydrothieno[3,2-*b*]azepine (1a) could be isolated, but was unstable. Therefore, benzoylation of 1a was carried out to study the results of DIBAH reduction. The regioselectivity of azepine synthesis was confirmed by X-Ray crystallographic analysis of compound (4a). As described above, Beckmann rearrangement of oxime benzenesulfonate (8a) with 3 eq of sodium acetate in aqueous ethanol under reflux for 12 h gave lactam (9a) as the sole compound in an 82 % yield. In contrast to this rearrangement, DIBAH reduction of oxime benzenesulfonates (7a) and (8a) affored a fair amount of compound (13a), in which the NMR signal of methine proton α to NH was observed at δ 5.33. Therefore, the reductive ring enlargement reaction should be carried out using oxime (6a) at a low temperature. Thus, synthesis of heterocyclic fused azepine, furoazepine (1b), and pyrroloazepines (1c) and (1d) was undertaken with 4.5 eq of DIBAH in toluene or methylene chloride at 0-14 °C. We separated the oximes (3b) (*E*) and (3b) (*Z*) of 4,5,6,7-tetrahydro-4-oxobenzo[*b*]furan (2b)[6] at a ratio of 1 to 1.[7] When oxime (3b) (*E*) was treated with DIBAH in toluene at 0-14 °C, followed by benzoylation with *p*-nitrobenzoyl chloride, furo[3,2-*b*]azepine (4b) was obtained in a moderate yield accompanied by a small amount of benzoylated oxime. On the other hand, the oxime regioisomer (3b) (*Z*)[7] was more slowly reduced by the reagent and converted to the same compound (4 b), but no regioisomer (14b) was detected with this reaction. This finding showed that the reaction mechanism might not involve Beckmann rearrangement, because each regioisomer of the azepine should be obtained from *E*- or *Z*-oxime, respectively, by Beckmann rearrangement. Thus, it is assumed that the oxime double bond of A and B was first reduced by the reagent, and then rearrangement of C resulted in D as shown in Scheme 5. Similarly, pyrroloazepine (1c) was selectively obtained from reduction of oxime (3c) (*E/Z*=1/1 mixture) of 1,5,6,7-tetrahydro-4*H*-indol-4-one (2c)[8] with DIBAH, and the *N*-methylpyrroloazepine derivative (1d) was obtained as well.[9] These azepines were benzoylated to give compounds (4c) and (4d), respectively. Although these azepines (1a-1d) were unstable, they might be useful as key intermediates for other derivatives. This method employing DIBAH will be used for the synthesis of heterocyclic chemical and pharmaceutical compounds in the future.

In conclusion, the novel construction of heterocyclic fused azepines (1a-1d) using DIBAH was found to be very effective and the mechanism of the reaction was different from that of Beckmann rearrangement.

EXPERIMENTAL

Melting points were determined with a Yanagimoto (Yanako) micro-melting point apparatus HK-10D and are uncorrected. ^{1}H-NMR spectra (ppm, δ) were recorded with a JEOL JNMA 300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. IR spectra (cm^{-1}) were obtained with a PERKIN ELMER FT 1650 infrared spectrophotometer. MS spectra were obtained with a Finigan TSQ 700. Column chromatography was performed using Merck silica gel (70-230 mesh).

Synthesis of 4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine (4a) *via* 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine (1a)

To a stirred solution of compound (2a) (2.27 g, 14.9 mmol) in pyridine (18 mL) was added hydroxylammonium chloride (2.07 g, 29.8 mmol) at rt and stirring was continued for 2 h. Pyridine was removed *in vacuo* at 30 °C to give the residue, which was diluted with water and extracted with ethyl acetate. The aqueous layer was extracted again with ethyl acetate and the combined extracts were washed with brine and dried over anhyd. $MgSO_4$. Evaporation under reduced pressure yielded crystals of 3a (*E/Z* =9/1 by ^{1}H-NMR) (2.36 g. 95 %).

To a stirred solution of 3a (*E/Z* mixture) (1.3 g, 7.78 mmol) in anhyd. methylene chloride (250 mL) was added 0.98 M diisobutylaluminum hydride (DIBAH) (35.7 mL, 35.0 mmol) over 10 min at 0-5 °C (internal temperature) under an argon atmosphere. Stirring was continued at 0 °C for 2 h. Sodium fluoride powder (7 g, 167 mmol) was added to the reaction solution and 2.24 g of water was added after 5 min. After stirring at 0 °C for 20 min, the reaction mixture was filtered through Celite (8 g) wetted with methylene chloride (25 mL) on a glass filter. The celite was washed with a small amount of methylene chloride and the combined solvent was evaporated to give 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine (1a) (0.988 g, 83 %) as a yellow solid. ^{1}H-NMR (δ, $CDCl_3$) : 1.60-1.75 (2H, m) 1.75-1.90 (2H, m), 2.65-2.80 (2H, m), 3.00-3.15 (2H, m), 6.31 (1H, d, J=5.0 Hz), 6.82 (1H, d, J=5.0 Hz). MS (FAB, m/z)=154 (M^++1). Since the compound was unstable, the filtrate may be used without concentration of the solvent for the next benzoylation. To a stirred solution of compound (1a) (0.9 g, 5.88 mmol) in methylene chloride (250 mL) was added triethylamine (1.4 mL, 10.1 mmol) and then a solution of *p*-nitrobenzoyl chloride (1.73 g, 9.32 mmol) in anhyd. methylene chloride (35 mL) at rt. After stirring at rt for 1 h, the reaction mixture was concentrated under reduced pressure to yield the residue, which was dissolved in chloroform (70 mL). The solution was washed successively with water, 1N aqueous HCl, 1N aqueous NaOH, and brine (70 mL each). The organic layer was dried over anhyd. $MgSO_4$ and evaporated to give pale yellow crystals. Recrystallization from ethanol gave 4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine (4a) (1.33 g, 75 %). mp 148.5-149.5 °C (EtOH), ^{1}H-NMR (δ, $CDCl_3$) 1.65-1.95 (2H, m), 1.95-2.15 (2H, m), 2.85-3.00 (2H, m), 3.50-4.30 (2H, m), 6.14 (1H, d, J=5.3 Hz), 6.67 (1H, d, J=5.3 Hz), 7.41 (2H, d, J=8.6 Hz), 8.07 (2H, d, J=8.6 Hz). MS (FAB, m/z)=303 (M^++1). Anal. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59 ; H, 4.67. Found : C, 59.45 ; H, 4.69.

Synthesis of 4-(3-methoxy-4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine (5a)

A solution of 3-methoxy-4-nitrobenzoic acid (2 g, 10.15 mmol) and thionyl chloride (2 mL, 27.4 mmol) in chloroform (2 mL) and *N*, *N*-dimethylformamide (0.2 mL) was refluxed for 3 h, and the reaction mixture was evaporated *in vacuo* to give 3-methoxy-4-nitrobenzoic chloride. A solution of the chloride in chloroform (10 mL) was added over 10 min to a stirred solution of 5,6,7,8-tetrahydro-4*H*-thieno[3,2-

b]azepine (1a) (1.1 g, 7.19 mmol) and triethylamine (3 mL, 21.5 mmol) in chloroform (10 mL) at 0 °C. After stirring at rt for 12 h, the solvent was removed under reduced pressure to leave the residue, which was dissolved in chloroform. The solution was washed successively with water, 1 N-HCl, brine, 1 N-NaOH, and brine, dried over anhyd. $MgSO_4$, and evaporated to yield crude crystals, which were recrystallized from EtOH to give colorless crystals (5a) (2.2 g, 92 %). mp 123.4-124.6°C (EtOH). ^{1}H-NMR (δ, $CDCl_3$) 1.55-1.65 (2 H, m), 1.75-1.85 (2H, m), 2.90-3.00 (2H, m), 3.81 (3H, s), 3.70-4.00 (2H, br s), 6.19 (1H, d, J=5.1 Hz), 6.71 (1H, d, J=5.1 Hz), 6.87 (1H, d, J=8.4 Hz), 7.03 (1H, s), 7.66 (1H, d, J=8.4 Hz). MS (FAB, m/z)=333 (M^+ +1). Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85. Found : C, 57.90; H, 4.77.

When reaction temperature for DIBAH reduction was increased to 25°C, the primary amine was produced as a by-product, which was benzoylated to give compound (13a). ^{1}H-NMR (δ, $CDCl_3$) 1.80-2.30 (4H, m), 2.75-2.95 (2H, m), 4.03 (3H, s), 5.25-5.40 (1H, m), 6.35 (1H, br d, J=7.8 Hz), 6.92 (1H, d, J= 5.1 Hz), 7.12 (1H, d, J=5.1 Hz), 7.24 (1H, dd, J=8.4, 1.8 Hz), 7.65 (1H, d, J=1.8 Hz), 7.83 (1H, d, J=8.4 Hz). MS (FAB, m/z)=319 (M^+ +1). Anal. Calcd for $C_{16}H_{16}NO_4S$: C, 60.36; H, 5.07. Found : C, 60.43 ; H, 5.01.

The following compounds (4b-d) were prepared in a similar fashion. In these cases, the fundamental skeleton,5,6,7,8-tetrahydro-4*H*-furo[3,2- *b*]azepine (1b), 1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine (1c), and 1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine (1d) were not isolated because of instability. Thus, the filtrate passing through the glass filter was used directly for benzoylation without concentration.

Synthesis of 4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4*H*-furo[3,2-*b*]azepine (4b)

The oximes were prepared by the usual procedure and were found to be a mixture of *E/Z* (1/1). Two isomers were separated by SiO_2 column chromatography and each isomer reacted independently with DIBAH. DIBAH reduction of oxime-(*E*) (3b) (1.00 g, 6.62 mmol) gave 1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine (1b), which was very unstable even on a SiO_2 TLC plate. Benzoylation of compound (1b) was immediately carried out to give sole compound (4b), which was recrystallized from $CHCl_3$-EtOH to yield compound (4b) (0.90 g, 48 %). mp 165.5-166.6 °C (EtOH). ^{1}H-NMR (δ, $CDCl_3$) 1.70-1.90 (2H, m), 1.95-2.15 (2H, m), 2.85-3.00 (2H, m), 3.80-4.00 (2H, m), 5.47 (1H, br s), 6.87 (1H, br s), 7.53 (2H, d, J=8.4 Hz), 8.07 (2H, d, J=8.4 Hz). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93. Found: C, 63.04; H, 5.09. In a similar manner, oxime-(*Z*) (3b) was converted to compound (4b) without any isomeric furoazepine (14b).

Synthesis of 4-(4-nitrobenzoyl)-1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine (4c)

Similarly, compound (4c) (6.20 g, 54 %) was obtained by reduction of oxime (3c) (6.00 g, 40.0 mmol) with 0.93 M DIBAH (215 mL, 200 mmol) (0 °C, 3 h), followed by benzoylation as described above. compound (4c). mp 232.0-233.0 °C (CH_2Cl_2-hexane). ^{1}H-NMR (δ, $CDCl_3$) 1.70-1.85 (2H, m), 1.95-2.10 (2H, m), 2.70-2.85 (2H, m), 3.85-4.00 (2H, m), 5.29 (1H, t, J=3.0 Hz), 6.18 (1H, t, J=3.0 Hz), 7.47 (2H, d, J=9.0 Hz), 7.74 (1H, br s), 8.07 (2H, d, J=9.0 Hz). MS (FAB, m/z)=286 (M^+ +1). Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30. Found : C, 63.22; H, 5.11.

Synthesis of 1-methyl-4-(4-nitrobenzoyl)-1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine (4d)

In a similar manner, compound (4d) (1.04 g, 37 %) was obtained *via* compound (1 d) from oxime (3d) (1.55 g, 9.40 mmol). This compound was also obtained by methylation of compound (4c) with NaH-MeI in THF-DMF. mp 164.0-166.0 °C ($CHCl_3$-Et_2O). IR (KBr) 3442, 1638 cm^{-1}. ^{1}H-NMR (δ, $CDCl_3$) 1.70-1.90 (2H, m), 1.95-2.10 (2H, m), 2.70-2.85 (2H, m), 3.49 (3H, s), 3.80-4.00 (2H, m), 5.19 (1H, d, J=2.9 Hz), 6.07 (1H, d, J=2.9 Hz), 7.47 (2H, d, J=8.8 Hz), 8.07 (2H, d, J=8.8 Hz). MS (FAB, m/z)=301 (M^+ +1). Anal. Calcd for $C_9H_{12}N_2O$: C, 64.20; H, 5.72. Found: C, 64.36; H, 5.61.

Synthesis of 4,6,7,8-tetrahydro-5*H*-thieno[3,2-*b*]azepin-5-one (9a) and 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepin-4-one (10a)

Phosphorus pentoxide (1.2 g, 8.5 mmol) was added to stirred methanesulfonic acid (12 g, 120 mmol) and stirring was continued for 2 h. Oxime (3a) (200 mg, 1.2 mmol) was then added to the stirred solution at 100 °C. After stirring for 5 h at 100-110 °C, the reaction mixture was cooled and quenched carefully with saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$. The organic layer was dried over anhyd. $MgSO_4$ and evaporated to give the residue. This was purified by SiO_2 column chromatography (EtOAc: hexane=1:1 then 3:1) to give the less polar compound (9a) (61 mg, 30 %) as a colorless powder and the more polar compound (10a) (120 mg, 60 %) as colorless crystals. The chemical structure of 10a was determined by X-Ray crystallographic analysis.

Synthesis of 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine (1a) from compound (9a)

To a stirred solution of compound (9a) (314 mg, 1.88 mmol) in toluene (19 mL) was added Red-Al [65 wt % solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene] (563 μL, 1.88 mmol) at 0 °C under an argon atomosphere. Stirring was continued for 1 h at rt and then for 1 h at 60°C. To the cooled reaction mixture were added 5 N aqueous NaOH and toluene. The organic layer was separated after shaking, dried over anhyd. $MgSO_4$ and evaporated to give the solid (1a) (220 mg, 76 %), the NMR spectrum of which was identical with that of 1a prepared by the DIBAH method.

Synthesis of compound (4a) from 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine-5, 8-dione (11a)

5,6,7,8-Tetrahydro-4*H*-thieno[3,2-*b*]azepine-5, 8-dione (11a) (2.0 g, 11.0 mmol) was added as small portions of powder to a stirred slurry of lithium aluminum hydride (754 mg, 19.84 mmol) in THF (75 mL) at 0°C. The mixture was refluxed for 3 h and then water (750 mL) and 15 % NaOH (750 mL) were added successively. After decantation, the solution was dried over anhyd. $MgSO_4$ and evaporated to give the solid (1a). To a stirred solution of 1a in $CHCl_3$ (100 mL) and Et_3N (6.1 mL, 43.8 mmol) was added *p*-nitrobenzoyl chloride (5.1 g, 27.5 mmol) at 0°C and stirring was continued at rt for 18 h. The reaction mixture was washed twice with water and dried over anhyd. $MgSO_4$. The solution was evaporated to leave the residue, which was chromatographed with SiO_2 (hexane/AcOEt=5/1, then gradually changed to 1/2) to afford 1.63 g (49 %) of compound (4a). The ^{1}H-NMR spectrum of the compound was identical with that of compound (4a) synthesized as described above.

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7. Assignment of the chemical structures (3b) (*E*) and (3b) (*Z*) was done by comparison of the ^{1}H-NMR chemical shifts of compounds (2b), (3b) (*E*), and (*Z*). Namely, the methylene protons (δ: 2.68-2.80) α on an oxime group of 3b (*E*) were observed at a lower field than the corresponding protons (δ ; 2.50) α on the carbonyl group of 2b, and the methine proton (δ: 7.13) at position-3 on the furan ring of oxime 3b (*Z*) appeared at a lower field than the corresponding proton of 2b (δ: 6.67) and that of 3b (*E*) (δ: 6.62), because of the deshielding effect of the hydroxy group.

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