

Short Communication

Reactions of 1-Aza-1,3-butadienes. An Expedient Synthesis of Unsymmetrically Substituted *N*-Benzyl-1,4-dihydropyridines and *N*-Benzyl-1,4-dihydronicotinamides

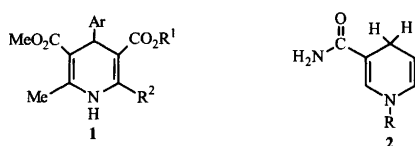
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The 1,4-dihydropyridines (1,4-DHP) continue to be the subject of considerable interest, mainly due to their properties as calcium channel blockers,^{1–3} the 4-aryl-1,4-dihydropyridines **1a,b** being examples of successfully introduced commercial products. Furthermore, the recognition that 1,4-dihydronicotinamide **2** is the chemically active component of NAD(P)H has created interest in dihydropyridines in general as potentially selective reducing agents.^{4,5}

The vast majority of reported synthetic procedures for the preparation of 1,4-DHP, particularly large-scale preparations, are based on the Hantzsch synthesis.^{6,7} More recent developments include the use of microwave irradiation^{8,9} and improved methods for the synthesis and isolation of chiral 1,4-dihydropyridine derivatives.^{10,11}



a: R¹=R²=Me; Ar=2-nitrophenyl (Nifedipine)
b: R¹=Et; R²=-CH₂OCH₂CH₂NH₂;
Ar=2-chlorophenyl (Amlodipine)

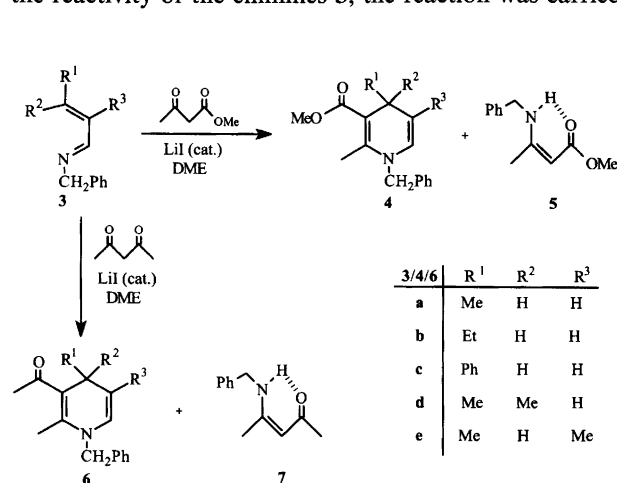
In continuation of our studies on the reactions of 1-aza-1,3-butadienes **3** with 1,3-dicarbonyl compounds,¹² we now report a convenient method for the preparation of unsymmetrically substituted 1,4-DHP from readily available starting materials. Moreover, this method produces derivatives that are unsubstituted at the 6-position, compounds reported to be difficult to obtain.¹

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Results and discussion

The 1-aza-1,3-butadienes (enimines) **3** were prepared by stirring a dichloromethane solution of an α,β -unsaturated aldehyde and benzylamine over molecular sieves under nitrogen at ambient temperature for 24 h. This afforded the air- and moisture-sensitive products **3** as colorless or pale yellow oils in 50–80% yield after distillation. This method was in all cases superior to conventional condensation using a Dean–Stark trap.

The reaction sequence for the reaction of **3** with methyl acetoacetate and acetylacetone is depicted in Scheme 1. Basic reaction conditions did not yield any isolable products which was ascribed to the diminished reactivity of the enamine toward nucleophiles, compared with the corresponding carbonyl compounds. In order to enhance the reactivity of the enamines **3**, the reaction was carried



Scheme 1.

out in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH). These mild, acid-catalyzed conditions afforded the 1,4-DHP **4a** from **3a** in 50–60% yield after chromatographic purification. Unfortunately, the employment of TsOH as a catalyst was not extendable to the other enamines, and further efforts to promote the reaction by conventional Lewis acids (AlCl₃, FeCl₃, TiCl₄, BF₃·OEt₂) did not furnish the products **4** in satisfactory yields. The enamines **3c** and **3d** proved to be particularly difficult substrates in this context, always giving rise to products that resulted from an initial 1,2-addition of the dicarbonyl compound to the enamine **3**. It is noteworthy that the use of catalytic amounts of Hg(OAc)₂ seemed generally to facilitate such a 1,2-addition of the dicarbonyl compound to **3** with subsequent elimination of the amino functionality. However, the isolated yields of such products remained low.

Recently, Scettri *et al.* reported on the use of lithium iodide as a preferred catalyst in Michael reactions performed under neutral reaction conditions.¹³ A minor modification of their procedure was successful with our compounds. Stirring of a 1,2-dimethoxyethane (DME) solution of the reactants in the presence of 10 mol% of lithium iodide at ambient temperature for 24 h afforded **4** in good to excellent yields (Table 1). Even the ‘difficult’ enamines, **3c** and **3d**, provided **4c** and **4d** in 55% and 44% yield, respectively.

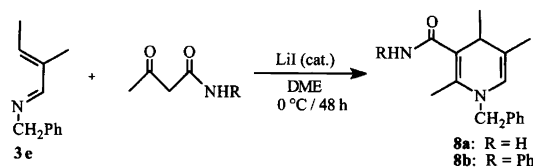
The formation of the 1,4-DHP can be rationalized as a Michael addition of the 1,3-dicarbonyl compound to the enamine with an ensuing ring closure. The function of the catalyst is presumably to polarize the π -system of **3** and such polarization is expected to activate the enamine towards nucleophilic attack. It was previously noted that the 1,2-addition competes to some extent with the desired 1,4-addition. Additionally, we observed the formation of the enamino ester **5** and the corresponding starting aldehyde as by-products in the reaction of **3c,d** with methyl acetoacetate. The enamines **3c,d** are less reactive Michael acceptors than the other enamines, and that might be partly responsible for the formation of **5**,

probably via an iminolysis of the 1,3-dicarbonyl compound.^{14,15} Alternatively, the hydrolysis of **3** would produce benzylamine which could condense with the 1,3-dicarbonyl compound to form **5**. In order to reduce the probability of hydrolysis, the reaction was carried out in the presence of activated molecular sieves, but without any noticeable effect on the results.

This latter reaction pathway constituted a more serious problem when **3** was reacted with acetylacetone to afford the 1,4-DHP **6** (Scheme 1, Table 1). The enamino ketone **7** was always formed in appreciable amounts and in the case of enamine **3d** it was the only isolable product (50% yield).

The products **4** and **6** were characterized on the basis of their ¹H and ¹³C NMR spectra. A very distinctive feature of their ¹H NMR spectra was the appearance of two doublets at δ 4.4–4.8 with a large coupling constant of between 16.5 and 17 Hz. These signals were assigned to the non-equivalent protons of the methylene group of the benzyl moiety. Only compound **4d** displayed a singlet for the methylene protons. The signal for 6-H appeared as a doublet at δ 5.5–6.5 with ³*J* in the range 7.5–9.5 Hz; the corresponding signals for compounds **4e** and **6e** showed a small allylic coupling (*J*_{allyl} 1.4 Hz). These characteristic features are given in Table 1.

In order to demonstrate the synthetic utility of the reaction sequence, we prepared two *N*-benzyl-1,4-dihydropyridinamides **8a,b**, as outlined in Scheme 2. In a somewhat modified procedure, a keto amide and **3e**, the least air- and moisture-sensitive of the enamines, were stirred in an ice–water bath for 48 h to afford **8a** and **8b** in 63% and 27% yield, respectively.



Scheme 2.

Table 1. Selected data for compounds **4**, **6**, and **8**.

Compound	R ¹	R ²	R ³	Yield (%)	b.p./°C (Torr) [m.p./°C]	¹ H NMR: δ	
						-CH ₂ Ph (² <i>J</i> in Hz)	H-6 (³ <i>J</i> in Hz)
4a	Me	H	H	61	120–130 (0.008)	4.47/4.62 (16.5)	
4b	Et	H	H	44	130–140 (0.03)	4.50/4.62 (17.0)	5.93 (7.6)
4c	Ph	H	H	55	180–200 (0.003)	4.59/4.72 (17.0)	5.98 (7.6)
4d	Me	Me	H	44	180–200 (0.005)	4.64 (s)	6.53 (9.6)
4e	Me	H	Me	72	140–150 (0.008)	4.45/4.62 (17.1)	5.68 (<i>J</i> _{allyl} 1.4)
6a	Me	H	H	55	110–120 (0.005)	3.84/4.37 (17.0)	6.37 (9.5)
6b	Et	H	H	20	100–120 (0.008)	4.34/4.92 (16.9)	6.50 (9.5)
6c	Ph	H	H	30	190–200 (0.008)	4.65/4.88 (16.8)	5.96 (7.6)
6e	Me	H	Me	45	120–140 (0.006)	4.50/4.64 (17.0)	5.70 (<i>J</i> _{allyl} 1.4)
8a	R = H			63	[173–174]	4.42/4.59 (17.1)	5.69 (<i>J</i> _{allyl} 1.3)
8b	R = Ph			27	[117–118]	4.44/4.60 (18.2)	5.72 (<i>J</i> _{allyl} 1.3)

An attempt to use *N,N*-diethylacetoacetamide was unsuccessful.

Spectroscopic features of **8a,b** were similar to those of the other 1,4-DHP, and are listed in Table 1 for comparison.

In summary, we report a convenient, easy-to-scale-up, procedure for the preparation of unsymmetrically substituted 1,4-DHP derivatives from readily accessible enamines, obtained from α,β -unsaturated aldehydes. All attempts to devise a similar procedure using α,β -unsaturated ketones as starting materials have been unsuccessful to date, and this constitutes a limitation to the reaction sequence.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer. Chemical shifts are reported in δ values relative to CHCl_3 . Multiplicities in the ^{13}C NMR spectra were determined using DEPT pulse sequences. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer. Elemental analyses were carried out on a Model 1106 Carlo Erba microanalyzer at the University of Iceland. Melting points were obtained on a Büchi 520 melting point apparatus and are uncorrected. Distillation of small amounts was effected with a bulb-to-bulb apparatus in a Büchi Kugelrohr oven, Model GKR-50 (only external or oven temperature reported).

General procedure for the preparation of N-benzyl-1,4-dihydropyridines (4, 6, 8). The reactions were carried out under nitrogen in thoroughly dried glassware. A solution of the dicarbonyl compound (0.01 mol) and lithium iodide (0.134 g, 0.001 mol) in dry DME (2–3 ml) was added dropwise to a stirred solution of the enamine **3** (0.01 mol) in dry DME (5–10 ml). The resulting mixture was stirred at ambient temperature for 24 h. After removal of the solvent under reduced pressure, the oily residues were purified by short column chromatography (silica gel, eluted with dichloromethane–ethyl acetate) and Kugelrohr distillation.

For the preparation of *N*-benzyl-1,4-dihydronicotinamides (**8**) the mixture was stirred over activated molecular sieves (2.5 g, 4 Å) at 0 °C for 48 h. If crystals formed during the reaction (**8a**), the solution was filtered and the product recrystallized from dichloromethane. A second crop could be obtained by removing the solvent *in vacuo* and purifying the residue by chromatography (silica gel, elution with CHCl_3). Otherwise (**8b**), after removal of the molecular sieves, the solvent was removed *in vacuo* and the residue purified by chromatography (silica gel, elution with CHCl_3). The product was recrystallized from 1-butanol or ethanol–petroleum ether.

N-Benzyl-2,4,5-trimethyl-1,4-dihydronicotinamide, **8a**. Yield 1.6 g (63%). M.p. 173–174 °C. Anal. $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$: C, H, N. IR (KBr): 1565, 1630, 1690, 3380 cm^{-1} .

^1H NMR (CDCl_3): δ 1.12 (d, $J=6.5$ Hz, 3 H), 1.68 (d, $J=1.3$ Hz, 3 H), 2.21 (s, 3 H), 3.09 (q, $J=6.5$ Hz, 1 H), 4.42 (d, $J=17.1$ Hz, 1 H), 4.59 (d, $J=17.1$ Hz, 1 H), 5.50 (br s, 2 H), 5.69 (q, $J=1.3$ Hz, 1 H), 7.16–7.37 (m, 5 H). ^{13}C NMR (CDCl_3): δ 15.8 (q), 18.3 (q), 21.4 (q), 35.3 (d), 53.0 (t), 103.0 (s), 114.8 (s), 125.7 (d), 126.0 (d, 2 C), 127.2 (d), 128.7 (d, 2 C), 138.8 (s), 143.0 (s), 172.8 (s).

N-Benzyl-*N'*-phenyl-2,4,5-trimethyl-1,4-dihydronicotinamide, **8b**. Yield 0.9 g (27%). M.p. 117–118 °C. Anal. $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}$: C, H, N. IR (KBr): 1580, 1620, 1690, 3320 cm^{-1} . ^1H NMR (CHCl_3): δ 0.84 (d, $J=6.5$ Hz, 3 H), 1.70 (d, $J=1.3$ Hz, 3 H), 2.16 (s, 3 H), 3.24 (q, $J=6.5$ Hz, 1 H), 4.44 (d, $J=18.2$ Hz, 1 H), 4.60 (d, $J=18.2$ Hz, 1 H), 5.72 (q, $J=1.3$ Hz, 1 H), 7.02–7.38 (m, 11 H). ^{13}C NMR (CDCl_3): δ 15.9 (q), 18.3 (q), 21.8 (q), 35.4 (d), 53.0 (t), 105.2 (s), 114.4 (s), 119.7 (d, 2 C), 123.6 (d), 125.9 (d), 126.0 (d, 2 C), 127.2 (d), 128.8 (d, 2 C), 128.9 (d, 2 C), 138.7 (s), 138.9 (s), 141.4 (s), 169.1 (s).

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