

## SOLID ACID CATALYZED REACTION OF AMINALS WITH METHYL 3-AMINOCROTONATE

Mária Balogh<sup>1\*</sup>, André Gerstmans<sup>2</sup>, István Hermecz<sup>1</sup>

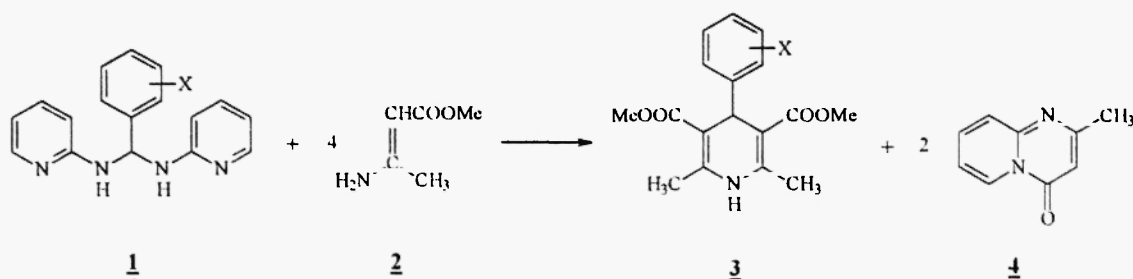
<sup>1</sup>CHINOIN Pharmaceutical and Chemical Works Ltd., Research Centre,  
H-1325 Budapest, P.O.Box 110, Hungary

<sup>2</sup>Université de Liège, Sart-Tilman par 4000 Liège, Belgium

**Abstract:** Solid acid catalyzed reaction of amins 1 with methyl 3-aminocrotonate 2 affords dimethyl 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates 3. 2-Methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one 4 is formed from 2-aminopyridine moiety of the amins.

Recently attention has been focused on the use of solid acids in organic syntheses as environmentally acceptable alternatives to conventional Brønsted and Lewis acids. Clays and zeolites are effective catalysts for a wide variety of organic reactions (1-3). The prowess of acid-treated montmorillonite clay (K10) and ZF520 zeolite, as strong Brønsted acidic catalysts, has been shown in carbon-carbon and carbon-nitrogen bond formation processes, such as addition and cyclization reactions (4-6). Azines (4) derived from aromatic aldehydes and *N*-benzylideneanilines (6) undergo clay-mediated cyclocondensation reaction with methyl 3-aminocrotonate to give symmetrically substituted 1,4-dihydropyridines, which are highly effective calcium antagonists (7).

Condensation reaction between aromatic aldehydes and 2-aminopyridine leads to the formation of amins instead of the expected Schiff bases (8-11). The easy access to amins 1 prompted us to examine their reaction with methyl 3-aminocrotonate 2. The presence of an acidic catalyst is a prerequisite for the success of the reaction. Solid acids tested include K10 montmorillonite, kaolinite, ZF520 zeolite and silica gel. The acid strength of a solid surface is defined as its proton-donating ability, quantitatively expressed by Hammett  $H_0$  function ( $H_0 = -3$  to  $-6$  for kaolinite and  $H_0 = -6$  to  $-8$  for acid treated montmorillonite) (12). K10 montmorillonite is a mesoporous solid having pores with the majority in the 60-100 Å diameter range (13). The Brønsted acidity in zeolites is linked to the Si/Al ratio (14). ZF520 is a highly acidic Y zeolite (Si/Al = 20). Besides microporosity of the faujasite structure (15) with diameters around 8 Å there is a secondary porous system in the range of 50-200 Å.

Table 1. Reaction of aminals **1** with methyl 3-aminocrotonate **2** (Toluene, 110 °C, 8 h)

| Entry | <b>1</b>  | X                        | Catalyst         | <b>3</b>  | Yield % | m.p. °C | Lit. m.p. °C | <b>4</b> | Yield % |
|-------|-----------|--------------------------|------------------|-----------|---------|---------|--------------|----------|---------|
| 1     | <b>1a</b> | H                        | -                | <b>3a</b> | -       | -       | -            | <b>4</b> | -       |
| 2     | <b>1a</b> | H                        | K10              | <b>3a</b> | 53      | 197-198 | 197-198 (16) | <b>4</b> | 90      |
| 3     | <b>1b</b> | 2-NO <sub>2</sub>        | K10              | <b>3b</b> | 49      | 172-174 | 171 (17)     | <b>4</b> | 79      |
| 4     | <b>1c</b> | 3-NO <sub>2</sub>        | K10              | <b>3c</b> | 70      | 208-209 | 209-210 (16) | <b>4</b> | 92      |
| 5     | <b>1c</b> | 3-NO <sub>2</sub>        | SiO <sub>2</sub> | <b>3c</b> | 59      | 207-208 | 209-210 (16) | <b>4</b> | -       |
| 6     | <b>1c</b> | 3-NO <sub>2</sub>        | ZF520            | <b>3c</b> | 59      | 208     | 209-210 (16) | <b>4</b> | 54      |
| 7     | <b>1c</b> | 3-NO <sub>2</sub>        | Kaolinite        | <b>3c</b> | 60      | 208-209 | 209-210 (16) | <b>4</b> | -       |
| 8     | <b>1d</b> | 4-NO <sub>2</sub>        | K10              | <b>3d</b> | 55      | 195-196 | 197 (18)     | <b>4</b> | 72      |
| 9     | <b>1e</b> | 3,4-(MeO) <sub>2</sub>   | K10              | <b>3e</b> | 72      | 146-147 | 145-146 (19) | <b>4</b> | 70      |
| 10    | <b>1f</b> | 3,4-(OCH <sub>2</sub> O) | K10              | <b>3f</b> | 66      | 186-187 | (20)         | <b>4</b> | 71      |
| 11    | <b>1g</b> | 2,3-Cl <sub>2</sub>      | K10              | <b>3g</b> | 61      | 187-188 | 185-187 (21) | <b>4</b> | 73      |

No reaction was observed in the absence of a catalyst. Yields of isolated products are given.

The elemental analyses for C, H, N, Cl were within  $\pm 0.3$  % of the theoretical values.

**4**, m.p. 124 °C (acetone). Lit. (22) m.p. 123 °C.

Treatment of aminals **1a-g** with four equivalents of methyl 3-aminocrotonate **2** gave dimethyl 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates **3a-g** in 49-72 % yields. (Table 1) Methyl 3-aminocrotonate **2** is cyclized with 2-aminopyridine, liberated from the aminals to afford 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one **4**. This cyclization can be promoted by K10 clay and ZF520 zeolite, but not by kaolinite and SiO<sub>2</sub>. We have examined the effect of the amount of the catalysts on the formation of 1,4-dihydropyridine **3c** (X = 3-NO<sub>2</sub>). Yields are influenced by the number of acidic sites on the catalyst surface. Best results were obtained by K10 montmorillonite. (Table 2) Reaction of **1c** (X = 3-NO<sub>2</sub>) was carried out in various solvents (e.g. in chloroform, methanol and acetic acid) under heterogeneous and homogeneous conditions. (Table 3) Higher yield of **3c** was achieved in

methanol under homogeneous conditions using hydrochloric acid as catalyst, but K10 montmorillonite can be recovered and reused (it was reused three times without loss of its activity).

Table 2. Effect of the amount of the catalyst on the formation of **3c** (X = 3-NO<sub>2</sub>, Toluene, 110 °C, 8 h)

| Catalyst / 0.01 mol of <b>1c</b> | <b>3c</b> Yield % |     |
|----------------------------------|-------------------|-----|
|                                  | 0.4 g             | 4 g |
| K10                              | 54                | 70  |
| ZF520                            | 39                | 59  |
| Kaolinite                        | 22                | 60  |

In summary, the solid acid catalyzed reaction of amins **1a-g** with methyl 3-aminocrotonate **2** represents a new environmentally friendly procedure for the synthesis of 1,4-dihydropyridines **3a-g** with minimal pollution and waste.

Table 3. Reaction of **1c** (X = 3-NO<sub>2</sub>) with **2** in different solvents

| Entry | Catalyst         | Solvent           | Temp.<br>°C | Time<br>h | <b>3c</b> <sup>a</sup><br>Yield % |
|-------|------------------|-------------------|-------------|-----------|-----------------------------------|
| 1     | K10              | Toluene           | 110         | 8         | 70                                |
| 2     | K10              | CHCl <sub>3</sub> | 61          | 8         | 50                                |
| 3     | K10              | MeOH              | 64          | 8         | 51                                |
| 4     | HCl <sup>b</sup> | MeOH              | 64          | 8         | 81                                |
| 5     | -                | AcOH              | 118         | 8         | 72                                |

<sup>a</sup>Yields of isolated pure product. <sup>b</sup>cc. HCl (1 ml) / 0.01 mol of **1c**

## Experimental

Melting points are uncorrected and were determined on a Büchi 535 apparatus. All products were characterized by their <sup>1</sup>H-NMR spectra, recorded in CDCl<sub>3</sub> with Bruker AC-200 spectrometer and are in agreement with the reported data (17,20,23). Silica gel 60 (Merck, 70-230 mesh ASTM) was used for column chromatography. Amins **1a-g** were prepared according to known procedures (8-11). Catalysts used were: K10 montmorillonite (Aldrich), Kaolinite (Fluka), ZF520 zeolite (Zéocat), Silica gel 60 (Merck, 70-230 mesh ASTM).

### Reaction of Amins **1a-g** with methyl 3-aminocrotonate **2** - General procedure

A mixture of amins **1a-g** (0.01 mol), methyl 3-aminocrotonate **2** (4.60 g, 0.04 mol), catalyst (4 g), and toluene (50 ml) was stirred at 110 °C for 8 h. The catalyst was filtered off from the hot reaction mixture and washed with CHCl<sub>3</sub> (50 ml). 1,4-Dihydropyridines (**3a**, 40 %; **3c**, 50 %, **3e**, 30 %, **3f**, 36 %) were filtered off from toluene after cooling. The combined filtrate (toluene and CHCl<sub>3</sub>) was evaporated then treated with methanol (35 ml) to isolate additional 20 % of **3c**. Evaporation of the filtrate then treated with isopropyl ether (20 ml) gave **4**. Column chromatography (*n*-hexane/ethyl acetate 100 : 10 - 1 : 1) was applied for the preparation of 1,4-dihydropyridines **3a,b,d-g** and 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one **4**. Yields are summarized in Table 1.

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