An Expeditious Synthesis of Highly Substituted 1,4-Diazepines and their Rearrangement into 2*H*-1,3-Oxazines

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

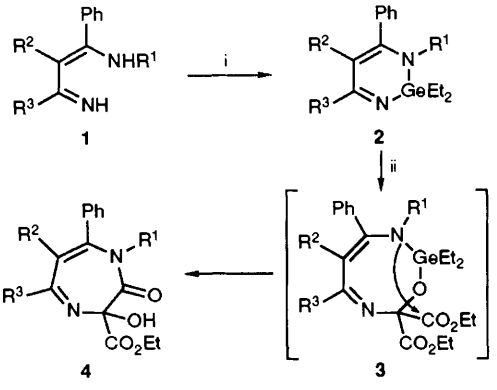
[a] *Departamento de Química Organometálica and* [b] *Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain*

3-Iminoprop-1-enylamines **1** react successively with diethylgermanium dichloride and diethyl oxomalonate to afford 1,3-dihydro-1,4-diazepin-2-ones **4**; the crystal structure of **4a** has been determined and its thermal behaviour leading to 2*H*-1,3-oxazines **5** studied.

In spite of the fact that fused 1,4-benzodiazepines have received intensive study in the last decades because of their pharmacological properties, the monocyclic derivatives remain much less explored and hence developing efficient routes to them are doubtless desired.[1,2] On the other hand, we have recently found novel silicon-[3] and germanium-assisted[4] rearrangements in the field of heterocyclic synthesis. On the basis of these features we report here the synthesis of 1,4-diazepine derivatives **4** from diethyl oxomalonate and 3-iminoprop-1-enylamines **1**, *via* their diazagermine derivatives **2**, as well as their transformation to substituted 1,3-oxazines **5**.

First, a solution of substituted 1,2-dihydro-1,3,2-diazagermines **2** in toluene was formed from **1** ($R^2 \neq H$) and diethylgermanium dichloride[4]; then, addition of 1.1 equiv. of diethyl oxomalonate at 25 °C followed by heating the mixture at 75 °C for 5 h resulted in the formation of 1,3-dihydro-1,4-diazepin-2-ones **4**, which were isolated in 65–78% overall yield from **1** after column chromatography (silica gel, hexane–diethyl ether 1 : 1) (Scheme 1, Table 1). The structure **4** was in agreement with spectroscopic (IR, ^1H and ^{13}C NMR and mass) and analytical data and was confirmed by an X-ray determination performed on compound **4a**† (R^1 = *p*-tolyl; R^2 = Me; R^3 = Ph) (Fig. 1).

Mechanistically, the conversion **2** → **4** seems to involve addition of the nitrogen–germanium bond of the diazagermine **2** onto the ketone function of the malonate diester[5] to form the eight-membered intermediate **3**, which undergoes attack of



Scheme 1 *Reagents and conditions*: i, Et_2GeCl_2, toluene–1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 25 °C overnight; ii, (*a*) EtO_2C–CO–CO_2Et, toluene, 75 °C, 5 h; (*b*) H_2O

Table 1 1,3-Dihydro-1,4-diazepin-2-ones **4** and 2*H*-1,3-oxazines **5**

Compd.[a]	R^1	R^2	R^3	Yield (%)[b]	M.p. (*T*/°C)[c]
4a	*p*-Tolyl	Me	Ph	78	161–163
4b	Ph	Me	Ph	73	154–156
4c	*p*-Tolyl	Me	*p*-Tolyl	75	159–161
4d	*p*-Tolyl	Cl	Ph	65	153–155
5a	Ph	Me	Ph	95	138–140
5b	*p*-Tolyl	H	Ph	90	170–172
5c	*p*-Tolyl	H	c-C_6H_{11}	87	179–181

[a] All new compounds reported here gave satisfactory analytical figures. [b] Overall yield of isolated products from iminopropenes **1**, except for **5a**. [c] Recrystallized from hexane–diethyl ether.

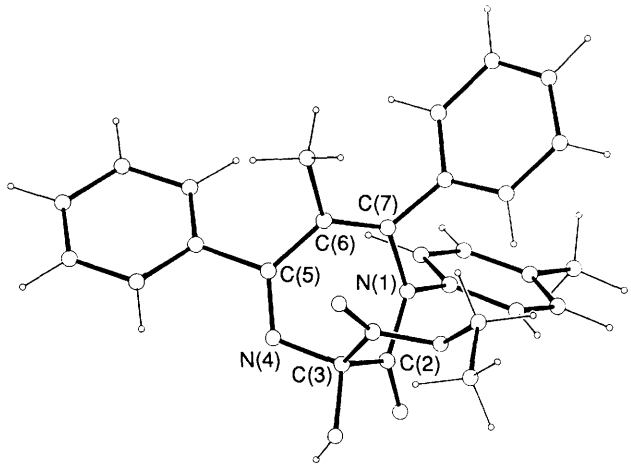
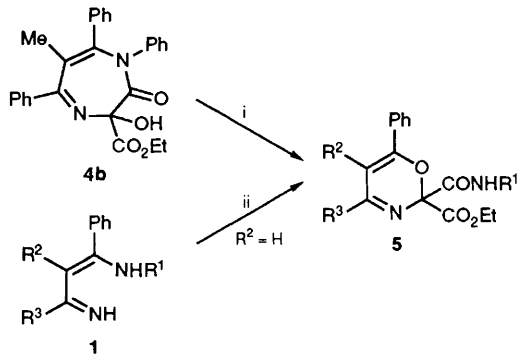


Fig. 1 PLUTON plot of the structure of **4a**, showing the atomic numbering of the seven-membered ring

† *Spectroscopic data* for compound **4a**: IR (KBr) ν_{max}/cm^{-1} 3406 (OH), 1751 (CO), 1674 (CO); ^1H NMR ($CDCl_3$; 300 MHz): δ 1.3 (t, 3H, *J* 7.2 Hz), 1.8 (s, 3H), 2.2 (s, 3H), 4.2 (q, 2H, *J* 7.2 Hz), 5.9 (br, 1H), 7.0 (s, 4H), 7.1–7.4 (m, 5H), 7.5–7.6 (m, 3H), 7.8–7.9 (m, 2H); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 169.3 (s), 167.5 (s), 167.2 (s), 142.9 (s), 137.4 (s), 136.8 (s), 135.7 (s), 133.9 (s), 130.8 (d), 129.9 (d), 129.3 (d), 128.9 (d), 128.8 (d), 128.6 (d), 128.1 (d), 127.4 (s), 127.2 (d), 89.0 (s), 62.4 (t), 20.9 (q), 18.9 (q), 13.8 (q); MS *m/z* 454 (M^+).

Crystal data for compound **4a**: $C_{28}H_{26}N_2O_4 \cdot C_4H_{10}O$, colourless crystal, monoclinic, space group $P2_1/n$, a = 18.379(4), b = 14.748(3), c = 21.138(6) Å, β = 109.79(2)°, V = 5391(3) Å^3, Z = 4, D_c = 1.21 g cm^{-3}, T = 293 K, crystal dimensions 0.20 × 0.20 × 0.16 mm^3. 9095 reflections measured, range ($0 < \theta < 25°$) and $-21 \leq h \leq 20$, $0 \leq k \leq 17$, $0 \leq l \leq 17$; 8885 unique reflections (R_{int} = 0.043, averaging double measured) and 1850 observed with $I > 3\sigma(I)$, μ = 0.762 cm^{-1}. Final R = 0.062 and R_w = 0.059 {376 parameters and $\omega = 1/|\sigma^2(F_o) + 0.0002F_o^2|$}; maximum shift/error = 0.001, ρ_{max} = 0.22 e Å^{-3}. ρ_{min} = −0.23 e Å^{-3}. X-Ray experimental procedures: Mo-Kα radiation (λ = 0.71073 Å)., graphite crystal monochromator, Enraf-Nonius CAD4 single crystal diffractometer (ω–2θ scan technique). Semiempirical and empirical absorption corrections were applied. The structure was solved by direct methods (SHELXS 86) and anisotropically refined (SHELX 76, local version). Drawing made using PLUTON. All calculations were made on a MicroVAX-3400 at the Scientific Computer Center of the University of Oviedo. 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.



Scheme 2 *Reagents and conditions*: i, toluene, 90 °C, 12 h; ii, (*a*) Et_2GeCl_2, toluene–DBU, 25 °C, overnight; (*b*) EtO_2C–CO–CO_2Et, toluene, 50 °C, 2 h; (*c*) hydrolysis

the remaining N–Ge bond to one of the ester groups and rearrangement leading to the diazepine ring **4**.‡

The thermal behaviour of compounds **4** was then tested and found that heating a toluene solution of **4b** at 90 °C for 12 h afforded quantitatively the 2*H*-1,3-oxazine **5a**. This ring transformation can be rationalized in terms of Michael-type addition of the hydroxy group followed by amide displacement. Therefore, this process should be faster in the case of C-6 unsubstituted diazepinones. Thus, applying the whole protocol to iminopropenes **1** with R^2 = H did not allow us to isolate the corresponding diazepine derivatives **4**, but substituted 1,3-oxazines **5b,c** were obtained in excellent yields upon heating **2** (R^2 = H) and diethyl oxomalonate at 50 °C for 2 h (Scheme 2, Table 1). Compounds **5b,c**§ were isolated by acid and basic workup, triturated with hexane and purified by recrystallization from hexane–diethyl ether.¶

In summary, we have devised a regioselective, one-pot synthesis of highly substituted 1,3-dihydro-1,4-diazepin-2-ones by germanium-mediated [5 + 2] annulation of 3-iminoprop-1-enylamines;[6] moreover, the process is simple in terms of availability of materials and experimental techniques. Finally, the thermal transformation of the diazepine ring takes place very easily giving rise to a scarcely found oxazine family, namely 2*H*-1,3-oxazines.[7]

This work was supported in part by the Dirección General de Investigación Científica y Técnica (DGICYT, PB88-0500). J.-S. K. thanks the Ministerio de Educación y Ciencia for a fellowship.

Received, 4th August 1992; Com. 2/04196K

References

1 J. T. Sharp, in *Comprehensive Heterocyclic Chemistry*, ed. W. Lwowski, Pergamon Press, Oxford, 1984, vol. 7, p. 608; D. Lloyd, H. P. Cleghorn and D. R. Marshall, in *Adv. Heterocycl. Chem.*, 1974, **17**, 1.

2 J. Barluenga, R. Pérez Carlón, F. J. González, F. López Ortiz and S. Fustero, *J. Chem. Soc., Chem. Commun.*, 1991, 1704; Y. Ohtsuka, *J. Org. Chem.*, 1976, **41**, 629; A. Padwa, L. Gehrlein and R. B. Kinnel, *J. Org. Chem.*, 1975, **40**, 1683; U. Schöllkopf and J. Mittendorf, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 613.

3 J. Barluenga, M. Tomás, A. Ballesteros and J.-S. Kong, *Synthesis*, 1992, 106.

4 J. Barluenga, M. Tomás, A. Ballesteros, J.-S. Kong, S. García-Granda and P. Pertierra, *Organometallics*, 1992, **11**, 2348.

5 P. Rivière, M. Rivière-Baudet and J. Satgé, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon Press, New York 1982, vol. 2, p. 399.

6 H. Hoberg and J. Barluenga, *Synthesis*, 1970, 140; J. Barluenga, M. Tomás, J. F. López-Ortiz and V. Gotor, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2273.

7 M. Sainsbury, in *Comprehensive Heterocyclic Chemistry*, ed. A. J. Boulton and A. McKillop, Pergamon Press, Oxford, 1984, vol. 3, p. 995.

‡ The formation of 2,2-bis(ethoxycarbonyl)-1,2-dihydropyrimidines was not observed although elimination of diethylgermanium oxide is expected to compete. On the other hand, neither 1,3,2-diazasiline derivatives nor iminopropenes **1** themselves furnish **4** on reaction with diethyl oxomalonate.

§ *Spectroscopic data* for compound **5c**; IR (KBr) ν_{max}/cm^{-1} 3213 (NH), 1764 (CO), 1624 (CO); ^1H NMR ($CDCl_3$; 300 MHz): δ 0.5–2.0 (m, 11H), 1.3 (t, 3H, *J* 7.0 Hz), 2.2 (s, 3H), 4.3–4.5 (m, 2H), 5.7 (s, 1H), 6.5 (d, 2H, *J* 8.3 Hz), 6.9 (d, 2H, *J* 8.3 Hz), 7.1–7.4 (m, 5H), 9.2 (br, 1H); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 175.3 (s), 169.1 (s), 162.8 (s), 156.4 (s), 146.2 (s), 136.4 (s), 132.9 (s), 132.8 (s), 128.7 (d), 128.1 (d), 128.0 (d), 127.5 (d), 121.5 (d), 117.4 (d), 80.6 (s), 62.1 (t), 36.1 (d), 29.6 (t), 25.5 (t,), 24.9 (t), 20.6 (q), 14.2 (q); MS *m/z* 446 (M^+).

¶ The structure **5** was confirmed by X-ray diffraction analysis, details of which will be published elsewhere.