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Synthesis of Fused *s*-Triazoles from 2-Methanesulfonyl-5-phenyl-1,3,4-oxadiazole and Binucleophilic Reagents by Means of Intramolecular Ring Transformation

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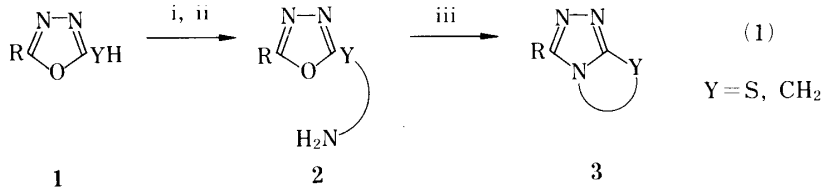
2-Methanesulfonyl-5-phenyl-1,3,4-oxadiazole (**4**) reacted with 3-aminopropanol and 2-aminoethanethiol in the presence of triethylamine to give displaced and rearranged products 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)- (**6b**) and 2-(2-thiazolin-2-yl)benzhydrazide (**9**), which were further cyclodehydrated by heating to give the corresponding fused *s*-triazoles (**7**) and (**10**), respectively. In the case of the reaction with a diaminoalkane only the 1 : 2 adduct (**8**) was obtained.

Keywords——intramolecular ring transformation; pyrolysis; 2-methanesulfonyl-5-phenyl-1,3,4-oxadiazole; binucleophilic reagent; 6,7-dihydro-5*H*-*s*-triazolo[3,4-*b*]oxazine; 5,6-dihydrothiazolo[2,3-*c*]-*s*-triazole

Some triazole-fused ring systems are known to possess biological activities (*e.g.*, insecticidal, bactericidal, *etc.*)[1,2] In order to access this class of compounds, we have developed the intramolecular ring transformation shown in Eq. 1.[3]



1 2 3

i: halo-ketone (or its equivalent) ii: amination iii: heat

Chart 1

During the course of our program, we were intrigued by the nucleophilic displacement of 2-methanesulfonyl-1,3,4-oxadiazole (**4**).[4] In view of this facile functionalization at the 2-position it seems reasonable to make use of **4** as a versatile starting material for the above synthetic route to fused *s*-triazoles; the reaction with binucleophilic reagents (**5**, Y=O, NH, S) may construct a requisite structure such as **2** in a single step, and the subsequent intramolecular ring transformation (iii in Eq. 1) might lead to the desired *s*-triazole. This report deals with the reactions of **4** with amino alcohols (**5a**, **b**), diamines (**5c**, **d**) and 2-aminoethanethiol (**5e**); in the last case we correct a previous erroneous assignment by other workers.

The reactions of **4** with 2-aminoethanol (**5a**) and 3-aminopropanol (**5b**) in the presence of triethylamine gave 2-(2-oxazolin-2-yl)-(**6a**) and 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)benzhydrazide (**6b**) in 41 and 72% yields, respectively, as the result of displacement and further rearrangement.[5] The hydrazide function of **6** was observed at around 3300 (NHNH) and 1620 (C=O) cm^{-1} in the infrared (IR) spectra and at δ 8.70 for **6a** and 8.50 for **6b** as a

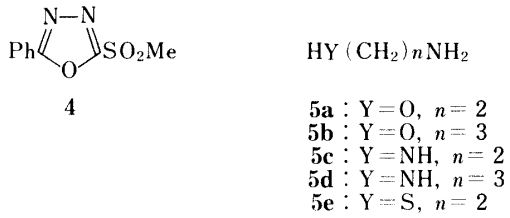


Chart 2

broad singlet (NHNH) in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. The cyclodehydration of **6b** to the 6,7-dihydro-5*H*-*s*-triazolo[3,4-*b*][1,3]oxazine **7** was performed by heating a solution of **6b** in *o*-dichlorobenzene at reflux temperature for 27 h. Structural assignment was based on spectral and elemental analyses; the ring closure was supported by the absence of absorptions due to amino and carbonyl groups in the IR spectrum and by the disappearance of an NHNH signal in the ^{1}H-NMR spectrum. Unfortunately the ring closure of **6a** did not take place under the same conditions.

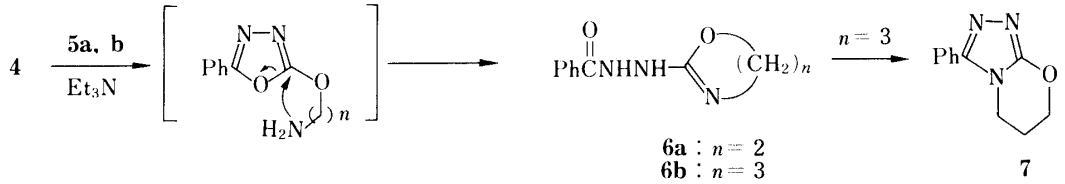


Chart 3

In the case of diaminoalkane (**5c, d**) the expected 1 : 1 adduct could not be obtained, but both amino groups of **5c** and **d** reacted with **4** to give the 1 : 2 adduct **8** which was identified from the mass spectrum. A similar result was obtained even with a large excess of diamine.

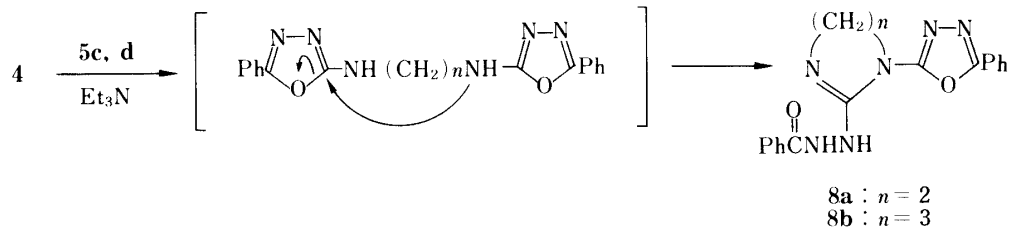


Chart 4

In the same manner as with the amino alcohols (**5a, b**) the reaction of **4** with 2-aminoethanethiol (**5e**) gave 2-(2-thiazolin-2-yl)benzhydrazide (**9**) in 73% yield; the structure of **9** was readily deduced from a spectral comparison with the analogous hydrazide which we had in hand.[3] On pyrolysis (neat, 280 °C/5 mmHg), the obtained hydrazide **9** was cyclodehydrated to the desired 5,6-dihydrothiazolo[2,3-*c*]-*s*-triazole **10** in 22% yield. This type of ring closure has already been demonstrated by us.[3]

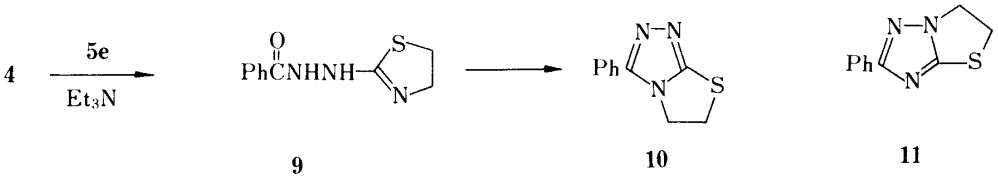


Chart 5

Indian chemists have reported cyclizations of 2-benzoylhydrazino-2-thiazoline hydrobromide and of 5-mercapto-3-phenyl-*s*-triazole with 1,2-dibromoethane, where the products ("A" and "B") were assigned as **10** and isomeric 2-phenyl-5,6-dihydrothiazolo[3,2-*b*]-*s*-triazole (**11**), respectively.[2] We repeated their experiments. However, the synthesized product "A" was not identical with our product in terms of mp, thin-layer chromatography (TLC), and IR and ^{1}H-NMR spectra; the characteristic absorptions at 1440 and 1475 cm^{-1} of "A" were quite different from those at 1435, 1465 and 1480 cm^{-1} of our product in the IR spectra. In the ^{1}H-NMR spectrum of "A", a D_2O-exchangeable broad singlet at δ 8.68 together with signals at δ 3.35—4.65 (4H, m) and 7.27—8.25 (5H, m) is decisively incompatible with the structure assigned by them. However, the IR and ^{1}H-NMR spectra of the product "B" were consistent with those of our product. As the present route to **10** should be valid by analogy with a previous example,[3] the product "A" is not **10** and the product "B" should be reassigned as **10**.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240B elemental analyzer. The ^{1}H-NMR spectra were determined with a JEOL C60HL spectrometer, and chemical shifts are reported in δ units downfield from internal tetramethylsilane. The IR spectra were determined on a JASCO IRA-1 spectrometer, and data are reported in units of cm^{-1}. All of the crystalline products were scanned in KBr disks. Mass spectra (MS) were obtained with a Hitachi RMS-4 mass spectrometer at 70 eV. Pyrolysis was carried out with a Shibata GTO-250 glass tube oven.

2-(2-Oxazolin-2-yl)benzhydrazide (6a)——2-Aminoethanol (0.24 ml, 4 mmol) and triethylamine (0.28 ml, 2 mmol) were added to a solution of **4**[4] (0.45 g, 2 mmol) in THF (15 ml) at room temperature and the mixture was stirred for 12 h. After removal of the solvent, the residue was washed with water and the resulting solids were collected to give 0.17 g (41%) of **6a**, mp 132—135 °C (EtOH–H_2O). IR ν_{max}: 3250, 3090, 2940, 2860, 1620, 1555, 1490, 1445. ^{1}H-NMR (CF_3COOH): 4.0—4.9 (4H, m, CH_2), 7.4—8.2 (5H, m, Ph), 8.75 (2H, br s, NHNH). *Anal.* Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.88; H, 5.23; N, 20.30.

2-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)benzhydrazide (6b)——By the same treatment as above, **6b** was obtained in 72% yield from **4** and 3-aminopropanol: mp 132—134 °C (EtOH–H_2O). IR ν_{max}: 3350, 3230, 3080, 2940, 2870, 1620, 1575, 1485, 1445. ^{1}H-NMR (CF_3COOH): 2.39, 3.90 and 4.68 (each 2H, quintet, tt, respectively, J=7 Hz, CH_2), 7.6—8.2 (5H, m, Ph), 8.50 (2H, br s, NHNH). *Anal.* Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.33; H, 5.89; N, 18.95.

3-Phenyl-6,7-dihydro-5*H*-*s*-triazolo[3,4-*b*][1,3]oxazine (7)——A solution of **6b** (0.22 g, 1 mmol) in *o*-dichlorobenzene (7 ml) was heated under reflux for 27 h. After removal of the solvent *in vacuo*, the residue was chromatographed on a silica gel column ($CHCl_3$/EtOH = 10/1) to give 0.11 g (54%) of **7**, mp 185—187 °C. IR ν_{max}: 2940, 1550, 1495, 1460, 1440. ^{1}H-NMR ($CDCl_3$): 2.18, 4.12 and 4.45 (each 2H, quintet, tt, respectively, J=6 Hz, CH_2), 7.3—7.9 (5H, m, Ph). *Anal.* Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.81; H, 5.61; N, 20.60.

Reactions of 4 with Diamines (5c, d)——The products **8a** and **8b** were obtained in 44% and 26% yields from **4** and ethylenediamine (**5c**) and from **4** and 1,3-diaminopropane (**5d**), respectively, by the same procedure as for **6a** except that stirring was carried out for 3 d (**5c**) or 9 d (**5d**). The yields were raised to 75% and 41%, respectively, when the ratio of **4** to the diamine was 2 : 1. **8a**: mp 250—252 °C (EtOH). IR ν_{max}: 3240, 3040, 1620, 1600, 1555, 1480, 1440. ^{1}H-NMR (CF_3COOH): 4.0—4.6 (4H, m, CH_2), 7.4—8.2 (10H, m, Ph), 9.05 (2H, m, NHNH). MS *m/e* (%): 348 (M^+, 32), 105 (87), 77 (100). *Anal.* Calcd for $C_{18}H_{16}N_6O_2$: C, 62.14; H, 4.80; N, 23.87. Found: C, 62.06; H, 4.63; N, 24.12. **8b**: mp 215—217 °C (EtOH). IR ν_{max}: 3225, 3030, 2950, 2870, 1620, 1560, 1485, 1465, 1440. ^{1}H-NMR (CF_3COOH): 2.2—2.7 (2H, m, CH_2), 3.6—4.3 (4H, m, NCH_2), 7.3—8.1 (10H, m, Ph), 8.95 (2H, br s, NHNH). MS *m/e* (%): 362 (M^+, 8), 105 (100), 77 (68). *Anal.* Calcd for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19. Found: C, 63.02; H, 5.14; N, 23.01.

2-(2-Thiazolin-2-yl)benzhydrazide (9)——2-Aminoethanethiol (0.18 g, 2.3 mmol) and triethylamine (0.33 ml, 2.4 mmol) were added to a solution of **4** (0.50 g, 2.2 mmol) in THF (20 ml) and the mixture was stirred at room temperature for 7 h. After removal of the solvent, the residue was washed with water and the resulting solids were collected by filtration to give 0.24 g of **9**. An additional 0.12 g (total yield, 73%) of **9** was extracted from the washings with $CHCl_3$: mp 210—211 °C (EtOH–H_2O). IR ν_{max}: 3180, 3100, 2910, 1600, 1570, 1535, 1490. ^{1}H-NMR (CF_3COOH): 3.80 and 4.32 (each 2H, t, J=7 Hz, CH_2), 7.4—8.1 (5H, m, Ph), 8.88 (2H, br s, NHNH). *Anal.* Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.27; 5.14; N, 18.83.

3-Phenyl-5,6-dihydrothiazolo[2,3-*c*]-*s*-triazole (10)——The hydrazide **9** (0.30 g, 1.4 mmol) was heated at 280 °C under a vacuum (5 mmHg) for 30 min in a glass tube oven with a trap bulb heated at 200 °C. After cooling to room

temperature, the trapped product was chromatographed on a silica gel column (AcOEt) to give 60 mg (22%) of **10**, mp 199—201 °C. IR ν_{max}: 2960, 1630, 1480, 1465, 1435. ^{1}H-NMR ($CDCl_3$): 3.9—4.6 (4H, m, CH_2), 7.3—7.9 (5H, m, Ph). *Anal.* Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.30; H, 4.58; N, 20.34.

References and Notes

1) D. S. Shridhar, M. Jogibhukta, P. P. Joshi, and P. Gopal Reddy, *Indian J. Chem.*, **20B**, 132 (1981).
2) K. S. Dhaka, J. Mohan, Vijay K. Chadha, and H. K. Pujari, *Indian J. Chem.*, **12**, 485 (1974).
3) *a*) T. Sasaki, E. Ito, and I. Shimizu, *J. Org. Chem.*, **47**, 2757 (1982); *b*) T. Sasaki, M. Ohno, E. Ito, and K. Asai, *Tetrahedron*, **40**, 2703 (1984).
4) R. Madhavan and V. R. Srinivasan, *Indian J. Chem.*, **7**, 760 (1969).
5) Such consecutive reactions in a single procedure have often been seen in the reductive amination of some keto-1,3,4-oxadiazoles; see ref. 3*b*.