RING TRANSFORMATION OF 1,2,6-THIADIAZINE 1,1-DIOXIDES INTO PYRAZOLES. A CONVENIENT SYNTHESIS OF N-ALKYLSULFAMIDES

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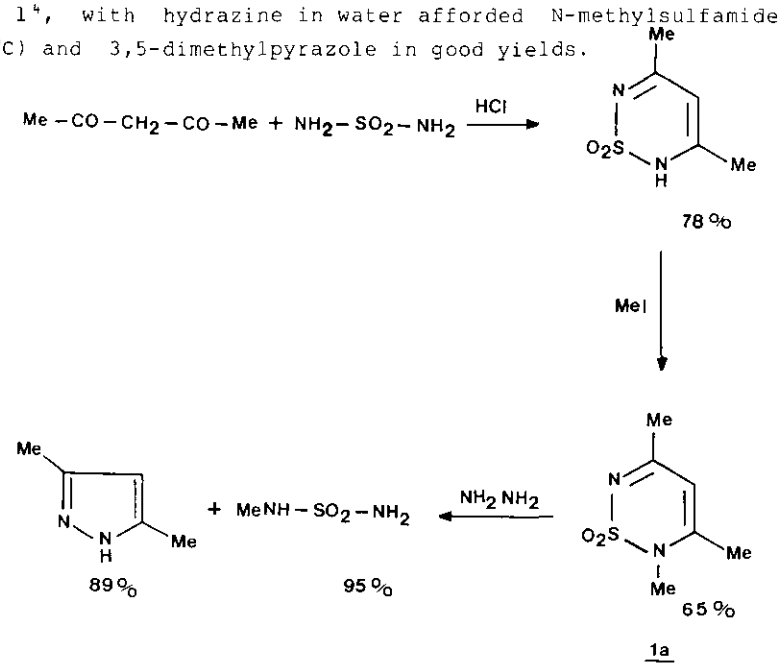
Abstract -Conversion of thiadiazines into pyrazoles by the action of hydrazine represents a new example of ring transformation and provides a new entry into N-methylsulfamide. The latter has been used to prepare an N-methyl-3,5-diaminothiadiazine which cannot be obtained by direct alkylation.

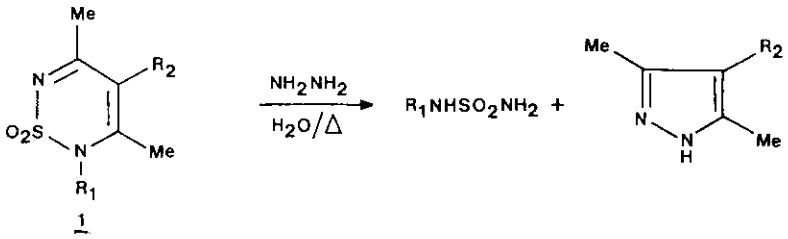
For many years, there has been considerable interest in ring transformations caused by the action of nucleophiles on heterocyclic compounds[1]. We now wish to report conversion of N-substituted 1,2,6-thiadiazine-1,1-dioxides into pyrazoles by reaction with hydrazine. When N-methylthiadiazines are used, this reaction has an additional interest since it provides a very convenient synthesis of N-methylsulfamide, a valuable key intermediate for many heterocycles containing the $N-SO_2-N$ moiety[2]. The general synthesis of N-alkylsulfamides involves reaction of sulfamide and alkylamines[3] but with methylamine this procedure does not work. Reaction of 2,3,5-trimethyl-1,2,6-thiadiazine-1,1-dioxide (1a) prepared according to Scheme 1[4], with hydrazine in water afforded N-methylsulfamide (mp 63-65°C Lit.[5] 63-64°C) and 3,5-dimethylpyrazole in good yields.



Scheme 1

The reaction proceeded in a very clean and smooth manner and the compounds were easily separated by crystallization. Other thiadiazines were used and the results are gathered in Table 1: 3,4,5-Trimethylpyrazole was obtained from 2,3,4,5-tetramethyl-1,2,6-thiadiazine 1,1-dioxide 1b[4], prepared in a similar way to 1a whilst 2-phenylethyl-3,5-dimethyl-1,2,6-thiadiazine-1,1-dioxide 1c[6] afforded N-phenylethylsulfamide and 3,5-dimethylpyrazole. This reaction was only performed in order to check the general scope of the method, since thiadiazine 1c was synthesized from N-phenylethylsulfamide and 2,4-pentanedione.

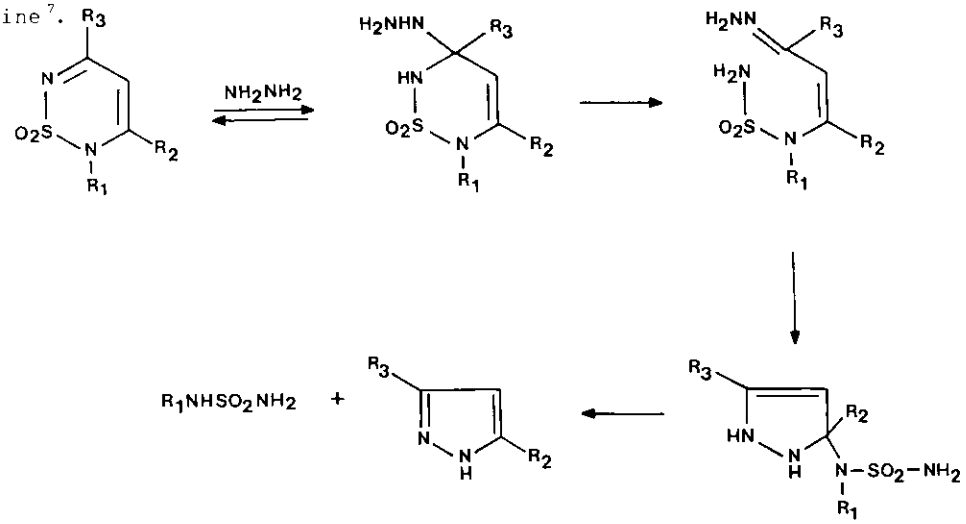
TABLE 1



1

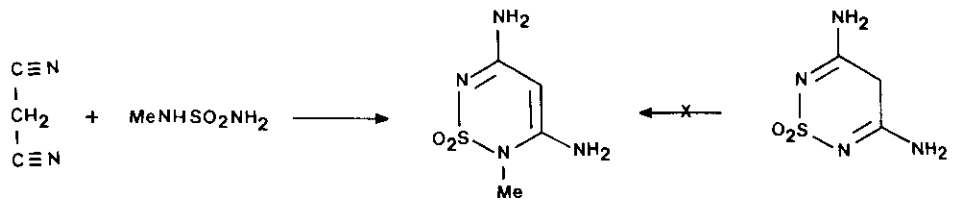
	R_1	R_2	%yield in sulfamide	%yield in pyrazole
a)	Me	H	95	89
b)	Me	Me	68	70
c)	CH_2CH_2Ph	H	67	59

The probable mechanism involved is depicted in Scheme 2. A similar mechanism has been postulated for the conversion of pyrimidines into pyrazoles by the action of hydrazine[7].



Scheme 2

The structures of the pyrazoles were established by comparison with authentic samples[8]. Since no recent reports have dealt with N-methylsulfamide its nmr spectra have been recorded: ^{1}H nmr (300 MHz) (DMSO-d_6) δ : 6.46 (s, NH_2), 6.28 (d, J=3.4 Hz, NH), 2.50 (d, J=3.5 Hz, CH_3); (acetone-d_6) δ : 5.81 (s, NH_2), 5.50 (bs, NH), 2.68 (d, J=5.3 Hz, CH_3). ^{13}C nmr (75 MHz) (DMSO-d_6) δ : 28.7 (q, J=137.7 Hz, CH_3).
Finally, the synthetic usefulness of N-methylsulfamide is exemplified in the preparation of 2-methyl-3,5-diamino-1,2,6-thiadiazine-1,1-dioxide (2). The parent compound, 3,5-diamino-2H-1,2,6-thiadiazine-1,1-dioxide[9] (3) is the starting material of many [6+6] and [6+5] fused thiadiazine derivatives[10]. Direct methylation of this compound afforded C-mono- and C,N-dimethyl derivatives[11] but the N-methyl derivative 2 could not be isolated. This compound can easily be obtained from N-methylsulfamide and malononitrile in dimethoxyethane[12] (Scheme 3).



2 3

Scheme 3

General procedure for conversion of 1,2,6-thiadiazines 1,1-dioxides into pyrazoles: An equimolar mixture of the thiadiazine and hydrazine hydrate in water (50-100 ml) was refluxed for 2h. After cooling, the precipitate (pyrazole) was collected by filtration and solvent evaporated under reduced pressure to afford the corresponding sulfamide.

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6. 2-Phenylethyl-3,5-dimethyl-1,2,6-thiadiazine-1,1-dioxide 1c.- A solution of phenylethylsulfamide (2g, 0.01 mol) and 2,4-pentanedione (1g, 0.01 mol) in ethanol (50 ml) was saturated with hydrogen chloride. The reaction mixture was refluxed for 4 h, the solvent evaporated in vacuo and the residue recrystallized from methanol to give 2.3 g (88%) of 1c, mp 185-186 C. Uv (MeOH) λ nm(ε): 217 (2800), 323 (4100); ir (nujol) ν cm^{-1}:1320, 1180 (SO_2); ^1H nmr (DMSO-d_6) δ: 7.4 (m, 5H, Ar-H), 5.9 (s, 1H, H-4), 4.1 (t, J=6 Hz, 2H, N-CH_2), 3.1 (t, J=6 Hz, 2H, CH_2), 2.2 (s, 3H, CH_3-3), 2.1 (s, 3H, CH_3-5). $C_{13}H_{16}N_2O_2S$ requires: C, 59.09; H,6.06; N,10.60; S,12.12. Found: C, 59.31; H, 6.11; N, 10.64; S,12.36.

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12. 2-Methyl-3,5-diamino-1,2,6-thiadiazine-1,1-dioxide 2.- A solution of malononitrile (3g, 0.045 mol) and methylsulfamide (5g, 0.045 mol) in dimethoxyethane[13] (30 ml) was saturated with hydrogen chloride for 15 min. The solid was collected by filtration and dissolved in a saturated solution of sodium bicarbonate. After cooling, a crystalline white precipitate appeared which was recrystallized from ethanol to give 2 g (26%) of 2, mp 175-177°C, uv (MeOH) λnm(ε): 205 (7500), 225 (6200), 285 (13950). Ir (nujol) ν cm^{-1} : 1330, 1180 (SO_2). ^1H Nmr (DMSO-d_6) δ: 6.8 (s, 2H, NH_2), 6.5 (s, 2H, NH_2), 4.6 (s, 1H, H-4) 3.1 (s, 3H, CH_3). $C_4H_8N_4O_2S$ requires: C, 27.27; H, 4.54; N, 31.81; S, 18.18. Found: C, 27.56; H, 4.61; N, 32.01; S, 18.01.

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