SYNTHESIS OF N-ALKYLISOTHIAZOLIDINES

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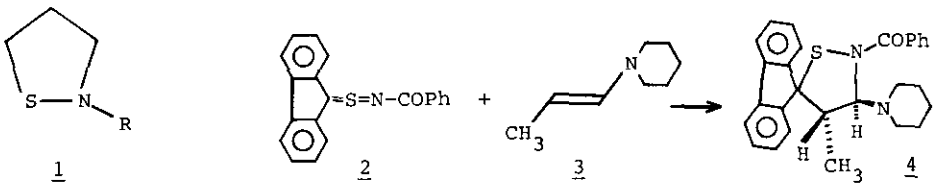
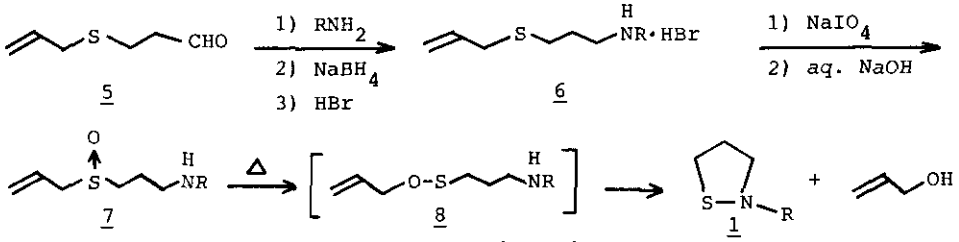
Abstract — N-Alkylisothiazolidines were prepared by [2,3]-sigmatropic rearrangement of allyl 3-alkylaminopropyl sulfoxides to the sulfenates, followed by intramolecular thiophilic substitution of N-alkylamino moieties.

Isothiazolidine framework (1) has been well known in heterocycles, but the synthesis of isothiazolidine and N-alkylisothiazolidines has not been reported. Burgess et al. have reported as a special case that the cycloaddition reaction of fluorenethione S-benzoylimide (2) with N-propenylpiperidine (3) gave isothiazolidine derivative (4).[1]



1 2 3 4

We now wish to report a simple and general synthetic method for N-alkylisothiazolidines (1) (R= alkyl) starting from an easily available β-allylmercaptopropionaldehyde (5) as shown in Scheme 1.



5 6 7 8 1

Scheme 1.

β-Allylmercaptopropionaldehyde (5) was prepared by addition of allyl mercaptan to acrolein in the presence of a triethylamine in benzene at room temperature.[2] Allyl 3-alkylaminopropyl sulfides were generated by $NaBH_4$ reduction of Shiff bases which were produced by the condensation reactions between 5 and primary amines. After oxidation reaction of allyl 3-alkylaminopropyl sulfide·HBr salts (6) by $NaIO_4$ in aqueous MeOH at 0 °C for 2 h and following treatment with base, allyl 3-alkylaminopropyl sulfoxides (7) were obtained. Finally, N-alkylisothiazolidines (1) were prepared in high yields by [2,3]-sigmatropic rearrangement (Mislow-Evans rearrangement)[3] of 7 to sulfenates (8), followed by intramolecular thiophilic substitution of N-alkylamino moieties liberating allyl alcohol.

Table 1. Yields, Mps and Some Properties of 6 and 7

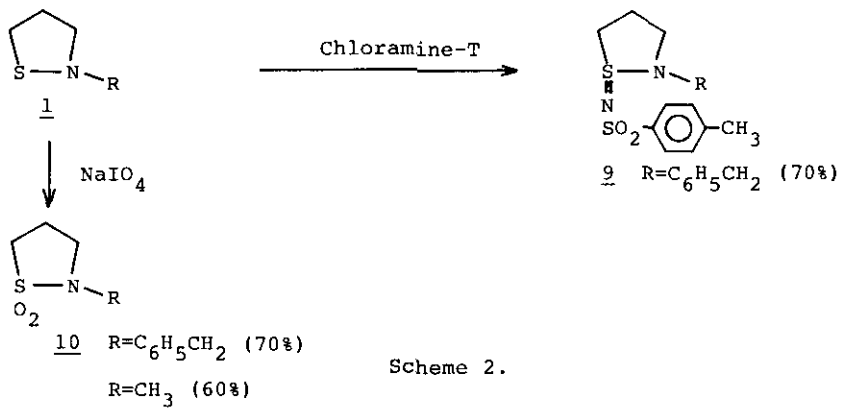
Compd	R	Yield (%) (5)→(6)	mp (°C)	Compd	R	Yield (%) (6)→(7)	ir (neat) ($\nu_{S=O}$, cm^{-1})
6a	CH_3	32	90-91	7a	CH_3	75	1030
6b	C_2H_5	37	85-86	7b	C_2H_5	89	1050
6c	$t\text{-}C_4H_9$	64	137-138	7c	$t\text{-}C_4H_9$	95	1020
6d	$C_6H_5CH_2$	54	102-103	7d	$C_6H_5CH_2$	96	1030

Table 2. Yields and Some Properties of 1

Compd	R	Yield (%) (7)→(1)	MS (m/e)	^{1}H-nmr Chemical Shifts [a]
1a	CH_3	66	103 (M^+)	1.8-2.3 (2H, m), 2.51 (3H, s), 2.9-3.3 (4H, m)
1b	C_2H_5	100	117 (M^+)	1.6 (3H, t, J= 7.2 Hz), 1.7-2.2 (2H, m), 2.44 (2H, q, J= 7.2 Hz), 2.75-3.2 (4H, m)
1c	$t\text{-}C_4H_9$	97	146 (M^++1)	1.13 (9H, s), 1.75-2.3 (2H, m), 2.78-3.26 (4H, m)
1d	$C_6H_5CH_2$	85	179 (M^+)	1.70-2.20 (2H, m), 2.83-3.16 (4H, m), 3.60 (2H, s), 7.16 (5H, s)

a) Peaks given as δ (ppm) from TMS; spectra were run in $CDCl_3$.

In a typical preparation, a primary amine (0.1 mole) was added to a solution of 0.1 mole of β-allylmercaptopropionaldehyde (5) in methanol at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. Then $NaBH_4$ (0.2 mole) was added slowly to the resulting solution at 0 °C. After the addition of $NaBH_4$ was completed, the solution was stirred overnight at room temperature. Water (20 ml) was added to the above solution and methanol was evaporated under vacuum. The residue was extracted with ether (x2). The ether solution was dried over sodium sulfate, filtered and concentrated. Hydrobromic acid (47%) was added to the methanol solution of the residue at 0 °C until it became a little acidic solution. Then the resulting solution was evaporated and the residual solid was recrystallized from acetone to give 6.[4] *$NaIO_4$ (0.05 mole) was added slowly to a solution of* allyl aminopropyl sulfide·HBr salt (6) in MeOH-H_2O (2:1) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Methanol was evaporated and 1N-NaOH was added slowly to the above solution at 0 °C until it became a strongly basic solution. The solution was extracted with dichloromethane (x3). The dichloromethane solution was dried over sodium sulfate, filtered and concentrated *in vacuo*. The sulfoxide (7) thus obtained was pure enough to use in the next step.[5] Allyl 3-alkylaminopropyl sulfoxides (7b-d) (15 mmol) were refluxed in cyclohexane (100 ml) overnight; allyl 3-methylaminopropyl sulfoxide (7a) was refluxed in n-hexane (100 ml) for a day. The solution was concentrated *in vacuo* and the residue was purified by molecular distillation to give 1. (Table 2) N-Alkylisothiazolidines (1) reacted with Chloramine-T (sodium p-toluenesulfonchloramide) in aqueous acetone at 0 °C for 1 h to give sulfimides in good yields.[6] N-Alkylpropanesultams (10) were also obtained by the oxidation of 1 with $NaIO_4$ in MeOH-H_2O at reflux for 10 h.[7] (Scheme 2)



Scheme 2.

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2. 5: bp 75-79 °C/8 mmHg (40% yield) (lit. bp 51-52.5 °C/1.2 mmHg); Y. Takano, T. Shichimi, R. Yamamoto, N. Yamamoto, and I. Yamashita, Nippon Gomu Kyokaishi, 45, 588 (1972).
3. a) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, J. Am. Chem. Soc., 90, 4869 (1968).
   b) D. A. Evans, G. C. Andrews, and C. L. Sims, J. Am. Chem. Soc., 93, 4956 (1971); D. A. Evans and G. C. Andrews, Acc. Chem. Res., 7, 147 (1974).
   c) R. W. Hoffmann and S. Goldmann, Chem. Ber., 111, 2716 (1978).
4. 6a: (R=CH_3) ^{1}H-nmr ($CDCl_3$) δ 1.95-2.4 (2H, m), 2.45-2.8 (5H, m), 2.9-3.3 (4H, m), 4.85-6.2 (3H, m), 8.9 (2H, broad s).
   6b: (R=C_2H_5) ^{1}H-nmr ($CDCl_3$) δ 1.50 (3H, t, J= 7.2 Hz), 1.9-2.75 (4H, m), 2.8-3.3 (4H, m), 4.85-6.2 (3H, m), 9.0 (2H, broad s).
   6c: (R=t-C_4H_9) ^{1}H-nmr ($CDCl_3$) δ 1.45 (9H, s), 2.0-3.2 (8H, m), 4.8-6.0 (3H, m), 8.7 (2H, broad s).
   6d: (R=$C_6H_5CH_2$) ^{1}H-nmr ($CDCl_3$) δ 1.9-3.2 (8H, m), 4.05 (2H, t, J= 5.4 Hz), 4.8-6.2 (3H, m), 7.2-7.7 (5H, m), 9.4 (2H, broad s).
5. 7a: (R=CH_3) ^{1}H-nmr ($CDCl_3$) δ 1.44 (1H, s), 1.62-2.20 (2H, m), 2.39 (3H, s), 2.56-2.90 (4H, m), 3.34-3.56 (2H, m), 5.1-6.3 (3H, m).
   7b: (R=C_2H_5) ^{1}H-nmr ($CDCl_3$) δ 1.02 (3H, t, J= 7.2 Hz), 1.07 (1H, s), 1.55-2.0 (2H, m), 2.27-2.71 (6H, m), 3.14-3.33 (2H, m), 4.95-6.2 (3H, m).
   7c: (R=t-C_4H_9) ^{1}H-nmr ($CDCl_3$) δ 1.03 (9H, s), 1.6-2.0 (3H, m), 2.4-2.8 (4H, m), 3.25-3.42 (2H, m), 5.0-6.2 (3H, m).
   7d: (R=$C_6H_5CH_2$) ^{1}H-nmr ($CDCl_3$) δ 1.45-2.0 (3H, m), 2.35-2.65 (4H, m), 3.0-3.25 (2H, m), 3.55 (2H, s), 4.9-6.1 (3H, m), 7.02 (5H, s).
6. 9: (R=$C_6H_5CH_2$) mp 114-115 °C (methanol); ^{1}H-nmr ($CDCl_3$) δ 1.90-2.80 (5H, m containing s at 2.32, CH_3 and C-CH_2-C), 2.9-3.5 (4H, m, S-CH_2, N-CH_2-C), 3.76 and 4.48 (2H, dd, J= 13.8 Hz, N-CH_2-Ph), 7.10-7.83 (9H, m containing s at 7.21, Ph and -C_6H_4-CH_3); ir (KBr) 1295, 1280, 1145, 1000 cm^{-1}.
7. 10: (R=$C_6H_5CH_2$) oil; ^{1}H-nmr ($CDCl_3$) δ 2.16-2.50 (2H, m), 3.08-3.36 (4H, m), 4.27 (2H, s), 7.52 (5H, s); ir (neat) 2960, 1300, 1140 cm^{-1}.
   (R=CH_3) mp 48-49 °C (acetone) (lit. mp 45-47 °C); W. F. Erman and H. C. Kretschmar, J. Org. Chem., 26, 4841 (1961).

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