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Convenient and Mild Method for Acylation of Betulin using Tetraacetyl Glycoluril

Salah Arrous[1]*, Abdigali Bakibaev[1], Phuoc Hoang [2], Imene Boudebouz[1],Viktor Malkov[1]

[1]Department of Chemistry, Faculty of Science, Tomsk State University, Lenin Avenue 36, Tomsk 634050, Russia
[2]Department of Chemistry, Faculty of Science, Tomsk Polytechnic University, Lenin Avenue 30, Tomsk 634050, Russia

Abstract : Betulin was reacted with tetraacetylglycoluril at room temperature in the presence of paratoluenesulfonic acid to produce corresponding diacetate with good yield. The acetylation of betulin was also carried out using mechanochemical method in the presence para toluene sulfonic acid to yield diacetatebetulin, while in the presence of formic acid the formylation took the place of acetylation, which gave allobetulinformiate. The reaction time for classical reaction was 2 hours, while for mechanochemical method the time was 5 to 15 minutes. The solvents used in these reactions were chloroform and dioxane.
Keywords : Betulin, Acylation, Glycoluril, Mechanochemistry, betulin Diacetate.

Introduction

Acetylation of alcohols is an important and routinely utilized transformation in organic chemistry [1]. Among the various protecting groups used for the hydroxyl group, acetyl is one of the most common groups, being stable in the acid reaction conditions and also eases of removal by mild alkaline hydrolysis.

Glycolurils have been received a great attention due to their applications as fertilizers [2], psychotropic agents, stabilizers of organic compounds against photo degradation [3], explosives [4], polymer crosslinking agents [5,6], catalysts, bleaching activators 7[7-9], and their use in combinatorial chemistry. [3]

Reaction of glycoluril with acyl anhydride such as acetic anhydride under acidic conditions gives the tetraacetylglycoluril[10], which has been used as bleaching activator [11, 12], in similar manner to other N- and O-acetyl species. This process occurs by reaction of hydrogen peroxide with the acetyl group to make peroxyacetic acid, which has greatly improved bleaching efficiency compared to hydrogen peroxide.

Tetraacetylglycoluril (TAGU, 2,4,6,8-tetraacetyl-2,4,6,8-tetraazabicyclo [3,3,0] octane-3,7-dione) also can acts as N-acetylating reagent for certain proteins [13] and amines [14] under the classical organic synthesis and under mechanochemical activation [15]. However, the use of TAGU as acetylating agent for alcohols is not reported under classical organic synthesis or under mechanochemical activation.

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It is well known that betulindiacetate has many interesting biological activities hepatoprotective, hypolipidemic, cholegogic, and antioxidant properties and is a promising pharmaceutical [16-20]. Furthermore the protection of C-3 and C-28 using acylation method can serves as the raw material for many organic syntheses such as the synthesis of betulinic acid, sulphur-containing betulin derivatives, amino derivatives of betulindiacetate, and especially conversions involving the isopropenyl group which are relatively unstudied. [21,22]

Generally, the acetylation of betulin is based on its reactions with acetic anhydride or acyl chloride in the presence of bases such as pyridine. An attempt to synthesize betulindiacetate was reported [23] using boiling acetic anhydride with betulin in the presence of sulfuric acid, which leads to the formation of 3-acetate of allobetulin instead of the target compound. Later levdansky and al have established [24] that substitution of sulfuric acid for orthophosphoric acid in these conditions has excluded isomerization process of betulin to allobetulin, giving only 3, 28-diacetate of betulin.

The present work highlighted the preparation of betulindiacetate using TAGU as new mild, cheap and recyclable acetylating reagent in the presence of para-toluene sulfonic acid as catalyst.

Experimental section

General

Melting points (mp) were determined in open capillaries using Buchi apparatus and are uncorrected.[1].

Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded on a Bruker Avance III D spectrometer at room temperature. Chemical shifts (d) are reported relative to tetramethylsilane peak set at 0.00 ppm. In the case of multiplets the signals are reported as intervals. Signals were abbreviated as s, singlet;d, doublet;t, triplet;m, multiplet. Coupling constants were expressed in Hz.

Reaction progress was controlled by thin-layer chromatography and observed under UV light (254/365 =λnm) with Ehrlich's reagent and C_6H_6:CH_2Cl_2:CH_3OH (5:5:1).) as eluent.

Fourier-transform infrared (FTIR) spectra were obtained directly from the products using the high-attenuated total reflectance technique in a Bruker Tensor 27 FT-IR Spectrometer.

The spectra were recorded in the range of 400 to 4000 cm-1 with a resolution of 4 cm-1 over 16 scans.

Betulin3,28-Diacetate (3). Method A*:*

0.3g (0.6mmol) of **1** and 0.2g (1mmol) of para-toluenesulfonic acid were dissolved in 30 ml of chloroform. The mixture was stirred until the solution became homogeneous, then 0.2g (0.5mmol) of **2** was added to the solution and stirred at 70 °C for 2 hours. After the solution being stirred for 1 hour **4a** and **4b** were precipitated as a white solid. After reaction completion, which was checked by TLC .The precipitate was filtered off and the solvent was evaporated to dryness. The resulting crude product was redissolved in methanol and then poured into water to form white precipitate. The resulting compound was filtered off to give 0.32g (89%)diacetatebetulin.

Method B*:*

A mixture of betulin 0.3g (0.6 mmol), TAGU 0.2g (0.5 mmol) and p-TsOH 0.2g (1mmol) in dioxane (4 mL) was grinded at room temperature. Reaction time was from 5 to15 minutes. After completion of the reaction (TLC monitoring) the mixture was dissolved in methanol and then poured into water to form white precipitate. The precipitate was filtered and washed with water. The crude product was recrystalized from isopropanol to give 0.3g (83%) pure betulindiacetate.

Compound(3):

Rf= 0.91(C_6H_6: CH_2Cl_2: CH_3OH / 5:5:1). Yield=89%. Mp=220°C. IR (cm^{-1}): 3070.90 (=C-H), 1739.93 (C=O), 1649.86 (C=C), 1246.14, 1085.78(C-O-C). ^{1}H NMR (300 MHz, CDCl3)), δH, ppm: 0.78 (m, 1H, 5-H), 0.83 (s, 3H, CH3), 0.85 (s, 6H, CH3), 0.97 (s, 3H, CH3), 1.03 (s, 3H, CH3), 1.03–1.95 (m, 10H, CH2); 1.30 (m, 1H, CH), 1.60 (m, 1H, CH), 1.65 (m, 1H, CH); 1.68 (s, 3H, C30H3), 2.04 (s, 3H, CH3CO), 2.07 (s, 3H, CH3CO),

2.44 (t.d, 1H, 19-H, *J* = 11.0, 5.8 Hz), 3.85 and 4.25 (d, 2H, 28-H, 2*J* = 11.0 Hz), 4.47 (m, 1H, 3-H), 4.59 and 4.69 (m, 2H, 29-H). ^{13}C NMR spectrum (75 MHz, CDCl3), δC, ppm: 14.7, 16.0, 16.2, 16.5 (CH3); 18.2 (C6), 19.1(C30), 20.8 (CH2), 21.1 (CH3CO), 21.4 (CH3CO), 23.7 (C2), 25.1 and 27.0 (CH2), 27.9 (CH3), 29.6 (C21); 29.7, 34.1, 34.5 (CH2); 37.1, 37.5 (C13), 37.8, 38.4 (CH2);40.9, 42.7, 46.3, 47.7 (C19), 48.7 (C18), 50.3 (C9), 55.3 (C5), 62.8 (C28), 80.9 (C3), 109.9 (C29), 150.1 (C20), 170.0 and 171.6 (C=O).

1,4-Diacetylglycoluril 4a+4b:

Mp>300 C. ^{1}H NMR (300 MHz, DMSO-d6): 8.81 and 7.7 (s, 2H, NH), 5.56 (s, 2H, CH), 2.33 and 2.26 (s, 6H, CH3). ^{13}C NMR (75 MHz, DMSO-d6): 170.6 and 170.1 (C=O acetyl), 154.3 (C=O glycoluril), 62.3 and 63.3 (CH), 23.7 and 24.5 (CH3).

Allobetulinformiate 5*:*

Betulin 0.3g (0.6 mmol), TAGU 0.2g (0.5 mmol) and formic acid (4 mL) were grinded together at room temperature. Reaction time was from 5 to15 minutes. After completion of the reaction (TLC monitoring) the mixture was dissolved in methanol and then poured into water to form white precipitate. The precipitate was filtered and washed with water to give 0.27g (82%) of allobetulinformiate.

Allobetulinformiate 5 :

Rf= 0.89 (C_6H_6: CH_2Cl_2: CH_3OH / 5:5:1). Yield=82%. Mp= 315 °C.IR (cm^{-1}): 2925 (=C-H), 1720(C=O), 1175 (C-O-C).^{1}H NMR (300 MHz, CDCl3): 0.73 (s, 3H, CH3), 0.79 (s, 3H, CH3), 0.80 (s, 3H, CH3), 0.84 (s, 3H, CH3), 0.86 (s, 3H, CH3), 0.89 (s, 3H, CH3), 0.97 (s, 3H, CH3), 3.36 (d, 1H, *J* 7.8, 28-Ha), 3.47 (s, 1H, 19a-H), 3.7 (d, 1H, *J* 7.8, 28-Hb), 4.54 (m, 1H, 3a-H), 8 (s, 1H, 3b-COH). ^{13}C NMR (75 MHz, CDCl3): 13.5, 15.7, 16.5, 16.5, 18.1, 21.0, 21.3, 23.7, 24.5, 26.2, 26.4 (2 C), 27.9, 28.8, 32.7, 33.8, 34.1, 36.2, 36.7, 37.1, 37.8, 38.6, 40.6, 40.7, 41.4, 46.8, 51.0, 55.5, 71.2, 81.0, 87.9, 161.24.

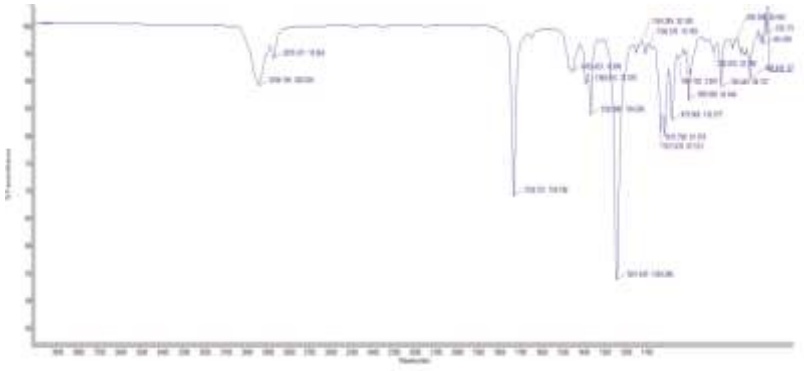


Figure 1.IR spectrum of compound 3.

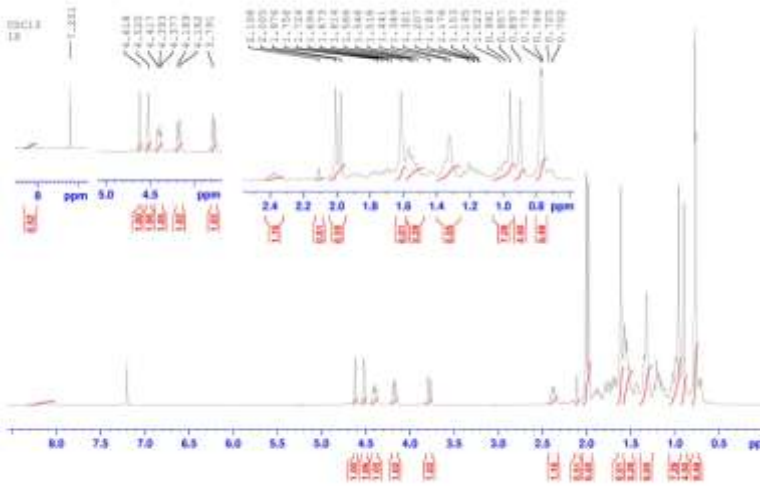


Figure 2.1HNMR Spectrum of Compound 3.

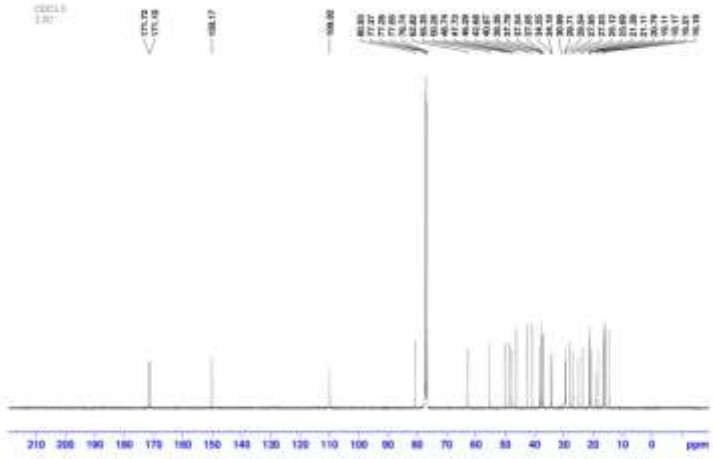


Figure 3.13C NMR Spectrum of Compound 3.

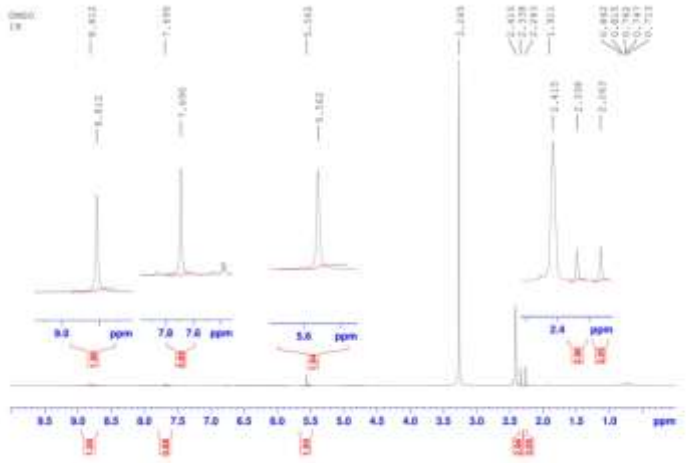


Figure 4.1H NMR Spectrum of Compounds 4a+4b.

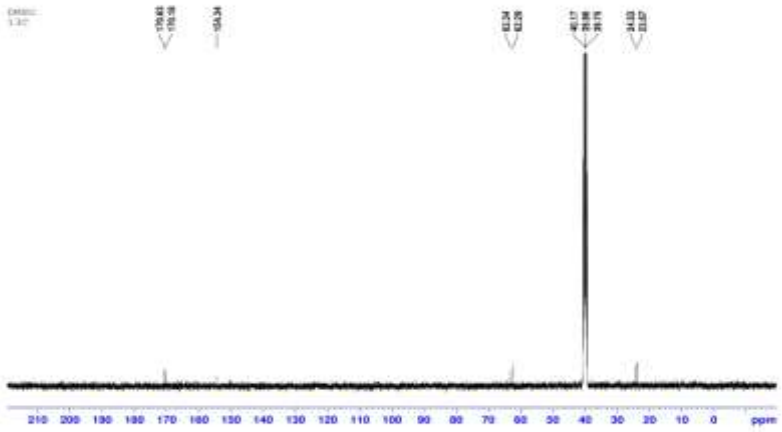


Figure 5.13 C NMR Spectrum of Compounds 4a+4b.

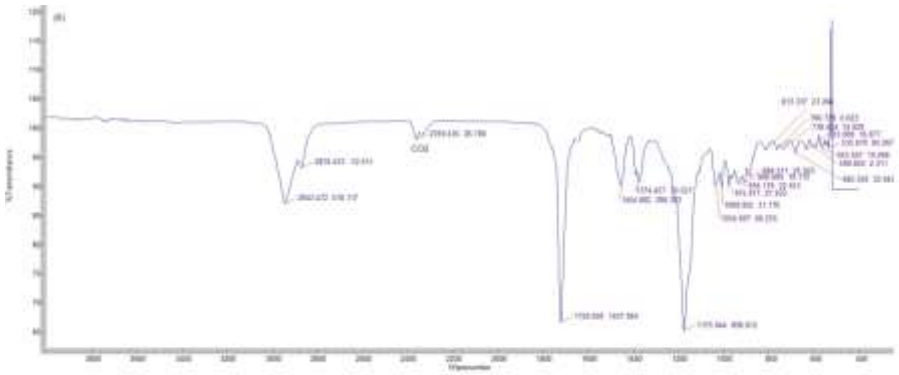


Figure 6.IR Spectrum of Compound 5.

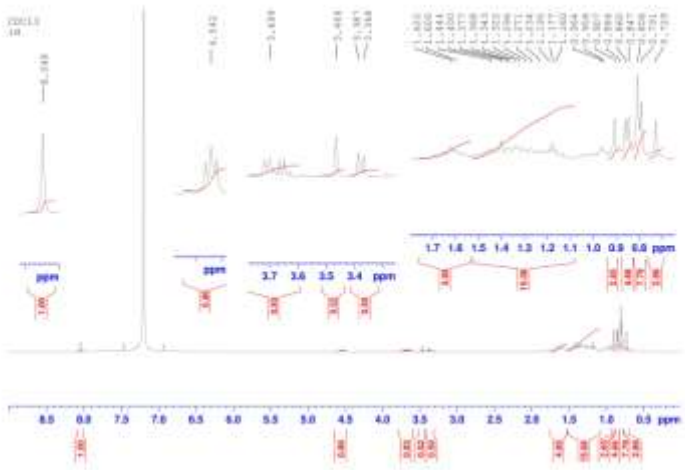


Figure 7.1H NMR Spectrum of Compound 5.

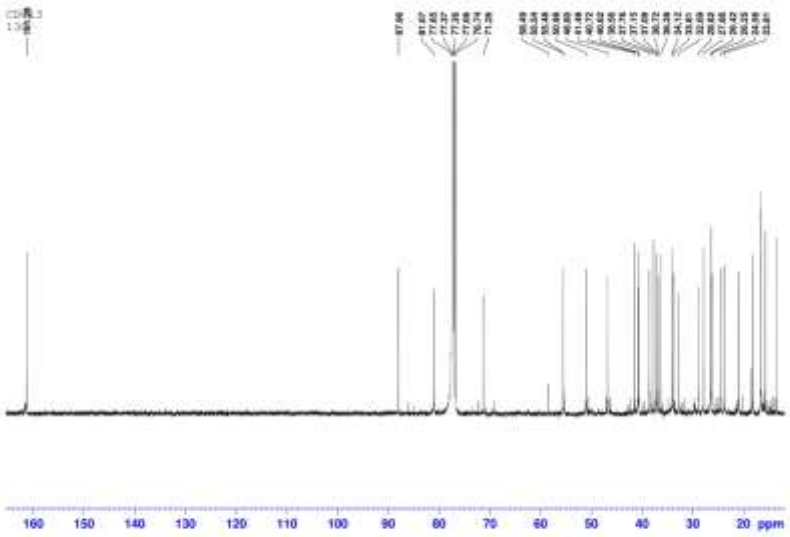
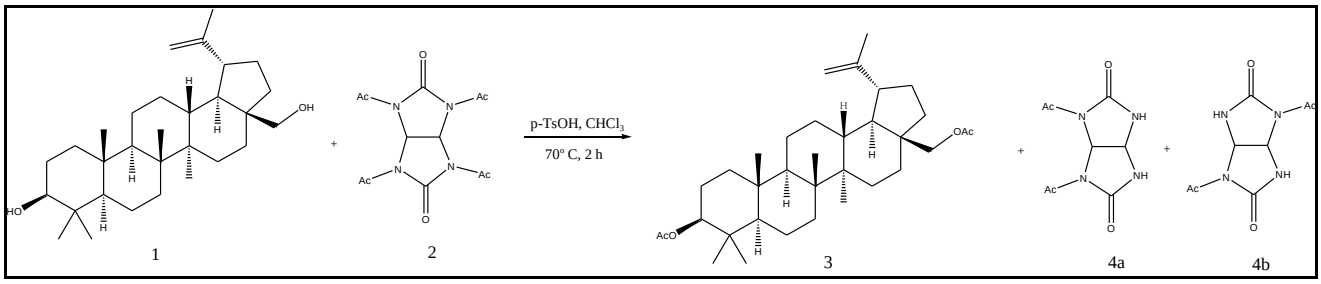
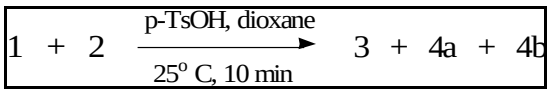


Figure 8.13 C NMR Spectrum of Compound 5.

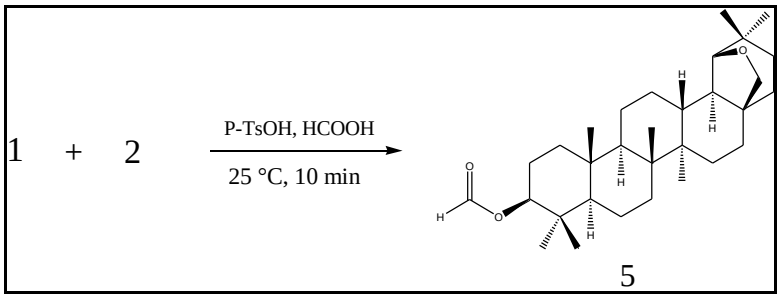
Results and Discussion



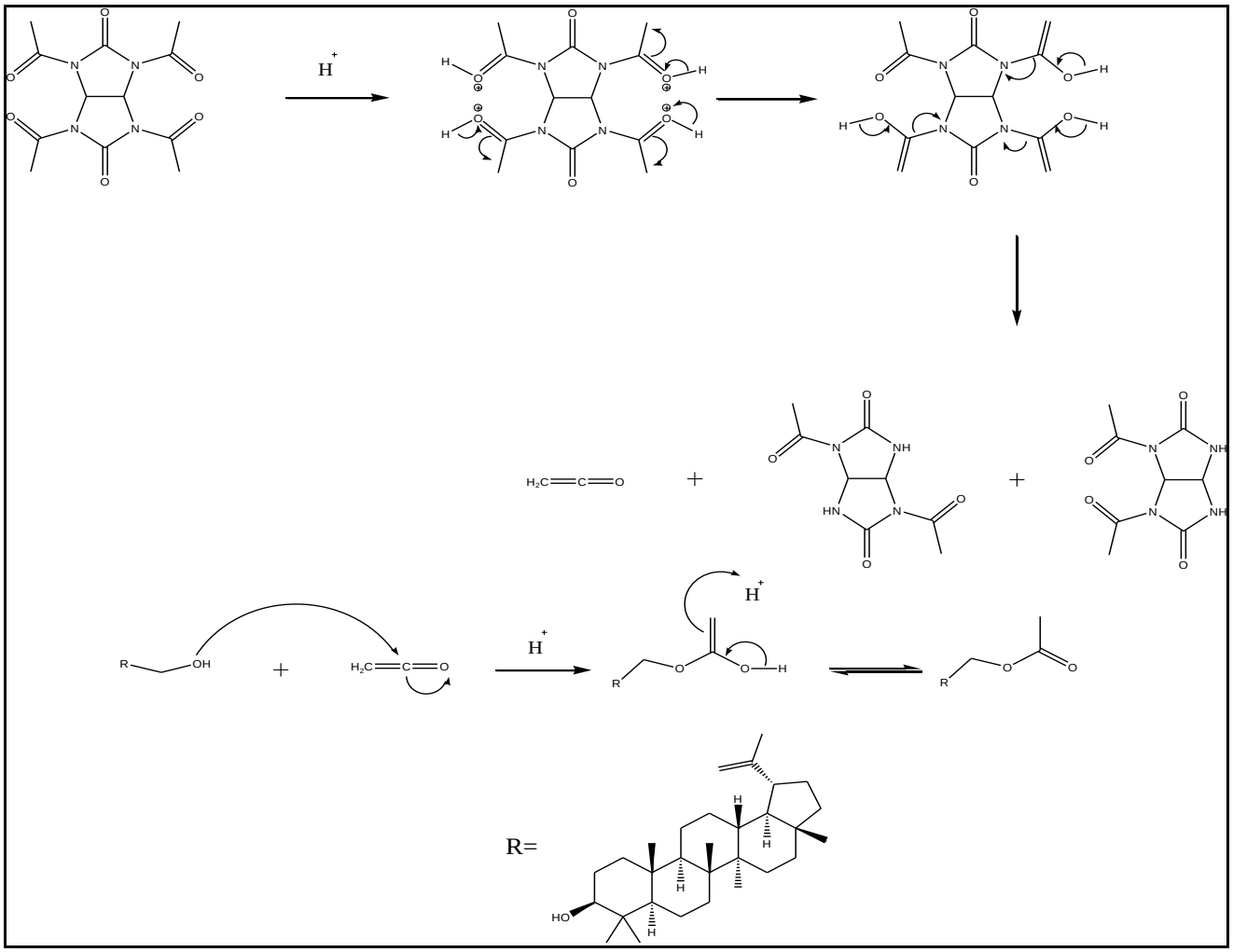
Schema 1. Reaction of Betulin with TAGU in Chloroform



Schema 2. Reaction of Betulin with TAGU in Dioxane.



Schema 3. Reaction of Betulin with TAGU in Formic Acid.



Schema 4. Mechanism of Acylation of Betulin.

In the present paper we prepared betulin diacetate from betulin using 1, 3, 4, 6-tetraacetylglycoluril, which was previously prepared by Kuhling and it was used as a mild N-acylating reagent for amino groups. However in the present study we developed two new, convenient and mild methods for the O-acetylation of betulin diacetate with good yield.

Thus, compound 1 was treated with 2 equivalents of TAGU (2) in chloroform at reflux in the presence of 2 equivalents of p-TsOH (schema 1), after one hour we observed the formation of white precipitate, which was identified by NMR as mixture of 4a and 4b. After 2 hour the reaction gave complete conversion of the starting compound 1 into the corresponding acetyl ester 3 (monitored by thin-layer chromatography, TLC).

It should be noted that after one hour of reaction only betulin monoacetate was observed using TLC plate ,and according to which explained that primary alcohol at the position 28 is more reactive than the secondary alcohol at the position 3. Furthermore the secondary alcohol is more hindered than the primary alcohol, which make this latter easy to react.

The reaction was carried out using the same experimental conditions but without para-toluenesulfonic acid, after 24 h we did not observe any formation of diacetate or monoacetate betulin, which means that the acetylation of betulin does not proceed without acidic catalyst.

Mechanochemical synthesis of compound 3 in this report has been studied by reacting 1eq of compound 1 with 2eq of TAGU and 2 eq of p-TsOH in dioxane as a solvent at room temperature for 10 min (schema 2). The reaction completion was checked by using TLC, which has shown the total conversion of betulin into its complete acetate.

The aim of the present work was also extended to investigate the formation of DAGU (4a+4b) as byproduct, its unreactivity as acetylating agent.Kuhling has shown in his report[10,13]that the reaction between TAGU and 2 equiv of monofunctional nucleophiles results in the formation of the acetylated nucleophiles and 1,4-diacetylglycoluril.

The crystal structure of TAGU(2) was studied by Marek et al[25], who have revealed that acetyl groups are attached to glycoluril unit with the different degree of twisting relative to the planes of the corresponding ureido moieties, and according to different values of dihedral angles comprising acetyl groups they have demonstrated that the acetyl groups bound in thepositions N1 and N4 are more twisted compared to those in positionsN3 and N2, which can rationalize their higher reactivity with nucleophiles.

Replacing p-TsOH with mild acid such as formic acid or acetic acid was done. Formic acid was used instead of acetic acid because this latter is a famous acetylating agent, which can achieve the acetylation without TAGU. There was a good conversion Utilizing formic acid but to formiate allobetulin (5) and not diacetate betulin (schema 3), which can be explained by the competition reaction between the acyl group and formyl group.

We have tried the reaction of betulin diacetate with betulin in chloroform at reflux to see if diacetate can also play the role of acetylating agent; the reaction was checked by TLC, which confirms that the reaction did not work.

The course of the reaction was monitored by thin layer chromatography (TLC). The workup and isolation of the products were easy. The acetylated betulin was characterized by comparison of its TLC, IR spectra, 1H-NMR spectra, and melting point with betulin.

The ^{1}H NMR spectrum of the betulin diacetate showed a doublet-like signal centered at δ 4.50 ppm and was attributable to the terminal methylene of an olefinic group. as well as a set of singlets representing six methyl groups at δ 0.72, 0.78, 0.96, 1.00, 1.20 and 1.62 ppm. A singlet at δ 2.04 ppm, assignable to the acetate methyl and a quartet, attributable to two protons, centered at δ 3.96.The multiplet at δ 4.40 ppm, which was suggested that attributable to a methine proton in the axial orientation bonded at C-3.

The ^{13}C NMR spectrum of the diacetate showed signals at δ 109.88 and δ 150.12 ppm were attributable to a terminal methylene carbon and a quaternary carbon atom.

The formation o f the diacetate was evidenced both by the appearance of two, three proton singlets, at 52.02 and 52.12 ppm, and the presence of resonances for two methyl groups at δ 21.04 and δ 21.30 ppm with the signals for the corresponding carbonyls at δ 171.02 and δ 171.63 ppm in its ^{13}C NMR.

Betulin diacetate was identified by infrared spectrum, which indicated the absence O-H stretching band and the presence of C-H (alkane) at 2916.65 cm^{-1} and 2850.02, -CH3 (bending) at 1374.99 cm^{-1}, C=C (stretching vibration) at 1644.49 cm^{-1}, C-O (stretching vibration) at 1086.83 cm^{-1} and 1246.14 cm^{-1} and C=O group (stretching vibration) at 1739.93 cm^{-1}.

Conclusion

In conclusion, this new method does not require any expensive catalysts or reagents and the ease of product separation, safe reaction medium, high selectivity, and low cost of the reagent promotes this method as a promising alternative to the other existing methods.

The results confirm that TAGU can be considered as eco-friendly and valid alternative to acetic anhydride or acetyl chloride as acetylating reagent. However, the use of TAGU significantly increases the range of acetylation substrates, making it highly effective and under mild reaction conditions.

The recyclability of the reagent was tested through the acetylation of DAGU using acetic anhydride, which make it reusable for other O-acetylation reaction.

Acknowledgments

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