Reaction of Azines with Aromatic Ketones; Synthesis of α,β-Unsaturated Azines and 5,6-Dihydro-4*H*-1,2-diazepines

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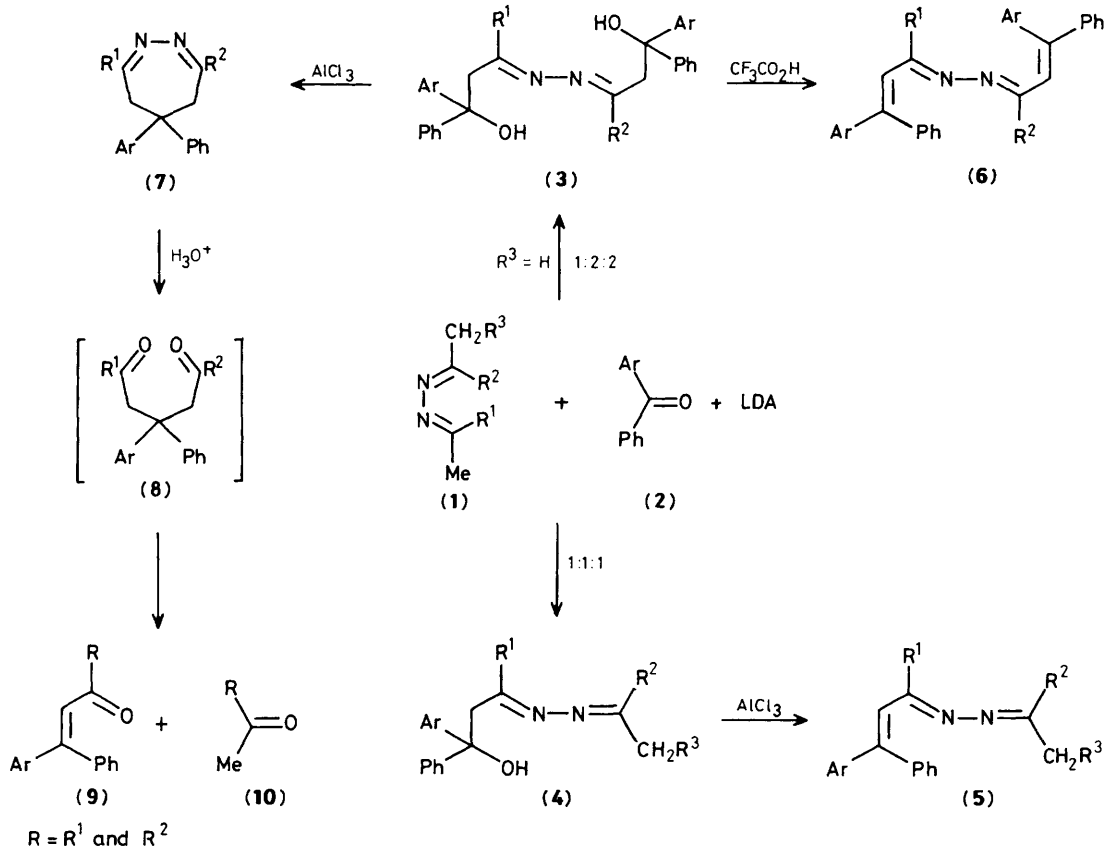
Azines react with aromatic ketones, in the presence of lithium di-isopropylamide (LDA), giving rise to mono- and di-hydroxyazines; the reaction of these compounds with $AlCl_3$ affords α,β-unsaturated azines and 5,5-disubstituted-5,6-dihydro-4*H*-1,2-diazepines, respectively.

In preliminary papers, we have reported on the reactivity of the ketazine (ketone azine) C_α–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[1] and hydrazine[2] derivatives, respectively. In the reaction of unsymmetrical substituted azines derived from aromatic hydrazones and aliphatic ketones with saturated nitriles[1] we have observed different C_α–H reactivities of the starting azines, since the addition occurs through the C_α–H group on the aliphatic side of the azine in a regioselective manner. Although C_α-metallated ketimines,[3] oximes,[4] and hydrazones[5] have been widely used in organic synthesis, the preparation of the corresponding lithiated azines has received little attention.[6] We thought it of interest to study the reaction of C_α-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. α,β-Unsaturated azines (**5**) and (**6**) from hydroxyazines (**4**) and (**3**) (Ar = Ph).

Compound[a]	R^1	R^2	R^3	Yield (%)	M.p./°C
(**5a**)	Me	Ph	H	93	116—118
(**5b**)	Me	Ph	Me	97	103—105
(**6a**)	*p*-MeC_6H_4	*p*-MeC_6H_4	–	96	235—236
(**6b**)	*p*-ClC_6H_4	*p*-ClC_6H_4	–	89	241—242
(**6c**)	Ph	Ph	–	85	208—210
(**6d**)	*p*-MeC_6H_4	Ph	–	83	195—197

[a] All new compounds gave satisfactory elemental analyses.

Table 2. 1,2-Diazepines (**7**) from dihydroxyazines (**3**).

Compound[a]	R^1	R^2	Ar	Yield (%)	M.p./°C
(**7a**)	Me	Ph	Ph	85	193—195
(**7b**)	*p*-MeC_6H_4	*p*-MeC_6H_4	Ph	88	252—254
(**7c**)	*p*-ClC_6H_4	*p*-ClC_6H_4	Ph	83	234—236
(**7d**)	Ph	Ph	Ph	80	173—175
(**7e**)	*p*-MeC_6H_4	*p*-MeC_6H_4	*p*-MeC_6H_4	90	177—179
(**7f**)	*p*-MeC_6H_4	Ph	Ph	85	158—160

[a] 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 stoicheiometric amounts of unsymmetrical azines, LDA, and carbonyl compounds were used. When the hydroxyazines (**4**) were allowed to react with aluminium chloride, α,β-unsaturated azines (**5**) were isolated. The ^{1}H n.m.r. spectra of these compounds display a singlet at δ *ca.* 7 corresponding to the β-hydrogen. On the other hand, the ^{13}C n.m.r. spectra show three characteristic signals at δ *ca.* 161 (s, *C*=N), 159 (s, *C*=N), and 124 (d, –C=*C*H). 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-4*H*-1,2-diazepines (**7**) were isolated as the sole product in excellent yields‡ (see Table 2). It is noteworthy that while 5,6-dihydro-4*H*-1,2-diazepines can be synthesized by condensation of 1,5-dicarbonyl compounds with hydrazine,[7] 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.[8,9]

Compounds (**7**) were characterized on the basis of their elemental analyses and spectral data. Thus, the ^{1}H n.m.r. spectrum of (**7b**) (R^1 = R^2 = *p*-MeC_6H_4; Ar = Ph) shows a signal at δ 3.4 due to the cyclic methylene groups. In the ^{13}C n.m.r. spectrum of (**7b**) signals at δ 38 (t), 61 (s), and 159 (s) corresponding to the ring carbon atoms are observed.

Acid hydrolysis of some 5,6-dihydro-4*H*-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.[10] However, treatment of (**7**) with mineral acid, under various conditions, did not lead to the formation of (**8**); ketones (**9**) and (**10**) in stoicheiometric 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 α,β-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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