GREEN SYNTHESIS OF NEW HYBRID MOLECULES OF IBUPROFEN AND 1,2,3,4-TETRAHYDROISOQUINOLINE

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Abstract

Herein we report an eco-friendly method for synthesis of 1,2,3,4-tetrahydroisoquinoline derivatives of ibuprofen. All five newly obtained compounds are fully characterized with their ^{1}H,^{13}C-NMR, IR, HRMS, and are interesting for the purpose of studying their biological activities.

Keywords: *ibuprofen, NSAIDs, hybrids, 1,2,3,4-tetrahydroisoquinoline, green chemistry, $TfOH/SiO_2$*

1. INTRODUCTION

The obtaining of hybrid molecules and their evaluation as a diverse range of pharmacological agents and as potent drugs have been under constant escalation for the last few decades. In the literature are reported many successfully synthesized hybrid molecules owning anti-malarial, anti-inflammatory, anti-tuberculosis, anti-fungal, anti-cancer, and many other activities [1]. In this article, the obtaining of new hybrid molecules of ibuprofen and 1,2,3,4-tetrahydroisoquinoline is presented (Fig. 1).

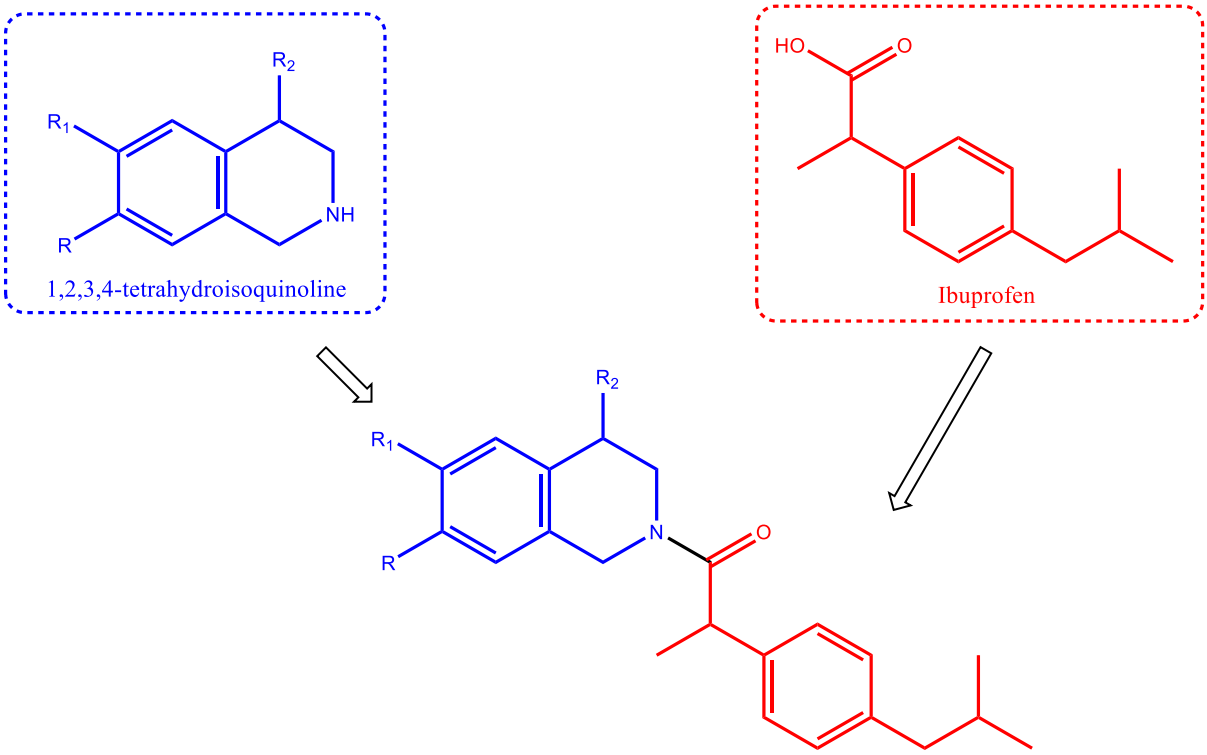
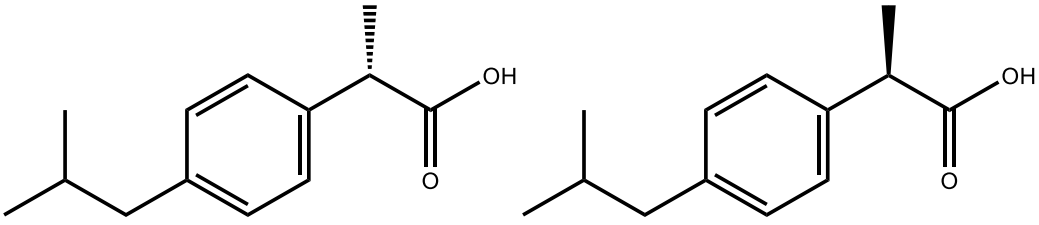


Fig. 1. Novel hybrids of 1,2,3,4-tetrahydroisoquinoline and ibuprofen.

Ibuprofen **1** or 2- (*p*-isobutylphenyl) propionic acid is a non-steroidal anti-inflammatory drug (NSAIDs) with a stronger antipyretic, anti-inflammatory, and analgesic effect than analgin. Ibuprofen is a drug used to treat inflammatory and painful diseases, such as rheumatoid arthritis, soft tissue damage,

osteoarthritis, etc. [2]. The medicinal product has been rapidly popularized since the late 1970s and is widely used throughout the world, becoming one of the most widely used drugs.

Ibuprofen is a chiral compound having an sp^3-hybrid tetrahedral asymmetric carbon atom in the side chain of the molecule and exists under the form of two enantiomers: *S*- (**1a**) and *R*- (**1b**) ibuprofen (Fig. 2.). However, only *S*-ibuprofen (**1a**) is used as a painkiller.



S-ibuprofen **1a** *R*-ibuprofen **1b**

Fig. 2. Structural formulas of *S*- and *R*- Ibuprofen.

The literature review shows that in recent years there has been no increased production of synthetic ibuprofen derivatives. The literature survey shows that most of the scientific reports in recent years are related to the use of ibuprofen in medical practice, as well as in the search for methods for obtaining various complexes of ibuprofen with metal ions.

An international scientific group [3] have studied the complexation of ibuprofen with a number of metal ions - Na^+, Ag^+, Ca^{2+}, Mg^{2+}, Cu^{2+}, Zn^{2+}, and Hg^{2+}. The authors have also evaluated their biological activity. Ibuprofen and its complexes with Ag^+ and Hg_2^{+} show antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* and *Listeria monocytogenes*). Metal complexes have been shown to be significantly more effective than Ibuprofen itself.

Cyclooxygenase-2 (COX-2) is one of the most important targets for the treatment of various inflammatory diseases. Other authors [4] successfully synthesized new biologically active substances derived from ibuprofen, ibuprofen amides, and ibuprofen acid hydrazones and investigated the selective inhibition of COX-2. The synthesized novel ibuprofen derivatives selectively inhibited COX-2, and some of the reported molecules showed higher inhibition compared to ibuprofen.

Ishii and co-workers [5] have synthesized *closo*-dodecaborate ibuprofen by forming an amide bond between ibuprofen activated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and 4-aminoethoxyethoxy-*closo*-dodecaborate, which is synthesized by ring-opening reaction of 1,4-dioxane-closo-dodecaborate complex with ammonia in an aqueous medium.

The isoquinoline structural motifs are widely distributed in nature. These alkaloids and their synthetic analogs have been studied since the end of the 19th century, and have been reported to display a wide spectrum of biological and pharmacological activities [6].

Easy-separable and reusable heterogeneous acid catalysts have been playing an important role in organic synthesis and in the production of industrially important chemicals. A number of scientists [7] have reported the successful use of Brönsted acids as catalysts in a number of organic transformations. To overcome limitations such as toxicity, evaporation, high cost, and hazardous nature of conventional methods, the acids that catalyze the reactions are adsorbed on a suitable support, such as silica gel. The use of such catalysts is gaining importance worldwide. The authors describe some of the common acid catalysts, namely, heteropolyacids, polyphosphoric acid, perchloric acid, hydrofluoric acid, and sulfuric acid. These catalysts are used in a number of reactions to produce compounds that are critical in both the chemical and pharmaceutical industries.

Trifluoromethanesulfonic acid or triflic acid, also known as, TFMS, TFSA, HOTf, or TfOH, is a sulfonic acid with the chemical formula CF_3SO_3H. It is one of the strongest acids. Trifluoromethanesulfonic acid

was mainly used in the study as a catalyst for esterification. It is a hygroscopic, colorless, slightly viscous liquid soluble in polar solvents. Triflic acid is a highly corrosive and fuming liquid. It is dangerous for storing and transportation, as well as during operation, so its use is severely limited. Immobilization of trifluoromethanesulfonic acid on an inorganic material such as silica gel and other inorganic materials results in "solid" acids that can be easily used because they are less toxic, non-corrosive, with high thermal and mechanical resistance under catalytic conditions.

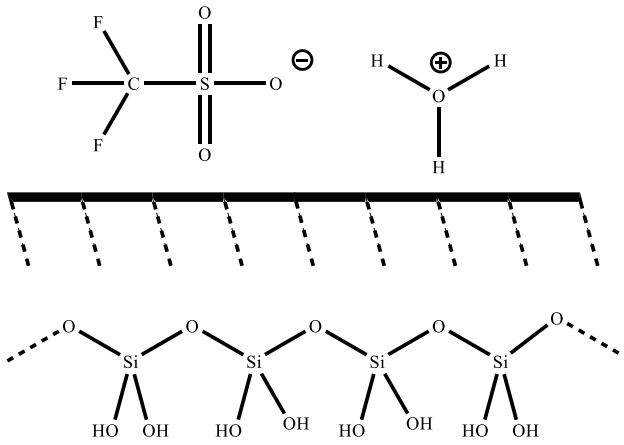


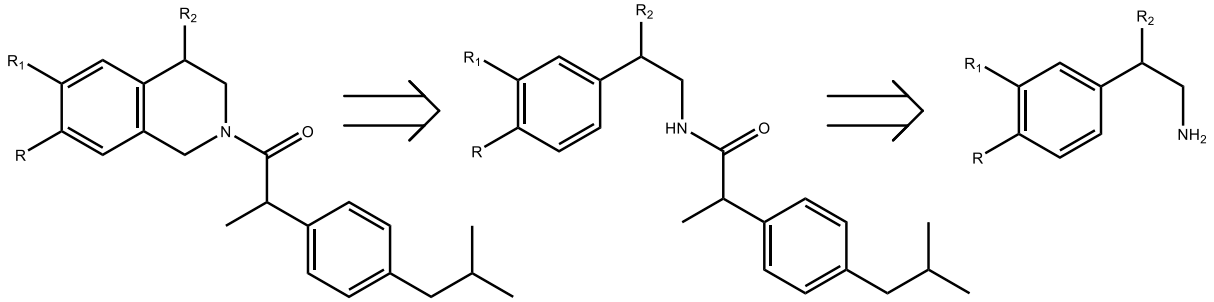
Fig. 3. General representation of triflic acid immobilized on silica gel.

In this regard, we are interested in the application of TfOH/SiO_2 as a “heterogeneous catalyst” for the synthesis of 1,2,3,4-tetrahydroisoquinoline derivatives of ibuprofen. The newly synthesized compounds are interesting because of their biological activity.

2. RESULTS AND DISCUSSION

It is known from the literature that ibuprofen is a widespread non-steroidal anti-inflammatory drug with a pronounced anti-rheumatic effect, which is widely used in medical practice. Due to a number of contraindications (renal impairment, prostate enlargement, hyperthyroidism, narrow-angle glaucoma, hypersensitivity, etc.), as well as the incompatibility of the drug with other drugs (aspirin, other nonsteroidal anti-inflammatory drugs, including inhibitors of COX-2), there is an interest in obtaining new organic compounds containing ibuprofen residue in the structure of its molecule. On the other hand, isoquinoline alkaloids are known for their broad spectrum of biological activities. The literature review also showed that the application of environmentally friendly and "green" methods for the preparation of organic compounds occupies a central place in organic synthesis. The application of heterogeneous acid systems applied to silica gel is widely used for the preparation of a number of new organic compounds.

In connection with our goal, it was necessary to solve the following main tasks, summarized in the following retrosynthesis scheme:



Scheme 1. Retrosynthesis scheme of *N*-(4-isobutylphenyl)propan-1-one substituted 1,2,3,4-tetrahydroisoquinolines.

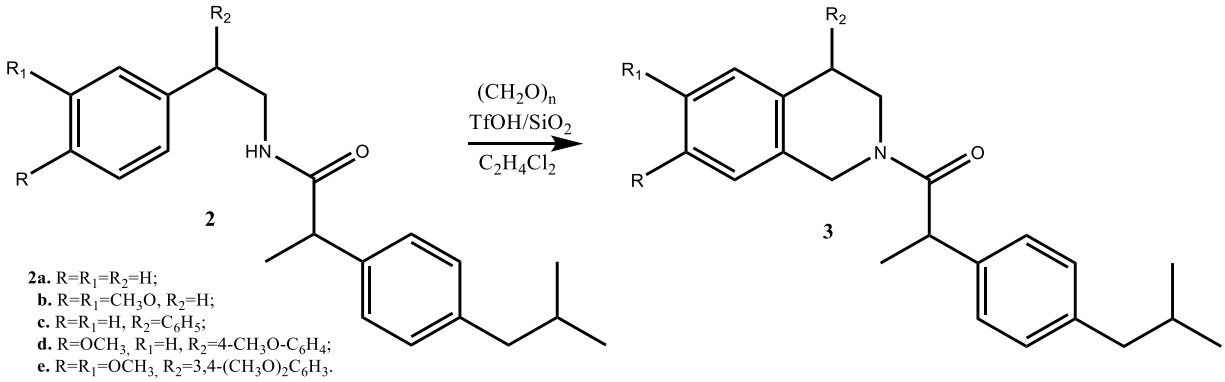
So, the first task is obtaining of different substituted ibuprofen amides following by cyclization of the newly formed amides to 1,2,3,4-tetrahydroisoquinoline derivatives of ibuprofen.

Searching for alternative methods for the synthesis of the starting amides, the method described in the literature with the use of amines and carboxylic acids using *N*, *N*-dicyclohexylcarbodiimide aroused our interest. *N*, *N*-dicyclohexylcarbodiimide (DCC) is a dehydrating agent commonly used to prepare esters, amides, or anhydrides. It is commercially available as a waxy crystalline substance with a low melting point of 34-35°C. DCC reacts with the carboxyl group of ibuprofen to form an activated acylating agent that reacts with the amino group of the other molecule to form an amide bond. All amides are successfully obtained and reported by us with their biological evaluation already [8].

For the cyclization step, we explored the possibility of using new "green" reagents, which are increasingly used in practice, representing strong protic acids immobilized on silica gel as heterogeneous acid catalysts in the intramolecular *α*-amidoalkylation reaction.

Both the electron donor substituents in the amide molecule and the proton reaction medium are extremely important for the successful course of the reaction. The course of the intramolecular *α*-amidoalkylation reaction in amides that do not contain electron-donating substituents in the aromatic nucleus becomes possible when a more acidic medium is used. This explains the importance of the proton medium on the course of the reaction, supporting the generation of intermediate-forming *N*-acyliminium ions.

We have investigated the possibility of using the $TfOH/SiO_2$ as a heterogeneous catalyst in the intramolecular *α*-amidoalkylation reaction. The same heterogeneous system has been successfully applied in recent years in a number of acid-catalyzed reactions. They are characterized as environmentally friendly methods with the separation of a minimum amount of waste products.



Scheme 2. Preparation of 1,2,3,4-tetrahydroisoquinolines **3**.

For this purpose, an excess of paraformaldehyde and $TfOH/SiO_2$ (0.03 g per 1 mmol amide, of which 0.015 mmol acid) was added to the amides **2** dissolved in dichloroethane. The reaction mixture was stirred on an electromagnetic stirrer at 80°C, observing that the reaction proceeded completely in 60 minutes under these reaction conditions (Scheme 2). The progress of the reaction is monitored by thin-layer chromatography. Chromatographically was observed obtaining of two new compounds after the completion of the reaction with amides **2c**, **2d**, and **2e**. Appropriate conditions for the separation of diastereoisomeric pairs are to be found. The results presented here are of the diastereoisomeric mixtures of compounds **3c-e**.

The newly synthesized cyclic compounds **3a-e** were obtained in the high yields shown in the experimental section. The resulting cyclic compounds **3a-e** are new compounds (*Reaxys*), and all are characterized by ^{1}H- and ^{13}C-NMR, IR, and HRMS spectra.

3. EXPERIMENTAL SECTION

All the reagents and chemicals were purchased from commercial sources (Sigma-Aldrich, S.A., Sofia, Bulgaria) and used as received. Melting points were determined on a Boetius hot stage apparatus and are non-corrected. The spectral data were recorded on a Bruker Avance II + 600 spectrometer (BAS IOCCP—Sofia, Sofia, Bulgaria). The ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ or DMSO at 600 MHz and 150.9 MHz, respectively. Chemical shifts are given in ppm relative and were referenced to TMS (δ = 0.00 ppm) as an internal standard with the coupling constants indicated in Hz. The NMR spectra were taken at room temperature (ac. 295 K). Mass analyses were carried out on a Q Exactive Plus mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). TLC was carried out on precoated 0.2mm Fluka silica gel 60 plates. Ibuprofen is isolated from a product available in the pharmacy market. For this purpose, the tablets were ground and extracted with isopropyl alcohol. Then, ibuprofen is filtered through silica gel and the solvent is removed using a rotary evaporator. The temperature range at which the resulting white crystals melt is 75-78°C. According to literature data, the melting point of ibuprofen is 76°C.

Synthesis of ibuprofen amides 2a-e [8]

Synthesis of 1,2,3,4-tetrahydroisoquinolines 3a-e

To the corresponding amide **2a-e** (1 mmol) dissolved in dichloroethane (20 ml) TfOH / SiO_2 (0.06 g) was added. The reaction mixture then was stirred on an electromagnetic stirrer at 80°C for 60 minutes. The progress of the reaction is monitored by thin-layer chromatography. After the reaction proceeds, the heterogeneous catalyst is removed by simple filtration, washed, and regenerated for further use. The dichloroethane was removed by distillation then the residue in the flask was dissolved in methylene chloride, washed with water, dried over anhydrous Na_2SO_4, and concentrated.

3a: 1-(3,4-dihydroisoquinolin-2(1H)-yl)-2-(4-isobutylphenyl)propan-1-one.

Yield = 94%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 – 7.06 (m, 4H), 7.01 (m, J = 5.8 Hz, 2H), 6.95 (m, J = 22.7, 7.6 Hz, 2H), 4.69 (dd, J = 110.9, 17.2 Hz, 1H), 4.42 (dd, J = 155.0, 16.0 Hz, 1H), 3.91 – 3.81 (m, 2H), 3.55 – 3.50 (m, 1H), 2.81 – 2.70 (m, 1H), 2.36 (d, J = 7.2 Hz, 2H), 1.79 – 1.70 (m, 1H), 1.39 (d, J = 6.8 Hz, 3H), 0.81 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.78, 140.19, 134.16, 133.57, 129.65, 128.30, 127.02, 126.92, 126.40, 126.16, 125.91, 45.00, 44.61, 43.47, 43.03, 30.22, 29.01, 22.37, 20.78. IR: 708, 748, 768, 849 $\gamma(C_{sp}^2\text{-H})$; 1279, 1343 ν(C-N), 1383 ($\delta_s CH_3$); 1431, 1454, 1559, 1647 (ν C=C); 1700 ν(C=O); 2867 ν_s (CH_2); 2930 $\nu_{as}(CH_2)$; 2953 $\nu_{as}(CH_3)$; 3023, 3069 $\nu(C_{sp}^2\text{-H})$. HRMS electrospray ionization (ESI) m/z calcd for $C_{22}H_{28}NO^+$ = 322.2171, found 322.2172 (mass error Δm = 0.31 ppm)

3b: 1- (6,7-dimethoxy-3,4-dihydroisoquinolin-2 (1H) -yl) -2- (4-isobutylphenyl) propan-1-one.

Yield = 99%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 – 7.07 (m, 3H), 7.05 – 6.96 (m, 2H), 5.23 (s, 2H), 4.52 (d, J = 16.9 Hz, 1H), 3.93 – 3.82 (m, 1H), 3.77 (d, J = 7.5 Hz, 2H), 3.73 (d, J = 8.4 Hz, 2H), 2.37 (dd, J = 7.3, 3.4 Hz, 1H), 2.33 (d, J = 7.2 Hz, 1H), 2.10 (s, 1H), 1.81 – 1.73 (m, 1H), 1.40 (d, J = 6.8 Hz, 1H), 0.82 (s, 1H), 0.81 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.69, 147.70, 147.49, 140.16, 139.29, 129.63, 129.58, 127.32, 127.00, 126.92, 125.36, 111.05, 109.31, 55.90, 53.46, 44.99, 44.25, 30.58, 28.48, 25.87, 20.78. IR: 708, 748, 768, 804, 850 $\gamma(C_{sp}^2\text{-H})$; 1279, 1343 ν(C-N), 1383 ($\delta_s CH_3$); 1465, 1518, 1647 (ν C=C); 1700 ν(C=O); 2867 $\nu(OCH_2\text{-H})$; 2932 $\nu_{as}(CH_2)$; 2953, $\nu_{as}(CH_3)$; 3023 $\nu(C_{sp}^2\text{-H})$. HRMS electrospray ionization (ESI) m/z calcd for $C_{24}H_{32}NO_3^+$ = 382.2382, found 382.2385 (mass error Δm = 0.78 ppm).

3c: 2-(4-isobutylphenyl)-1-(4-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)propan-1-one

Yield = 98%, ^{1}H NMR (600 MHz, CDCl3) δ 7.19 – 7.14 (m, 4H), 7.13 – 7.09 (m, 2H), 7.07 – 6.99 (m, 4H), 6.93 – 6.87 (m, 3H), 4.68 (t, J=7.5 Hz, 2H), 4.00 (t, J = 8.0 Hz, 1H), 3.83 – 3.62 (m, 2H), 3.33 (q, J = 7.2 Hz, 1H), 2.35 (d, J = 7.2 Hz, 2H), 1.80 – 1.72 (m, 1H), 1.36 (d, J = 7.3 Hz, 3H), 0.82 (dd, J = 6.6, 3.5 Hz, 6H). ^{13}C NMR (151 MHz, CDCl3) δ 174.45, 141.73, 141.69, 140.59, 138.06, 129.58, 129.55, 128.74, 128.66, 128.64, 128.03, 127.99, 127.32, 127.30, 126.72, 50.36, 46.70, 45.03, 43.84, 30.21, 22.44, 18.20. IR: 705, 747, 768, 806, 852 $\gamma(C_{sp}^2\text{-H})$; 1281, 1340 ν(C-N), 1383 ($\delta_s CH_3$); 1467,

1517, 1648 ν(C=C); 1700 ν(C=O); 2867 ν(OCH$_2$-H); 2932 ν_{as}(CH$_2$); 2953, ν_{as}(CH$_3$); 3023 ν(C$_{sp}^2$-H). HRMS electrospray ionization (ESI) m/z calcd for $C_{28}H_{32}NO^+$ = 398.2484, found 398.2486 (mass error Δm = 0.50 ppm).

3d: 2-(4-isobutylphenyl)-1-(7-methoxy-4-(4-methoxyphenyl)-3,4-dihydroisoquinolin-2(1H)- yl)propan-1-one

Yield = 92%, ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.12 – 7.07 (m, 2H), 7.04 – 7.00 (m, 2H), 6.94 – 6.88 (m, 4H), 6.75 – 6.65 (m, 3H), 5.21 (s, 2H), 3.88 (t, J = 8.0 Hz, 1H), 3.69 (d, J = 0.8 Hz, 6H), 3.64 (d, J = 5.2 Hz, 2H), 3.42 (q, J = 7.2 Hz, 1H), 2.37 (d, J = 4.6 Hz, 2H), 1.76 (m, 1H), 1.42 (dd, J = 7.2, 2.7 Hz, 3H), 0.82 (dd, J = 4.8, 1.8 Hz, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 178.37, 174.50, 173.68, 129.66, 129.58, 129.50, 129.47, 129.34, 129.13, 128.89, 128.84, 127.32, 127.29, 113.96, 113.73, 110.74, 55.21, 48.70, 46.69, 45.01, 44.10, 43.13, 30.21, 22.41, 18.50. IR: 703, 751, 765, 809, 850 γ(C$_{sp}^2$-H); 1280, 1342 ν(C-N), 1384 (δ_sCH$_3$); 1466, 1519, 1644 ν(C=C); 1702 ν(C=O); 2869 ν(OCH$_2$-H); 2933 ν_{as}(CH$_2$); 2952, ν_{as}(CH$_3$); 3021 ν(C$_{sp}^2$-H). HRMS electrospray ionization (ESI) m/z calcd for $C_{30}H_{36}NO_3^+$ = 458.2695, found 458.2697 (mass error Δm = 0.44 ppm).

3e: 1-(4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-(4-isobutylphenyl)propan-1-one

Yield = 94%, ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.15 – 7.05 (m, 2H), 7.04 – 7.00 (m, 2H), 6.92 – 6.86 (m, 3H), 6.71 – 6.67 (m, 2H), 5.21 (s, 2H), 3.86 (t, J = 7.8 Hz, 1H), 3.71 (s, 12H), 3.62 (d, J = 5.1 Hz, 2H), 3.43 (q, J = 7.2 Hz, 1H), 2.03 (d, J = 5.0 Hz, 2H), 1.77 (tq, J=13.6, 6.8 Hz, 1H), 1.42 (dd, J = 7.2, 1.7 Hz, 3H), 0.82 (d, J = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, CDCl3) δ 179.52, 173.86, 170.28, 129.86, 129.68, 129.45, 129.42, 129.35, 129.14, 128.88, 128.80, 127.33, 127.30, 113.94, 113.72, 110.71, 55.20, 48.72, 46.68, 45.00, 44.15, 43.12, 30.19, 25.82, 22.40, 18.24. IR: 699, 745, 763, 811, 856 γ(C$_{sp}^2$-H); 1285, 1341 ν(C-N), 1383 (δ_sCH$_3$); 1467, 1514, 1646 ν(C=C); 1701 ν(C=O); 2867 ν(OCH$_2$-H); 2932 ν_{as}(CH$_2$); 2951, ν_{as}(CH$_3$); 3022 ν(C$_{sp}^2$-H). HRMS electrospray ionization (ESI) m/z calcd for $C_{32}H_{40}NO_5^+$ = 518.2906, found 518.2908 (mass error Δm = 0.39 ppm).

4. CONCLUSIONS

In conclusion, we have successfully applied an eco-friendly method for obtaining 1,2,3,4-tetrahydroisoquinoline derivatives of ibuprofen. The applied green catalyst TfOH/SiO$_2$ in the reaction of intramolecular α-amidoalkilation was regenerated and prepared for another use. No waste products were observed at the end of the reaction. The obtained five molecules are new compounds (*Reaxys*).

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