Smiles Rearrangement of 2-(1-Methyl-1*H*-tetrazol-5-ylthio)acetamides and Their Sulfonyl Derivatives

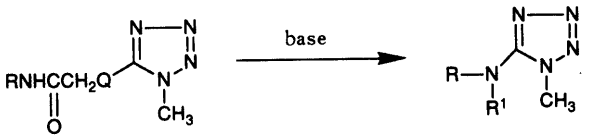
Katsuyuki ISHII, Minoru HATANAKA and Ikuo UEDA*

The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan. *Received May 20, 1991*

The Smiles rearrangement of 2-(1-methyl-1*H*-tetrazol-5-ylthio)acetamides and their sulfonyl derivatives occurred under basic conditions to yield 5-amino-1-methyl-1*H*-tetrazole derivatives in excellent yields.

Keywords Smiles rearrangement; 2-(1-methyl-1*H*-tetrazol-5-ylthio)acetamide; 5-amino-1-methyl-1*H*-tetrazole; 5-mercapto-1-methyl-1*H*-tetrazole

The Smiles rearrangement is generally considered to be an intramolecular nucleophilic aromatic substitution reaction resulting in the migration of an aromatic ring from one hetero atom to another. The scope of the reaction has been extended to diverse molecular systems.[1] However, little is known about Smiles rearrangement of migrating tetrazole groups.[2] This paper describes the base-promoted Smiles rearrangement of 2-(1-methyl-1*H*-tetrazol-5-ylthio)-acetamides and their sulfinyl and sulfonyl derivatives to 1-methyl-5-(*N*-substituted amino)-1*H*-tetrazoles (Chart 1).



1 : R = H, Q = S
2 : R = C_6H_5, Q = S
3 : R = C_6H_5, Q = SO
4 : R = C_6H_5, Q = SO_2
5 : R = $C_6H_5CH_2$, Q = S
6 : R = $C_6H_5CH_2CH_2$, Q = S
7 : R = A, Q = S
8 : R = A, Q = SO
9 : R = A, Q = SO_2

10 : R = R^1 = H,
11 : R = C_6H_5, R^1 = H
12 : R = C_6H_5, R^1 = $COCH_3$
13 : R = $C_6H_5CH_2$, R^1 = H
14 : R = $C_6H_5CH_2CH_2$, R^1 = H
15 : R = A, R^1 = H
16 : R = A, R^1 = $COCH_3$

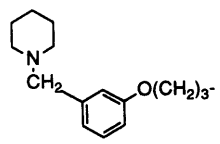
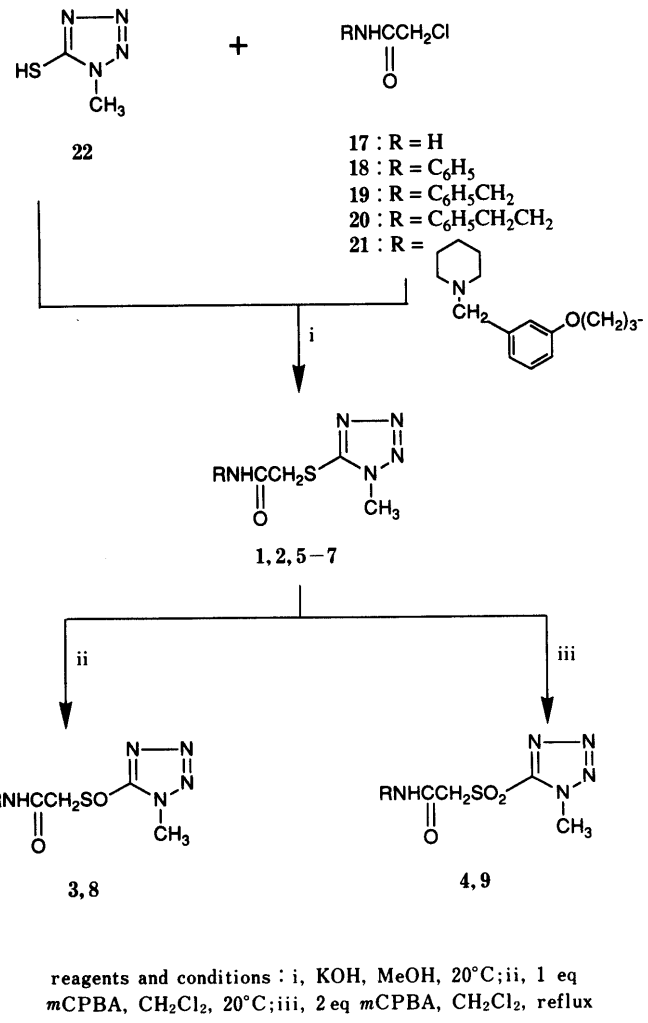
A = 

Chart 1

A series of 2-(1-methyl-1*H*-tetrazol-5-ylthio)acetamides and their sulfinyl and sulfonyl derivatives was prepared according to Chart 2. 2-(Tetrazol-5-ylthio)acetamides (**1**, **2**, **5**, **6** and **7**) were prepared in good yields by condensation of 5-mercapto-1-methyl-1*H*-tetrazole[3] (TzSH: **22**), using 1 eq of KOH in MeOH, with 2-chloroacetamides (**17**—**21**). Corresponding sulfinyl (**3** and **8**) and sulfonyl derivatives (**4** and **9**) were obtained by treating **2** and **7** with 1 eq of *m*-chloroperbenzoic acid (*m*CPBA) in CH_2Cl_2 at 20 °C or 2 eq of *m*CPBA in refluxing CH_2Cl_2. The elemental analysis and spectral data of compounds **1**—**9** are given in Tables I and III.



reagents and conditions : i, KOH, MeOH, 20°C; ii, 1 eq *m*CPBA, CH_2Cl_2, 20°C; iii, 2 eq *m*CPBA, CH_2Cl_2, reflux

Chart 2

TABLE I. 2-(1-Methyl-1*H*-tetrazol-5-ylthio)acetamides and Their Sulfinyl and Sulfonyl Derivatives

Compd.	Yield (%)	mp (°C) (Recrystn. solvent)[a]	Formula	Analysis (%) Calcd (Found)		
				C	H	N
1	88	187.0—188.0 (MeOH)	$C_4H_7N_5OS$	27.74 (27.76	4.07 3.98	40.44 40.16)
2	92	168.4—168.5 (AcOEt)	$C_{10}H_{11}N_5OS$	48.18 (47.96	4.45 4.24	28.09 27.92)
3	81	165.5—166.0 (dec.) (CH_2Cl_2–IPE)	$C_{10}H_{11}N_5O_2S$	45.27 (45.16	4.18 4.25	26.40 26.18)
4	88	126.0—126.5 (CH_2Cl_2–IPE)	$C_{10}H_{11}N_5O_3S$	42.72 (42.91	3.94 3.78	24.90 24.72)
5	86	105.5—106.0 (CH_2Cl_2–IPE)	$C_{11}H_{13}N_5OS$	50.18 (50.34	4.98 4.92	26.60 26.72)
6	87	81.5—82.5 (AcOEt–IPE)	$C_{12}H_{15}N_5OS \cdot 1/13H_2O$	51.71 (52.01	5.48 5.67	25.13 24.90)
7[b]	93	90.0—90.5 (IPE)	$C_{19}H_{28}N_6O_2S$			
8[b]	63	Oil	$C_{19}H_{28}N_6O_3S$			
9[b]	58	Oil	$C_{19}H_{28}N_6O_4S$			

a) IPE: isopropyl ether. *b*) Reference 8.

When compounds **1**, **2**, **5**, **6** and **7** were refluxed in ethanolic sodium hydroxide, corresponding rearrangement products (**10**, **11**, **13**, **14** and **15**) were obtained in excellent yields. Under mild reaction conditions such as ethanolic sodium hydroxide at room temperature and with *N*-methylpiperidine in refluxing toluene, compounds **1**, **2**, **5**, **6** and **7** remained unchanged. When the sulfinyl derivative (**3**) was treated in ethanolic sodium hydroxide at room temperature or with *N*-methylpiperidine in refluxing toluene, **3** was completely decomposed into unidentified polar materials. Two-phase reaction of **3** with $NaHCO_3$ in a mixture of H_2O and CH_2Cl_2 (1 : 1) at room temperature for 4 h gave **11** in 11% yield. Unchanged starting material **3** was recovered in 64% yield from the reaction mixture. Reaction of sulfonyl derivatives (**4** and **9**) in ethanolic sodium hydroxide at room temperature gave the corresponding rearrangement products (**11** and **15**) in 95% and 80% yields, respectively. When **4** was allowed to react with *N*-methylpiperidine in refluxing toluene for 30 min, 5-acetylamino-1-methyl-1*H*-tetrazole (**12**) was obtained in 89% yield. Reaction of **9** in refluxing toluene for 13 h gave **16** in 73% yield. The results are summarized in Table II.

The Smiles rearrangement of $RNHCOCH_2QTz$, in which Tz is the 1-methyl-1*H*-tetrazole moiety and Q represents S, SO and SO_2 functions, was shown to occur easily under basic conditions, giving two types of *N*-acetylamino and

Table II. Preparation of 5-Amino-1-methyl-1*H*-tetrazoles *via* the Smiles Rearrangement

Starting material	Method[a]	Time (min)	Rearrangement product						
			Compd.	mp (°C) (Recrystn. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
1	E	60	10	224 (H_2O) (lit.,[9] 223—225)	93	$C_2H_5N_5$	24.24 (24.30	5.09 5.00	70.68 70.35)
2	E	180	11	185.6—185.9 (AcOEt) (lit.,[10] 185.5—186.5)	97	$C_8H_9N_5$	54.84 (54.59	5.18 5.30	39.98 40.03)
3	C	240	11		11			[b]	
4	D	120	11		95			[b]	
4	B	30	12	Oil	89	$C_{10}H_{11}N_5O$	HRMS: 217.0963 (217.0964)		
5	E	35	13	133—134 (C_6H_6–hexane) (lit.,[10] 99)	95	$C_9H_{11}N_5$	57.12 (57.01	5.86 5.90	37.02 36.89)
6	E	40	14	153—154 (C_6H_6–hexane)	94	$C_{10}H_{13}N_5$	59.10 (59.20	6.45 6.44	34.46 34.41)
7	E	60	15	124.5 (IPE) (lit.,[11] 118—120)	97	$C_{17}H_{26}N_6O$	61.79 (61.96	7.93 8.03	25.44 25.17)
8	C	240	15		20			[b]	
9	D	120	15		80			[b]	
9	A	(13 h)	16	Oil	73	$C_{19}H_{28}N_6O_2$	HRMS: 372.2273 (372.2247)		

a) Conditions: A, without base in refluxing toluene; B, with *N*-methylpiperidine in refluxing toluene; C, with $NaHCO_3$ in a mixture of H_2O and CH_2Cl_2 (1 : 1); D, with NaOH in EtOH at room temperature; E, with NaOH in refluxing EtOH. *b*) The structure of each compound was confirmed by direct comparision with an authentic sample.

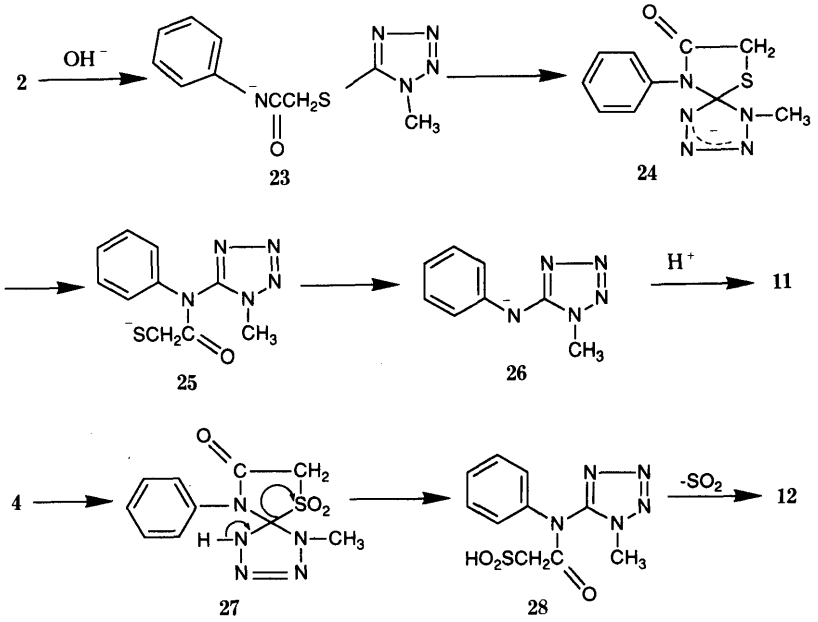


Chart 3

free amino derivatives. The ease of rearrangement was shown to depend on the leaving group in the order $SO_2 \gg SO > S$, which is the general order for base-catalyzed β-elimination of these groups in production of olefins from aliphatic sulfonyl, sulfinyl and sulfenyl compounds.[4] The rearrangement in this series may proceed through a stabilized intermediate **24**, as opposed to a transition state and an intermediate **27** (Chart 3). In the Smiles rearrangement of **2** in refluxing ethanolic sodium hydroxide the initial step of the reaction involves the removal of a proton from the $-NHCOCH_2-$ group of **2** to give an amide anion **23**, which then acts as the attacking nucleophile to give the anionic spiro-intermediate (**24**). The intermediate **24** is converted *via* **25** into an intermediate **26** and thence to the final product **11**. The rearrangement of **4** to **12** occurs through an intermediate **28** (not isolated) produced *via* the neutral spiro-intermediate **27**, followed by conversion into **12**, with loss of sulfur dioxide.

Experimental

Melting points were measured in a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 infrared spectrophotometer and proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on Hitachi R-90 (90 MHz) and Bruker AM 360 (360 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), m (multiplet), q (quartet), qt (quintet) or br (broad). All spectra were consistent with the assigned structures. Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained on a JMS-DX 300 spectrometer operating at an ionization potential of 70 eV. Combustion analyses were performed on a Perkin-Elmer Model 240C elemental analyzer.

2-Chloroacetamide (**17**) was commercially available. *N*-Substituted 2-chloroacetamides (**18**—**20** and **21**) were prepared by procedures described in the literature.[5-8]

Preparation of 2-(1-Methyl-1*H*-tetrazol-5-ylthio)acetamides (1, 2, 5, 6 and 7) 2-(1-Methyl-1*H*-tetrazol-5-ylthio)-*N*-phenylacetamide (**2**): A mixture of 2-chloro-*N*-phenylacetamide (**18**)[5] (1.19 g, 7 mmol), TzSH[3] (1.22 g, 10.5 mmol) and KOH (85% purity; 695 mg) in MeOH (20 ml) was stirred for 3 h at room temperature. After removal of the solvent, the residue was treated with H_2O to give a crystalline powder, which was recrystallized from AcOEt to give pure **2** (1.61 g). 2-(1-Methyl-1*H*-tetrazol-5-ylthio)acetamide (**1**), and 2-(1-methyl-1*H*-tetrazol-5-ylthio)-*N*-benzyl- and -*N*-phenethylacetamides (**5** and **6**) were prepared by a procedure similar to that used for **2**. 2-(1-Methyl-1*H*-tetrazol-5-ylthio)-*N*-[3-{3-(piperidinomethyl)phenoxy}propyl]acetamide (**7**) was prepared according to the procedure described in the literature.[8] The elemental analysis and spectral data are given in Tables I and III.

2-(1-Methyl-1*H*-tetrazol-5-ylsulfinyl)-*N*-phenylacetamide (**3**): A mixture of **2** (100 mg, 0.4 mmol) and *m*CPBA (80% purity; 86 mg, 0.4 mmol) in CH_2Cl_2 (25 ml) was stirred for 24 h at room temperature, washed with chilled saturated $NaHCO_3$ aqueous solution and brine successively, dried over $MgSO_4$ and evaporated *in vacuo* to give a crystalline powder. The powder was recrystallized from a mixed solvent of CH_2Cl_2 and isopropyl ether (IPE) to give pure **3** (86 mg).

2-(1-Methyl-1*H*-tetrazol-5-ylsulfinyl)-*N*-[3-{3-(piperidinomethyl)-phenoxy}propyl]acetamide (**8**) was prepared from **7** and 1 eq of *m*CPBA in the presence of methanesulfonic acid in CH_2Cl_2 according to the procedure described in the literature.[8] The elemental analysis and spectral data of **3** and **8** are given in Tables I and III.

2-(1-Methyl-1*H*-tetrazol-5-ylsulfonyl)-*N*-phenylacetamide (**4**): A mixture of **2** (100 mg, 0.4 mmol) and *m*CPBA (80% purity; 172 mg, 0.8 mmol) in CH_2Cl_2 (25 ml) was stirred for 3 h under reflux. Work-up by a procedure similar to that used for **3** gave pure **4** (99 mg).

2-(1-Methyl-1*H*-tetrazol-5-ylsulfonyl)-*N*-[3-{3-(piperidinomethyl)phenoxy}propyl]acetamide (**9**) was prepared from **7** and 2 eq of *m*CPBA in the presence of methanesulfonic acid in refluxing CH_2Cl_2 according to the procedure described in the literature.[8] The elemental analysis and spectral data of **4** and **9** are given in Tables I and III.

The Smiles Rearrangement of 2-(1-Methyl-1*H*-tetrazol-5-ylthio)acetamides and Their Sulfinyl and Sulfonyl Derivatives: General Procedures Method A: A solution of **9** (100 mg, 0.22 mmol) in toluene (10 ml) was refluxed for 13 h with stirring. After removal of the solvent, the residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (10 : 1) to give pure **16** as an oil (62 mg).

Method B: A mixture of **4** (450 mg, 1.6 mmol) and *N*-methylpiperidine (160 mg, 1.6 mmol) in toluene (50 ml) was refluxed for 30 min. After removal of the solvent, the residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (15 : 1) to give pure **12** as an oil (310 mg).

Method C: A solution of **3** (280 mg, 1.1 mmol) in a mixture of saturated $NaHCO_3$ aqueous solution and CH_2Cl_2 (50 ml) was vigorously stirred for 4 h. The reaction mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and brine successively, and dried over $MgSO_4$. After removal of the solvent, the oily residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (10 : 1) to give pure **11** (20 mg). Unchanged starting material **3** was recovered in 64% yield. Compound **8** was treated under conditions similar to those used for **3** to give **15**.

Method D: A solution of **4** (560 mg, 2.0 mmol) and NaOH (80 mg, 2.0 mmol) in EtOH (50 ml) was stirred at room temperature for 2 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and brine successively, dried over $MgSO_4$ and evaporated to give a crystalline material, which was recrystallized from AcOEt to give pure **11** (340 mg). Compound **9** was treated under conditions similar to those used for **4** to give **15**.

TABLE III. Spectral Data for 2-(1-Methyl-1*H*-tetrazol-5-ylthio)acetamides and Their Sulfinyl and Sulfonyl Derivatives

Compd.	IR ν cm^{-1} (KBr)	^{1}H-NMR δ	
		Solvent[a]	Chemical shift
1	3350 (NH), 1695 (C=O)	D	3.96 (3H, s), 4.03 (2H, s), 7.11—7.37 (1H, br), 7.46—7.72 (1H, br)
2	3290 (NH), 1675 (C=O)	C	3.96 (3H, s), 4.05 (2H, s), 6.98—7.59 (5H, m), 9.14—9.42 (1H, br)
3	3320 (NH), 1675 (C=O), 1050 (SO)	C	4.27 (3H, s), 4.57 (2H, dd, J=14 Hz), 6.98—7.58 (6H, m, Ar-H and NH)
4	3350 (NH), 1670 (C=O), 1350 and 1145 (SO_2)	D	4.34 (3H, s), 4.73 (2H, s), 7.13—7.56 (5H, m), 10.15—10.20 (1H, br)
5	3240 (NH), 1650 (C=O)	D	3.90 (3H, s), 3.97 (2H, s), 4.40 (2H, d, J=6 Hz), 7.23 (5H, m), 7.26—7.58 (1H, br)
6	3290 (NH), 1670 (C=O)	D	2.80 (2H, t, J=7 Hz), 3.54 (2H, q, J=7 Hz), 3.65 (1H, br), 3.86 (2H, s), 3.90 (3H, s), 7.10—7.30 (5H, m)
7	3300 (NH), 1640 (C=O)	C	1.39—1.47 (2H, m), 1.53—1.62 (4H, m), 1.98 (2H, qt, J=6.0 Hz), 2.33—2.41 (4H, m), 3.43 (2H, s), 3.47 (2H, q, J=6.0, 6.5 Hz), 3.90 (3H, s), 3.93 (2H, s), 3.98 (2H, t, J=6.0 Hz), 6.71—7.23 (5H, m)
8	1660 (C=O)	C	1.38—1.74 (6H, m), 1.74—2.13 (2H, m), 2.23—2.57 (4H, m), 3.27—3.73 (2H, m), 3.48 (2H, s), 3.99 (2H, t, J=6.0 Hz), 4.26 (3H, s), 4.37 (2H, dd, J=4.0 Hz), 6.62—7.53 (5H, m)
9	1690 (C=O), 1335 and 1260 (SO_2)	C	1.40—1.78 (6H, m), 2.01—2.27 (2H, m), 2.31—2.65 (4H, m), 3.38—3.67 (4H, m), 3.97 (3H, s), 4.05 (2H, t, J=6.0 Hz), 4.32 (2H, s), 6.63—7.58 (5H, m)

a) C, $CDCl_3$; D, dimethyl sulfoxide-d_6 (DMSO-d_6).

TABLE IV. Spectral Data for 5-Amino-1-methyl-1*H*-tetrazoles

Compd.	IR ν cm^{-1}		^{1}H-NMR δ	
			Solvent[a]	Chemical shift
10[b]	KBr	3320 (NH), 1665 (C=N)	D	3.71 (3H, s), 8.28 (1H, s), 8.29 (1H, s)
11[b]	KBr	3300 (NH), 1620 (C=N)	C	3.88 (3H, s), 6.20—6.38 (1H, br), 7.26—7.44 (5H, m)
12[b]	$CHCl_3$	1695 (C=O)	C	2.14 (3H, s), 3.93 (3H, s), 7.43 (5H, s)
13[b]	KBr	3350 (NH), 1620 (C=N)	C	3.74 (3H, s), 4.60 (3H, s), 7.35 (5H, s)
14[b]	KBr	3290 (NH), 1610 (C=N)	C	2.99 (2H, t, J=6.5 Hz), 3.65 (3H, s), 3.74 (2H, q, J=6.5 Hz), 3.90—4.09 (1H, br), 7.26 (5H, s)
15[c]	KBr	3280 (NH), 1630 (C=N)	C	1.42—1.46 (2H, m), 1.53—1.59 (4H, m), 2.16 (2H, qt, J=6 Hz), 2.31—2.41 (4H, m), 3.42 (2H, s), 3.67 (2H, q, J=6 Hz), 3.73 (3H, s), 4.09 (2H, t, J=6 Hz), 5.47 (1H, t, J=6 Hz), 6.70—7.20 (4H, m)
16[c]	Neat	1690 (C=O)	C	1.51—1.55 (2H, m), 1.62—1.69 (4H, m), 2.21 (2H, m), 2.41—2.49 (7H, m), 3.52 (2H, s), 3.92—4.03 (5H, br), 4.10 (2H, t, J=6 Hz), 6.79—7.31 (4H, m)

a) C, $CDCl_3$; D, DMSO-d_6. *b*) 90 MHz. *c*) 360 MHz.

Method E: A mixture of **1** (173 mg, 1 mmol) and NaOH (40 mg) in EtOH (10 ml) was stirred for 1 h under reflux. After removal of the solvent, the crude residue was washed with H_2O and recrystallized from H_2O to give pure **10** (92 mg). Compounds **2**, **5**, **6** and **7** were treated under conditions similar to those used for **1** to give corresponding rearrangement products (**11**, **13**, **14** and **15**).

The results and spectral data are given in Tables II and IV.

Acknowledgements We would like to express our thanks to the Material Analytical Center of ISIR, Osaka University, for spectral measurements and microanalyses. The present work was partially supported by a grant from the Research Program on "Creation of New Materials through Intelligent Design" of ISIR, Osaka University.

References

1) W. E. Truce, E. M. Kreider and W. W. Brand, "Organic Reactions," Vol. 18, Chap. 2, ed. by W. G. Dauben, John Wiley & Sons, Inc., New York, 1970, pp. 99.
2) H. W. Altland, *J. Org. Chem.*, **41**, 3395 (1976).
3) R. Stolle and Fr. Hencke-Stark, *J. Prakt. Chem.*, [2], **124**, 275 (1930); E. Lieber and J. Ramachandran, *Can. J. Chem.*, **37**, 101 (1959).
4) T. L. Wallace, J. E. Hofmann and A. Schriesheim, *J. Am. Chem. Soc.*, **85**, 2739 (1963); J. E. Hofmann, T. J. Wallace, P. A. Argabright and A. Schriesheim, *Chem. Ind.* (London), **1963**, 1243.
5) H. K. Iwamoto and deCamp Farson, *J. Am. Pharm. Assoc.*, **35**, 50 (1946) [*Chem. Abstr.*, **40**, 2440^5 (1946)].
6) E. Schraufstaetter and R. Goennert, *Z. Naturforsch*, **17b**, 505 (1962) [*Chem. Abstr.*, **57**, 13666 (1962)].
7) S. J. Hasan, V. S. B. Roa, S. Husain and P. B. Sattur, *Indian J. Chem.*, **9**, 1022 (1971).
8) I. Ueda, K. Ishii, K. Shinozaki, M. Seiki and M. Hatanaka, *Chem. Pharm. Bull.*, **39**, 1430 (1991).
9) R. J. Spear, *Aust. J. Chem.*, **37**, 2453 (1984).
10) W. G. Finnegan, R. A. Henry and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).
12) I. Ueda, M. Nagano and A. Akabane, Japan. Kokai Tokkyo Koho JP 58 90569 [*Chem. Abstr.*, **99**, 175769*d* (1983)].