Obtaining of new Ibuprofen functionalized 4-aryl-1,2,3,4-tetrahydroisoquinoline derivatives *via* heterogeneous-catalyzed cyclisation: A green method for synthesis of new Cherylline derivatives

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1,2,3,4-Tetrahydroisoquinolines are very important class of synthetic and natural compounds, which display a broad range of medicinal activities such as antitumor, antibacterial, antiplasmodial, and β-adrenergic receptor antagonism. Tetrahydroisoquinolines arylated at C-4 shows prominent pharmaceutical activities. *Cherylline* is a naturally occurring 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid which has one stereo center in the molecule.

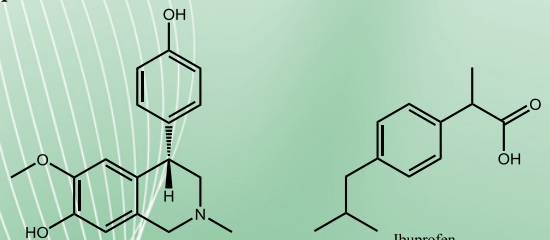
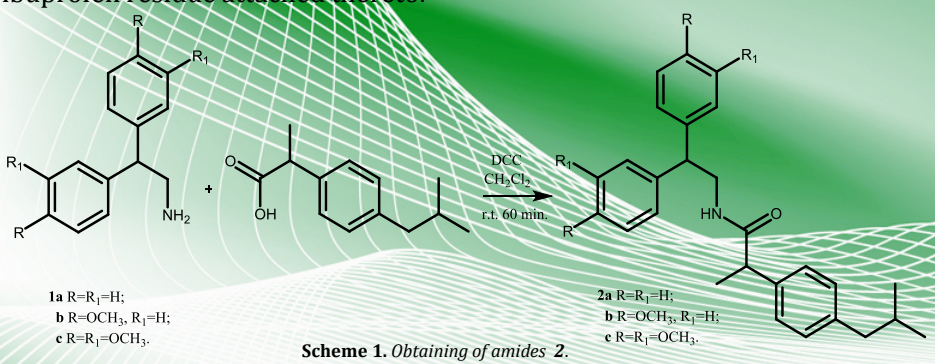


Figure 1. *Structural formulas of Cherylline and Ibuprofen.*

Ibuprofen or 2-(*p*-isobutylphenyl) propionic acid belongs to the non-steroidal anti-inflammatory agents with anti-inflammatory activity which has superior to that of salicylate and is similar to phenylbutazone and indomethacin. Ibuprofen has an analgesic and antipyretic effect and is widely used in medical practice in rheumatoid arthritis, osteoarthritis, Behreve's disease, coxarthrosis, bursitis, tendinitis, disorder, trizmus, etc.

From this point of view what interested us was the synthesis of new compounds structurally containing a *Cherylline* moiety as well as an ibuprofen residue attached thereto.

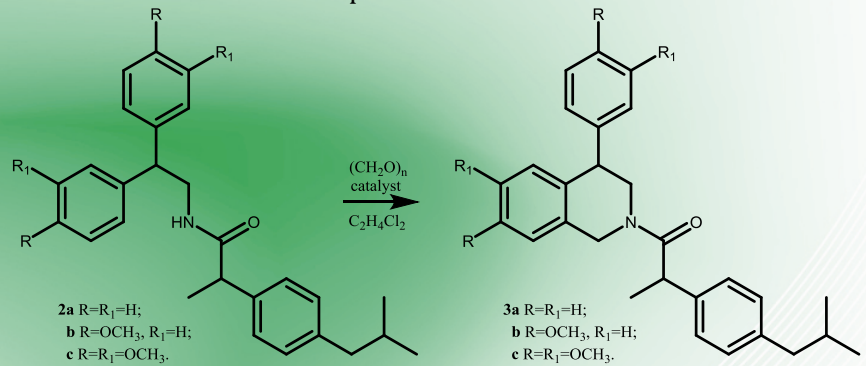


Scheme 1. *Obtaining of amides* ***2****.*

We have first synthesize the required amides **2** from the reaction between amines **1** with ibuprofen and *N*,*N'*-dicyclohexylcarbodiimid(***Scheme1***). The reaction mixture was stirred at room temperature for 60 minutes.

The next step was the cyclization of the newly obtained amides **2** in the reaction conditions of intramolecular α-amidoalkylation.

In recent years in the practice as acid catalysts increasingly find use the catalytic systems of acid absorbed on silica. Their application allows both the successful carried out of the reaction, as well as recovery and repeated their consistent application, which identifies them as environmentally friendly – "green reagent". In searching of "green" agents we studied the possibility of application of the system $TfOH/SiO_2$ as heterogeneous acid catalyst in the reaction of intramolecular α-amidoalkylation. The same systems in the recent years successfully were applied in a number of acid-catalyzed synthetic procedures, characterized as environmentally friendly methods with minimized harmful waste products.



Scheme 2. *Obtaining of Cherylline derivatives* ***3****.*

For the cyclisation step to the newly obtained amides **2** (Scheme 2) in $C_2H_4Cl_2$, paraformaldehyde in excess and $TfOH/SiO_2$ (0.03g per mmol of amide, of which 0.015mmol acid) were added. The reaction mixture was stirred at 80°C, observing that for 60 minutes under these reaction conditions the reaction proceeded completely for **3b** and **3c** . For obtaining of the compound **3a** was required longer reaction time (180mins) due to the lack of electron-donating substitutions activating the benzene nuclei. The resulting new compounds **2** and **3** (Reaxys) are characterized by IR, ^{1}H- and ^{13}C-NMR and MS.

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