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Stereochemistry of the 2-Hydroxy-1,2,3,4-tetrahydropyridine Intermediate of Hantzsch Cyclization

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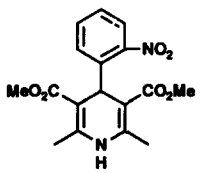
Abstract: Hantzsch cyclization of cyanoethyl 3-aminocrotonate and (*E,Z*)-4-dialkoxymethyl-2-benzylidene-acetoacetates (**5a,b**) afforded 3,4-*trans*-2-hydroxy-1,2,3,4-tetrahydropyridines (**7a,b**) in high stereoselectivity.

In the last decade, synthetic studies of 1,4-dihydropyridine derivatives have been carried out in many research institutes all over the world because of their attractive biological activities as calcium antagonists.[1] The Hantzsch-type condensation reaction[2] has been widely used to prepare 1,4-dihydropyridines, the most popular of which are the 2,6-dimethyl derivatives such as nifedipine (**1**)[3]. By employing the Hantzsch method, 1,4-dihydropyridines were obtained directly without formation of the reaction intermediates 2-hydroxy-1,2,3,4-tetrahydropyridines. Contrary to the ordinary reaction, the Hantzsch reaction using ethyl 4-trifluoromethyl acetoacetate instead of methylacetoacetate yielded 2-hydroxy-1,2,3,4-tetrahyropyridines (**2a,b**).[4] However, the stereochemistry remains unclear. In this paper, we report a Hantzsch-type reaction of using 4-dimethoxylmethyl acetoacetate which gives 3,4-*trans*-2-hydroxy-1,2,3,4-tetrahydropyridine (**7a,b**) predominance with high stereoselectivity.



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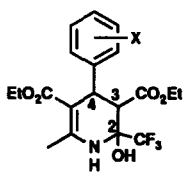
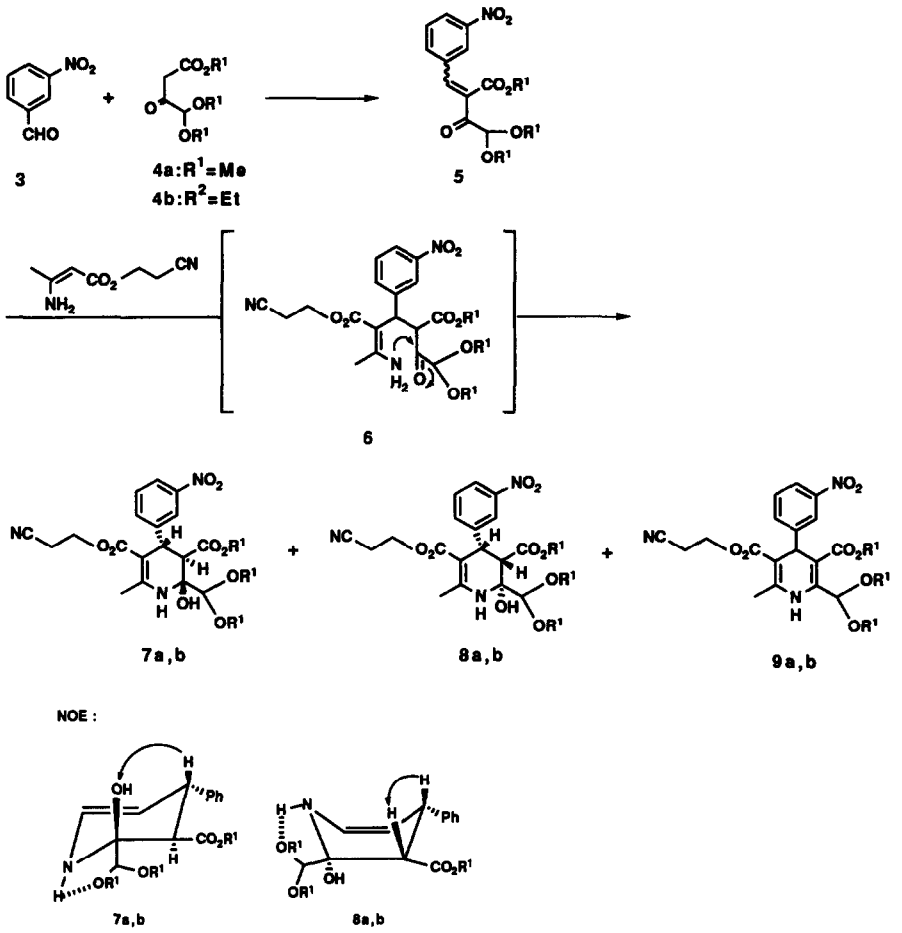


2a : X = 4-NO_2
2b : X = 3,4-Cl_2

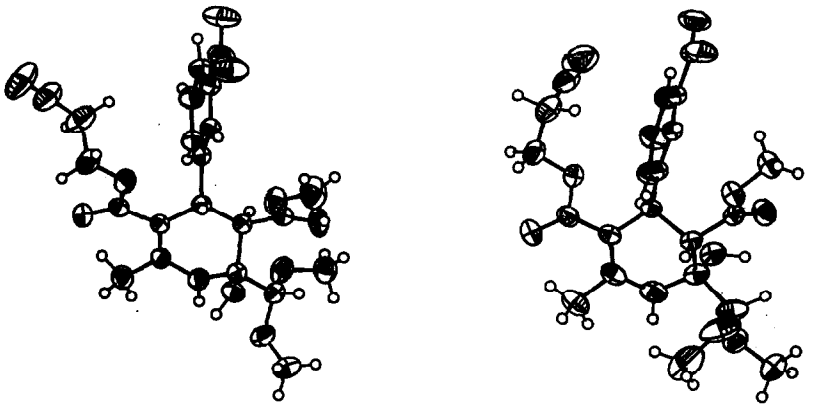
Hantzsch cyclization of cyanoethyl 3-aminocrotonate and 4-dimethoxymethyl-2-benzylidene acetoacetate (**5**), derived from 3-nitrobenzaldehyde (**3**) and 4-dimethoxymethyl acetoacetate (**4a**) were performed in refluxing 2-propanol in the presence of piperidine acetate to give a mixture of 2-hydroxy-1,2,3,4-tetrahydropyridines (**7a** and **8a**) in a ratio of 4.6:1 in 66% yield and 1,4-dihydropyridine (**9a**) in a 16% yield (Scheme 1).[5] The structures of **7a** and **8a** were assigned from their spectral data and ready conversion into the corresponding dihydropyridines (**9a,b**) by the treatment with camphorsulfonic acid in methanol. The ^{13}C-NMR spectrum (75 MHz, $CDCl_3$) of **7a** confirms the presence of two sp3-methine groups at δ[41.83 and 52.12 for C3 and C4]. The ^{1}H-NMR spectrum (200 MHz, $CDCl_3$, δ) of **7a** shows a singlet at 2.80 (J=12 Hz) for H-3, and a doublet of doublet at 4.26 (J=12 and 1.2 Hz) for H-4, having a long range coupling with CH_3-6. It can, therefore, be presumed that the dihedral angle between H-3 and H-4 of **7a** must be close to 0° or 180°, according to the Karplus equation. The ^{13}C-NMR spectrum (75 MHz, $CDCl_3$) of **8a** confirms the presence of two sp3-methine

groups at δ[40.40 and 46.56 for C3 and C4]. The ^{1}H-NMR spectrum (200 MHz, $CDCl_3$, δ) of **8a** shows a doublet at 3.42 (J=8 Hz) for H-3 and a doublet at 4.53 (J=7.5 Hz) for H-4 , suggesting the dihedral angle between H-3 and H-4 of **8a** must be 10° or 150°. The relative stereochemistry of **7a** and **8a** was established by the NOE experiments (Scheme 1).

Scheme 1

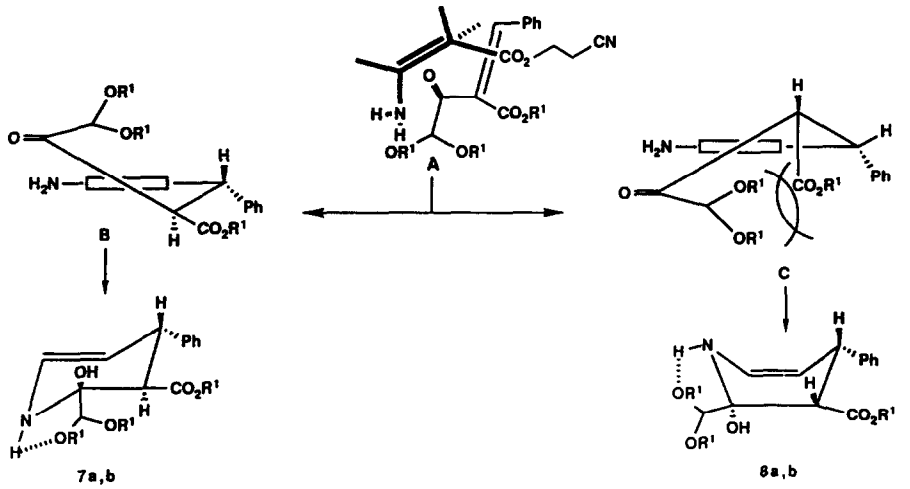


In order to ascertain the stereochemistry of 2-OH in both isomers, the crystal X-ray diffraction analyses of **7a** and **8a** were carried out. The crystal X-ray diffraction analysis of **7a** indicates that the relative configuration of H-3 and H-4 of tetrahydropyridine ring is *trans* and that of H-3 and 2-OH is also *trans*.[6] On the other hand, the analysis of **8a** indicates the relative configuration of H-3 and H-4 to be *cis* and that of H-3 and 2-OH to be *trans*.[6] Thus, the stereochemistry of **7a** and **8a** was unambiguously assigned as shown in Scheme 1. Hantzsch cyclization of cyanoethyl 3-aminocrotonate under the same conditions as for **5b** proceeded similarly in a high stereoselectivity to give a mixture of **7b** and **8b** (**7b**:**8b**=5.2:1, 64% yield), and **9b** in a 15% yield.



Crystal Structure of 7a and 8a

In the first step of the Hantzsch method, the most favorable formation of the Michael adduct should be via six-membered ring transition state A[7], which leads to the 3- and 4-*trans* intermediate B avoiding the repulsion between the phenyl group and the ester substituents. Although stereochemical course of the present Hantzsch cyclization is unclear at the second stage, the results described in this paper strongly suggest that the observed stereoselection may reflect steric interaction alone. Assuming two transition states B and C leading to **7a,b** and **8a,b**, transition state B would be favored over C, because in transition state C steric repulsion between the acetal and 3-alkyl ester is present. According to such a transition state, ring closure of the nitrogen nucleophile, in its energetically preferred conformation, takes place predominantly on the *si*-face of the carbonyl. It seems likely that the predominant formation of stable **7a,b** and **8a,b** has been attributed to a hydrogen-bond formation between the amino proton and acetal oxygen.



In summary we have offered a new insight into the mechanism of Hantzsch cyclization, suggesting that Michael addition of cyanoethyl 3-aminocrotonate to Z- and *E*-benzylidene acetate(5), which leads to 3-and 4-*trans* intermediate B, gives 3,4-*trans*-2-hydroxy-1,2,3,4-tetrahydropyridines (**7a,b**) predominance with high stereoselectivity.

References and Notes

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5. All new compounds gave satisfactory spectroscopic and analytical data. **7a**: mp 156-157 °C; ^{1}H NMR (200MHz, $CDCl_3$, δ) 2.22 (2H, m), 2.39 (3H, d, J=1.2 Hz), 2.80 (1H, d, J= 12 Hz, δ), 3.50, 3.55, 3.57 (3Hx3, each s), 4.94 (2H, t, J= 5 Hz), 4.96 (1H, s), 4.20 (1H, s), 4.26 (1H, dd, J= 12, 1.2 Hz), 5.36 (1H, br),7.40-8.11 (4H, m, ArH). **8a**: mp 130-131 °C; 2.42 (2H, m), 2.49 (3H, s), 3.40 (3H, s), 3.42 (1H, d, J= 7.5 Hz), 3.63, 3.84 (3Hx2, each s), 3.89 (1H, s), 4.10 (2H, m), 4.18 (1H, s), 4.53 (1H, d,J= 7.5 Hz), 5.71 (1H, br s), 7.30-8.10 (4H, m). **9a**: mp 100-101°C; 2.41 (3H, s), 2.66 (2H, t, J=6Hz), 3.46, 3.51, 3.69 (3Hx3, each s), 4.28 (2H, m), 5.15 (1H, s), 6.03 (1H, s), 6.92 (1H, br s), 7.46-8.17 (4H, m). **7b**: mp 146-147°C; 0.94 (3H, t, J= 7.5 Hz), 1.22 (3H, t, J= 7.5 Hz), 1.24 (3H, t, J= 7.5 Hz), 2.21 (2H, m), 2.38 (3H, d, J= 1.2 Hz), 2.84 (1H, d, J= 12 Hz), 3.49-3.98 (6H, m), 4.19 (1H, s), 4.26 (1H, dd, J= 12, 1.2 Hz), 4.36 (1H, s), 5.44 (1H, br s), 7.39-8.12 (4H, m). **8b**: mp 139-140 °C; 1.18, 1.27, 1.43 (3Hx3, each s), 2.41 (2H, m), 2.49 (3H, s), 3.42 (2H, m), 3.44 (1H, d, J= 8 Hz), 3.79(2H, m) , 3.90 (1H, s), 4.09 (2H, m), 4.26 (2H, m), 4.45 (1H, s), 4.54 (1H, d, J= 8 Hz), 5.77 (1H, br s), 7.30-8.09 (4H, m). **9b**: mp 112-113 °C; 1.25 (9H, m), 2.40 (3H, s), 2.66 (2H, t, J= 5 Hz), 3.56-3.87 (6H, m), 4.11 (2H, m), 4.26 (2H, m), 5.12 (1H, s), 6.18 (1H, s), 6.97 (1H, br s), 7.38-8.15 (4H,ArH).
6. Single crystals of **7a** and **8a** suitable for X-ray diffraction study were obtained from a mixture of methanol/ether under concentration of mother liquor by evaporation of the solvent at 293K. Data collections were performed by Mac-Science MXC18 diffractometer. The structures were solved by direct methods using SHELXS86 (Sheldrick, 1986) and refined with a full matrix least-squares method. Crystal Data of **7a**: $C_{21}H_{25}N_3O_9$, Mr= 463.00, triclinic, space group $P\bar{1}$, a=9.381(2)Å, b=14.858(2)Å, c=9.188(2)Å, α= 101.85(2)°, β=111.07(2)°,γ=100.81(1)°, V=1120.5(3)Å^3 , T=293K, Z=2, Dx =1.37gcm^{-1}, (Cu-Kα)= 1.54178Å, μ=8.23cm^{-1}, R= 0.049 over 3696 independent reflections. Crystal Data of **8a**: $C_{21}H_{25}N_3O_9$, Mr= 463.00, triclinic, space group $P\bar{1}$, a=11.065(4)Å, b=12.613(3)Å, c=9.573(5)Å, α=96.80(2)°, β= 111.89(2)°, γ=109.34(1)°, V= 1124.3(3)Å^3, T= 293K, Z=2, Dx=1.37 gcm^{-1}, (Cu-Kα)=1.54178Å, μ= 8.20cm^{-1},0.093 over 3673 independent reflections. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
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