Short Communication

Reactions of 1-Aza-1,3-butadienes. A Convenient Synthesis of *N*-Benzyl-1,4-dihydropyridines

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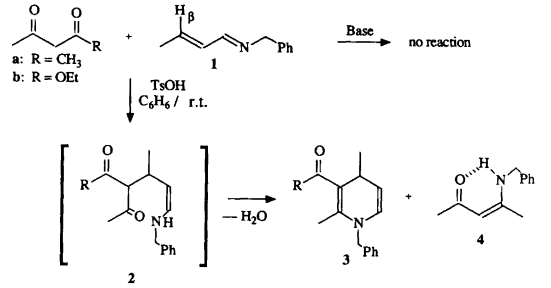
1,4-Dihydropyridines (1,4-DHP)[1-3] are biologically interesting substances because of their natural occurrence[4,5] and medical applications.[6-8]

A recent review on the synthesis of 1,4-DHP prompted us to disclose our synthetic approach towards these substances using 1-aza-1,3-butadienes (enimines) as starting materials.[9]



Scheme 1.

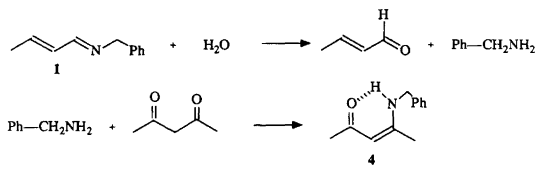
Due to its electronic structure, an enimine system (e.g. **1** in Scheme 1) could be expected to behave in a similar fashion to an α,β-unsaturated carbonyl compound in a Michael addition. It was therefore surprising to find that the reaction of **1** with various 1,3-dicarbonyl compounds (ethyl acetoacetate, acetylacetone, dimethyl malonate, ethyl cyanoacetate) under basic conditions did not yield any isolable products; instead the starting compounds were always contaminated with tarry material. These results indicate the enimine compounds to be considerably less reactive toward nucleophiles than the corresponding carbonyl compounds,[10,11] i.e. the partial positive charge on the β-carbon in enones is greater than in enimines, owing at least partly to the greater electronegativity of oxygen as compared with nitrogen. This was indeed supported by NMR spectroscopy as β-H in **1** appears at δ 5.78 whereas in crotonaldehyde it appears at δ 6.9, indicating a lower electron density at the β-carbon of the aldehyde,[12] hence the aldehyde is more reactive in a Michael reaction.

We therefore changed to acid-catalysed reaction conditions in order to enhance the reactivity of the enimine, by protonating the nitrogen atom. In this communication we report the results of the reactions of *N*-benzyl-1-aza-1,3-pentadiene (**1**) with ethyl acetoacetate and acetylacetone. By adding a catalytic amount of *p*-toluenesulfonic acid (TsOH) to the reaction mixture, the enimine **1** becomes reactive enough to react with ethyl acetoacetate and acetylacetone. The corresponding 1,4-DHP was isolated as the main product, identified by its ^{1}H and ^{13}C NMR spectra.

The reaction of **1** with acetylacetone at ambient temperature afforded, after chromatographic purification, 50 % of the 1,4-DHP **3a**, 18 % of the enamino ketone **4** and 6 % of an unidentified air-sensitive compound, the ^{1}H NMR spectrum of which agrees with structure **2**. Refluxing of the mixture resulted in 16 % of **3a** and 33 % of **4**. The ^{1}H NMR spectrum of **3a** revealed for the vinyl protons one signal at δ 6.49 (d, J=9.5 Hz) and another at δ 5.07 (dd, J=5.5 and 9.5 Hz). The non-equivalent benzyl protons appeared as doublets at δ 4.40 and 4.86 with J=17 Hz. The IR spectrum showed a strong band at 1610 cm^{-1} in agreement with this conjugated system.

The reaction of **1** with ethyl acetoacetate at ambient temperature gave 60 % of **3b** as the only product. It is noteworthy that we did not observe any product corresponding to an attack of nitrogen on the ester carbonyl. This is actually in accordance with the fact that the use of dimethyl malonate as the active methylene compound only resulted in tar formation, probably because the ring closure in the second step did not occur.

The proposed formation of **4** is demonstrated in Scheme 2.



Scheme 2.

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Water from the dehydration step (**2** to **3**) hydrolyses the enimine **1** and the so-formed benzylamine reacts with acetylacetone to afford **4**. When benzylamine and acetylacetone were stirred together in benzene at ambient temperature, the only product isolated was a compound, which had spectroscopic properties identical with those of **4**.

Experimental

Distillation of small amounts was effected by bulb-to-bulb distillation in a Büchi Kugelrohr oven, Model GKR-50 (only external or oven temperature reported). IR: Perkin-Elmer Spectrophotometer, Model 283. ^{1}H NMR: Varian EM 360; ^{13}C NMR:Varian CFT 20. Chromatographic purifications were performed with a preparative HPLC instrument from Waters, Model Prep-LC 500A.

N-*Benzyl-1-aza-1,3-pentadiene* (**1**). Crotonaldehyde (0.24 mol) and benzylamine (0.24 mol) were disolved in benzene (200 ml), stirred for 60 min under N_2 at ambient temperature and then heated in a Dean–Stark apparatus until water formation had ceased (ca. 1 h). After the solution had been cooled to room temperature, it was washed with water and dried over $MgSO_4$. The solvent was removed and the residue was distilled (Kugelrohr distillation). Yield 22.1 g (58%), b.p. 110–120°C (0.02 mmHg). ^{1}H NMR (60 MHz, C_6D_6): δ 1.54 (3 H, d, *J* 6 Hz), 4.50 (2 H, s), 5.78 (1 H, qd, *J* 6 Hz and 15 Hz), 6.30 (1 H, dd, *J* 8 Hz and 15 Hz), 7.15 (5 H, s), 7.70 (1 H, d, *J* 8 Hz). IR (neat): 1625, 1655 cm^{-1}.

General procedure for the formation of the 1,4-dihydropyridine derivatives. To a solution of the enimine **1** (0.12 mol) in 200 ml of dry benzene at room temperature was added a solution of the 1,3-dicarbonyl compound (0.12 mol) and TsOH (0.0024 mol; 2%) in benzene (50 ml), and the mixture was stirred for 24 h under N_2. The solution was washed with water and dried over $MgSO_4$. After the solvent had been removed, the residue was chromatographed on silica gel (light petroleum–ethyl acetate) to afford the products.

N-*Benzyl-3-acetyl-2,4-dimethyl-1,4-dihydropyridine* (**3a**): Yield 50%; b.p. 110–120°C (0.005 mmHg). IR (neat): 1610 cm^{-1}. MS [*m/z* (% rel. int.)]: 241 (M^+, 5), 226 (22), 189 (13), 174 (8), 172 (4), 91 (100). ^{1}H NMR (C_6D_6): δ 0.90 (3 H, d, *J* 6 Hz), 2,14 (3 H, s), 2.40 (3 H, s), 3.60 (1 H, dq, *J* 5.5 and 6 Hz), 3.84 (1 H, d, *J* 17 Hz), 4.37 (1 H, d, *J* 17 Hz), 4.84 (1 H, dd, *J* 5.5 and 9.5 Hz), 6.37 (1 H, d, *J* 9,5 Hz), 7.15 (5 H, s). ^{13}C NMR ($CDCl_3$, TMS): δ 17.16 (q), 19.35 (q), 28.86 (q), 52.95 (t), 55.70 (d), 108.88 (s), 111.67 (d), 125.03 (d), 126.14 (d), 127.57 (d), 128.91 (d), 136.87 (s), 156.45 (s), 194.12 (s).

N-*Benzyl-3-ethoxycarbonyl-2,4-dimethyl-1,4-dihydropyridine* (**3b**). Yield 60%; b.p. 120–130°C (0.01 mmHg). IR (neat): 1630, 1675 cm^{-1}. MS [*m/z* (% rel. int.)]: 271 (M^+, 6), 256 (31), 242 (1), 226 (8), 205 (3), 91 (100). ^{1}N NMR ($CDCl_3$): δ 1.12 (3 H, d, *J* 6 Hz), 1.29 (3 H, t, *J* 7 Hz), 2.44 (3 H, s), 3.97 (1 H, dq, *J* 5.5 and 6 Hz), 4.16 (2 H, 1 *J* 7 Hz), 4.37 (1 H, d, *J* 16.5 Hz), 4.84 (1 H, dq *J* 16.5 Hz), 5.05 (1 H, dd, *J* 5.5 and 9,5 Hz), 6.60 (1 H, d, *J* 9.5 Hz), 7.22–7.34 (5 H, m). ^{13}C NMR ($CDCl_3$, TMS): δ 14.60 (q), 16.46 (q), 19.45 (q), 53.05 (t), 55.52 (d), 58.91 (t), 98.40 (s), 111.96 (d), 123.98 (d), 126.14 (d), 127.39 (d), 128.84 (d), 137.57 (s), 154.93 (s), 167.48 (s).

*4-(*N*-Benzylamino)-3-penten-2-one* (**4**). ^{1}H NMR (C_6D_6): δ 1.83 (3 H, s), 1.96 (3 H, s), 4.45 (2 H, d, *J* 6.5 Hz), 5.07 (1 H, s), 7.40 (5 H, s), 13.08 (1 H, broad t, *J* 6.5 Hz). IR (neat): 1610, 1575 cm^{-1}.

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