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S. Arrous, A. Bolde, I. Boudebouz, M.V. Lyapunova, A.A. Bakibayev

National Research Tomsk State University, Russia
(E-mail: parroussalinkov@yahoo.com)

«Solvent-less» mechanochemical approach to the synthesis of allobetulin and some of its esters

Various significant biological activities have been recently found for allobetulin and its derivatives which in combination with their low toxicities lead to an increased research effort. In the present work allobetulin and some its acyl derivatives have been synthesized by different reactions using a grindstone method. All reactions were carried out at room temperature. Allobetulin (**1a**) and allobetulin 3-O-formate (**1b**) were prepared by reacting betulin with trifluoroacetic acid (TFA) and HCOOH, consecutively. The reactions time was 30–40 min, and the yield of the products was 82 and 98 %, respectively. Allobetulin (**1a**) under the action of TFA for 2 hours affords allobetulin 3-O-trifluoroacetate (**3**) in 95 % yield. Whereas, the treatment of betulin diacetate with TFA for 30 min gives allobetulin 3-O- acetate (**2a**) in 92 % yield. The formation of products was detected by TLC using C_6H_6:CH_2Cl_2:CH_3OH (5:5:1) as eluent and the spots were revealed after spraying the TLC plates with reagent (1 % phosphomolybdic acid-water) followed by heating at 110 ºC for 5 minutes to show a characteristic blue colour. The present procedure is simple, efficient, and environmentally benign. The structures of all products were confirmed by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy.

Keywords: betulin, allobetulin, trifluoroacetic acid, mechanochemistry, grindstone, formic acid, allobetulinformate, betulin diacetate.

Introduction

The organic solvents are volatile and harmful, causing risks to people who inhale them as well as the environment. Thus, development of less hazardous synthetic methods for organic reactions is one of our objectives in current research. One of the methods belonging to such a protocol is a grindstone method. This mechanically activated solvent-free reaction helps in reducing the toxic waste produced, and therefore, becomes less harmful to the environment. Solvent-less organic reactions based on grinding of two macroscopic particles together mostly involves the formation of a liquid phase prior to the reaction, i.e. formation of an eutectic melt of uniform distribution where the reacting components being in close proximity react in a controlled way [1].

The grindstone method has been successfully applied for many reactions like Reformatsky reaction [2], Aldol condensation [3], Dieckmann condensation [4], Knoevenagel condensation [5], Biginelli reaction [6], synthesis of carbamates [7], and others [8]. On the other hand, allobetulin has been utilized as an important precursor in the further transformation of triterpenoids [9–22] and as a sample for biological studies. Recently, considerable attention is paid to the study of their biological activity among which are compounds with anti-inflammatory, antiulcerous [23], antiviral [24, 25], and immunoregulatory activities [26], an antibacterial, hepatoprotective, and antifeedant activity [9, 27, 28].

We report herein a simple and highly efficient method for the synthesis of allobetulin and its derivatives bearing acyl moiety at C-3 by a grindstone method.

Experimental

^{1}H and ^{13}C NMR spectra have been recorded with Bruker AVANCE 400 III HD spectrometer (Bruker, Billerica, MA, USA), 400.17 and 100.63 MHz, respectively. Chemical shifts are reported relative to tetramethylsilane peak set at 0.00 ppm. In the case of multiplets the signals were reported as intervals. Signals were abbreviated as s, singlet; d, doublet; t, triplet; m, multiplet. Coupling constants were expressed in Hz.

TLC was conducted on Sorbfil plates using C_6H_6: CH_2Cl_2: CH_3OH (5:5:1). Spots were detected by spraying TLC plates with 1 % phosphomolybdic acid and heating at 110 ºC for 5 minutes to show a characteristic blue colour.

Infrared spectra were obtained directly from the products using Bruker Tensor 27 FT-IR Spectrometer. The spectra were recorded in the range of 400 to 4000 cm^{-1}. Melting temperatures have been detected in open capillaries using Buchi apparatus. Finely cut birch bark was extracted with hot ethanol to give crude betulin **1** [29].

Synthesis of compound allobetulin **1a**

0.5 g (1.1mmol.) of betulin, 15 ml of TFA were added into a porcelain mortar (8 cm diameter). After few seconds of grinding with the aid of a pestle, the reaction mixture became a dark paste. The mixture was grinded for a period of 40 minutes until totally solidified when a beige solid powder became. At the end of grinding, 10 ml of methanol was added to the mortar (to facilitate the product precipitation) and further well mixed with the product so obtained using the pestle and a spatula to remove the solid from mortar wall. The resulting solid was collected by vacuum filtration on a Büchner funnel. Yield is 98 %. R_f is 0.56 (in system A), mp is 265 ºC (lit., [30] 264–266 ºC). IR spectrum (KBr, ν, cm^{-1}): 3423.4 — OH, 2934.5–2880.7 (-CH_3 and -CH_2), 1451.6, 1381.6 (-CH_3 and -CH_2), 1039.0 (C-O-C). ^{1}H NMR spectrum (400.17 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 0.78 (3H, s, CH_3), 0.81 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.99 (6H, s, CH_3), 1.20–1.73 (24H, m, CH_2, CH), 3.22 (1H, t, C_3H, *J* 5.6 Hz), 3.45 (1H, d, $C_{28}H_2$, *J* 8 Hz), 3.54 (1H, s, $C_{19}H$), 3.78 (1H, dd, $C_{28}H_2$, *J* 7.2 Hz). ^{13}C NMR spectrum (100.63 MHz, $CDCl_3$, δ, ppm): 13.52 (C27), 15.39 (C24), 15.72 (C26), 16.50 (C25), 18.26 (C6), 21.00 (C11), 24.56 (C29 or C30), 26.28 (CH_2), 26.45 (CH_2), 27.43 (C2), 27.99 (C23), 28.83 (C29 or C30), 32.72 (C21), 33.92 (C7), 34.16 (C13), 36.28 (C17), 36.76 (C16), 37.27 (C10), 38.90 (C4), 38.92 (C1), 40.62 (C), 40.72 (C), 41.49 (C), 46.84(C18), 51.09 (C9), 55.49 (C5), 71.29 (C28), 78.99 (C3), 87.94 (C19).

Synthesis of allobetulin 3-O-acetate **2a**

Betulin diacetate 0.5 g (1.1 mmol) and 15 ml of TFA were mixed and placed in a mortar and ground by hand with a pestle. Grinding was continued until the mixture appeared homogeneous and the reaction was complete (TLC), which took 0.5 h. After removal of most solvent, the residue was diluted with methanol, and the white precipitate was collected by filtration to afford white product. Yield is 92 %. R_f is 0.64 (C_6H_6:CH_2Cl_2:CH_3OH / 5:5:1), and mp is 283 ºC (lit., [31] 285–287 ºC). IR spectrum (KBr, ν, cm^{-1}): 2924.4–2856 (-CH_3 and -CH_2), 1726 (C=O), 1247.5 and 1023.3 (C-O-C). ^{1}H NMR spectrum (400.17 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 0.70 (3H, s), 0.74 (3H, s), 0.75 (3H, s), 0.77 (3H, s), 0.83 (3H, s), 0.87 (3H, s), 0.94 (3H, s), 2.08 (3H, s, 3b-$COCH_3$), 3.35 (1H, d, *J*=7.6, 28-H_a), 3.46 (1H, s, 19-H), 3.70 (1H, d, *J*=7.6, 28-H_b), 4.38 (1H, m, 3α-H). ^{13}C NMR spectrum (100.63 MHz, $CDCl_3$, δ, ppm): 13.52 (C27), 15.69 (C24), 15.77 (C26), 16.50 (C25), 18.14 (C6), 20.99 (C11), 21.37, 24.55 (C29 or C30), 26.23 (CH_2), 26.42 (CH_2), 27.93 (C2), 28.36 (C23), 28.80 (C29 or C30), 32.69 (C21), 33.83 (C7), 34.13 (C13), 36.26 (C17), 36.70 (C16), 37.17 (C10), 38.59 (C4), 39.66 (C1), 40.62 (C), 40.71 (C), 41.49 (C), 46.80 (C18), 51.00 (C9), 55.56 (C5), 71.26 (C28), 80.96 (C3), 88.04 (C19), 171.15 ($CH_3\underline{C}OO$).

Synthesis of compound allobetulin 3-O-trifluoroacetate **3**

0.5 g of allobetulin (1.1 mmol), and 50 ml of TFA were added in a mortar and ground continuously. The mixture was ground until completion of the reaction, which was monitored by TLC (2h). 10 ml of methanol was added to the syrupy formed product to give a white precipitate, which filtered through the filtration flask to afford the pure product without further purification. Yield is 95 %, R_f is 0.63 (C_6H_6:CH_2Cl_2:CH_3OH / 5:5:1), and mp is 268 ºC (lit., [24] 265.5–266.8 ºC). IR spectrum (KBr, ν, cm^{-1}): 2944.6–2869.0 (-CH_3 and -CH_2), 1770.1 (C=O), 1219.3, 1188.6 and 1033.0 (C-O-C), 1166.6 (C-F). ^{1}H NMR spectrum (400.17 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 0.72 (3H, s), 0.81 (3H, s), 0.82 (3H, s), 0.84 (3H, s), 0.85 (3H, s), 0.87 (3H, s), 0.91 (3H, s), 3.37 (1H, d, *J*= 7.6, 28-Ha), 3.47 (1H, s, 19a-H), 3.70 (1H, d, *J*=7.6, 28-Hb), 4.63 (1H, m, 3a-H). ^{13}C NMR spectrum (100.63 MHz, $CDCl_3$, δ, ppm): 12.46 (C27), 14.73 (C24), 15.22 (C26), 15.49 (C25),

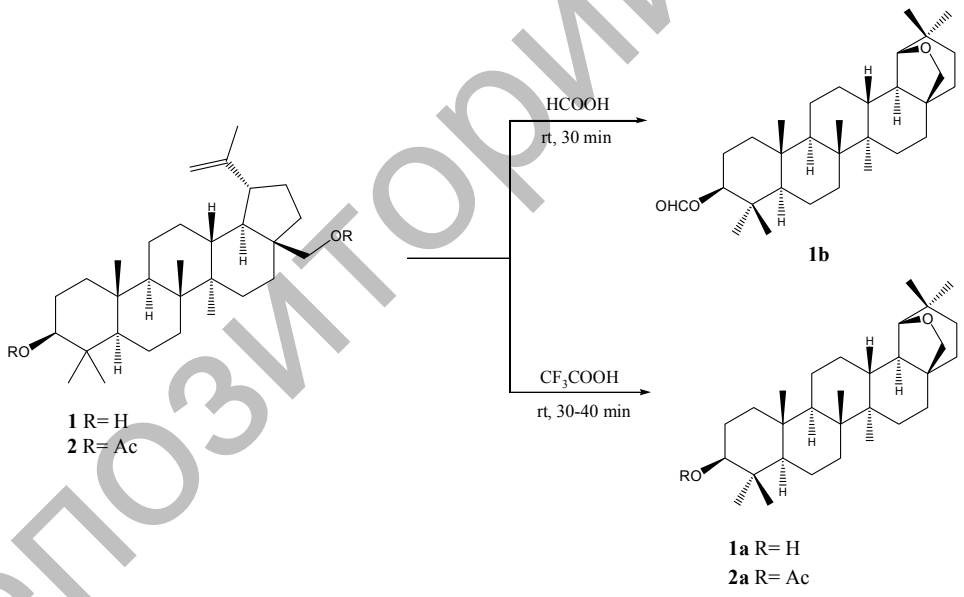
17.04 (C6), 20.01 (C11), 22.23 (CH2), 23.52 (C29 or C30), 25.49 (CH_2), 26.73 (CH_2), 26.84 (C2), 27.77 (C23), 31.66 (C29 or C30), 32.74 (C21), 33.09 (C7), 35.24 (C13), 35.69 (C17), 36.12 (C16), 37.05 (C10), 37.39 (C4), 39.60 (C1), 39.71 (C), 40.44 (C), 45.77(C18), 49.94 (C9), 54.40 (C5), 70.22 (C28), 85.25 (C3), 86.93 (C19). 115.09 ($\underline{C}F_3COO$), 156.57 ($CF_3\underline{C}OO$).

Synthesis of compound allobetulin 3-O-formate **1b**

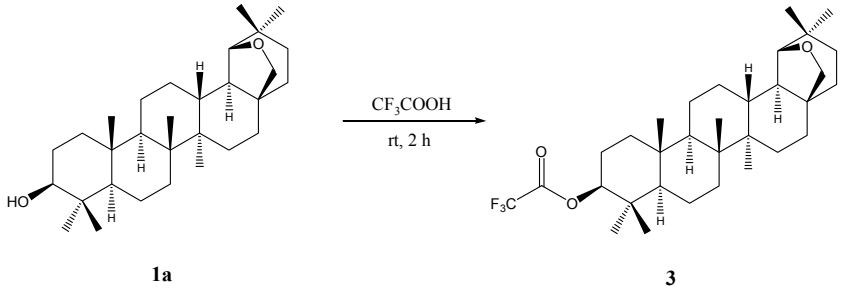
Betulin 0.5 g (1.1 mmol) and 25 ml TFA were taken in a pestle; the mixture was grounded till the reaction completion, which was monitored by TLC. The reaction was completed about 30 min at room temperature, after completion 10 ml of methanol was added, the precipitated product was filtered, and recrystallized in ethanol solvent. Yield is 82 %, R_f is 0.63 (C_6H_6:CH_2Cl_2:CH_3OH / 5:5:1), and mp is 314 ºC (lit., [32] 315 ºC). IR (KBr, ν, cm^{-1}): 2925 (=C-H), 1720 (C=O), 1175 (C-O-C).^{1}H NMR (400.17 MHz, $CDCl_3$, δ, ppm): 0.73 (s, 3H, CH3), 0.79 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 3.36 (d, 1H, *J* 7.6, 28-Ha), 3.47 (s, 1H, 19a-H), 3.7 (d, 1H, *J* 7.6, 28-Hb), 4.54 (m, 1H, 3a-H), 8 (s, 1H, 3b-COH). ^{13}C NMR(100.63 MHz, $CDCl_3$, δ, ppm): 13.52 (C27), 15.39 (C24), 15.72 (C26), 16.50 (C25), 18.26 (C6), 21.00 (C11), 23.81, 24.56 (C29 or C30), 26.25(CH_2), 26.42(CH_2), 27.86 (C23), 28.82 (C29 or C30), 32.69 (C21), 33.81 (C7), 34.12 (C13), 36.28 (C17), 36.72 (C16), 37.15 (C10), 37.76 (C4), 38.56 (C1), 40.62 (C), 40.72 (C), 41.48 (C), 46.80 (C18), 50.98 (C9), 55.48 (C5), 71.26 (C28), 81.07 (C3), 87.96 (C19), 161.24 (H$\underline{C}$OH).

Results and Discussion

The combination of solvents and long reaction time, costly chemicals makes this method environmentally hazardous. This provided the stimulus to synthesize allobetulin **1a** and its derivatives **1b**, **2a** and **3** using a grinding technique. In grindstone technique, reaction occurs through generation of heat by grinding of substrate and reagent by a mortar and a pestle.



Scheme 1. Synthesis of compounds **1a**, **1b** and **2a**



Scheme 2. Synthesis of compound **3**

More recently, a new process for the isomerisation of betulin **1** to allobetulin **1a** using trifluoroacetic acid has been reported by Medvedeva and co-workers [30] by stirring compound **1** with TFA at room temperature for 8 minutes. Whereas, the mechanochemical method required a simple grinding of compound **1** and TFA for 40 min to give allobetulin **1a** in 98 % (Scheme 1). The products obtained by both methods were found to be identical by mp.

The transformation of **1** to **1b** was reported as early as in 1922 by Schulze and Pieroh [32] in which **1** was isomerised by formic acid under reflux during 2 hours to give **1b** in moderate yield. While, the treatment of betulin **1** with formic acid under grinding at 20 ºC for 1h provided **1b** in 82 % isolated yield (Scheme 1).

It should be noted that compound **3** was previously being synthesized starting with betulin using a two-stage method including the stage of 3-monoacetate betulin synthesis that directly reacted with TFA and trifluoroacetic anhydride at 0 ºC for 1.5 hour to afford of allobetulin 3-O-trifluoroacetate. The total yield of allobetulin 3-O-trifluoroacetate **3** was 40 % calculated with reference to betulin [24]. While, in our study the starting compound was allobetulin **1a** which was ground with TFA at room temperature for 2 hours to give allobetulin 3-O-trifluoroacetate **3** in 95 % (Scheme 2).

Compound **2a** was also previously being synthesized from betulin diacetate **2** and formic acid under reflux according to the reported method in trichloromethane at reflux during 1.5 hour [33]. Replacing formic acid by trifluoroacetic acid using a grinding method the compound **2** was converted to allobetulin 3-O-acetate **2a** after 30 min in 92 % (Scheme 1).

Chemical structure of compound **1a** is confirmed using IR spectroscopy, ^{1}H and ^{13}C NMR, and their properties have been compared with literary data [31]. In its IR spectrum we observed the presence of hydroxyl group at 3423.4 cm^{-1} and also the appearance of intense bands at 1039 cm^{-1}, which could be attributed to C–O groups. ^{1}H NMR spectrum of the allobetulin **1a** showed that the signals at 4.59 and 4.69 ppm of the olefinic region were missing, along with the formation of tetrahydrofuran ring which appeared as doublets of protons of $C_{28}H_2$ group (*AB* system) at δ 3.45 and 3.78 ppm, and a singlet of CH group at 3.54 ppm. The ^{13}C NMR spectrum confirmed the absence of two olefinic carbons at 110 and 150 ppm and the presence of new signal at 87.94 ppm corresponding to C-19.

The structures of the synthesized compounds **1b, 2a** and **3** were established by ^{1}H and ^{13}C NMR spectroscopy in comparison with the analogous data published for related triterpenoids [24, 31, 32]. The ^{1}H NMR spectra of allobetulin esters synthesized **1b, 2a** and **3** contain characteristic signals of tetrahydrofuran ring, which appears as doublets of protons of CH_2 group (*AB* system), δ 3.45–3.78 ppm, and a singlet of CH group at 3.53–3.57 ppm. Comparison of the ^{1}H NMR spectra of **1b, 2a, 3** and allobetulin revealed an appreciable downfield shift of the C-3 proton signals as a result of introduction of an acyl group (the very characteristic resonance signal from an unsubstituted derivatives is usually at around 3.22 ppm, while substitution of carbon C-3 shifts this signal downfield by 1.16–1.41 ppm).

The allobetulin esters **1b, 2a** and **3** have been characterized by IR spectra, which display the disappearance of OH band of allobetulin and appearance of new bands such as the C=O group at 1720–1770 cm^{-1} and of the C–O ester group at 1000–1275 cm^{-1}.

Conclusion

We reported simple, faster method for the synthesis of allobetulin and its acyl derivatives by a mechanochemical method. This procedure offers several advantages including time saving, very easy work-up, and it is free from usage of organic solvents. The generality of this method has been demonstrated by the successful conversion with 82–98 % yields in 30–120 minute reaction completion.

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С. Арроус, А. Болде, И. Будебу, М.В. Ляпунова, А.А. Бакибаев

Аллобетулин және оның кейбір күрделі эфирлерінің синтезіне «еріткішсіз» механохимиялық тәсілдеме

Аллобетулин және оның туындылары үшін соңғы кезде биологиялық белсенділік табылған, бұл олардың төмен улылығымен біріккенде ғалымдардың назарын өзіне тартады. Мақалада аллобетулин және оның кейбір ацетил тобы бар туындылары, механохимиялық белендіруге негізделген, әртүрлі әдістермен синтезделді. Барлық реакциялар бөлмелік температурада жүргізілді. Аллобетулин (**1a**) және аллобетулин 3-О-формиат (**1b**) бетулиннің трифторсірке қышқылымен (TFA) және HCOOH әрекеттесу реакциясы арқылы алынды. Реакцияның жүру уақыты 30–40 мин құрды, және өнімдердің шығымы сәйкесінше 82 және 98 % тең болды. Аллобетулин 3-О-трифторацетат (**4**) 95 % шығыммен аллобетулиннің (**1a**) TFA 2 сағаттық реакциясы нәтижесінде алынды. Ал аллобетулиннің 3-О-ацетаты (**2a**) бетулин диацетатының трифторсірке қышқылымен 30 мин ішінде өңделуі нәтижесінде 92 % шығыммен алынды. Өнімдердің түзілуі ЖҚХ әдісімен, элюент ретінде C_6H_6:CH_2Cl_2:CH_3OH (5:5:1) қолданылуымен анықталды, дақтар ЖҚХ пластиналарын реагентпен (1 % фосфомолибден қышқылы – су) бүркіп, соңынан көк түсті бояу пайда болғанша 110 ºС температурада 5 мин қыздырғанда анықталды. Бұл процедура қарапайым, тиімді және экологиялық қауіпсіз. Барлық өнімдердің құрылымдары ^{1}H ЯМР, ^{13}C ЯМР және ИҚ-Фурье-спектроскопия әдістерінің мәліметтерімен дәлелденді.

Кілт сөздері: бетулин, аллобетулин, трифторсірке қышқылы, механохимия, механохимиялық белсендіру, құмырсқа қышқылы, аллобетулиннің формиаты, бетулиннің диацетаты.

С. Арроус, А. Болде, И. Будебу, М.В. Ляпунова, А.А. Бакибаев

Механохимический подход «без растворителя» к синтезу аллобетулина и некоторых его сложных эфиров

Для аллобетулина и его производных не так давно была обнаружена биологическая активность, что, в сочетании с их низкой токсичностью, привлекает внимание ученых. В данной работе аллобетулин и некоторые его производные, содержащие ацетильную группу, синтезируются различными методами, основанными на механохимической активации. Все реакции проведены при комнатной температуре. Аллобетулин (**1a**) и аллобетулин 3-О-формиат (**1b**) были получены реакцией взаимодействия бетулина с трифторуксусной кислотой (TFA) и HCOOH. Время проведения реакции составляло 30–40 мин, выход продуктов составил 82 и 98 % соответственно. Аллобетулин 3-О-трифторацетат (**4**) с выходом 95 % получается реакцией аллобетулина (**1a**) с TFA в течение 2 часов. В то время как 3-О-ацетат аллобетулина (**2a**) получается обработкой диацетатабетулина трифторуксусной кислотой в течение 30 минут с выходом 92 %. Образование продуктов определяли методом ТСХ с использованием C_6H_6:CH_2Cl_2:CH_3OH (5:5:1) в качестве элюента, пятна были обнаружены после опрыскивания пластин ТСХ реагентом (1 % фосфомолибденовая кислота – вода) с последующим нагреванием при 110 ºС в течение 5 минут до появления характерного синего окрашивания. Данная процедура проста, эффективна и экологически безопасна. Структуры всех продуктов были подтверждены данными ^{1}H ЯМР, ^{13}C ЯМР и ИК-Фурье-спектроскопии.

Ключевые слова: бетулин, аллобетулин, трифторуксусная кислота, механохимия, механохимическая активация, муравьиная кислота, формиат аллобетулина, диацетатбетулина.