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Proceeding Paper

Uranyl Acetate, a Lewis Acid Catalyst for Acetoxylation of Monoterpenic and Steroidal Alcohols †

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Abstract: The use of heterogeneous catalytic systems in the production of esters of secondary alcohols (monoterpenic and steroidal) allows us to obtain satisfactory yields of these derivatives widely used in the industry. The use of the heterogeneous system uranyl acetate/chloroform-acetonitrile, under laboratory conditions, allows us to reach yields higher than 90%, optimizing the purification steps and without the use of extreme conditions (inert atmosphere, high temperatures or corrosive agents). All compounds were characterized by the use of spectroscopic techniques.

Keywords: uranyl acetate; esterification; monoterpenic and steroidal alcohols; esters

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1. Introduction

Esters have high potential in industry and pharmaceutics because of their wide use in fragrances, flavors, surfactants, plasticizers, drugs and as solvents [1]. Generally, they are synthesized by catalytic acetylation of alcohols with, pyridine, 4-(dimethylamino) pyridine (DMAP) or 4-pyrrolidinopyridine (PPy) in the presence of acyl chlorides or acid anhydrides [2,3]. Acetylation is one of the primary reactions in organic synthesis, since acetyl groups are useful for protecting various kinds of functional groups, such as alcohols, amines, phenols and thiols, among others [4–7]. It has been developed, at laboratory or industrial scale, under heterogeneous and homogeneous catalytic conditions as well as in the presence of acidic or basic catalysts, including biogenic catalytic extracts [8–12].

These methods suffer from inherent disadvantages such as the high cost of the catalysts employed at laboratory and industrial scales, low stability of catalytic systems in the presence of moisture, poor regioselectivity in case of allylic alcohols, elimination byproducts in tertiary alcohols, racemization of optically active alcohols, epimerization of steroidal and tedious workup during and purification procedures. In this context, one of the most versatile ways for protecting hydroxyl groups in alcohols is the Lewis-mediated esterification using a variety of acylation reagents such as acid anhydrides and proper catalysts.

In [13], it was reported that terminal olefins were converted selectively towards the Markovnikov's products, 1-methylalkylacetate without isomerization using vanadium oxide in the presence of trifluoroacetic acid. This prompted us to develop a new Lewis acid catalyst with acetate ligands on uranium oxide and its acetoxy salts for acetylation reactions in a different solvent system.

We report herein a heterogeneous system, uranyl (VI) acetate/acetonitrile/chloroform, for acetylation of alcohols (monoterpenic and steroidal) with acetic anhydride at laboratory

scale. Incidentally, this is one of the few reports on the heterogenization of a homogeneous system, guided by the simple principle of insolubility, that evolves and functions as a genuine 'heterogeneous system' facilitating the recyclability and reusability of catalyst [14].

Uranyl acetate has been used in the photochemical oxidation of imidazolyl thione derivatives. It has also been reported for use in catalytic mixtures, alongside other uranyl salts, for highly efficient photocatalytic conversion processes from C-H to C-C bonds. Additionally, it has been utilized in photo assisted selective oxidation processes of alcohols and sulfides, as well as in the organic pollutant control [15–17].

2. Materials and Methods

2.1. General Procedures

All commercial reagents (oxides, acetoxy salts, acetic anhydride, acetic acid, and selected monoterpenic alcohols) and solvents ($CHCl_3$, CH_3CN) were purchased from Sigma-Aldrich/Merck Life Science (Darmstadt, Germany), and they were used without any further purification or synthetic modification. All yields refer to the isolated products. Determination of the purity of substrates, related acetoxylated derivatives and the monitoring of the acetoxylating reaction were accomplished by means of thin layer chromatography (TLC) on silica-gel plates 60 F-254 (Merck KGaA, Darmstadt, Germany). All O-acetoxy derivatives were identified by their spectra and physical data. Melting points were determined by using the capillary tube method with an electrothermal 9100 apparatus. ^{1}H-NMR spectra ($CDCl_3$) were registered on Brucker AC-250 MHz spectrometer (2005, Bruker Center AXS, Karlsruhe, Germany), at 25 °C, using tetramethylsilane as internal standard.

2.2. Preparation of the Catalyst

Uranyl (VI) acetate was prepared by refluxing uranium oxide UO_3 (1.82 g) in excess of acetic anhydride (50 mL) for 2 h. The slight-yellow solid product was then filtered, washed with $CHCl_3$ (150 mL) and dried in a vacuum at room temperature for 1 h (yield 3.5 g, 95%, $UO_2(CH_3COO)_2$, powder insoluble in organic solvents, with a slight odor of vinegar). The product obtained is kept in a closed flask at 18 °C in the absence of light until it is used in the acetylation process.

Precautionary Measures

Uranyl acetate, a water-soluble uranium compound, is often used as a stain in electron microscopy. However, it requires the adoption of basic safety precautions, emphasizing the avoidance of any possibility of inhalation or ingestion of the material. Given the inherent toxicity of uranyl salts, when working with uranium oxide and uranyl acetate, the use of NK-45 masks, protective eyewear, and a lab coat is mandatory for amounts up to 10 g. Work periods should never exceed four hours, and gloves must be worn when handling or weighing uranyl acetate. To prevent bench surface contamination, use spill trays (metal or plastic) with disposable coverings such as bench coats, and clean the surface after use. Adopting appropriate control measures is essential to minimize risk, including:

- Reducing the amount of material handled as much as possible.
- Not exceeding a working temperature of 200 °C to avoid the thermal decomposition of uranyl acetate.
- Containing unsealed sources to prevent contamination.
- Maintaining a high level of cleanliness.
- Not disposing of uranyl acetate as ordinary waste.

2.3. Acetylation Procedure

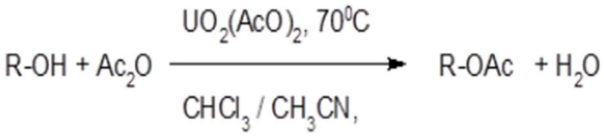
The alcohol (2.0 mmole), acetic anhydride (3 mmole) and the catalysts (0.2 mmole, 10 %w) were stirred in acetonitrile-chloroform (5 mL 3:2 v/v) at 70 °C for 3–4 h. The progress of the reaction was controlled by TLC using an ethyl-acetate-dichloromethane eluent mixture and vainilline-sulphuric acid (10%) as chromogenic agent. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (3 × 30 mL). Combined organic

layers were washed with brine and dried over Na_2SO_4. The solvent was removed and the crude products were column chromatographed on a silica gel column to afford pure acetate esters which were subjected to NMR-^{1}H spectroscopy. The catalyst was then filtered, removed, and kept for another cycle (5×) with the previous activation at 50 °C for 2 h.

3. Results and Discussion

The conversion of various alcohols, including, steroidal, and monoterpenic derivatives, to their corresponding esters was easily achieved, almost quantitatively, by treating the alcohol with 1.5 equivalents of acetic anhydride at 70 °C for 3–4 h in the presence of 10% mol of the catalyst in the described solvent mixture.

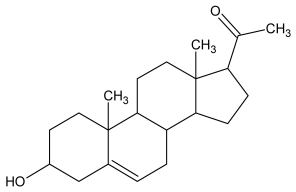
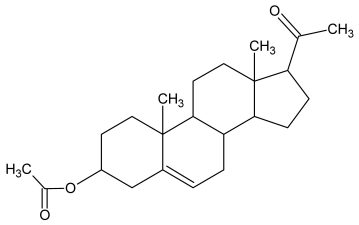
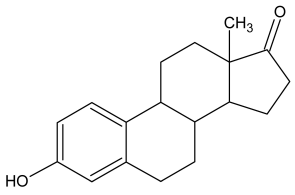
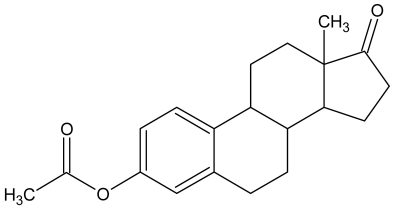
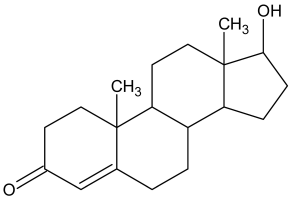
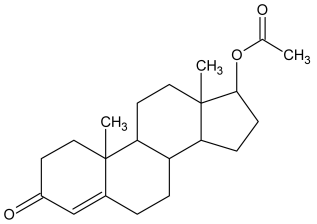
The process of acetoxylation takes place according to the proposed Scheme 1.



Scheme 1. Acetoxylation of alcohols with Ac_2O in the presence of Uranyl Acetate.

The results of the acetoxylation process, using the proposed catalytic system, (*grosso modo*), are shown in Table 1.

Table 1. Acetoxylation of alcohols (steroidal and monoterpenic) with $Ac_2O/UO_2(CH_3COO)_2$.

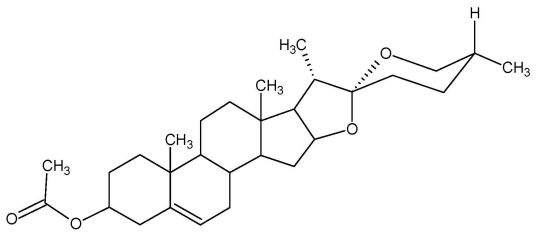
Entry	Substrate	O-Acetoxy-Derivative [a]
1	 Pregnenolone	 Pregnenolone acetate (m.p:191.7 °C/96.8%)
2	 Estrone	 Estrone acetate (m.p.: 129.7 °C/97.3%)
3	 Δ-4-androsten-17β-ol	 Δ-4-androsten-17β-ol-acetate (m.p.: 142.6 °C/83.4%)
4	(−)-Menthol	Menthyl acetate (b.p.: 57.8 °C/82%)
5	(+/−)-endo-Norborneol	Norbornyl acetate (b.p.: 202 °C/85%)
6	α-Terpineol	(±)-α-Terpinyl acetate (b.p: > 185 °C) [b]

[a] The reported yields of isolated products are an average from over five subsequent batches. [b] Was observed a sudden darkening of the reaction mixture.

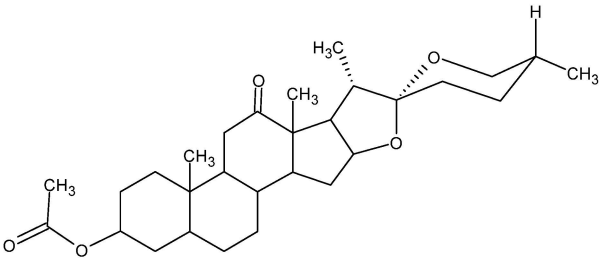
Steroidal alcohols such as progesterone, estrone and androstenol react smoothly with the catalytic system (uranyl acetate/acetonitrile-chloroform) within 3–4 h with very satisfactory yields.

In the spirostannic series, in the presence of this catalytic system, similar behavior of the diosgenin and hecogenin substrates is observed, generating their corresponding acetates with excellent yields.

The Figure 1 depicts the results obtained for spirostannic alcohols. The reported yields of isolated products are an average from over five subsequent batches. The final product was re-chromatographed twice on silica-gel.



Diosgenin Acetate (m.p.: 195.80 °C/yield: 93.1%)



Hecogenin Acetate (m.p.: 243.60 °C/yield: 90.4%)

Figure 1. Spirostannic alcohol acetates obtained in the presence of $Ac_2O/UO_2(CH_3COO)_2$/ Acetonitrile-Chloroform/3–4 h/70 °C.

An important features worth describing is that the selective acetylation of hydroxy carbonyl compounds (entries 2 and 3, Table 1) is achieved without the formation of α,β-unsaturated carbonyl compounds due to the elimination of the resulting acetate.

The most significant achievement is the reusability of the salt of transition metal catalyst for several number of cycles (5×) with almost high consistent activity. The synergetic effect of Lewis acids of the insoluble solid salt, and solvent mixture, influences the acetoxylation reaction for higher activity as solid acid. The advantage of using this catalytic system, at laboratory scale, can be summarized as follows: Uranyl acetate can be easily prepared directly from uranium oxide and acetic anhydride; the mixture of $UO_2(AcO)_2$/Acetonitrile-Chloroform is stable and not revealed any toxic or hazardous action during the storage (1 year) and utilization at laboratory scale; the spirocetalic unit of spirostene derivatives (diosgenin and hecogenin, Figure 1) remains intact and was not observed any isomerization of the olefinic bound in steroidal alcohol; it is not necessary any inert atmosphere or dry conditions for performing the reaction; the catalyst is easy recovered by filtration and centrifugation; and could be re-used in 5 catalytic cycles after thermal activation; not observed any formation of by-products like ketene, olefine o acetoacetate derivatives. It should be noted that, under the reaction conditions, no decomposition of uranyl acetate is observed.

Some implications in kinetic resolution and mechanistic studies are underway, as well as their application to other hydroxy functionalized substrates (carbohydrates and tertiary alcohols). The mechanistic perception of the acetoxylation process in the presence of uranyl acetate as a catalyst will be published soon.

In conclusion, the monoterpenic and secondary steroidal alcohols are acetoxylated satisfactorily, with remarkable selectivity, and yields, using acetic anhydride in the presence of uranyl (VI) acetate as a catalyst.

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