Tandem Cycloaddition–Rearrangement of 2-Aza-1,3-dienes. A Simple and Efficient Synthesis of 1*H*-1,4-Diazepine-7(6*H*)-thiones

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1*H*-1,4-Diazepine-7(6*H*)-thiones **7** have been synthesized in two steps from 2-aza-1,3-dienes **2** and trimethylsilyl isothiocyanate *via* 1,2-dihydropyrimidine-4(3*H*)-thiones **6**.

In our studies concerning the reactivity of neutral 2-aza-1,3-dienes **1**, we have shown the synthetic utility of these systems in the preparation of six-membered nitrogen-containing heterocycles, mainly *via* [4 + 2] cycloaddition reactions.[1] In addition, we have found that their mono-halogenated derivatives **2** (Scheme 1),[2] because of the introduction of asymmetry in the molecule, are suitable for studying the face selectivity in Diels–Alder processes. Thus, we have recently reported[2] that compounds **2** react with dienophiles such as dialkyl azodicarboxylates and carbonyl compounds showing several levels of facial selectivity depending on the nature of dienophile.

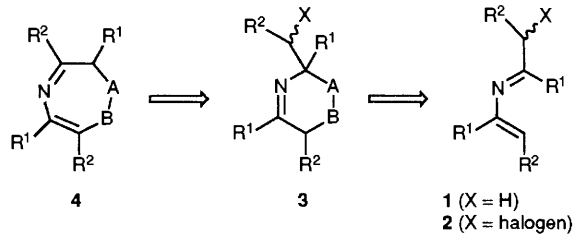
On the basis of the behaviour of 2-aza-1,3-dienes **2**, we thought that an easy synthetic approach to seven-membered heterocyclic ring systems could be the one shown in Scheme 1. Our approach involves a two-step process, in which the cycloadducts **3** initially formed might undergo a ring expansion to the corresponding seven-membered ring **4** by treatment with a base.

As a dienophile we chose reactive heterocumulenes such as trimethylsilyl isothiocyanate **5**, because these types of compounds gave [4 + 2] cycloadducts with 2-aza-1,3-dienes **1**[3] exclusively in the enamine form (which seems to be more reactive than its imino tautomer **3** from which the ring expansion has been not yet possible).†

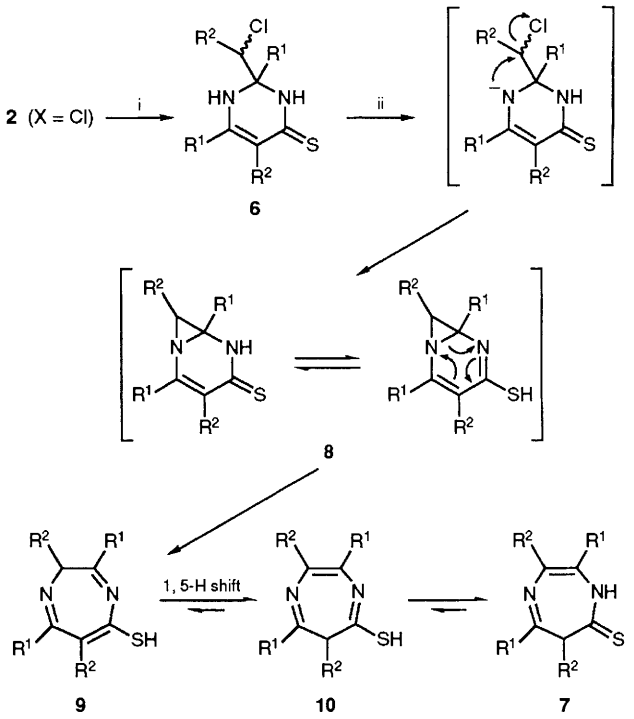
We now report a simple and efficient method for preparing 1,2-dihydropyrimidine-4(3*H*)-thiones **6** and 1*H*-1,4-diazepine-7(6*H*)-thiones **7** from 2-aza-1,3-diene derivatives **2** (X = Cl).

In sharp contrast with their pharmacologically important 1,4-benzo derivatives[4] the monocyclic 1,4-diazepines have received much less attention. In fact, and with exception of the 2,3-dihydro-1*H*-1,4-diazepines,[5] only a few isolated reports related to the preparation of fully unsaturated 1,4-diazepines have appeared.[6] Condensation of 1,3-dicarbonyl compounds with 1,2-diamino alkenes[6b] and ring expansion of diazabicyclo derivatives[6c,d] are some of the methods described for the synthesis of these systems.

The synthesis of 1*H*-1,4-diazepine-7(6*H*)-thiones **7** starts with the preparation of 1,2-dihydropyrimidine-4(3*H*)-thiones **6**, which are easily obtained in good yields by reaction of **2** (X = Cl) and trimethylsilyl isothiocyanate **5** (1.1 equiv.) under mild conditions (toluene; room temperature or 40 °C; 16 h). The process takes place apparently with complete regioselectivity,[3] and cycloadducts **6**‡ were obtained as yellow solids and isolated as a mixture of diastereoisomers, the process showing moderate facial selectivity (Scheme 2 and Table 1).[1,2] The mixture of epimers **6** was used in the ring expansion step. Thus, compounds **6** were subjected to treatment with an equivalent of NaH in tetrahydrofuran at room temperature for 48 h affording 1,4-diazepines **7** in high yields (Scheme 1 and Table 1).



Scheme 1



Scheme 2 *Reagents and conditions*: i, $Me_3SiN{=}C{=}S$ **5** (1.1 equiv.), toluene, 25–40 °C, 16 h; ii, NaH (1 equiv.), tetrahydrofuran, 25 °C, 48 h

† All attempts to isolate compounds of type **4** by reaction of **2** with azo derivatives and carbonyl compounds (A=B ≡ $RO_2C{-}N{=}N{-}CO_2R$, O=CHR) were unsuccessful. The reason for this behaviour could be that in these cases the cycloadduct was isolated in the imino form **3** (Scheme 1) which prevents the consequent cyclization process, probably for steric reasons.

‡ *Spectroscopic data* for compound **6a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.5 (d, 3H), 1.5 (d, 3H), 1.9 (s, 3H), 4.6 (m, 2H), 5.1, 5.3 (br s, 1H), 7.3–7.7 (m, 10H Ar) and 8.5 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.1, 145.7, 145.1, 140.7, 139.7, 134.9, 130.3 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.9 (CH), 126.0 (CH), 125.9 (CH), 125.1 (CH), 117.1, 115.9, 14.8, 74.5, 61.4 (CH), 60.6 (CH), 19.7 (CH_3) and 16.27 (CH_3); MS *m/z* 344, 342 (M^+); R_f 0.052 (hexane–ether, 5:1). For compound **7a**. * Refers to the minor component. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.2 (d, 3H), 1.5 (d, 3H), 2.1 (s, 6H), 3.1 (q, 3H) 5.3 (dq, 3H)*, 7.3–8.0 (m, 10H, Ar) and 9.3 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.1, 190.6*, 156.1, 155.9*, 136.9, 136.4, 135.2, 135.1, 130.6 (CH), 129.9 (CH), 129.6 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.4 (CH), 126.8 (CH), 125.1, 122.6*, 54.8 (CH), 51.8 (CH), 20.6 (CH_3)*, 20.3 (CH_3), 15.8 (CH_3) and 8.4 (CH_3)*; MS *m/z* 306 (M^+); R_f 0.40 (hexane–AcOEt, 6:1).

Table 1 Preparation of 1,2-dihydropyrimidine-4(3*H*)-thiones **6** and 1*H*-1,4-diazepin-7(6*H*)-thiones **7**

Compd.[a,b]	R^1	R^2	Yield (%)	Epimer (conformer) ratio[c]	M.p., *t*/°C
6a	Ph	Me	70	64:36	204–208[d]
6b	Ph	Et	80	62:38	87–92[d]
6c	Ph	Pr	75	68:32	151–155[d]
6d	*p*-Tolyl	Me	80	56:44	151–154[d]
7a	Ph	Me	80	(74:26)	133–136
7b	Ph	Et	91	(53:47)	Oil
7c	Ph	Pr	83	(62:38)	Oil
7d	*p*-Tolyl	Me	75	(74:26)	181–183

[a] All reactions take place at room temperature, except for **6a**, which needs a slight warming to 40 °C. [b] All compounds gave satisfactory elemental analyses. [c] Determined by ^{1}H NMR (300 MHz). In parentheses, conformer ratio for compounds **7**. [d] M.p. of the epimer mixture.

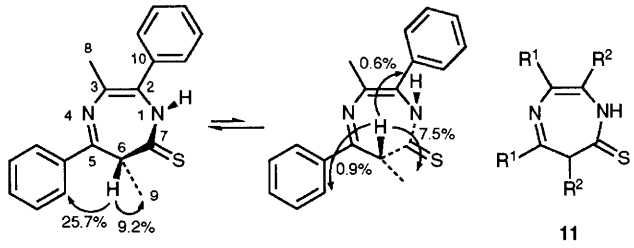


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Fig. 1 Selected NOEs for **7a**

The formation of 1,4-diazepines **7** and **6** could be understood by assuming a three-step mechanism, in which the initial deprotonation of **6** at N-1 is followed by formation of the unisolated heteronorcaradiene **8**, which rearranges electrocyclically to the 1,4-diazepine **9**. A subsequent [1,5]sigmatropic shift of hydrogen affords **10** which finally tautomerizes to the 1*H*-isomer **7** (cf. ref. 6*d*). Alternatively, the 1,4-diazepines **9** would evolve to **7** under the basic conditions of the reaction.

Compounds **7** were isolated as a mixture of two conformational isomers (Table 1) and characterized on the basis of their spectroscopic data and mass spectrometry.‡ Taking **7a** (Fig. 1) as an example, the COLOC spectrum afforded the carbon–carbon connectivity shown.§ The correlations of CH-6 with C-5 and C-7 and those of C-3, C-6 and C-10 with the NH show unequivocally that the diazepines **7** have the configuration represented in Scheme 2. This rules out the formation of compound **11**, a regioisomer of **7** which can be formed by deprotonation of the thioamide hydrogen, followed by an analogous process to that shown in Scheme 2.

^{15}N{^{1}H}INEPT spectra further confirm this point.[7] When optimized to detect long-range couplings (^{1}H–^{15}N), the same types of antiphase multiplets were obtained for both isomers, which correlate the methyne ring proton and the methyl group 8 with the tertiary nitrogen. Otherwise, the enhancements observed in NOE difference experiments (Fig. 1) are only compatible with a pair of conformers pivoting around the sp^3 centres of the ring. Furthermore, variable temperature NMR studies showed that both conformers coalesce at a temperature of 400 K, using [^{2}H$_8$]toluene as solvent.[8]

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§ NOE difference, INEPT and COLOC experiments were performed with the standard software of the Bruker AC 300 spectrometer. Details of the parameters employed will be published elsewhere.