SYNTHESES AND REACTIVITY OF 1,2,4-THIADIAZOLO-[2,3-a] PYRIDINES AND SOME RELATED SYSTEMS

Bojan Verček, Branko Stanovnik, and Miha Tišler*
Department of Chemistry, University of Ljubljana,
61000 Ljubljana, Yugoslavia

Treatment of N-ethoxycarbonylmethyl-N'-(pyridyl-2)-thiourea and derivatives (1) with bromine yielded 1,2,4-thiadiazolo [2,3-a] pyridines (2) in good yield. Other synthetic paths to 6 and the tricyclic compound 11 as well as some other transformations are described.

1,2,4-Thiadiazolo [2,3-a] pyrimidines and some other 1,2,4-thiadiazolo[2,3-x] azines have been the subject of our previous investigations.[1] Besides of their synthetic potential as precursors for other heterocyclic systems these compounds are also of particular structural interest.

In view of these findings iz seemed of interest to extend investigations on some related derivatives and systems.

N-Ethoxycarbonylmethyl-N'-(pyridyl-2) thiourea (1, R = OEt)[3] was prepared from 2-aminopyridine und ethoxycarbonylmethyl isothiocyanate[4] in hot cloroform solution, mp 141-143° (from ethanol); m/e 211 (M^+) and nmr δ ($CDCl_3$) 6.91 (ddd, H_3), 7.57 (ddd, H_4), 6.84 (ddd, H_5), 8.15 (ddd, H_5), 8.15 (ddd, H_6), 4.52 (d, CH_2), 9.64 (broad s, NH), 12.20 (t, NH), $J_{3,4}$=8.0, $J_{4,5}$=7.0, $J_{5,6}$=5.0, $J_{3,5}$=1.2, $J_{4,6}$=2.0, $J_{3,6}$=0,8 Hz.

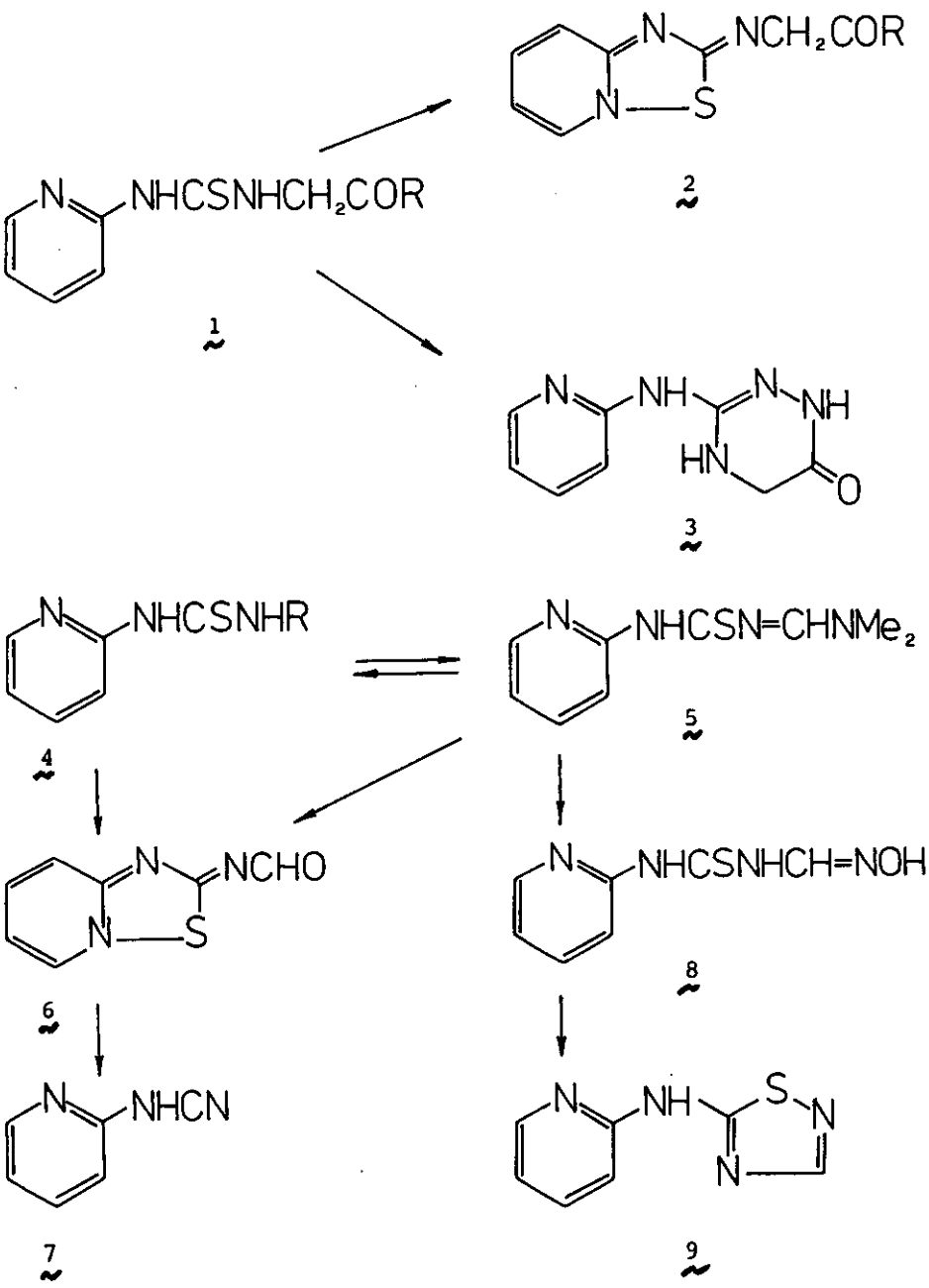
The ester (1, R = OEt) was saponified to the acid (1, R = OH), mp 182-185°; m/e 211 (M^+) and with ammonia and hydrazine the corresponding amide (1, R = NH_2) (mp 196-199°; m/e 210 (M^+) and hydrazide (1, R = $NHNH_2$) (mp 185-190°; m/e 225 (M^+) were prepared.

However, the ester (1, R = OEt) or hydrazide (1, R = $NHNH_2$) when heated with 80 % hydrazine hydrate was transformed into 3, mp 278-280°; m/e 191 (M^+) and nmr δ (DMSO-d_6) 7.17 (ddd, H_3), 7.69 (ddd, H_4), 6.88(ddd, H_5), 8.16 (ddd, H_6), 3.80 (d, CH_2), 8.22, 9.15 and 9.95 (broad s, NH groups), $J_{3,4}$ = 8.0, $J_{4,5}$ = 7,0, $J_{5,6}$ = 5.2, $J_{3,5}$ = 1.2, $J_{4,6}$ = 2.0, $J_{3,6}$ = 0.8, J_{NHCH_2} = 1.2 Hz.

The ester (1, R = OEt), when treated with bromine in glacial acetic acid at room temperature, gave, after neutralization, the thiadiazolopyridine derivative 2 (R = OEt) in 82 % yield, mp about 80° (dec); nmr δ ($CDCl_3$) 8.65 (ddd, H_5). 7.35 (ddd, H_6), 8.05 (ddd, H_7), 7.71 (ddd, H_8), 4.90 (s, CH_2), $J_{5,6}$ = 6.0, $J_{6,7}$ = 7.0, $J_{7,8}$ = 8.0, $J_{5,7}$ = 1.6, $J_{6,8}$ = 2.0, $J_{5,8}$ = 0.8 Hz. The bicyclic compound is more stable as hydrobromide, mp 193-194°. Also the acid 1 (R = OH) could be cyclized into the corresponding bicycle 2 (R = OH), obtained as the hydrobromide in 68 % yield, mp 166-180° (dec), and upon neutralization converted into the free acid, mp 138-142 °.

With dilute aqueous sodium hydroxide the ester 2 (R = OEt) was converted at room temperature by ring opening into the corresponding acid 1 (R = OH) in 24 % yield. Similarly, upon treatment with aqueous ammonia or hydrazine hydrate at room temperature the ester 2 (R = OEt) is cleaved to give the pyridine derivative 1 (R = OEt).

Oxidative cyclization was successful also with the amide 1 (R = NH_2) and the corresponding thiadiazolopyridine 2 (R = NH_2) was obtained in 88 % yield, mp about 160° (dec); nmr δ (DMSO-d_6) 9.05 (ddd, H_5), 7.42 (ddd, H_6), 8.15 (ddd, H_7), 7.78 (ddd, H_8), 4.55 (s, CH_2), 7.15 (broad s, NH), $J_{5,6}$ = $J_{6,7}$ = 7.0, $J_{7,8}$ = 8.0 Hz.



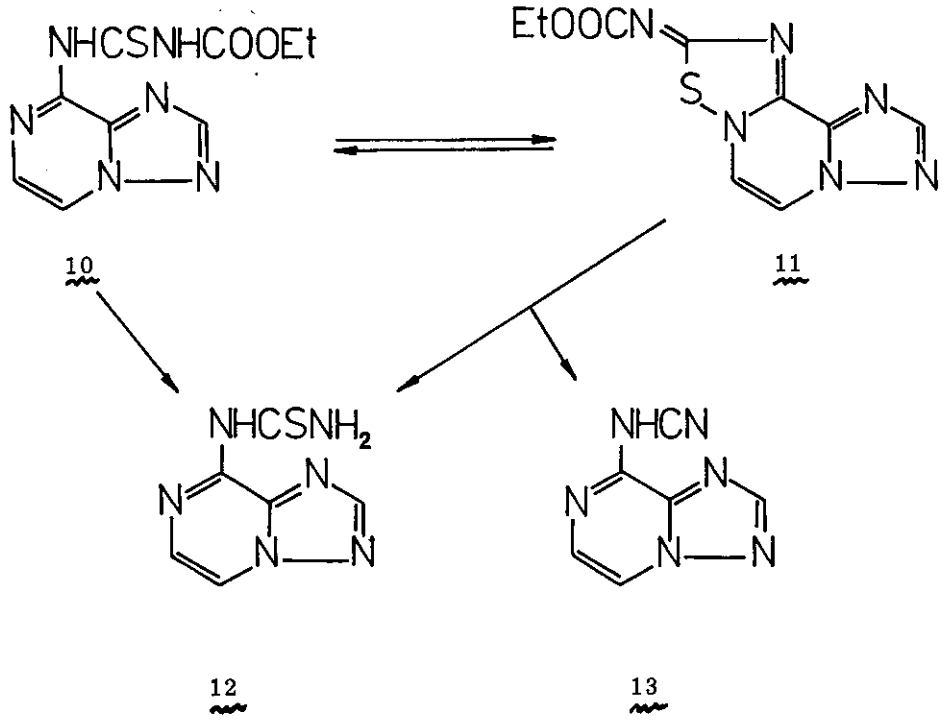
The thiadiazolopyridine ring can be formed also in an alternative manner. N-(Pyridyl-2) thiourea was converted with N,N-dimethylformamide dimethyl acetal into the corresponding N,N-dimethylaminomethylene derivative 5, mp 163-165°; m/e 208 (M^+).

This, when treated with bromine in chloroform at room temperature gave after neutralization the formylimino derivative 6 in 25 % yield, mp 158-161°; m/e 179 (M^+) and nmr δ (DMSO-d_6) 9.02 (ddd, H_5), 7.40 (ddd, H_6), 8.11 (ddd, H_7), 7.82 (ddd, H_8), 8.98 (s, CHO), $J_{5,6}$ = 6.2, $J_{6,7}$ = 6.2, $J_{7,8}$ = 8.0, $J_{5,7}$ = 1.6, $J_{5,8}$ = 0.8, $J_{6,8}$ = 2.0 Hz. The same compound could be prepared by converting the formamidine 5 with formic acid at room temperature into the formyl derivative 4 (R = CHO) and then by oxidative cyclization to give 6. In an attempt to deformylate 6 in the presence of a base at room temperature ring cleavage occurred and 2-cyanaminopyridine 7[5,6] was formed in 55 % yield.

Upon treatment of the formamidine 5 with hydroxylamine hydrochloride at room temperature the hydroxyiminomethylene derivative 8 was obtained in 96 % yield, mp 193-197°; m/e 196 (M^+). When heated in decaline 8 was transformed in 39 % yield in the thiadiazole 9, mp 270-280° (dec); m/e 178 (M^+) and nmr δ (DMSO-d_6) 8.43 (s, H_3), 7.27 (ddd, $H_{3'}$), 7.95 (ddd, $H_{4'}$), 7.17 (ddd, $H_{5'}$), 8.55 (ddd, $H_{6'}$), $J_{3',4'}$ = 8.0, $J_{4',5'}$ = 7.0, $J_{5',6'}$ = 5.0, $J_{3',5'}$ = 1.2, $J_{4',6'}$ = 1.8, $J_{3',6'}$ = 0,9 Hz.

In an analogous manner, oxidative cyclization of N-ethoxycarbonyl-N'-(s-triazolo [1,5-a] pyrazinyl-8) thiourea (10), mp 201-203°, prepared from 8-amino-s-triazolo [1,5-a] pyrazine[7] and ethoxycarbonyl isothiocyanate, afforded in 77 % yield the tricyclic compound 11, mp > 305°; nmr δ (DMSO-d_6) 8.74 (s, H_2), 8.44 and 8.67 (d, H_5 and H_6), $J_{5,6}$ = 6.0 Hz. Upon hydrogenolysis in the presence of palladized carbon (3 at, 18 hours) 11 is easily converted back to 10 in almost quantitative yield. With hot aqueous sodium hydroxide compound 11 is transformed into a mixture of the thiourea 12 (8 % yield) and the cyanamino derivative 13

(56 % yield), the former being formed also from 10 in cold aqueous sodium hydroxide. Thus, the above reaction leads to a new heterocyclic system 11.



REFERENCES AND NOTES

1 B. Koren, B. Stanovnik, and M. Tišler, J. Heterocyclic Chem., 1977, 14, 621.

2 I. Leban, Acta Cryst. B, 1976, 32, 1601.

3 Satisfactory analytical data have been obtained for all compounds described in this communication.

4 Houben-Weyl, "Methoden der Organischen Chemie, Bd. IX: Schwefel-, Selen-, Tellur-Verbindungen", Thieme Verlag, Stuttgart, 1955, p. 876.

5 P. Charonnet and F. Le Perdriel, Ann. Pharm. Fr., 1968, 26, 469.

6. S. Polanc, B. Verček, B. Šket, B. Stanovnik and M. Tišler, J. Org. Chem., 1974, 39, 2143.

7. B. Verček, B. Stanovnik, and M. Tišler, Tetrahedron Letters, 1974, 4539.

Received, 1st September, 1978