A New Class of Fused 1,4-Diazepines: Synthesis of Substituted 8,8*a*-Dihydrofuro[2,3-*b*][1,4]diazepin-2-ones

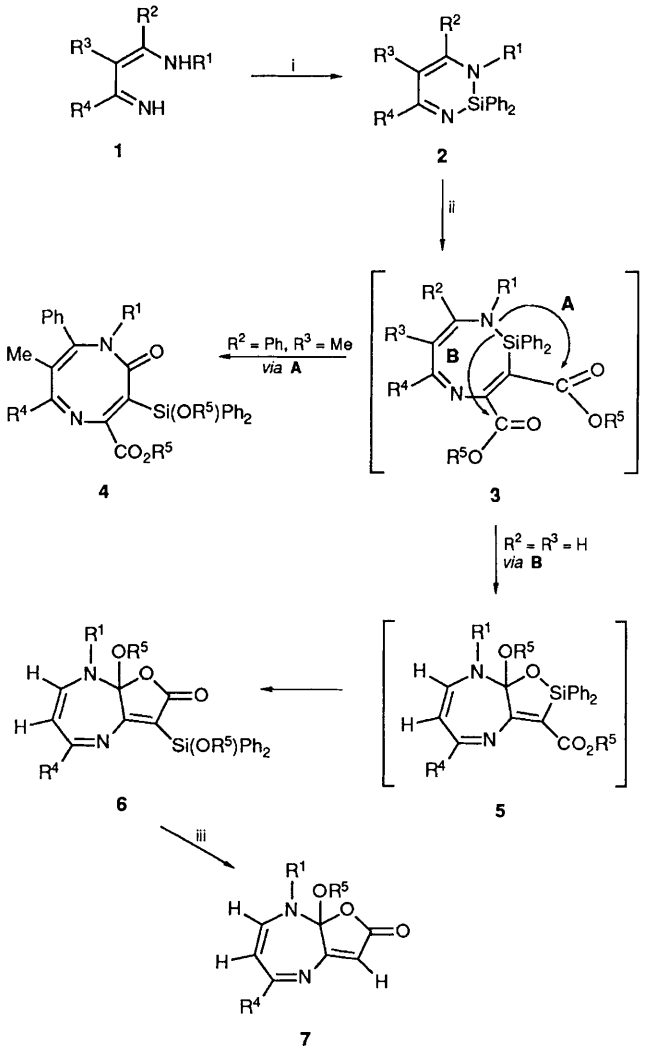
José Barluenga,*[a] Miguel Tomás,[a] Alfredo Ballesteros,[a] Jian-She Kong,[a] Santiago García Granda[b] and Enrique Pérez-Carreño[b]

[a] Departamento de Química Organometálica and [b] Departamento de Química-Física y Analítica, Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain

The novel furo[2,3-*b*][1,4]diazepines **7** have been synthesized in two steps from acetylenedicarboxylic acid esters and 4-amino-1-azabutadienes **1** *via* their 1,3,2-diazasiline derivatives **2** and the crystal structure of **7a** has been determined.

Recently we have shown that 4-amino-1-azabutadienes are valuable building blocks for the synthesis of five- and six-membered nitrogen-containing heterocycles as well as open-chain compounds.[1] In addition, we have found that the reactivity of these azadienes dramatically changes when they are first transformed into 1,2-dihydro-1,3,2-diazasilines.[2,3] Thus, we have reported[2a] that azadienes **1** (R^2 = Ph; R^3 = Me) furnish 1,5-diazocine derivatives **4** by reaction of their diazasiline derivatives **2** with esters of acetylenedicarboxylic acid (Scheme 1, pathway **A**). The reaction seems to involve formation of the silicon-containing heterocycle **3**, from which intramolecular rearrangement following pathway **A** (1,4-attack) takes place. We realized that rearrangement involving 1,5-attack of the enamine nitrogen on another alkoxycarbonyl group, which would give seven-membered heterocycles, could be feasible; in fact, the nature of the transition state in the rearrangement step leading to **4** might be determined primarily from steric interactions since the intermediate **3** is highly substituted.

We report here that seven-membered heterocycles are selectively formed starting from appropriate 4-amino-1-azabutadienes **1**. Thus, azadienes **1**, in which both C^{α}- and C^{β}-enamine carbon atoms are unsubstituted (R^2 = R^3 = H), were treated with dichlorodiphenylsilane in toluene at room temperature to produce the diazasilines **2**, which were not isolated; heating **2** with acetylenedicarboxylic acid esters at 60 °C allowed the silicon substituted fused heterocycles **6** to be identified (IR, ^{1}H and ^{13}C NMR, and mass spectra); without purification, compounds **6** were subjected to protodesilylation with trifluoroacetic acid in dichloromethane (25 °C; 12 h) to yield the furodiazepinones **7**† in 40–75% overall yield from **1** (Scheme 1, Table 1).

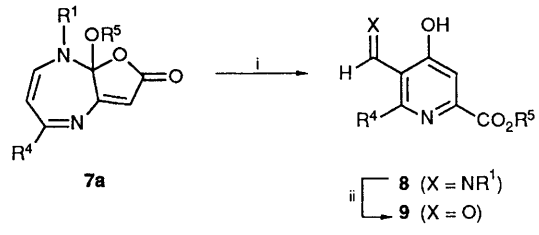


Scheme 1 *Reagents and conditions*: i, Cl_2SiPh_2, toluene–Et_3N, 25 °C, 12 h; ii, R^5O_2C–C≡C–CO_2R^5, toluene, 60 °C, 24 h; iii, CF_3CO_2H, CH_2Cl_2, 25 °C, 12 h

Table 1 Furo[2,3-*b*][1,4]diazepines **7** and pyridines **8** and **9**

Compound[a,b]	R^4	R^5	Yield (%)	M.p. (*t*/°C)[c]
7a	*p*-MeC_6H_4	Me	75	145–147
7b	Ph	Me	73	144–146
7c	*p*-$MeOC_6H_4$	Me	72	164–166
7d	*p*-$MeOC_6H_4$	Et	66	114–116
7e	4-Pyridyl	Me	40	164–166
8	*p*-MeC_6H_4	Me	90	137–139
9	*p*-MeC_6H_4	Me	98	141–142

[a] R^1 = cyclo-C_6H_{11}. [b] All new compounds reported here gave satisfactory elemental analytical figures. [c] Recrystallized from hexane–chloroform.



R^1 = cyclo-C_6H_{11}, R^4 = *p*-MeC_6H_4, R^5 = Me

Scheme 2 *Reagents and conditions*: i, toluene, 120 °C, 8 h; ii, 1 mol dm^{-3} HCl, tetrahydrofuran, 25 °C, 3 h

† *Spectroscopic data* for compound **7e**: IR (KBr) ν_{max} 1760 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 1.1–2.2 (m, 10H), 3.2 (s, 3H), 4.1 (m, 1H), 5.7 (d, 1H, *J* 9.7 Hz), 5.73 (s, 1H), 6.9 (d, 1H, *J* 9.7 Hz), 7.7 (d, 2H, *J* 6.1 Hz) and 8.7 (d, 2H, *J* 6.1 Hz); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 167.96 (s), 163.29 (s), 160.37 (s), 150.00 (d), 146.23 (s), 141.40 (d), 121.56 (d), 107.77 (s), 102.09 (d), 94.55 (d), 60.67 (q), 49.31 (d), 34.07 (t), 33.28 (t), 25.87 (t), 25.38 (t) and 24.93 (t); *m/z* 339 (M^+).

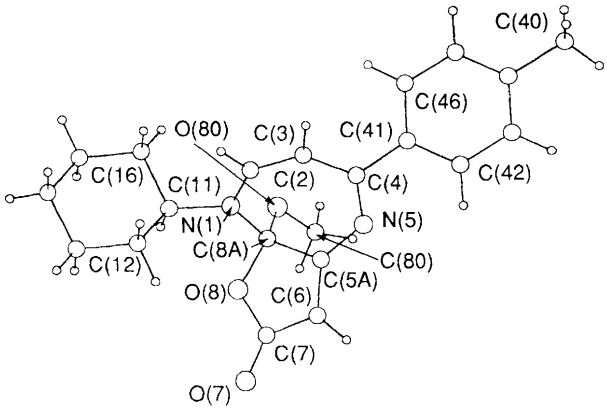


Fig. 1 PLUTO plot of the structure of **7a**, showing the atomic numbering

Compounds **7** gave the expected spectral data and showed satisfactory microanalysis; an X-ray structure of **7a** confirmed the assignment (Fig. 1).‡

In the formation of the heterocycles **7**, rearrangement of the intermediate **3** must involve nucleophilic attack of the enamine nitrogen on the carbonyl carbon attached to the Cβ-vinylsilane carbon (1,5-attack) to give the intermediate **5**; subsequent lactone formation and silicon group removal would account for the process (Scheme 1, pathway **B**).

The different reaction course leading to either eight- **4** or seven- **7** membered rings can be accounted for by steric interactions between the substituents R^1 and R^2 in the intermediate **3**. Molecular models show that structure **3** having R^2 = Ph (see Scheme 1) is rigid, the rearrangement being dominated by the more stable conformer (*via* **A**), whereas in the case of R^2 = H the conformational equilibrium is much less hindered allowing the rearrangement to involve the ester function placed four atoms away (*via* **B**).

Finally, fused diazepines **7** display unusual thermal behaviour; thus, heating a deoxygenated solution of **7a** in a sealed tube (toluene, 120 °C; 8 h) led to C(2)–C(6) carbon–carbon bond formation to give the highly functionalized pyridine **8** (90%, m.p. 137–139 °C), which in turn was quantitatively hydrolysed (1 mol dm^{-3} HCl, tetrahydrofuran, 25 °C, 3 h) to the formylpyridine **9** (m.p. 141–142 °C) (Scheme 2, Table 1).

Compounds **7**, which can be regarded as 1,4-diazepines with a fused butenolide ring, are members of a class of heterocycle which has not been previously described, to the best of our knowledge. 1,4-Benzodiazepines have been studied intensively, but recent attention has concentrated on the synthesis of analogues having heterocycles in place of the benzene ring because of their biological and pharmacological properties.[4] Our approach starts with the easily available 1-azadienes and provides an efficient, short entry to furo[2,3-*b*][1,4]diazepines.

This work was supported in part by the Dirección General de Investigación Científica y Técnica (DGICYT, PB86-0254). J.-S. K. thanks the Ministerio de Educación y Ciencia for a fellowship.

Received, 9th November 1990; Com. 0/05050D

‡ *Crystal data* for **7a**, M_r = 352.43, triclinic, $P\bar{1}$, a = 7.350(2), b = 15.033(3), c = 17.86(1) Å, α = 91.06(9), β = 101.8(1), γ = 104.13(2)°, V = 1868(2) Å^3, Z = 4, D_c = 1.25 mg m^{-3}, μ(Mo-Kα) = 0.79 cm^{-1}, T = 293 K, yellowish crystal, 0.49 × 0.26 × 0.20 mm size, Mo–Kα radiation (λ = 0.71073 Å), graphite monochromator. 11 144 reflections measured on a Enraf-Nonius CAD4 (ω–2θ scan technique), range $0 < \theta < 30$ and $-10 \leq h \leq 10$, $-21 \leq k \leq 21$, $0 \leq l \leq 25$; 10 820 unique reflections (R_{int} = 0.020, averaging some doubly measured reflections) and 5413 observed [$I > 3\sigma(I)$]. Semiempirical and empirical absorption corrections were applied. The structure was solved by direct methods (SHELXS 86) and anisotropically refined (SHELX 76) to a final R = 0.076 (262 parameters and unit weights). Maximum shift/error = 0.33, maximum residual electron density 0.46 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

References

1 J. Barluenga, *Bull. Soc. Chim. Belg.*, 1988, **97**, 545.
2 (*a*) J. Barluenga, M. Tomás, A. Ballesteros, V. Gotor, C. Krüger and Y.-H. Tsay, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 181; (*b*) J. Barluenga, M. Tomás, A. Ballesteros and V. Gotor, *Synthesis*, 1987, 489.
3 For the use of diazasilolidines in synthesis of macrocyclic systems, see E. Schwartz, H. E. Gottlieb, F. Frolow and A. Shanzer, *J. Org. Chem.*, 1985, **50**, 5469.
4 J. T. Sharp in *Comprehensive Heterocyclic Chemistry*, ed. W. Lwowski, vol. 7, Pergamon Press, Oxford 1984, p. 608; R. Pauwels, K. Andries, J. Desmyter, D. Schols, M. J. Kukla, H. J. Breslin, A. Raeymaeckers, J. V. Gelder, R. Woestenborghs, J. Heykants, K. Schellekens, M. A. C. Janssen, E. D. Clercq and P. A. J. Janssen, *Nature*, 1990, **343**, 470; D. E. Thurston, G. B. Jones and M. E. Davis, *J. Chem. Soc., Chem. Commun.*, 1990, 874.