Tetrahedron Letters No.33, pp. 2875-2877, 1969. Pergamon Press. Printed in Great Britain.

UNUSUAL HETEROCYCLIC TRANSFORMATION IN LIQUID AMMONIA[1]

Akira Takamizawa and Saichi Matsumoto

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

(Received in Japan 16 May 1969; received in UK for publication 16 June 1969)

Cycloadditions of alkylisothiocyanates with N-substituted-4-methyl-5-β-hydroxyethylthiazolium ylids were previously reported to give the fused heterocycles (Ia-d) containing a new spiro ring system.[2] This communication describes a facile transformation of the cycloadducts to the thiirane derivatives (IIa-c) involving a novel carbanion reaction catalyzed by liquid ammonia.

When the cycloadduct Ia (R_1 = Ph, R_2 = Me) was allowed to stand in liquid ammonia in a sealed tube for 20 hours at room temperature, the thiazolidine ring was smoothly cleaved and a new compound IIa (R_1 = Ph, R_2 = Me) [$C_{12}H_{11}N_3S_3$, m.p. 118-121°] was obtained in 83% yield.[3] The spectral data of IIa [IR ν_{max}^{nujol} cm^{-1}: 1674 (C=N), 1290 (C=S), UV λ_{max}^{EtOH} mμ (log ε): 274 (3.99), NMR ($CDCl_3$) τ: 6.15, 6.23 (2 x N-Me), 2.4-2.9 (5H Ar.)] were in good agreement with the proposed structure. On heating in toluene at 100° for 30 min., sulfur was readily extruded from IIa to give a quantitative yield of 2-phenyl-4,6-dimethyldihydroimidazo[4,5-d]thiazole-5-thione (IIIa) (R_1 = Ph, R_2 = Me) which is obtainable directly from Ia by heating in glac. AcOH at 100° or by treating with NaOEt in EtOH.[2]

Reaction of p-nitrophenyl derivative Ib (R_1 = Ph-NO_2 (p), R_2 = Me) in liquid ammonia at room temperature proceeded more rapidly to give IIb (R_1 = Ph-NO_2 (p), R_2 = Me) [$C_{12}H_{10}N_4O_2S_3$, m.p. ca. 120° (decomp.), IR ν_{max}^{nujol} cm^{-1}: 1673 (C=N), 1280 (C=S), UV λ_{max}^{EtOH} mμ: 281.5] within 3 hours, although the isolated yield of the product varied from 15-30% because of its considerable instability. Thermal desulfurization of IIb to IIIb (R_1 = Ph-NO_2 (p), R_2 = Me, m.p. >270°) was also carried out quantitatively at 100°.

In case of p-methoxyphenyl derivative Ic (R_1 = Ph-OMe (p), R_2 = Me), however, the thiazolidine ring was found to be more stable in liquid ammonia than those of Ia and Ib. Thus, the action of liquid ammonia upon Ic for 20 hours at room temperature resulted in the formation of only a trace quantity of IIc (R_1 = Ph-OMe (p), R_2 = Me) which could not be isolated in a pure state but was confirmed by the desulfurization to

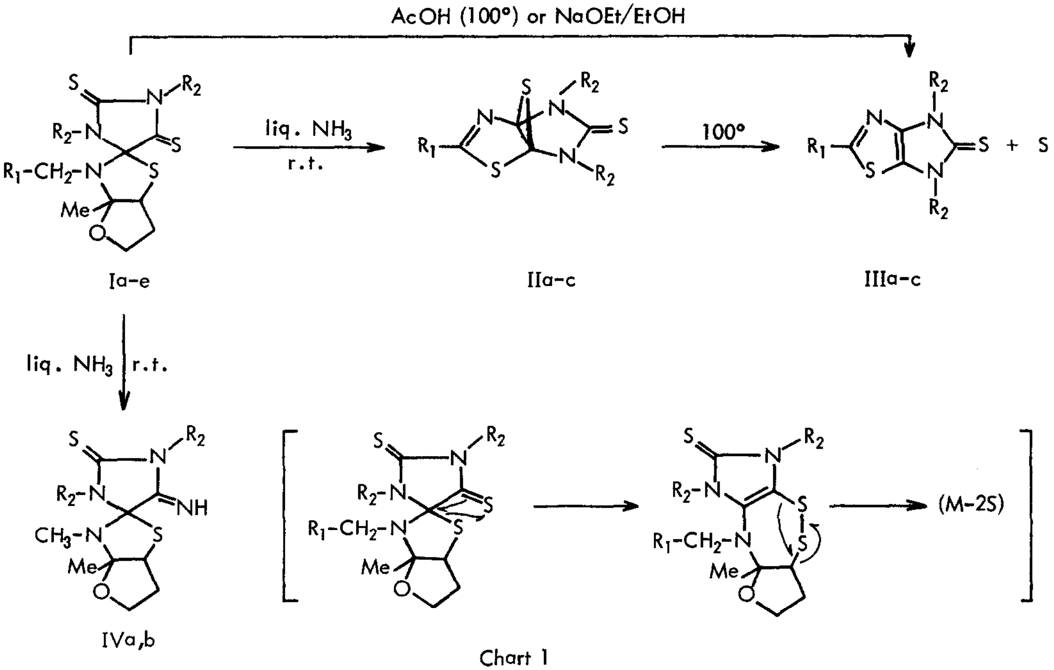

Chart 1

IIIc (R_1 = Ph-OMe (p), R_2 = Me) [$C_{13}H_{13}N_3OS_3$, m.p. 240–243°] by heating the reaction mixture. IIIc was also derivable directly from Ic in 20% yield by heating in glac. AcOH at 100°.

On the other hand, by the treatment of N-methyl derivatives Id (R_1 = H, R_2 = Me) and Ie (R_1 = H, R_2 = Ph-Cl (p)) with liquid ammonia for 20 hours at room temperature, the whole ring system was found to be quite stable and, in stead of the thiirane type product, the corresponding imino derivatives IVa (R_2 = Me) [$C_{11}H_{18}N_4OS_2$, m.p. 118-120°, IR ν_{max}^{nujol} cm^{-1}: 3245 (NH), 1669 (C=N), 1280 (C=S), UV λ_{max}^{EtOH} mμ: 271] (5%) and IVb (R_2 = Ph-Cl (p)) [$C_{21}H_{20}N_4OS_2Cl_2$, m.p. 120-123°, IR ν_{max}^{nujol} cm^{-1}: 3240 (NH), 1670 (C=N), 1283 (C=S), UV λ_{max}^{EtOH} mμ: 273] (56%) were obtained respectively. Assignments of the structures IVa,b were based both on the spectral data cited above and on the formation of thioureas RNHCSNHR (R = Me or Ph-Cl (p)) by treating with aq. HCl. Mass spectra of IVa,b showed that their fragmentations were essentially same as those of the original compounds Ia-e[4] except that the ions corresponding to (M-2S) which is a typical fragment observed for Ia-e were absent. This indicated therefore that the proposed mechanism of the formation of this unusual ion is valid and, as a result, confirmed the structures of IVa,b.

The foregoing results indicate that the ring cleavage reactions of Ia-c leading to IIa-c may largely be

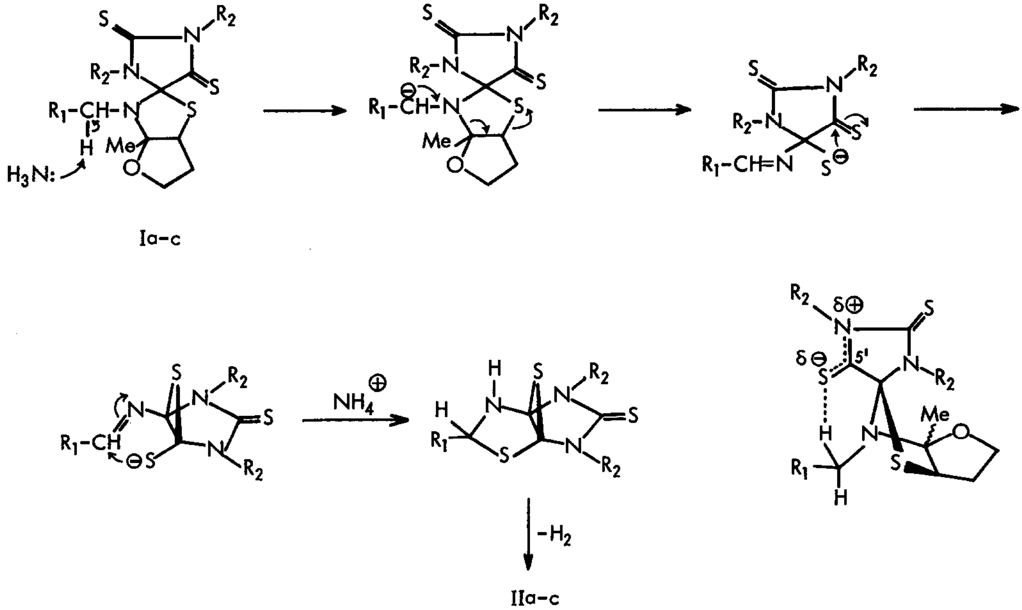

Chart 2

influenced by the stability of carbanion α to the thiazolidine nitrogen. Many carbanion reactions in liquid ammonia usually require a strong base such as metal amide as the proton acceptor. It is of interest to note that the present cleavage reactions however proceeded in the absence of the strong base. Although details are to be further investigated, the present reactions will probably be initiated by the abstraction of the benzylic proton by liquid ammonia, and a possible path way is illustrated in the Chart 2. This enhanced reactivity at the benzylic position of Ia-c may be attributed to the ring strain or more likely to the neighbouring group participation by the thiocarbonyl group on 5' position.

The authors acknowledge their indebtedness to Dr. K. Takeda, Director of this laboratory, for his encouragement and also to Dr. Y. Nakagawa for his valuable discussions on the mass spectra.

REFERENCES

1. A part of this work was presented at the 88th Assembly of the Pharmaceutical Society of Japan, April, 1969 (Nagoya).
2. A. Takamizawa, K. Hirai and S. Matsumoto, Tetrahedron Letters 4027 (1968); A. Takamizawa, K. Hirai, S. Matsumoto, S. Sakai and Y. Nakagawa, Chem. Pharm. Bull. (Tokyo), in press.
3. The counter part which would arise from the hydrofuran moiety of the starting material was obtained as a complex mixture consisting of nitrogen containing substances which could not be characterized.
4. Y. Nakagawa, S. Matsumoto and A. Takamizawa, Mass Spectrometry (Japan), in contribution.