# A Ring-enlargement Procedure for the Conversion of 4,5-Dihydro-1,3,4-thiadiazolest into Dihydro-4*H*-1,3,4-thiadiazines

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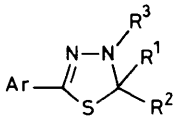
A new ring expansion reaction of 4,5-dihydro-1,3,4-thiadiazoles, which leads to the formation of dihydro-1,3,4-thiadiazines, is reported.

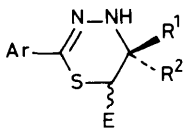
During the course of our investigations into the chemistry of 4,5-dihydro-1,3,4-thiadiazoles (**1**),[1] we have found a useful ring-expansion reaction which leads to 5,6-dihydro-4*H*-1,3,4-thiadiazines (**2**). To date there are only a few reported methods for the synthesis of this class of heterocycle,[2] and because our method may be applicable in other ring systems the details are now reported.

Although 4,5-dihydro-1,3,4-thiadiazoles (**1a, b**) are readily converted into 4-acyl derivatives (**1c**) by standard acylation procedures,[3] we have found them resistant to 4-alkylation under a variety of conditions [*e.g.* MeI, ethanol; MeI, NaH–*N*,*N*-dimethylformamide (DMF); MeI, lithium diisopropylamide (LDA)–tetrahydrofuran (THF); MeI, KOH–acetone]. The main product of such reactions of (**1a**) is the corresponding 1-(alkylthio)-2,3-diazabutadiene (**3a—d**), presumably formed *via* an intermediate diazabutadienylthiolate (**4**). However, when the electrophile provided for attack by this thiolate is of the type $ClCH_2E$, where E is an electron-withdrawing group (CN, $CO_2Et$, or COPh), spontaneous ring-closure to 5,6-dihydro-4*H*-1,3,4-thiadiazines (**2a—f**) occurs under the influence of the base required to generate the thiolate (Scheme 1). A typical procedure, developed for the preparation of (**2a**), involves the suspension of powdered potassium hydroxide (10.5 mmol) in a solution of the dihydrothiadiazole (**1a**) (0.67 mmol) in acetone (15 $cm^3$), followed by the addition of chloroacetonitrile (0.93 mmol). Reaction was complete after 2 h, and the yield of (**2a**), m.p. 149—152 °C, was 74% after recrystallisation from ethanol.



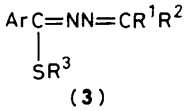
(**1**)

**a**; Ar = 4-$MeOC_6H_4$, $R^1 = R^3 = H$, $R^2$ = Ar
**b**; Ar = 4-$MeOC_6H_4$, $R^1 = R^2$ = Me, $R^3$ = H
**c**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, $R^3 = COCH_2X$, X = H, Cl, CN



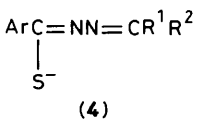
(**2**)

**a**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, E = CN
**b**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, E = COPh
**c**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, E = $CO_2Et$
**d**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, E = Ph
**e**; Ar = 4-$MeOC_6H_4$, $R^1 = R^2$ = Me, E = CN
**f**; Ar = Ph, $R^1 = R^2$ = Me, E = CN

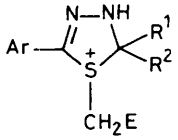


(**3**)

**a**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, $R^3$ = Me
**b**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, $R^3 = Pr^n$
**c**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, $R^3 = Pr^i$
**d**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, $R^3 = CH_2Ph$
**e**; Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^2$ = Ar, $R^3 = CH_2CH{=}CH_2$



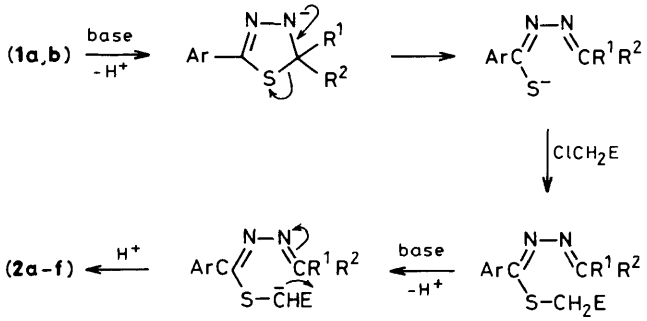
(**4**)



(**5**)

A somewhat higher ratio of *trans* : *cis* isomers was observed when (**2b**) was generated by ring-enlargement of the same dihydrothiadiazole (**1a**) with chloroacetylbenzene, using either sodium hydride in DMF (82% yield, *trans* : *cis* 4 : 1) or a phase-transfer system (66% yield, *trans* : *cis* 8 : 1). The analogous *trans*-isomer of (**2c**) was almost the sole isomer formed, irrespective of the procedure used, in the ring enlargement of (**1a**) with ethyl chloroacetate.

The formation of geometrical isomers is not possible when the 5,5-dimethyl-1,3,4-thiadiazole (**1b**) is the substrate for ring enlargement and this simplifies the interpretation of the n.m.r. spectra of the resulting dihydrothiadiazines (**2e, f**)



Scheme 1

† Formerly 1,3,4-thiadiazolines; see *Pure Appl. Chem.*, 1983, **55**, 409.

**Table 1.** $^1$H N.m.r. and $^{13}$C n.m.r. data for 5,6-dihydro-4*H*-1,3,4-thiadiazines (**2a**—**f**).[a]

| Compound | Isomer | $\delta_H$ (*J*/Hz) C-5 | $\delta_H$ (*J*/Hz) C-6 | $\delta_C$ C-5 | $\delta_C$ C-6 |
|---|---|---|---|---|---|
| (**2a**) | *trans* | 4.49 (9.4) | 4.14 (9.4) | 54.16[b] | 34.36[b] |
| (**2a**) | *cis* | 4.42 (3.6) | 4.19 (3.6) | 54.16[b] | 34.0[b] |
| (**2b**) | *trans* | 4.2 (10) | 4.45 (10) | 49.13 | 55.7 |
| (**2c**) | *trans* | 4.48 (9.8) | 5.35 (9.8) | 49.58 | 54.61 |
| (**2c**) | *cis* | 4.76 (4.75) | 5.22 (4.75) | 49.58 | 53.75 |
| (**2d**) | *trans* | 4.67 (9.8) | 3.98 (9.8) | 64.05 | 46.49 |
| (**2d**) | *cis* | 4.77 (4.9) | 4.53 (4.9) | 61.08 | 51.22 |
| (**2e**) | | | 4.0 | 46.25 | 37.62 |
| (**2f**) | | | 3.95 | 46.47 | 37.59 |

[a] All spectra were run at 220 MHz, and in $CDCl_3$ unless otherwise indicated. [b] Spectra run in [$^2H_6$]acetone.

(45—62%). The spectroscopic data of the dihydrothiadiazines (**2**) so far obtained are displayed in Table 1; all new compounds had satisfactory elemental analyses.

We have obtained supporting evidence for the mechanism proposed (Scheme 1) as follows. Treatment of (**1a**) with benzyl chloride in the presence of sodium hydride in DMF yields, after 18 h, the dihydrothiadiazine (**2d**) (70% yield) as a mixture of the *trans* and *cis* isomers (essentially pure *trans*-isomer was obtained using LDA at −78 to −20 °C). If the benzyl chloride–NaH–DMF reaction is stopped after only 1 h, the product (80%) is the 1-(benzylthio)-2,3-diazabutadiene (**3d**) m.p. 88—89 °C; treatment of this material with LDA in THF at −78 °C for 18 h gave the dihydrothiadiazine (**2d**) obtained previously, as before mainly in the *trans* configuration.

Although it is possible that ring-opening of the dihydrothiadiazoles is assisted electrophilically, *e.g.* by prior formation of a sulphonium ion (**5**), we consider this less likely than a base-initiated ring-opening. As earlier workers have shown,[4] n.m.r. spectroscopic analysis of these dihydro-4*H*-thiadiazoles in basic media indicates that they are in equilibrium with the acyclic thiolate. However, we are unable to detect acyclic isomers in neutral or acid solution.

We are indebted to Reckitt & Colman PLC and to the S.E.R.C. for financial support.

*Received, 31st May 1984; Com. 756*

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