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A New Method for the Introduction of Arylthio Groups at the α-Position of Alicyclic Amines

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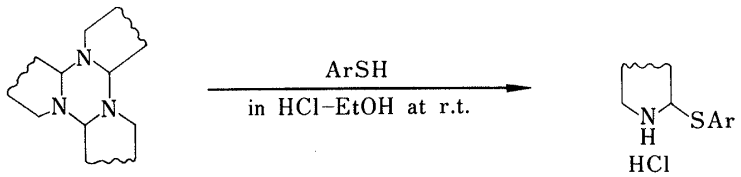
It has been found that tetracyclic hexahydro-1,3,5-triazines react with arenethiols to give 2-arylthio-substituted alicyclic amines. This new reaction provides a useful method for the introduction of arylthio groups at the α-position of alicyclic amines. The reaction with thioglycolate gives bicyclic thiazolidine derivatives, some reactions of which are also described.

Keywords——alicyclic imine trimer; 2-arylthio-substituted alicyclic amine; thiazolizine; oxidation; thermolysis

Introduction of functional groups at the α-position of alicyclic amines is an important area of synthetic organic chemistry, because many alkaloids contain pyrrolidine, pyrrolizidine and indolizidine nuclei that are α-substituted. Conversion of alicyclic amines to imine trimers *i.e.*, tetracyclic hexahydro-1,3,5-triazines (**1**), is one of the methods for activating the α-position of alicyclic amines.[1] We now wish to describe a simple method for introducing an arylthio group at the α-position of alicyclic amines by means of the reaction of **1** with arenethiols.

Trimers of 1,2-didehydropiperidine (**1a**) and 1,2-didehydropyrrolidine (**1b**) are available from alicyclic amines by N-chlorination with sodium hypochlorite[2] or *N*-chlorosuccinimide,[3] followed by dehydrochlorination with a base. We have found that reaction of the trimers (**1**) with arenethiols in ethanolic hydrogen chloride gave a new series of 2-arylthio-substituted alicyclic amine hydrochlorides in high yields. The reaction can be interpreted as a nucleophilic attack of the thiols on the protonated ammonium ion of **1** or the intermediary alicyclic iminium ion. The results of experiments with several arenethiols are summarized in Table I.



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In general, 2-arylthio-substituted alicyclic amines were isolated as pure crystals of their hydrochlorides, but not as the free amines. Nevertheless, hydrochlorides of 2-phenylthio- and 2-benzylthiopyrrolidines were not obtained in a pure state, because of their lability and hygroscopic character. The reaction of **1** with alkanethiols failed to yield the 2-alkylthio-substituted alicyclic amines, except for that of **1a** with phenylmethanethiol, where 2-benzylthiopiperidine (**6**) was obtained in good yield.

The structures of the products were determined on the basis of the spectral data and elementary analyses. The α-position of the arylthio groups was confirmed by the carbon-13

TABLE I. Synthesis[a] of 2-Aryl(or Aralkyl)thio-Substituted Alicyclic Amines

Thiol	1a	Yield (%)	1b	Yield (%)
CH_3-C$_6$H$_4$-SH	2a	90	2b	87
Cl-C$_6$H$_4$-SH	3a	81	3b	88
C$_6$H$_5$-SH	4	75		
C$_{10}$H$_7$-SH	5	83		
C$_6$H$_5$-CH$_2$SH	6	63		

a) General procedures are given in Experimental.

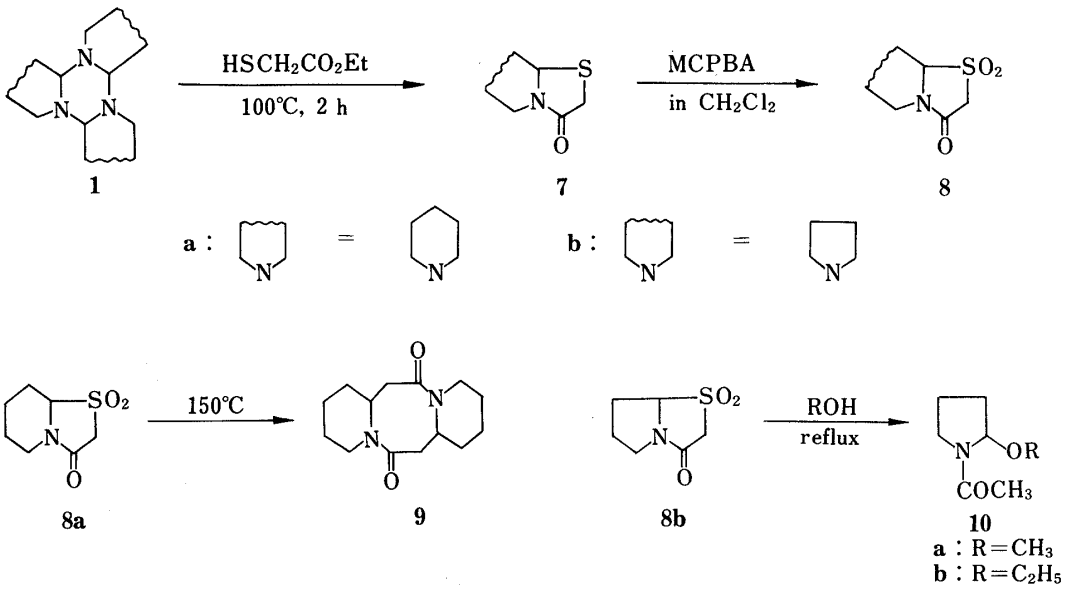

Chart 1

nuclear magnetic resonance (^{13}C-NMR) spectrum. In the spectrum of a representative compound, **2a**, the low magnetic field of the signal at 65.39 ppm (doublet) is consistent with assignment to the tertiary carbon adjacent to the ring nitrogen, because the signals of the tertiary carbons at C-3 and C-4 of piperidine should appear at much higher field.

TABLE II. Analytical Data

Compound No.	mp °C (recryst. solv.) or bp °C (mmHg)	Formula	Analysis (%) Calcd (Found)		
			C	H	N
2a	129—130 (CH_3CN)	$C_{12}H_{18}ClNS$	59.12 (58.78	7.44 7.44	5.75 6.08)
2b	111—112 (CH_3CN)	$C_{11}H_{16}ClNS$	57.50 (57.18	7.02 7.01	6.10 6.25)
3a	128—129 (CH_3CN)	$C_{11}H_{15}Cl_2NS$	50.05 (49.82	5.72 5.77	5.30 5.54)
3b	108—109 (CH_3CN)	$C_{10}H_{13}Cl_2NS$	48.01 (47.84	5.24 5.17	5.60 5.83)
4	133—135 (CH_3CN)	$C_{11}H_{16}ClNS$	57.50 (57.20	7.02 7.07	6.10 6.29)
5	129—130 (CH_3CN)	$C_{15}H_{18}ClNS$	64.39 (64.43	6.48 6.43	5.01 5.01)
6	128—129 (iso-PrOH)	$C_{12}H_{18}ClNS$	59.12 (59.01	7.44 7.32	5.75 5.94)
7a	94—96 (0.01)	$C_7H_{11}NOS$	53.46 (53.28	7.05 6.98	8.91 8.81)
7b	82—83 (0.01)	C_6H_9NOS	50.32 (50.19	6.33 6.35	9.78 9.57)
8a	143—145 (EtOH)	$C_7H_{11}NO_3S$	44.43 (44.28	5.86 5.73	7.40 7.32)
8b	88—89 (EtOH)	$C_6H_9NO_3S$	41.13 (41.16	5.18 5.18	7.99 7.99)
10a	61—62 (0.1)	$C_7H_{13}NO_2$	58.72 (58.71	9.15 9.18	9.78 9.61)
10b	68—69 (0.5)	$C_8H_{15}NO_2$	61.21 (61.01	9.62 9.53	8.91 9.01)

Further examination of the reaction of **1** was carried out with ethyl thioglycolate. Attempts to obtain a 2-ethoxycarbonylmethylthio-substituted compound under similar conditions failed, but heating of **1** with ethyl thioglycolate without any solvent was found to give bicyclic thiazolidine derivatives (**7**) in good yields, as illustrated in Chart 1. This finding led us to examine the chemical properties of **7**. Oxidation of the products (**7**) with *m*-chloroperbenzoic acid (MCPBA) gave 1,1-dioxo derivatives (**8**). In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **7b** and **8b**, the signal of one of the methylene protons at the 5-position was observed to shift to lower field than that of the other owing to the deshielding effect of the carbonyl group at the 3-position.

Thermolysis of **8a** at 150 °C gave the dimer (**9**) with the release of sulfur dioxide. Interestingly, heating of **8b** in alcohol gave 2-alkoxy-1-acetylpyrrolidine (**10**). This reaction may be initiated by alcoholysis at the 8-position, followed by release of sulfur dioxide. The product **10a** has been reported previously as a potential intermediate for alkaloid synthesis.[4] The NMR spectra of **10a** and **10b** revealed that they are mixtures of two isomers due to restricted rotation about the amide bond.

Experimental

All boiling and melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a JASCO IRA-2 spectrometer, and NMR spectra on a JEOL FX-90-Q spectrometer (with tetramethylsilane as an internal standard).

General Procedure for Synthesis of 2-Arylthio- or 2-Benzylthio Alicyclic Amines——A solution of an arenethiol or phenylmethanethiol (6 mmol) in EtOH (1 ml) was added dropwise to an ice-cooled solution of the trimer of an alicyclic imine (**1**) in EtOH (10 ml) containing hydrochloric acid (6 mmol), with stirring. The solution was stirred at room temperature for 3 h. The deposited precipitates were collected by filtration and the filtrate was concentrated under reduced pressure to give a further amount of the product.

The yields and analytical data of the products are listed in Tables I and II. The ^{1}H-NMR and ^{13}C-NMR spectra of 2-*p*-tolylthiopiperidine hydrochloride (**2a**) and 2-*p*-tolylthiopyrrolidine hydrochloride (**2b**) are described below. **2a**: ^{1}H-NMR δ ($CDCl_3$): 1.50—2.40 (6H, m), 2.32 (3H, s), 2.60—3.40 (2H, m), 4.50—4.70 (1H, m), 6.88 and 7.88 (4H, 2×d), 9.10—9.40 (2H, br). ^{13}C-NMR δ ($CDCl_3$): 21.18 (q), 21.56 (t), 22.05 (t), 30.05 (t), 44.54 (t), 65.39 (d), 129.82 (s), 130.36 (d), 135.02 (d), 139.62 (s). **2b**: ^{1}H-NMR δ ($CDCl_3$): 1.60—2.40 (4H, m), 2.32 (3H, s), 2.90—3.40 (2H, m), 4.50—4.70 (1H, m), 6.88 and 7.88 (4H, 2×d), 9.10—9.40 (2H, br). ^{13}C-NMR δ ($CDCl_3$): 21.18 (q), 23.57 (t), 31.86 (t), 45.40 (t), 66.21 (d), 129.82 (s), 130.36 (d), 134.26 (d), 139.41 (s).

Synthesis of Thiazolidinone Derivatives (7)——The trimer of an alicyclic imine (**1**) (25 mmol) and ethyl thioglycolate (100 mmol) were heated at 100 °C with stirring for 2 h. After removal of insoluble material by filtration, the filtrate was subjected to distillation under reduced pressure. **7a**: Yield 71%, bp 121—122 °C (0.16 mmHg). IR ν_{max}^{neat} cm^{-1}: 1655 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.43—2.10 (6H, m), 2.58—2.90 (1H, m), 3.56 (2H, s), 4.10—4.33 (1H, m), 4.33—4.67 (1H, m). ^{13}C-NMR δ ($CDCl_3$): 24.22 (2×t), 32.08 (t), 36.19 (t), 42.86 (t), 60.36 (d), 169.37 (s). **7b**: Yield 74%, bp 96—98 °C (0.1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1675 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.55—2.45 (4H, m), 2.90—3.80 (2H, m), 3.46 (1H, d, J=14 Hz), 3.96 (1H, d, J=14 Hz), 4.91 (1H, t, J=6 Hz). ^{13}C-NMR δ ($CDCl_3$): 20.17 (t), 32.81 (t), 37.87 (t), 42.97 (t), 62.53 (d), 171.05 (s).

Oxidation of 7——MCPBA (40 mmol) was added in portions to an ice-cooled solution of **7** (20 mmol) in CH_2Cl_2 (80 ml) with stirring. The mixture was stirred overnight at room temperature. After removal of *m*-chlorobenzoic acid by filtration, the filtrate was washed with aq. $KHCO_3$ and then aq. NaCl, dried over $MgSO_4$, and concentrated to give the product (**8**). **8a**: Yield 66%, mp 144—145 °C (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O), 1310, 1114 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 1.20—2.30 (6H, m), 2.58—2.90 (1H, m), 3.76 (2H, s), 4.37—4.58 (2H, m). ^{13}C-NMR δ ($CDCl_3$): 21.94 (t), 23.35 (t), 24.00 (t), 40.96 (t), 51.15 (t), 75.20 (d), 161.24 (s). **8b**: Yield 61%, mp 88—89 °C (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O), 1310, 1119 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 1.99—2.58 (4H, m), 3.24 (1H, dt, J=7.1, 11.7 Hz), 3.78 (1H, d, J=11.7 Hz), 3.85 (1H, dt, J=6.05, 11.7 Hz), 4.09 (1H, d, J=11.7 Hz), 4.90 (1H, t, J=6.6 Hz). ^{13}C-NMR δ ($CDCl_3$): 23.19 (t), 25.68 (t), 44.75 (t), 56.29 (t), 78.72 (d), 162.43 (s).

Thermolysis of 8——A solution of **8b** (3 mmol) in MeOH or EtOH (3 ml) was refluxed for 2 h. After removal of the alcohol, an almost pure oil was obtained. **10a**: Yield 91%, bp 61—62 °C (0.1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1650 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.60—2.50 (4H, m) 2.08 and 2.14 (3H, 2×s), 3.20—3.70 (2H, m), 3.30 and 3.38 (1H, 2×s), 4.93—4.97 and 5.38—5.50 (1H, m). ^{13}C-NMR δ ($CDCl_3$): 21.29 (t), 21.90 (q), 31.21 (t), 45.46 (t), 53.96 (q), 89.62 (d), 170.36 (s), 23.08 (t), 22.70 (q), 31.64 (t), 46.97 (t), 56.40 (q), 86.96 (d), 170.78 (s). **10b**: Yield 89%, bp 65—67 °C (0.1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1650 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.14 and 1.22 (3H, t, J=7.0 Hz), 1.60—2.20 (4H, m), 2.08 and 2.14 (3H, s), 3.46 and 3.48 (2H, q, J=7.0 Hz), 3.10—3.80 (2H, m), 5.01—5.05 and 5.44—5.53 (1H, m). ^{13}C-NMR δ ($CDCl_3$): 15.28 (q), 21.29 (t), 21.94 (q), 31.85 (t), 45.40 (t), 62.09 (t), 88.37 (d), 170.23 (s), 15.44 (q), 23.08 (t), 22.70 (q), 32.07 (t), 40.92 (t), 64.15 (t), 85.49 (d), 170.51 (s).

Compound **8a** (400 mg) was heated at 150 °C until the evolution of SO_2 subsided. The resultant viscous oil was subjected to preparative thin-layer chromatography (silica gel, $CHCl_3$: acetone = 1 : 1 as an eluent) to give an oil (30 mg) (Rf=0.6), which was presumed to be the dimer (**9**) based on the following data. IR ν_{max}^{neat} cm^{-1}: 1630 (C=O). MS m/z: 250 (M^+). *Anal.* Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.85; H, 8.86; N, 10.82.

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