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NUCLEOPHILIC SUBSTITUTION IN THE AZOMETHINE SERIES: AN IMPROVED SYNTHESIS OF 1,4-DIHYDROPYRIDINES

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ABSTRACT: A new convenient synthetic method for 1,4-dihydropyridines from azomethines is presented

The preparation of 1,4-dihydropyridine derivatives continues to be of significant interest due to their application as important pharmaceuticals. For example, Adalat (Nifedipine; dimethyl 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylate) is well known as a valuable calcium antagonist

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widely used in the treatment of hypertension of all kinds and of heart muscle diseases.[1]

The preparation of this compound was first realised by the Hantzsch synthesis[1]. Owing to the ever increasing quality requirements with respect to pharmaceuticals, this method was later found to be unsuitable for the manufacture of a high quality product. The great number of side reactions due to the strong alkaline medium (ammonia) applied in this reaction results in dark-coloured resinous products, which greatly decrease the yield and purity.

These problems are eliminated in Knoevenagel's synthesis[2], where no free ammonia is used. In this method methyl o-nitrobenzylideneacetoacetate is reacted with methyl 3-aminocrotonate to give Nifedipine in good yield and without impurities.

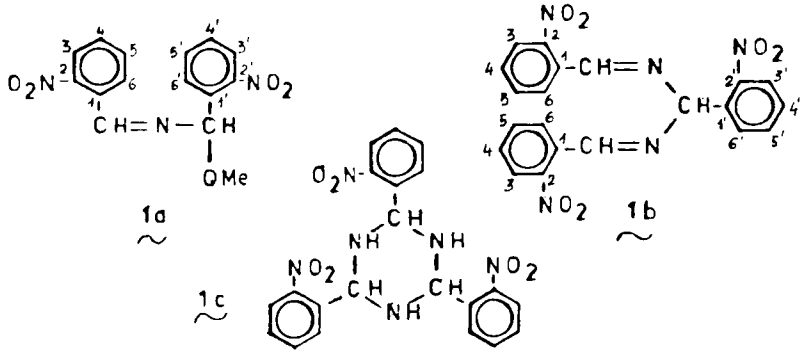
In a search for a convenient and optimal method for the synthesis of 1,4-dihydropyridines we made an effort to avoid the use of strong alkaline medium and free aldehyde in the initial reaction.

Our new synthesis presents a general method of preparing substitued symmetrical 1,4-dihydropyridines starting from azomethines. As an example, the synthesis of Nifedipine is described here in detail.

The method consists of reacting the azomethine with a mixture of methyl acetoacetate and methyl 3-aminocrotonate in methanolic solution to give 1,4-di-

hydropyridine (Nifedipine). When an aldimine is used as starting material it is reacted with methyl acetoacetate alone.

As starting materials two types of azomethines (1a, 1b) or the trimer aldimine (1c) can be used.



1a 1b 1c

These new compounds (1a, 1b, 1c) were prepared from o-nitrobenzaldehyde in the presence of the appropriate source of ammonia in a suitable solvent[3]. Their stability was examined in refluxing methanol, as a blank experiment, and in all cases the unchanged materials were recovered.

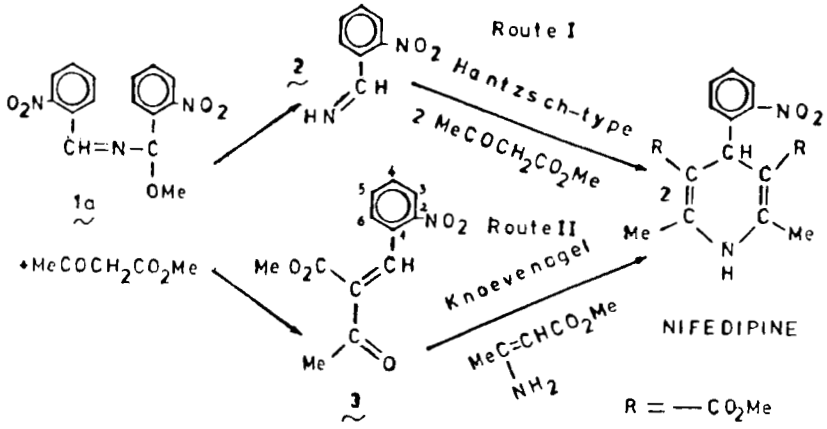
For 1a: 2 o-$NO_2C_6H_4CHO$ + 2 $CH_3CO_2NH_4$ $\xrightarrow{\text{methanol}}$ 1a

For 1b: 3 o-$NO_2C_6H_4CHO$ + 3 $CH_3CO_2NH_4$ $\xrightarrow{\text{isopropanol}}$ 1b

For 1c: 3 o-$NO_2C_6H_4CHO$ + NH_3(excess) $\xrightarrow{\text{methanol}}$ 1c

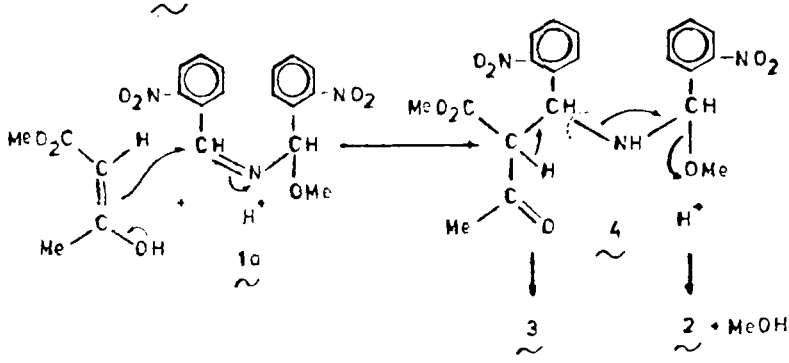
According to our new method, Nifedipine is formed in a very unusual way, by the following mechanism.

When starting from the azomethine (1a), the nucleophilic reaction between (1a) and methyl acetoacetate gives rise to two intermediates: o-nitrobenzaldimine (2) and methyl o-nitrobenzylideneacetoacetate (3). These two intermediates then react simultaneously by two different parallel routes: the o-nitrobenzaldimine (2) in a Hantzsch-type reaction (Route I) and the methyl o-nitrobenzylideneacetoacetate (3) according to the Knoevenagel synthesis (Route II), resulting in the same end-product (Nifedipine).

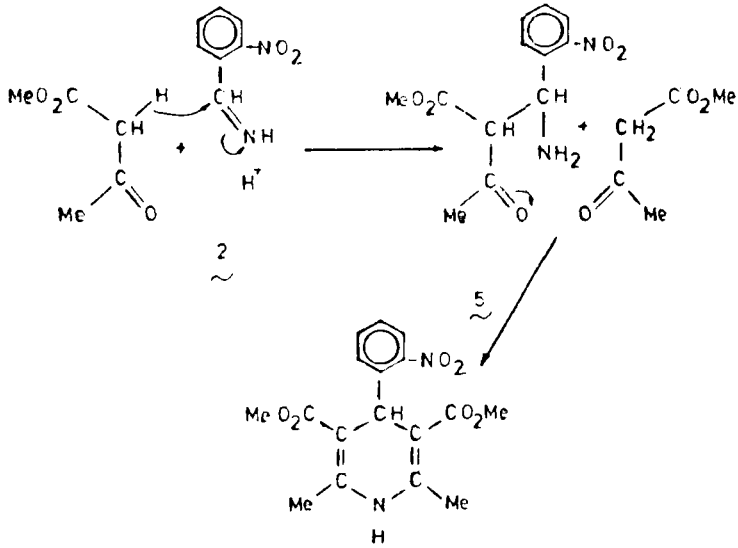


In the initial reaction the nucleophile (methyl acetoacetate) attacks on the methine carbon of (1a) to give a secondary amine (4), and then the second intramolecular nucleophilic attack on the same methine

carbon of (4) splits the amine to ylidene (3) and aldimine (2).



For Route I (Hantzsch type) we suppose that one mol of the nucleophile (methyl acetoacetate) attacks on the methine carbon of the aldimine (2) giving the unstable intermediate amino-adduct (5)[4],

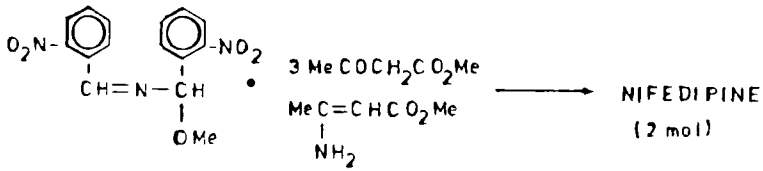


NIFEDIPINE

which is then converted with another mol of methyl acetoacetate to yield one mol of Nifedipine.

In Route II (Knoevenagel) one mol of the ylidene (3) reacts with one mol of methyl 3-aminocrotonate according to the Knoevenagel reaction, yielding one mol of Nifedipine.

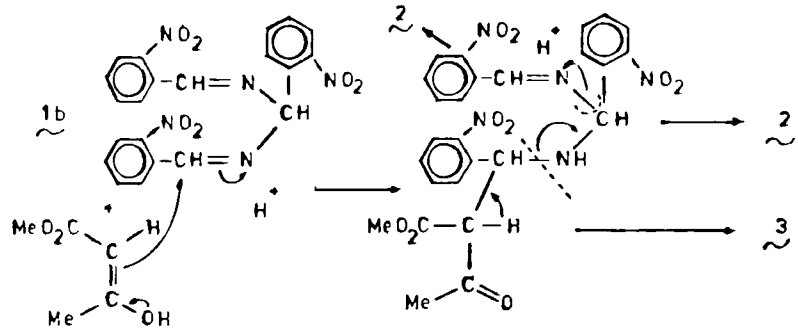
The overall synthesis (Route I + II) from azomethine (1a) is the following.



1a

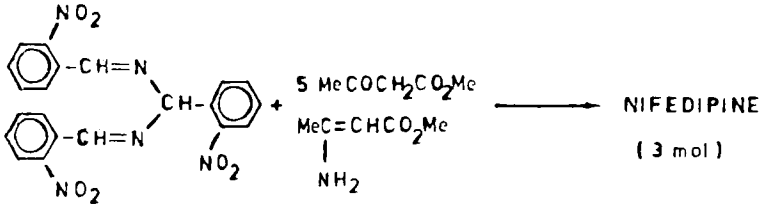
The overall yield, calculated for azomethine (1a) (Route I + II) is 83 %.

Using the other azomethine (1b) as the starting material, the mechanism is similar to the case of (1a).



The two mols of aldimine (2) and one mol of the ylidene (3) then react further as described above to give 3 mols of Nifedipine.

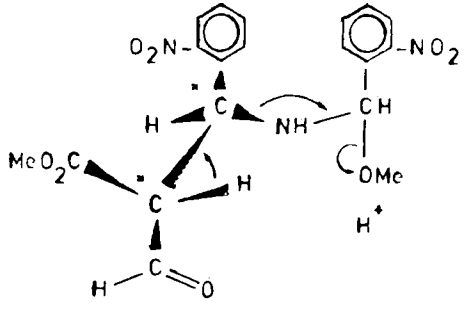
The overall reaction is then as follows:



1b

The trimer aldimine (1c) takes part in the reaction in the form of the aldimine monomer following Route I.

Some interesting stereochemical observations have been also made in the course of the synthesis. The ylidene compound (3) formed in the initial reaction is a mixture of two geometric isomers. The two diastereomers of the secondary amine (4)



4 R* R* and S* S*

formed transiently in the initial reaction - described previously by the synthesis of Nifedipine from (1a) - are responsible for the formation of the two isomers.

The intramolecular nucleophilic attack on the chiral carbons of the two diastereomers results in the aldimine (2) with the simultaneous formation of the two geometric isomers (Z and E) of the ylidene (3).

From the diastereomer R* R* the E isomer, from R* S* the Z isomer of the ylidene (3) is formed.

The reaction mechanism proposed by us for our new synthesis of 1,4-dihydropyridines has been proved by kinetic measurements using HPLC technique and spectroscopic methods, and will be published in an other paper.

Experimental

1-Methoxy-1-(2'-nitrophenyl)-N-(2'-nitrophenyl) methylenemethaneamine (1a). - 2-Nitrobenzaldehyde (15,1 g, 0,1 mol) was dissolved in methanol (25 ml) and ammonium acetate (8,0 g, 0,1 mol) was added to the solution, with stirring. The reaction mixture was stirred at 40 °C for 15 min, and then at room temperature for 7 h. After cooling, the precipitated product

was filtered off, washed with water and dried to give (1a) (15,4 g, 98 %), m.p. 117-118 °C.
IR (KBr, cm^{-1}): 1524, 1363, 1345, (NO_2 bands), 1100 (C-O), 785, 742 (δ CH=)
^{1}H-NMR ($CDCl_3$) δ : 3.56 (3H, s, OCH_3); 6.38 (1H, d, J = 1.3 Hz, -OCH); 7.4-8.1 (8H, m, ArH); 8.98 (1H, d, J = 1.3 Hz, =CH)
^{13}C-NMR ($CDCl_3$) δ : 56.9 OCH_3; 92.8 OCH ; 124.0 and 124.1 C-3 and C-3'; 128.3 and 128.9 C-6 and C-6'; 129.7 and 131.1 C-4 and C-4'; 130.6 and 134.0 C-1 and C-1'; 132.7 and 133.3 C-5 and C-5'; 149.0 and 149.3 C-2' and C-2; 156.7 -CH=.

Anal. Calc for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33. Found: C, 57.67; H, 4.15; N, 13.33.

1-(2'-Nitrophenyl)-N,N-bis-(2'-nitrophenyl methylenemethanediamine (1b). - 2-Nitrobezaldehyde (15.1 g 0.1 mol) and ammonium acetate (8.0 g, 0.1 mol) were added to isopropanol (50 ml). The procedure described for (1a) was followed to obtain (1b) (14.2 g, 98 %), m.p. 124-127 °C.
IR (KBr, cm^{-1}): 1525, 1344 (NO_2 bands)
^{1}H-NMR ($CDCl_3$) δ : 6.85 (1H, s, $\geq$CH); 7.50 (1H, $\sim$t, ArH-4'); 7.65 (5H, m, ArH 4, 6, 6'); 7.85 (1H, t, ArH-5'); 7.95 (1H, d, ArH-3'); 8.01 (4H, m, ArH-3,5); 9.05 (2H, s, =CH-).

^{13}C-NMR ($CDCl_3$) δ : 84.5 CH—; 124.2 C-3, C-3'; 128.8 C-4', 129.8 C-4; 130.6 C-1; 131.2 C-6; 133.0 C-5'; 133.5 C-5; 134.6 C-2'; 149.0 C-2; 159.0 =CH-.

Anal. Calcd for $C_{21}H_{15}N_5O_6$: C, 58.20; H, 3.49; N, 16.16. Found: C, 58.36; H, 3.51; N, 15.92.

Trimeric 2-nitrobenzaldimine (1c). - To a solution of 2-nitrobenzaldehyde (15.1 g, 0.1 mol) in methanol (40 ml) was added a methanolic solution of ammonia (1.7 g, 0.1 mol) by drops, with stirring. The reaction mixture was stirred at room temperature for 20 h. The precipitated product was filtered off, washed with methanol and dried to give (1c) (11.3 g, 75.3 %), m.p. 117-119 °C.

IR (KBr, cm^{-1}): 3276 (NH); 1535, 1358 (NO_2 bands); 784 (δ CH=).

^{1}H-NMR (DMSO-d_6) δ : 2.58 (3H, t J=9 Hz, CH); 5.60 (3H, t, -NH-); 7.60 (3H, td, ArH-4); 7.75 (3H, td, ArH-5); 7.85 (6H, dd, ArH-3,6).

Anal. Calcd for $C_{21}H_{18}N_6O_6$: C, 56.00; H, 4.03; N, 18.66. Found : C, 56.08; H, 4.08; N, 18.18.

Nifedipine from (1a). - A suspension of (1a) (9.45 g, 0.03 mol) was prepared in methanol (30 ml), and methyl acetoacetate (10.45 g, 0.09 mol) then methyl 3-aminocrotonate (3.45 g,0.03 mol) were added. The reaction mixture was refluxed for 36 h. The pro-

duct which precipitated on cooling was filtered off with suction, dried and dissolved in warm acetic acid. A precipitate formed on the addition of water. It was filtered off, washed with methanol and dried to give nifedipine (17.16 g, 82.6 %), m.p. 172-174 °C.

HPTLC (Kieselgel 60 plates, developing solvent diisopropil ether) showed that the product was homogeneous.

Nifedipine from (1b). - A suspension of (1b) (13.0 g, 0.03 mol) was prepared in methanol (45 ml). Methyl acetoacetate (17.42 g, 0.15 mol) and methyl 3-aminocrotonate (3.45 g, 0.03 mol) were added, with stirring. The reaction mixture was stirred for 46 h, and then worked up as described above to yield nifedipine (23.22 g, 75 %), m.p. 173-174 °C.

Nifedipine from (1c). - Compound (1c) (9 g, 0.02 mol) and methyl acetoacetate (14 g, 0.12 mol) were dissolved in methanol (25 ml). The mixture was stirred and refluxed for 25 h. The crystalline product which separated was filtered off after cooling, dissolved in warm acetic acid and processed as described above to give nifedipine (12.4 g, 60 %), m.p. 170-173 °C.

Geometric isomers of the ylidene comp. (3). For the identification of the geometric isomers of the ylidene compound (3) from the reaction mixture,

it was necessary to have a stereochemically homogeneous mixture of the two isomers containing no nifedipine. A suitable method for this was the termic isomerisation of the readily available one of the "ylidene" isomers prepared by the method given in reference 2. The refluxing of this compound in toluene gave a pure mixture of the two isomers, without any impurities, as described below.

Isomerisation of methyl 2-nitrobenzylideneacetoacetate. - Methyl 2-nitrobenzylideneacetoacetate (6.23 g) was refluxed in toluene (22.5 ml) for 6 h, then cooled to 0 °C, allowed to stand for 1 h, and filtered with suction. The product was washed with isopropanol and dried (3.3 g, m.p. 102-104 °C). From the mother liquor the solvent was evaporated in vacuo to leave an oil (1.75 g).

The structure of the solid product (3.3 g) was determined by means of NMR and found to have the E configuration.

The oil (1.75 g) was a stereochemically homogeneous mixture of the two isomers without any impurities.

Anal. Calc for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 58.00; H, 4.60; N, 5.54.

The structure was verified by NMR measurements showing the mixture to consist of the E and Z iso-

mers. The E/Z ratio was 1:1. This ratio was confirmed by HPLC and GC as well (retention times in HPLC, E isomer: 4.84 min; Z isomer: 5.85 min). From the correspondence of the NMR and HPLC data ratio of ylidene isomers in the reaction mixture could be determined. The value of this is; $\frac{E}{Z} = \frac{9}{5} = 1.8$.

NMR analysis of the above oil fraction (1.75 g) of isomers: ^{1}H-NMR (250 MHz, $CDCl_3$) δ : 2.22, 2.49 (3H, 2 s, Ac); 3.62, 3.88 (3H, 2xs, OCH_3); 7.38, 7.46 (1H, 2xd, ArH-6); 7.6-7.8 (2H, overlapping multiplets, ArH-4,5); 8.20, 8.23 (1H, 2xd, ArH-3).

The ^{1}H-NMR spectra were taken on a Bruker WM (250 MHz) - Ft type NMR spectrometer, while by the ^{13}C-NMR spectra a Bruker WP-80 SY (20 MHz) type spectrometer was used.

Acknowledgement:

We are indebted to Professor Pál Sohár helpful discussions and for NMR measurements.

References and Notes.

1. In the Hantzsch synthesis of Nifedipine one mol of an aldehyde is made to react with two moles of an alkyl acetoacetate in the presence of excess ammonia to obtain 1,4-dihydropyridines; a) F. Bossert, W. Vater, U.S. Pat. 3 485 847, 1969 Dec 23; b) Hantzsch, Liebigs Ann. Chem. 1, 215, (1882). This

patent specification also includes the appreciation of the pharmaceutical importance of this compound.

2. Teller, Werner, et.al., B.R.D. Pat. Offenlegungsschrift DE 33 12216 A1 C 07 D 211/90 1985 Apr 5.

The reaction where the ylidene is reacted with the alkyl 3-aminocrotonate can be found in the literature under very different names; Knoevenagel, Knoevenagel - Ruschaupt, Hantzsch - Beyer, "Mixed Hantzsch Synthesis", et.al. See a) Knoevenagel, Ber. Dtsch. Chem. Ges. 31, 743, (1898); b) K.Torre, J.Org. Chem. 29, 3102, (1964); c) H. Meyer, F. Bossert, et. al., Arzneim.-Forsch/Drug Res. 31 (I), Nr. 3, 407, (1981).

In our opinion the most favourable name will be "The Knoevenagel synthesis" because of the confused authors situation. However, the mechanism of this reaction is a classical Michael addition's mechanism. See above under 2. b).

3. Our patent specification relating to Nifedipine contains also the description of the preparing of these new starting compounds; P. Benkó, D. Bózsing, L. Lévai, et. al., B.R.D. Pat. Offenlegungsschrift DE 3 907 508 A1 C 07 119/10, C 07 D 211/90, C 07 D 251/04, 1988 Marc 8, 1988 Aug 2.

4. The same amino adduct is mentined in the paper; D. Lyubomir, C. Raev... etc., Arch. Pharm. (Weinheim) 253, (1989).

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