A Hantzsch 1,4-Dihydropyridine Synthesis Producing an Unusual By-product

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Received April 6, 1987

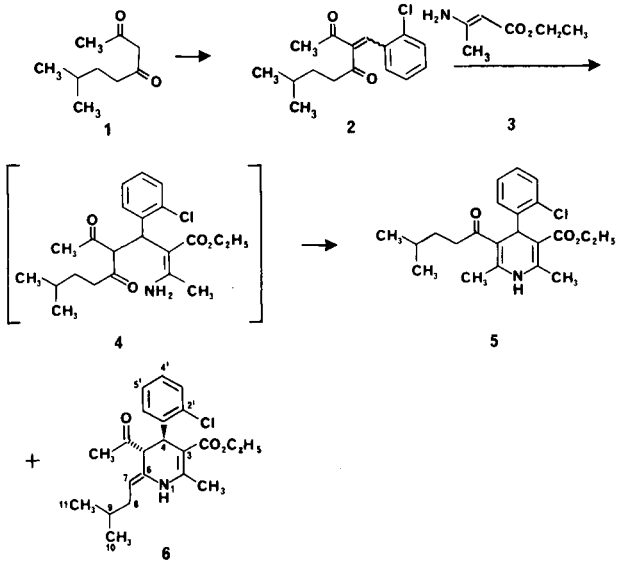
The reaction of 2-acetyl-1-(2-chlorophenyl)-6-methylhept-1-en-3-one (**2**) with ethyl 3-aminocrotonate gave an unusual isomer of a 1,4-dihydropyridine (**6**), having an exocyclic double bond. The structure and stereochemistry of **6** was established with ^1H and ^{13}C nmr spectroscopy.

J. Heterocyclic Chem., **25**, 125 (1988).

The venerable Hantzsch reaction [2] has been widely used to prepare 1,4-dihydropyridines and remains the method of choice for the synthesis of many 1,4-dihydropyridines possessing electron withdrawing groups at positions 3 and 5 of the pyridine ring. These compounds have received increasing amounts of attention by medicinal chemists in recent years because of their ability to regulate calcium concentrations in cardiovascular cells [3]. In spite of this renewed interest in the Hantzsch reaction there are remarkably few reports of unexpected by-products from this interesting multi-component condensation reaction [4,5]. The subject of this report is an unusual dihydropyridine tautomer observed in a case where the β-dicarbonyl component possesses a bulky alkyl group.

This study used a modification of the Hantzsch reaction in which the intermediate benzylidene dione **2** is prepared and isolated and then subjected to reaction with an aminocrotonate **3** in a separate step. The requisite benzylidene dione **2** was readily available by alkylation of 2,4-pentanedione with isobutyl bromide to give 7-methyl-2,4-octanedione (**1**) [6]. The reaction of dione **1** with 2-chlorobenzaldehyde gave the benzylidene dione **2** as a mixture of (*E*)- and (*Z*)-isomers. The condensation of **2** with ethyl 3-aminocrotonate was found to give two products, **5** and **6**, as illustrated in Scheme 1.

Scheme 1



The first of these (**5**) is an ordinary 1,4-dihydropyridine expected as the product from the Hantzsch reaction derived from the condensation of the amine function of intermediate **4** with the methyl ketone carbonyl followed by dehydration.

The second product (**6**) arises from condensation of the amine function of intermediate **4** with the isopentyl ketone carbonyl, however in this case dehydration leads to an exocyclic double bond as shown in structure **6**. The structure of compound **6** has been established by ^1H and ^{13}C nmr spectroscopy. The ^1H and ^{13}C nmr spectral assignments are summarized in Tables 1 and 2. The ^1H nmr nuclear Overhauser effect difference spectra were measured on a degassed sample of **6** and the results were consistent with the proposed structure, where the C5α acetyl methyl group is *cis* to the C4α-H and the C7 olefinic proton is *syn* to C5. The nOe experimental results are detailed in Table 3. Resolution enhancement and decoupling experiments provided the exact coupling constants for the H4, H5, H7 and H6′ resonances. Spectral simulation (Figure 1) using PANIC [7] was used to aid the analysis of the anisochronous methylene of the ethyl ester of **6**. The ^{13}C nmr spectrum was interpreted with the aid of nine single frequency decoupling experiments (SFDR) and an attached proton test (APT) experiment [8]. Calculation of the estimated chemical shifts for the aromatic ring carbons based on the model compound 2-chloroethylbenzene [9] was used to identify C3′, C4′, C5′ and C6′. The assignments of C3′ and C6′ were also confirmed by SFRD experiments.

Table 1

^{1}H NMR Chemical Shifts (ppm) of **6** in Deuteriochloroform

Proton	Chemical Shifts and Multiplicity	Coupling Constants in Hz	Number of H's
4	5.01 ddd	$J_{4,5}$ = 1.8, $J_{4,2Me}$ = 0.7, $J_{4,6'}$ = 0.2	1
5	3.15 ddd	$J_{4,5}$ = 1.8, $J_{5,7}$ = 0.8, $J_{5,NH}$ = 0.5	1
7	4.26 ddt	$J_{5,7}$ = 0.8, $J_{5,NH}$ = 0.7, $J_{7,8}$ = 7.4	1
8	1.86 dd	$J_{7,8}$ = 7.4, $J_{8,9}$ = 7.1	2
9	1.54 m	- - - - - - - - -	1
10,11	0.75 d, 0.83 d	$J_{9,10}$ = 6.6, $J_{9,11}$ = 6.6	3,3
2-Me	2.45 bd	$J_{4,2Me}$ = 0.7, $J_{2Me,NH}$ = 0.5	3
3-COOEt	3.97 [a], 4.02 [a] 1.10t [a]	J = 10.79, 7.07, 7.15, J = 7.15, 7.07	2 3
5-Ac	2.32 s	- - - - - - - - -	3
3'	7.35 dd	$J_{3',4'}$ = 7.3, $J_{3',5'}$ = 2.0	1
4'	7.11 ddd	$J_{3',4'}$, $J_{4',5'}$ = 7.8, $J_{4',6'}$ = 1.8	1
5'	7.08 ddd	$J_{3',5'}$ = 2.0, $J_{4',5'}$ = 7.8, $J_{5',6'}$ = 7.5	1
6'	6.84 ddd	$J_{5',6'}$ = 7.5, $J_{4',6'}$ = 1.8, $J_{4',6'}$ = 0.2	1
NH	5.85 bm	$J_{NH,7}$ = 0.7, $J_{NH,5}$ = 0.5, $J_{NH,2Me}$ = 0.5	1

s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, ddt = doublet of doublet of triplet, m = multiplet, bd = broad doublet, bm = broad multiple. [a] Assignment made by spectral simulation using PANIC.

Table 2

^{13}C NMR Chemical Shifts (ppm) of **6** in Deuteriochloroform

Carbon	Chemical Shift and Multiplicity
2	141.15 s
3	95.98 s
4 [a]	37.45 d
5 [a]	57.02 d
6	129.46 s
7 [a]	110.82 d
8 [a]	34.64 t
9 [a]	28.65 d
10,11	22.13 q, 22.45 q
2-Me [a]	20.74 q
3-COOEt	167.42 s, 59.25 t, 14.22 q
5-Ac [a]	27.47 q, 205.41 s
1'	149.00 s
2'	132.72 s
3' [a]	129.40 d
4'	127.63 d
5'	126.63 d
6' [a]	128.97 d

s = singlet, d = doublet, t = triplet, q = quartet. [a] Assigned by SFDR experiments.

Table 3

Nuclear Overhauser Effect in **6**

Position Saturated	nOe Observed
H4	H5, C5-Ac
C5-Ac	H4, H5
H5	C5-Ac, H4, H7
H7	H5, H8, H9

Although there are reports of Hantzsch-type dihydropyridine syntheses using 2,4-pentanedione as the 1,3-dicarbonyl component to produce 3,5-diacetyl-1,4-dihydropyridines [10], we are unaware of any previous report of a product of the type of compound **6** having an exocyclic double bond. The most obvious difference between these literature reports and our example is the bulky alkyl group on the dione component. In order to verify that the formation compound **6** was not the result of our particular reaction conditions, the synthesis was repeated under identical conditions using 2,4-pentanedione. Thus the aldol condensation between 2-chlorobenzaldehyde and 2,4-pentanedione gave 3-acetyl-4-(2-chlorophenyl)-3-buten-2-one (**7**). The condensation of **7** with ethyl 3-aminocrotonate (**3**) gave

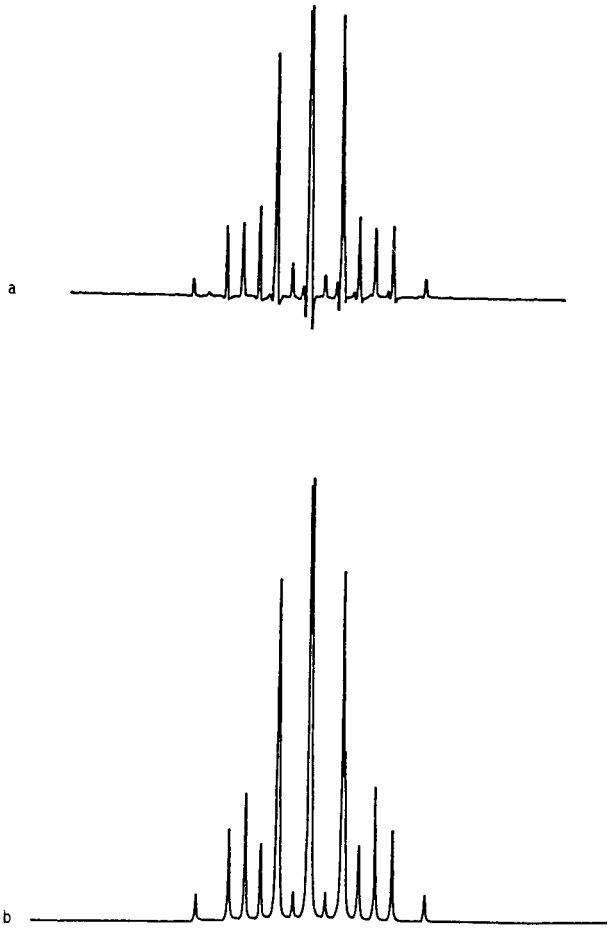
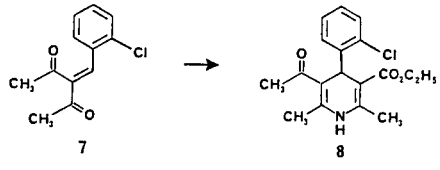


Figure 1. a) Experimental 300 MHz ^{1}H nmr spectrum of methylene protons of ethyl ester of compound 6. b) Simulation of methylene protons using PANIC.

Scheme 2



ethyl 5-acetyl-4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (**8**) in 36% yield. There were minor products in this Hantzsch condensation, one of which was unstable on silica gel, however even with considerable effort we were unable to isolate any product analogous to compound **6**.

EXPERIMENTAL

Infrared spectra were recorded on a Pye Unicam 3-200 spectrometer as neat films or potassium bromide pellets. The 300 MHz ^{1}H and 75.5 MHz ^{13}C nmr data for compound **6** were obtained on a Bruker WM 300 Fourier transform spectrometer in deuteriochloroform solution using tetramethylsilane as internal reference. The ^{1}H nmr spectra were recorded with a 3600 Hz sweep width using a pulse width of 4 μsec (8.2 μsec = 90° flip angle), 32K data points and an acquisition time of 2.28 sec. The ^{13}C nmr spectra were recorded using a 18,500 Hz sweep width, a pulse width of 6.4 μsec (16.5 μsec = 90° flip angle), 32K data points and an acquisition time of 0.44 sec. The nOe spectra were acquired using Bruker Instrument microprogram HOMNOEDF with a relaxation delay of 1 second, nOe generation time of 4 seconds and an irradiation power of 401 Hz. The resulting FID's were substracted using HOMNOEPR and the resulting spectra were not quantitized. The nmr spectra of the other compounds were recorded on a Varian EM-390 spectrometer (90 MHz). Melting points are uncorrected and were observed on a Hoover-Thomas apparatus.

Table 4

Spectral Data

Compound #	IR (cm^{-1})	^{1}H-NMR (ppm)
(*Z*)-**2**	2960, 2880, 1700, 1670, 1620, 1370, 1200, 1060, 760	7.78 (s, 1H), 7.5-7.2 (m, 4H), 2.8-2.6 (m, 2H), 2.15 (s, 3H), 1.7-1.4 (m, 3H), 0.90 (d, 6H, J = 6 Hz)
(*E*)-**2**	2960, 2880, 1700, 1670, 1610, 1380, 1240, 1060, 760	7.75 (s, 1H), 7.5-7.2 (m, 4H), 2.40 (s, 3H), 2.4-2.2 (m, 2H), 1.5-1.2 (m, 3H), 1.69 (d, 6H, J = 6 Hz)
5	3340, 2960, 2930, 2880, 1700, 1470, 1300, 1190, 1100	7.4-6.9 (m, 4H), 5.8 (brs, 1H, N-H), 5.4 (s, 1H), 4.13 (q, 2H, J = 7.5 Hz), 2.2-2.4 (m, 1H), 2.30 (s, 3H), 2.20 (s, 3H), 2.00 (s, 3H), 1.5-1.2, (m, 2H), 1.20 (t, 3H, J = 7.5 Hz), 0.82 (d, 6H, J = 6 Hz)
6	3320, 2950, 2860, 1700, 1680, 1590, 1390, 1190, 1085, 750	see Table 1
7	3060, 3000, 1700, 1675, 1615, 1380, 1235, 1050, 760	7.75 (s, 1H), 7.5-7.2 (m, 4H), 2.42 (s, 3H), 2.15 (s, 3H)
8	3380, 2990, 1690, 1640, 1600, 1470, 1300, 1210	7.4-7.0 (m, 4H), 5.7 (s, NH), 5.4 (s, 1H), 4.10 (q, 2H, J = 8 Hz), 2.25 (s, 3H), 2.20 (s, 6H), 1.2 (t, 3H, J = 8 Hz)

(*Z*)- and (*E*)-2-Acetyl-1-(2-chlorophenyl)-6-methylhept-1-en-3-one (**2**).

A mixture of 8.00 ml (71 mmoles) of 2-chlorobenzaldehyde, 10.0 g of 7-methyl-2,4-octanedione (64 mmoles) [6], 0.6 ml of acetic acid and 0.6 ml of piperidine in 120 ml of toluene was refluxed with a Dean-Stark trap for 2 hours, at which time 1.8 ml of water had separated. The toluene was evaporated and the residue passed through 400 g of silica gel, eluting with 10% ether-hexane to remove some colored polar impurities. Evaporation of the solvents gave 16.21 g (91%) of a mixture of (*Z*)- and (*E*)-**2**. Integration of the acetyl signals of the nmr spectrum of this mixture indicated an *E*/*Z* ratio of 70/30. Chromatography of this mixture on a larger amount of silica gel and eluting with ether-hexane mixtures separated the (*Z*)- and (*E*)-isomers of **2**, with the (*E*)-isomer (a liquid) eluting first.

Anal. Calcd. for $C_{16}H_{19}ClO_2$: C, 68.93; H, 6.87. Found: C, 68.81; H, 6.84.

Further elution gave the more polar (*Z*)-isomer of **2** (a liquid).

Anal. Calcd. for $C_{16}H_{19}ClO_2$: C, 68.93; H, 6.87. Found: C, 68.85; H, 6.87.

Ethyl (*Z*)-5α-Acetyl-4β-(2-chlorophenyl)-2-methyl-6-(3-methylbutylidene)-1,4,5,6-tetrahydropyridinecarboxylate (**6**).

A solution of 1.43 g (5.13 mmoles) of a mixture of (*E*)- and (*Z*)-**2**, 0.67 g (5.2 mmoles) of ethyl 2-aminocrotonate (**3**) in 5 ml of ethanol was refluxed 4 hours. The ethanol was evaporated *in vacuo* and the residue was purified by chromatography on 200 g of silica gel, eluting with 10% methanol in methylene chloride. Fractions containing **6** were combined, evaporated and recrystallized from methanol to give 0.168 g of **6**, mp 153-156°.

Anal. Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.76; H, 7.24; N, 3.59. Found: C, 67.79; H, 7.24; N, 3.59.

Further elution gave 0.90 g the 1,4-dihydropyridine **5** as a viscous oil.

Anal. Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.76; H, 7.24; N, 3.59. Found: C, 67.63; H, 7.46; N, 3.26.

3-Acetyl-4-(2-chlorophenyl)-3-buten-2-one (**7**).

A solution of 11.2 ml (0.10 mole) of 2-chlorobenzaldehyde, 12.3 ml (0.12 mole) of 2,4-pentanedione, 0.6 ml of acetic acid, 0.6 ml of piperidine and 120 ml of toluene was refluxed with a Dean-Stark trap for 2 hours. The cooled reaction mixture was washed with water and brine and dried over magnesium sulfate. Evaporation of the solvent and distillation thru a kugelrohr apparatus gave 17.61 g (79%) of **7**, bp 110-120°/0.01 mm.

Anal. Calcd. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98. Found: C, 64.76; H, 5.20.

Ethyl 5-Acetyl-4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (**8**).

A mixture of 1.11 g (5 mmoles) of enone **7**, 0.75 g (5.8 mmoles) of ethyl 3-aminocrotonate (**3**) and 5 ml of ethanol was refluxed 2 hours. The solvent was evaporated and the residue chromatographed on 150 g of silica gel, eluting with 2 percent methanol in hexane. The largest product was collected and recrystallized from ethyl acetate/hexane to give 0.597 g of **8**, mp 159-160°.

Anal. Calcd. for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; N, 4.20. Found: C, 64.67; H, 5.98; N, 4.16.

Acknowledgment.

The authors wish to thank the following members of Syntex Analytical and Environmental Research for elemental analysis and infrared and nmr spectra: L. Bautista, H. Levens, B. Arellano, L. Guzzo, L. Kurz, and M. Chung.

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