

## Reaction of Azines with Aromatic Ketones; Synthesis of $\alpha,\beta$ -Unsaturated Azines and 5,6-Dihydro-4*H*-1,2-diazepines

José Barluenga,\* María José Iglesias, and Vicente Gotor

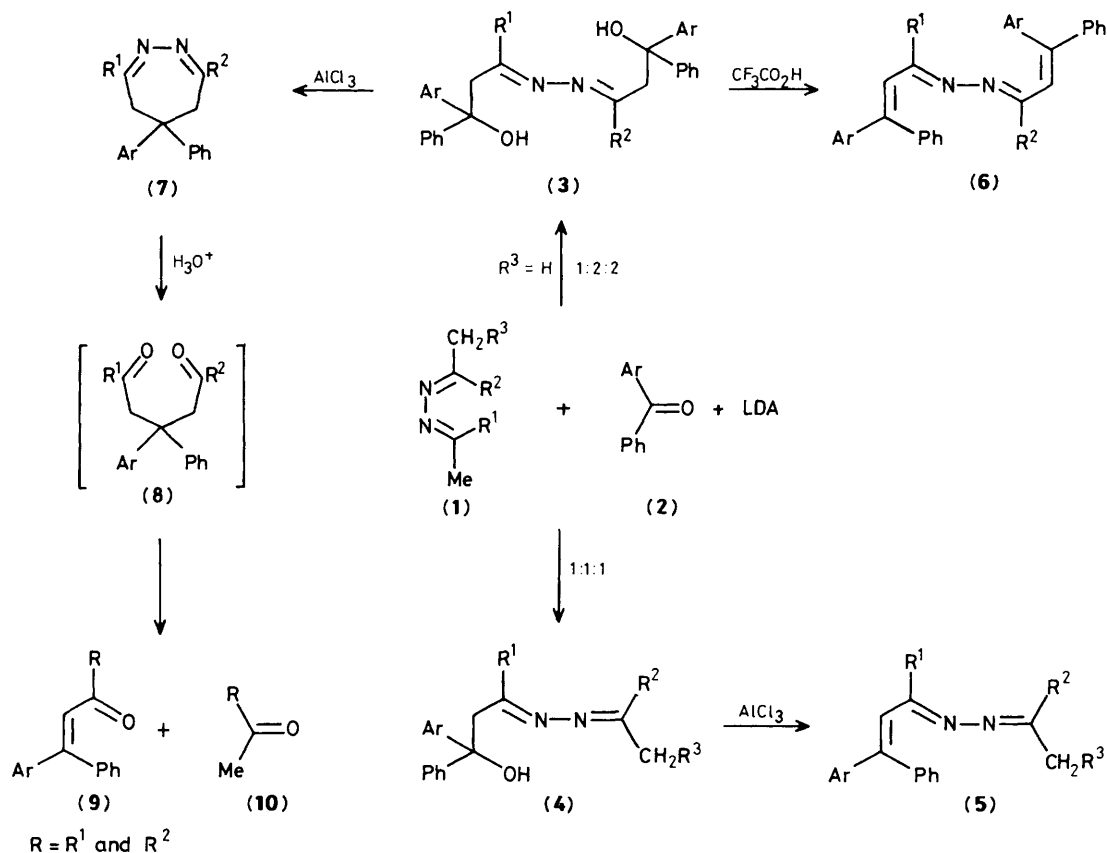
*Departamento de Química Orgánica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain*

Azines react with aromatic ketones, in the presence of lithium di-isopropylamide (LDA), giving rise to mono- and di-hydroxyazines; the reaction of these compounds with  $\text{AlCl}_3$  affords  $\alpha,\beta$ -unsaturated azines and 5,5-disubstituted-5,6-dihydro-4*H*-1,2-diazepines, respectively.

In preliminary papers, we have reported on the reactivity of the ketazine (ketone azine)  $\text{C}_\alpha\text{-H}$  bond towards saturated nitriles. This reaction takes place with addition of one or two molecular equivalents of nitrile to the starting azine to yield hydrazone<sup>1</sup> and hydrazine<sup>2</sup> derivatives, respectively. In the reaction of unsymmetrical substituted azines derived from aromatic hydrazones and aliphatic ketones with saturated nitriles<sup>1</sup> we have observed different  $\text{C}_\alpha\text{-H}$  reactivities of the starting azines, since the addition occurs through the  $\text{C}_\alpha\text{-H}$  group on the aliphatic side of the azine in a regioselective

manner. Although  $\text{C}_\alpha$ -metallated ketimines,<sup>3</sup> oximes,<sup>4</sup> and hydrazones<sup>5</sup> have been widely used in organic synthesis, the preparation of the corresponding lithiated azines has received little attention.<sup>6</sup> We thought it of interest to study the reaction of  $\text{C}_\alpha$ -anions of symmetrical and unsymmetrical azines with carbonyl compounds and to use the resulting compounds in the preparation of 1-azabutadiene derivatives, which are difficult to prepare by other methods.

Treatment of azine (1) with two equivalents of lithium di-isopropylamide (LDA) followed by addition of two equiv-



Scheme 1

**Table 1.**  $\alpha,\beta$ -Unsaturated azines (5) and (6) from hydroxyazines (4) and (3) (Ar = Ph).

Compound <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)	M.p./°C
(5a)	Me	Ph	H	93	116–118
(5b)	Me	Ph	Me	97	103–105
(6a)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	–	96	235–236
(6b)	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	–	89	241–242
(6c)	Ph	Ph	–	85	208–210
(6d)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ph	–	83	195–197

<sup>a</sup> All new compounds gave satisfactory elemental analyses.**Table 2.** 1,2-Diazepines (7) from dihydroxyazines (3).

Compound <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	Ar	Yield (%)	M.p./°C
(7a)	Me	Ph	Ph	85	193–195
(7b)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ph	88	252–254
(7c)	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ph	83	234–236
(7d)	Ph	Ph	Ph	80	173–175
(7e)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	90	177–179
(7f)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ph	Ph	85	158–160

<sup>a</sup> All new compounds gave satisfactory elemental analyses.

alents of ketone (2) resulted in the formation of dihydroxyazines (3) in high yield (see Table 1). On the other hand, hydroxyazines (4) were easily formed when stoichiometric amounts of unsymmetrical azines, LDA, and carbonyl compounds were used. When the hydroxyazines (4) were allowed

to react with aluminium chloride,  $\alpha,\beta$ -unsaturated azines (5) were isolated. The <sup>1</sup>H n.m.r. spectra of these compounds display a singlet at  $\delta$  ca. 7 corresponding to the  $\beta$ -hydrogen. On the other hand, the <sup>13</sup>C n.m.r. spectra show three characteristic signals at  $\delta$  ca. 161 (s, C=N), 159 (s, C=N), and 124 (d, –C=CH). In the same way, compounds (3) were converted into (6) by treatment with trifluoroacetic acid.†

Surprisingly, when the dihydroxyazines (3) were treated with aluminium chloride, the 5,5-disubstituted-5,6-dihydro-4H-1,2-diazepines (7) were isolated as the sole product in excellent yields‡ (see Table 2). It is noteworthy that while 5,6-dihydro-4H-1,2-diazepines can be synthesized by condensation of 1,5-dicarbonyl compounds with hydrazine,<sup>7</sup> the synthesis of the corresponding 5,5-disubstituted derivatives is rather difficult, and only in a few instances has the preparation of this class of compounds been described.<sup>8,9</sup>

Compounds (7) were characterized on the basis of their elemental analyses and spectral data. Thus, the <sup>1</sup>H n.m.r. spectrum of (7b) (R<sup>1</sup> = R<sup>2</sup> = *p*-MeC<sub>6</sub>H<sub>4</sub>; Ar = Ph) shows a signal at  $\delta$  3.4 due to the cyclic methylene groups. In the <sup>13</sup>C n.m.r. spectrum of (7b) signals at  $\delta$  38 (t), 61 (s), and 159 (s) corresponding to the ring carbon atoms are observed.

Acid hydrolysis of some 5,6-dihydro-4H-1,2-diazepines yields the corresponding 1,5-dicarbonyl compounds and

† The ability of azadienes (5) and (6) to participate in the cycloaddition processes is currently being investigated.

‡ The formation of the diazepine (7) can be explained through dehydration of (3) followed by loss of ketone and formation of a dihydropyrazole intermediate, which can be transformed into (7) via a mechanism similar to that proposed by Burger *et al.* for the formation of other 5,5-disubstituted-1,2-diazepine derivatives (see ref. 9).

hydrazine.<sup>10</sup> However, treatment of (7) with mineral acid, under various conditions, did not lead to the formation of (8); ketones (9) and (10) in stoichiometric ratio were isolated instead. The formation of these ketones can be explained through a *retro*-Michael reaction on the initially formed dicarbonyl compounds (8).

In conclusion, this work demonstrates the utility of hydroxyazines for the preparation of  $\alpha,\beta$ -unsaturated azines and their suitability for the synthesis of 5,5-disubstituted-5,6-dihydro-4*H*-1,2-diazepines, whose preparation by other methods is not easy.

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### References

- 1 J. Barluenga, L. Muñiz, M. J. Iglesias, and V. Gotor, *J. Chem. Soc., Perkin Trans. 1*, 1984, 611.
  - 2 J. Barluenga, L. Muñiz, and V. Gotor, *J. Chem. Soc., Chem. Commun.*, 1982, 454.
  - 3 L. Duhamel, J.-M. Poirier, and N. Tedga, *J. Chem. Res. (S)*, 1983, 222.
  - 4 (a) J. D. Wilson, T. D. Fulmer, L. P. Dasher, and Ch. F. Beam, *J. Heterocycl. Chem.*, 1980, **17**, 389; (b) D. Enders and P. Wenster, *Tetrahedron Lett.*, 1978, 2853; (c) T. Cuvigny, J. F. le Borgne, M. Larchevêque, and H. Normant, *Synthesis*, 1976, 237.
  - 5 M. Bellassoned, R. Chtara, F. Dardoize, and M. Gaudemar, *Synthesis*, 1983, 951, and references cited therein.
  - 6 S. E. David, N. L. Shealy, L. M. Shaffer, K. D. Shealy, and Ch. F. Beam, *Can. J. Chem.*, 1978, **56**, 1236.
  - 7 C. G. Overberger and J. J. Monagle, *J. Am. Chem. Soc.*, 1956, **78**, 4470.
  - 8 O. Tsuge, K. Kamota, and S. Yogi, *Bull. Chem. Soc. Jpn.*, 1977, 2153.
  - 9 K. Burger, H. Schickander, and C. Zette, *Liebigs Ann. Chem.*, 1982, 1741.
  - 10 H. E. Zimmerman and W. Eberbach, *J. Am. Chem. Soc.*, 1973, **95**, 3970.
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