View Article Online / Journal Homepage / Table of Contents for this issue

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

José Barluenga,*[a] Raquel Pérez Carlón,[a] Francisco Javier González,[a] Fernando López Ortiz[a] and Santos Fustero*[b]

[a] *Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain*
[b] *Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, 46010-Valencia, Spain*

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**.

Published on 01 January 1991. Downloaded by State University of New York at Stony Brook on 22/10/2014 21:30:29.

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.

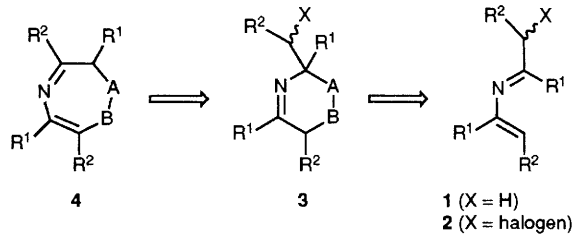
On the basis of the behaviour of 2-aza-1,3-dienes **2**, we thought that an easy synthetic approach to seven-membered heterocyclic ring systems could be the one shown in Scheme 1. Our approach involves a two-step process, in which the cycloadducts **3** initially formed might undergo a ring expansion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

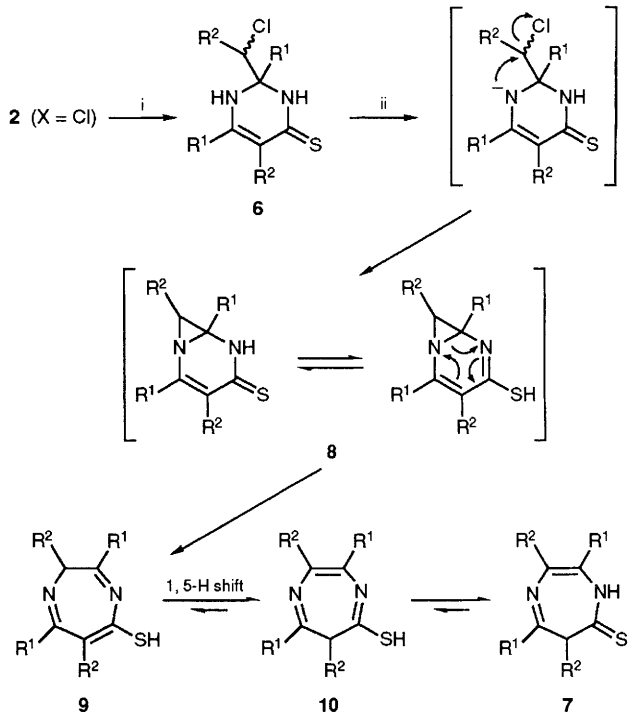
We now report a simple and efficient method for preparing 1,2-dihydropyrimidine-4(3*H*)-thiones **6** and 1*H*-1,4-diazepine-7(6*H*)-thiones **7** from 2-aza-1,3-diene derivatives **2** (X = Cl).

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).

View Article Online

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.

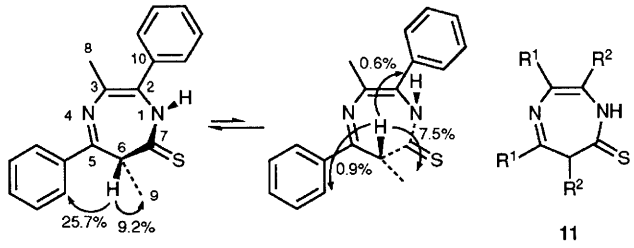


Fig. 1 Selected NOEs for **7a**

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]

This work was supported in part by the Dirección General de Investigación Científica y Técnica (DGICYT, BP86-0254). R. P. C. thanks the Ministerio de Educación y Ciencia for a predoctoral fellowship. We thank Dr Pablo Bernad for mass spectral measurements and helpful discussions.

Received, 30th July 1991; Com. 1/03962H

References

1 J. Barluenga, J. Joglar, F. J. González and S. Fustero, *Synlett*, 1990, 129.
2 J. Barluenga, F. J. González and S. Fustero, *Tetrahedron Lett.*, 1990, **31**, 397.
3 J. Barluenga, F. J. González, S. Fustero and V. Gotor, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1739.
4 N. W. Gilman, P. Rosen, J. V. Earley, C. Cook and L. J. Todaro, *J. Am. Chem. Soc.*, 1990, **112**, 3969 and references cited therein.
5 D. Lloyd, H. P. Cleghorn and D. R. Marshall, *Adv. Heterocycl. Chem.*, 1974, **17**, 2.
6 (*a*) J. Barluenga, M. Tomás, A. Ballesteros, J-S. Kong, S. García and E. Pérez-Carreño, *J. Chem. Soc., Chem. Commun.*, 1991, 353; (*b*) Y. Ohtsuka, *J. Org. Chem.*, 1976, **41**, 629; (*c*) A. Padwa, L. Gehrlein and R. B. Kinnel, *J. Org. Chem.*, 1975, **40**, 1683; (*d*) U. Schöllkopf and J. Mittendorf, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 613.
7 T. A. Scahill and S. L. Smith, *Org. Magn. Reson.*, 1983, **21**, 621.
8 P. Linscheid and J. M. Lehn, *Bull. Soc. Chim. Fr.*, 1967, **5**, 992.

§ 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.

Published on 01 January 1991. Downloaded by State University of New York at Stony Brook on 22/10/2014 21:30:29.