Tetrahedron Letters, Vol.22, No.24, pp 2285 - 2288, 1981
Printed in Great Britain

0040-4039/81/242285-04$02.00/0

DIAMINOTHIAZOLES AND DIAMINOTHIOPHENES

Masataka Yokoyama*, Masahiko Kurauchi, and Tsuneo Imamoto

Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho,
Chiba City, Japan

Summary: Several 2,4-diaminothiazoles and 2,4-diaminothiophenes could be easily obtained by metallation using LDA from aminomethylthiomethylenecyanamides **2** and aminomethylthiomethylenemalononitrile, respectively.

Five-membered aromatic heterocycles having electron-donating substituents such as amino and hydroxy groups have been generally known to be unstable.[1] Therefore, a few 2,4-diaminothiazoles[2-6] and 2,4-diaminothiophenes[7] have been reported so far.

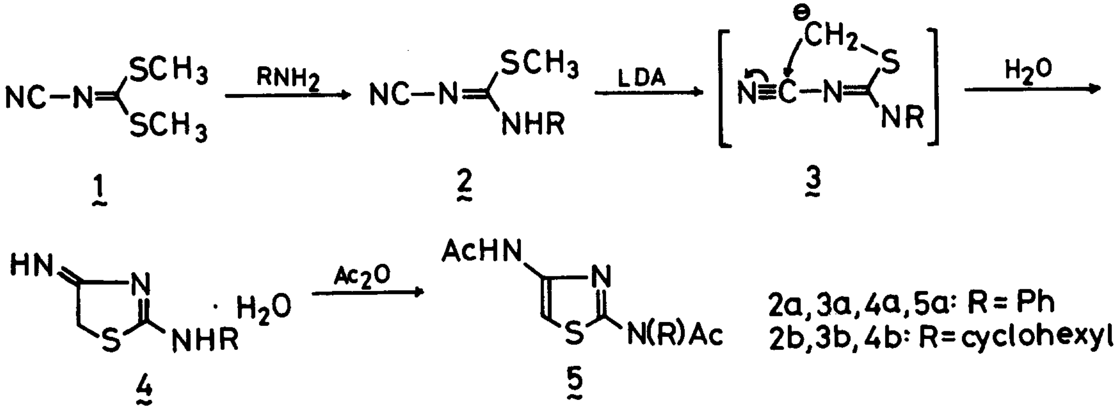
We intended to prepare such unstable heterocycles by a convenient procedure and found that they could be readily prepared by metallation using lithium diisopropylamide (LDA) from aminomethylthiomethylenecyanamides (**2** and **2'**)[8]or aminomethylthiomethylenemalononitrile.

The following preparation of 4-imino-2-phenylamino-4,5-dihydrothiazole **4a**[9] is representative. To a solution of LDA (2.5 mmol) in 5 ml of dry THF was added phenylaminomethylthiomethylenecyanamide **2a** (191 mg, 1 mmol) in 2 ml of dry THF. The mixture was stirred for 20 min under nitrogen atomosphere at - 30°C and then quenched with 10 ml of water to give white precipitates, which were collected and washed with ether-hexane (1:1). Recrystallization from pyridine-H_2O afforded white plates of mp 164-165°^{dec}C (**4a**) in 71 % yield.

Similarly, 2-cyclohexylamino-4-imino-4,5-dihydrothiazole **4b** was obtained in 75 % yield. These compounds **4** were unchanged in crystalline state in a vacuum desiccator at least one week, but they decomposed rapidly in a solution. Acetylation of **4a** with acetic anhydride afforded a stable derivative, 4-acetylamino-2-acetylphenylaminothiazole **5a**[10] as white prisms of mp 218-220°^{dec}C (recry. from benzene) in 80 % yield.

In contrast to the above results, an unusual cyclization occurred when compounds **2'** derived from dimethyl cyanodithioimidocarbonate **1**[11] with secondary amines were used. That is, treatment of **2'** with LDA at - 30°C gave 2-amino-5-cyano-4-substituted aminothiazoles **12** instead of **4**.

Scheme I



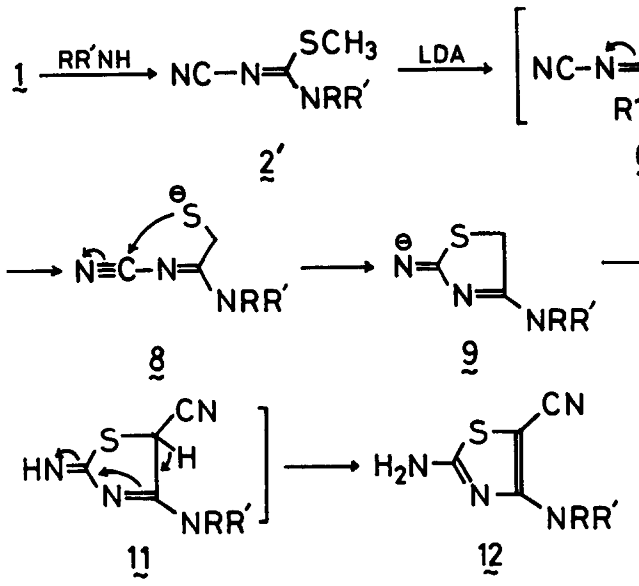
The structures of 12 were determined on the basis of spectroscopic evidence together with elemental analyses. The nmr spectrum (DMSO-d_6) of 12c showed a broad amino signal and a singlet methylene signal for morpholine at δ8.0 and 3.65, respectively. In its ir spectrum a strong CN stretching band appeared at 2170 cm^{-1}. The positions of the three functional groups on the thiazole ring were assigned on the basis of mass fragmentation patterns. The mass data of 12 showed fragmentation pattern to an ion (M- $H_2NC{=}N)^{\oplus}$ together with a parent and other ions.

Furthermore, 2-amino-5-cyano-4-methylthiothiazole 13[12] was prepared directly from 1 by the present reaction as white needles of mp 183-184°C (recry. from $CHCl_3$) in 30 % yield. This compound 13 was compared with its isomer 14 which corresponded to 4. Compound 14 was synthesized from the cyclization reaction of cyanomethylthiomethylthiomethylenecyanamide according to the method described in the literature.[13] On comparison with mass data of 13 and 14, their characteristic fragment ions were (M- $H_2NC{=}N)^+$ and (M- $H_3CSC{=}N)^+$, respectively. These results support the structures of 12 and 13.

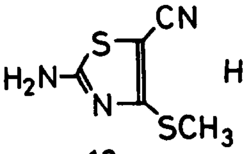
The unusual cyclization to form 12 can be explained by assuming several intermediates 6, 7, 8, 9, 10, and 11. The reaction pathway is very interesting (Scheme II); an anion $SCH_2^{\ominus}$ attacks methylene carbon to form a thiiran ring 7, followed by ring-opening to generate an anion 8, which in turn creates a thiazoline ring 9. The intermediate 9 is then converted to 10. This key species 10 abstracts cyano group from remaining 2' to afford 12 via 11.

On the other hand, a simple intramolecular cyclization is considered to occur exclusively in the reaction of 2 derived from 1 with primary amines. In this case two equivalents of LDA generate a dianion 3 and its $SCH_2^{\ominus}$ attacks directly cyano group to form thiazoline ring (Scheme I).

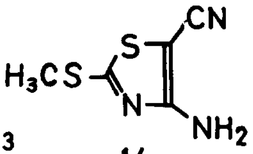
Scheme II



2'c, 6c, ...12c: NRR'= morpholino
2'd, 6d, ...12d: NRR'= piperidino



13



14

In order to extend this reaction, phenylaminomethylthiomethylenemalononitrile[14] was treated with LDA to give 3-cyano-4-imino-2-phenylamino-4,5-dihydrothiophene[15] as white needles of mp 197-$198^{\circ\,\mathrm{dec}}$C (recy. from pyridine-$H_2O$) in 56 % yield.

Aminothiazoles synthesized by the present procedure are as follows; 2-cyclohexylamino-4-imino-4,5-dihydrothiazole 4b[16] (white plates of mp 147-$148^{\circ\,\mathrm{dec}}$C, recry. from pyridine-$H_2O$); 2-amino-5-cyano-4-morpholinothiazole 12c[17] (white needles of mp 194-195°C, recry. from $CHCl_3$, yield 33 % based on 2'c); 2-amino-5-cyano-4-piperidinothiazole 12d[18] (white prisms of mp 145-146°C, recry. from benzene, yield 30 % based on 2'd).

Judging from the properties of 2,4-diaminothiazoles synthesized, it is deduced that first, diaminothiazoles exist exclusively in 4-imino structures and can be isolated as somewhat stable crystals containing a water of crystallization, and second, introduction of cyano group or acylation of amino groups can stabilize the thiazole ring.

References and Notes

All Compounds synthesized showed satisfactory results of elemental analyses.

(1) A.R.Katritzky and J.M.Lagowski, "The Principles of Heterocyclic Chemistry", Metheuen & Co (1967).

(2) A.H.Land, C.Ziegler, and J.M.Sprague, J. Org. Chem., 11, 617 (1946).

(3) W.Davies, J.A.Maclaren, and L.R.Wilkinson, J. Chem. Soc., 3491 (1950).

(4) R.M.Dodson and H.W.Turner, J. Amer. Chem. Soc., 73, 4517 (1951).

(5) K.Gewald, P.Blauschmidt, and R.Mayer, J. Prakt. Chem., 35, 97 (1967).

(6) O.Ceder and B.Beijer, Tetrahedron, 31, 963 (1975).

(7) R.Gompper and E.Kutter, Angew. Chem., 74, 251 (1962).

(8) Compounds **2** and **2'** were prepared from **1** and amines in refluxing ethanol: **2a**, white plates (recry. from EtOH), mp 199-200°C; **2b**, white plates (recry. from 1:1 MeOH-H_2O), mp 120-121°C; **2'c**, white prisms (recry. from EtOH), mp 125-126°C; **2'd**, white prisms (recry. from EtOH), mp 58-59°C.

(9) nmr (DMSO-d_6) δ 8.2 (br, 1H, N$\underline{H}$), 8.0 (br, 1H, N$\underline{H}$), 7.1 (m, 5H, Ph), 4.05 (s, 2H, C$\underline{H}_2$); mass m/e 191.0520 (M^+), 150 (M-CH_2CNH), 118 (PhNHCN), 104 (PhNHC), 92 (PhNH), 73 (phCCH_2S); ir (KBr) 3380 cm^{-1} (s, H_2O), 3240, 3050 (s, NH), 1555 (vs), 780, 700 (m, Ph).

(10) nmr (DMSO-d_6) δ 10.45 (br, 1H, N$\underline{H}$), 7.60 (s, 5H, Ph), 7.20 (s, 1H, C$\underline{H}$), 1.95 (s, 6H, 2C$\underline{H}_3$); mass m/e 275 (M^+), 233, 191, 119; ir (KBr) 3300 cm^{-1} (s, NH), 1680, 1660 (vs, CO), 780, 700 (m, Ph); uv $\lambda_{max}^{99\ \%\ EtOH}$ 221 nm (ε = 38300), 244 (sh, 16800), 288 (9200).

(11) L.S.Wittenbrook, C.L.Smith, and R.J.Timmons, J. Org. Chem., 38, 465 (1973).

(12) nmr (Py-D_5) δ 9.60 (br, 2H, N$\underline{H}_2$), 2.7 (s, 3H, C$\underline{H}_3$); mass m/e 170.9933 (M^+); ir (KBr) 3345, 3125 cm^{-1} (s, NH_2), 2940 (w, CH_3), 2190 (vs, CN), 1645 (s); uv $\lambda_{max}^{99\ \%\ EtOH}$ 249 nm (ε = 23600), 310 (21600).

(13) W.Wobig, Justus Liebigs Ann. Chem., 764, 125 (1972).

(14) This compound was prepared from dimethylthiomethylenemalononitrile and aniline in refluxing ethanol; white plates of mp 175-176°C (recry. from EtOH).

(15) nmr (DMSO-d_6) δ 8.35 (br, 2H, 2N$\underline{H}$), ca. 7.2 (m, 5H, Ph), 4.01 (s, 2H, C$\underline{H}_2$); mass m/e 215 (M^+), 143, 123, 77; ir (KBr) 3410, 3340, 3190 cm^{-1} (s, NH), 2200 (s, CN), 1580 (vs), 770, 700 (s, Ph).

(16) nmr (DMSO-d_6) δ 7.8 (br, 2H, 2N$\underline{H}$), 4.05 (s, 2H, C$\underline{H}_2$), 1.5 (m, 11H, cyclohexyl); mass m/e 197.0969 (M^+), 115 (M-C_6H_{10}), 83 (C_6H_{11}), 73 (NHCCH_2S); ir (KBr) 3420 cm^{-1} (s, H_2O), 3290, 3050 (s, NH), 2920, 2850 (s, CH), 1575 (vs).

(17) uv $\lambda_{max}^{99\ \%\ EtOH}$ 239 nm (ε = 23400), 310 (12600).

(18) nmr ($CDCl_3$) δ 5.3 (br, 2H, N$\underline{H}_2$), 3.65 (m, 4H, 2C$\underline{H}_2$), 1.64 (m, 6H, 3C$\underline{H}_2$); ir (KBr) 3310, 3150 cm^{-1} (s, NH_2), 2940, 2850 (m, CH), 2180 (vs, CN), 1660 (s); uv $\lambda_{max}^{99\ \%\ EtOH}$ 240.5 nm (ε = 31000), 313 (15900).

(Received in Japan 5 March 1981)