HETEROCYCLES, Vol. 31, No. 9, 1990

THE REACTION OF 3-SUBSTITUTED 2-(*N*-CYANOIMINO)THIAZOLIDINE DERIVATIVES WITH HYDRAZINE: NOVEL SYNTHESIS OF TRIAZOLES

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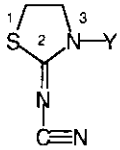
Abstract - The reaction of 3-substituted 2-(*N*-cyanoimino)thiazolidine (NCT) derivatives with hydrazine hydrate afforded two types of 1,2,4-triazoles *via* a selective C_2-S or C_2-N_3 bond fission, in which the selectivity was controlled by the N_3-substituent.

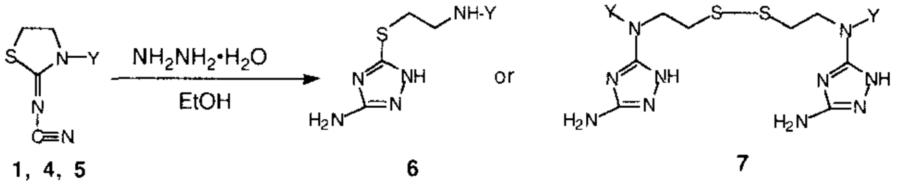
2-(*N*-Cyanoimino)thiazolidine (NCT)(1)[1] has various functionalities in its small molecule, and therefore it is expected to exhibit diverse reactivities and to be a useful synthon for many heterocycles. In the previous papers, we have reported the synthesis of imidazo[*2,1-b*]thiazole and thiazolo[*3,2-b*]-1,2,4-triazole derivatives by the cyclization of the compounds bearing active methylene group at N_3 (**2**) and through the N_3-amination of **1**, respectively, and also reported a selective cleavage of N_3-CO bond of 3-acyl-NCT (**3**) by amines, alcohols, and thiols to afford amides, esters, and thiolesters, respectively.[2] As one of the continuous studies on reactivity of NCT derivatives, we now report a novel synthetic route to 1,2,4-triazoles by the reaction of compound (**1**) and 3-substituted NCTs (**4**[3] and **5**[2]) with hydrazine hydrate *via* the N_3-substituent-directed bond fission at C_2-S or C_2-N_3 (Scheme 1).



1: Y = H
2: Y = CH_2Z
(Z = electron withdrawing group)
3: Y = COR
4: Y = SO_2R
5: Y = alkyl (R)

Scheme 1

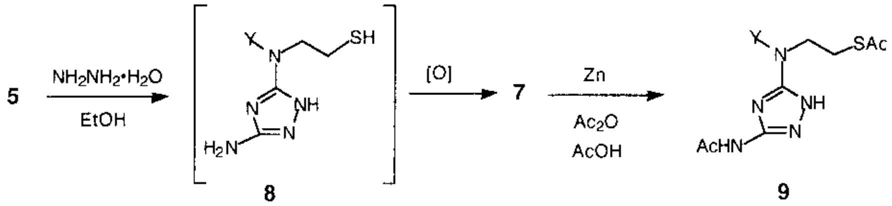
TABLE. The Reaction of 3-Aralkylsulfonyl-, Nonsubstituted and 3-Alkyl-NCTs with Hydrazine Hydrate



Y	yield (%)		mp	ir	^{1}H-nmr
	6*	**7***	(°C)	(KBr: cm^{-1})	(DMSO-d_6: δ)
$MeSO_2$	61	-	134.5-136	3400, 3300- 2800, 1650, 1580, 1500, 1140	2.93 (s, 3H) 2.99-3.41 (m, 4H) 5 84-6.00 (br s, 1H) 7.00-7.28 (m. 1H)
p-$MeC_6H_4SO_2$	67	-	140-141.5	3400, 3300, 1660, 1600, 1500, 1300, 1150	2.36 (s, 3H) 2.92-3.03 (m, 4H) 5.91-6.00 (br s, 2H) 7.28-7.70 (AA'BB', 4H)
p-$ClC_6H_4SO_2$	58	-	137-137.5	3400-3300, 1660, 1600, 1500, 1300, 1280, 1150	2.90-3.37 (m, 4H) 5.91-6.01 (br s, 1H) 7.56-7.88 (AA'BB', 4H)
H	-	90	231-233	3430, 3320, 1625, 1610, 1595, 1560, 1520	2.79 (m, 4H) 3.28 (m, 4H) 5.50-6.75 (m, 8H)
Me	-	66	206-208	3430, 3320, 1640, 1610, 1560, 1540	2.82 (s, 6H) 2.82-2.96 (m, 4H) 3.40-3.56 (m, 4H) 4.60-8.00 (m, 6H)
i-Pr	-	85	157-158.5	3450, 3300, 1640, 1610, 1550	1.18 (d, *J*=7 Hz, 12H) 2.83-3.00 (m, 4H) 3.40-3.58 (m, 4H) 4.13 (hep, *J*=7 Hz, 2H) 4.78 (br s, 6H)
$PhCH_2$	-	64	200-203	3450, 3300, 1650, 1640, 1610, 1600, 1560	2.67-2.83 (m, 4H) 3.30-3.46 (m, 4H) 4.45 (s, 4H) 5.10-6.00 (m, 6H) 7.20 (s, 10H)

* Satisfactory microanalyses were obtained for all compounds.

Treatment of 3-methanesulfonyl-NCT (**4**: R=Me) with 3 equivalents of hydrazine hydrate in boiling ethanol gave the 1,2,4-triazole (**6**: R=Me) in 61% yield. Other 3-arylsulfonyl-NCTs (**4**: R=*p*-MeC_6H_4, *p*-ClC_6H_4) also gave the similar results. On the other hand, the reaction of the nonsubstituted NCT (**1**) with hydrazine hydrate under the same conditions produced another type of 1,2,4-triazole (**7**: Y=H) exclusively in 90% yield. The same type of 1,2,4-triazoles (**7**) was also obtained in the case of 3-alkyl-NCTs (**5**). The results are summarized in Table. Since more rapid formation of the disulfides (**7**) is observed in an oxygen atmosphere than in air, compound (**7**) is assumed to be generated by the air oxidation of the initially formed thiol (**8**). Compound (**7**) was treated with zinc in a mixture of acetic acid and acetic anhydride to afford a triacetate (**9**; Y=Ac: when Y=H in **7**) or a diacetate (**9**; Y=alkyl)[4](Scheme 2).

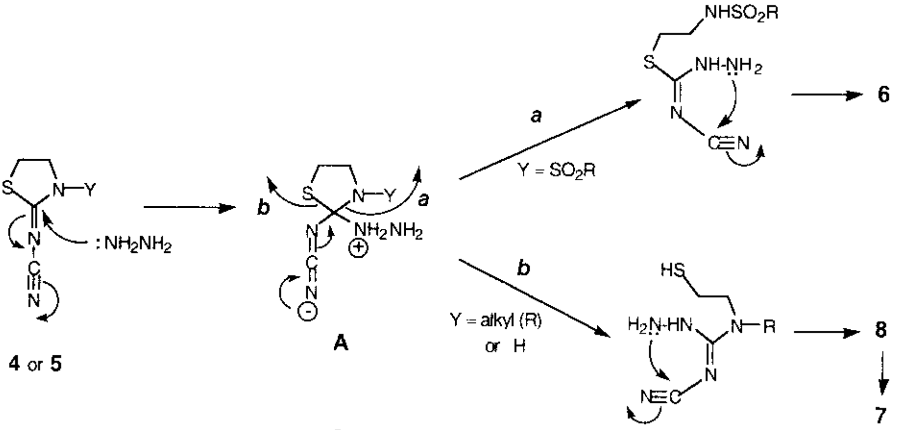


Scheme 2

In these ractions, the addition of hydrazine at C_2 would afford a carbodiimide intermediate (**A**). When the carbodiimide part returns to a cynoimine, a bond fission (***a*** or ***b***) would occur. Namely, in the 3-aralkylsulfonyl derivatives (**4**), the C_2-N_3 bond fission (***a***) followed by the intramolecular cyclization between the nitrile group and the hydrazine moiety gives the triazole (**6**). Contrary to the sulfonylated derivatives, the C_2-S bond cleavage (***b***) takes place in nonsubstituted or 3-alkyl-NCT (**1** or **5**), and subsequent intramolecular cyclization produces a triazole thiol (**8**), which is readily oxidized in the air to affoed the disulfide (**7**)(Scheme 3).

The fission ***a*** would afford a nitrogen anion and the fission ***b*** afford a thio anion. When Y is a sulfonyl group, the former is more stable than the latter. On the other hand, when Y is a hydrogen or an alkyl, the latter is more stable. Accordingly, the N_3-substituent controlled the direction of the bond cleavage and different type 1,2,4-triazoles were obtained.

As NCT is obtainable by one-step from the commercially available starting materials and various alkyl or sulfonyl group can easily be introduced at N_3, new facile synthetic route to two types of 1,2,4-triazoles were developped by changing the substituent of N_3.[5]



Scheme 3

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2. C. Iwata, M. Watanabe, S. Okamoto, M. Fujimoto, M. Sakae, M. Katsurada, and T. Imanishi, *Synthesis*, **1988**, 261; *Idem*, *Heterocycles*, 1988, **27**, 323.
3. 3-Aralkylsulfonyl-NCTs (**4**) were easily obtained by the reaction of NCT (1) with corresponding aralkylsulfonyl chloride in $CHCl_3$ in the presence of Et_3N. For example Y=SO_2Me: Yield 86%, mp 143-145 °C; Y=*p*-$MeC_6H_4SO_2$: Yield 81%, mp 154.5-155.5 °C; *p*-$ClC_6H_4SO_2$: Yield 79%, mp 181.5-183.0 °C
4. **9** (Y=CH_2Ph): Yield 85%; mp 109-110 °C; ir ($CHCl_3$: cm^{-1}) 3510, 3390, 1740, 1710, 1640, 1590,1580; ^{1}H-nmr ($CDCl_3$: δ) 2.31, 2.48 (each s, 3H), 2.98-3.14 (m, 2H), 3.35 (m, 2H), 4.61 (s, 2H), 6.82 (br s, 2H), 7.28 (s, 5H). **9** (Y=Me): Yield quant.; mp 89.5-91.0 °C; ir ($CHCl_3$: cm^{-1}) 3500, 3380, 1700, 1630, 1590; ^{1}H-nmr ($CDCl_3$: δ) 2.35, 2.51, 3.01 (each s, 3H), 3.08-3.16 (m, 2H), 3.41 (m, 2H), 6.63 (br s, 2H). **9** (Y=Ac): Yield 33%; mp 127-130 °C; ir ($CHCl_3$: cm^{-1}) 3500, 3440, 1690, 1680, 1630, 1570; ^{1}H-nmr ($CDCl_3$: δ) 2.31, 2.37, 2.60 (each s, 3H), 3.13-3.22 (m, 2H), 3.92-4.09 (m, 2H), 4.01 (br s, 2H).
5. Many kinds of 1,2,4-triazoles are known to exhibit various biological activities (*e.g.*, É. Bozó, G. Szilágyi, and J. Janáky, *Arch. Pharm.*, 1989, **322**, 583; R. Boehm and C. Karow, *Pharmazie*, 1981, **36**, 243 and references cited therein). There have been several methods for the synthesis of 1,2,4-triazoles to date (*e.g.*, V. J. Ram, L. Mishra, N. H. Pandey, D. S. Kushwaka, L. A. C. Pieters, and A. J. Vlietinck, *J. Heterocycl. Chem.*, 1990, **27**, 351; A. Bojilova, N. A. Rodios, C. A. Tsoleridis, and N. E. Alexandrou, *ibid.*, 1990, **27**, 735; Y. Miyamoto and C. Yamazaki, *ibid.*, 1989, **26**, 327 and 763; W. A. Kleischick, J. E. Dunbar, S. W. Snider, and A. P. Vinogradoff, *J. Org. Chem.*, 1988, **53**, 3120; H. Kristinsson and T. Winkler, *Helv. Chim. Acta*, 1983, **66**, 1129; C. Temple, Jr., "The Chemistry of Heterocyclic Compounds," Vol. 37, ed. by J. A. Montgomery, John Wiley & Sons, New York, 1981 and references cited therein).

Received, 26th July, 1990