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A combined experimental and theoretical study of highly chemioselectivity acetylation of diterpene

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ABSTRACT

Practical and simple techniques are described for using no modified domestic microwave ovens as safe and convenient laboratory devices to obtain numerous esters. In this work, an optimization of the solvent-free acetylation of natural product (diterpenoids) with acetic anhydride under microwave heating with iodine as a catalyst was performed in an eco-friendly process. The reactions were carried out under solvent-free conditions and the acetates were obtained in nearly quantitative yields with dramatic reduction of reaction time compared to standard oil-bath heating at room temperature. A complete theoretical study of the reaction has also been carried out using density functional methods (B3LYP/6-31G)*

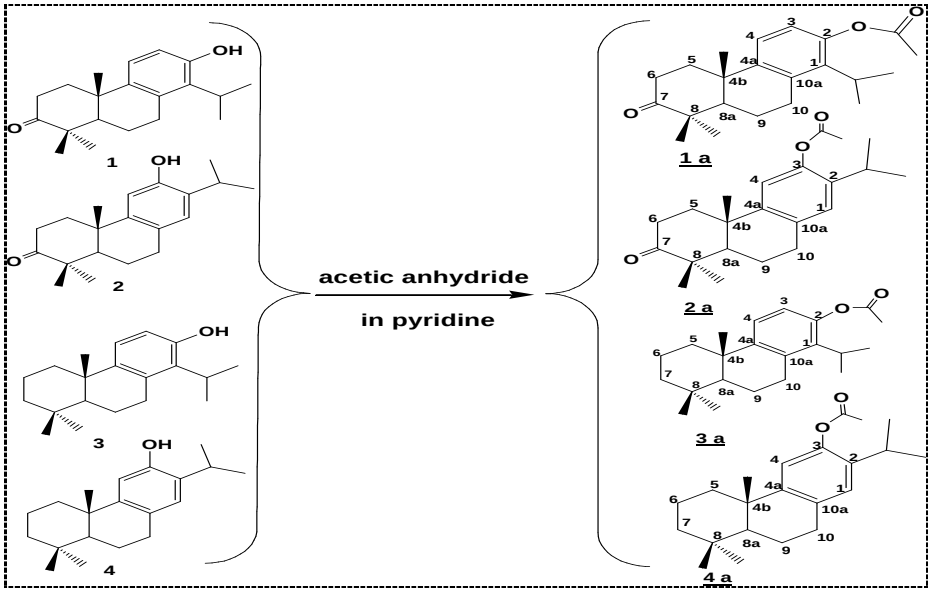
Keywords: Totarolone, Hinikione, Acetylation, diterpene, DFT.

INTRODUCTION

Acetylation of alcohols is an important and routinely utilized transformation in organic chemistry [1-4]. 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 eases of removal by mild alkaline hydrolysis. For this purpose, acetic anhydride is commonly employed [5-7] with an acid or base catalyst, such as zinc chloride, concentrated sulphuric acid, anhydrous sodium acetate or, most often, pyridine [8-12]. Ketones (totarolone 1, hinikione 2) and alkenes (totarol 3, ferruginol 4) were isolated from *Tetraclinis articulata* plant. The structures of these compounds were identified by the spectral data ^{1}H, ^{13}C NMR and mass spectroscopy [13-15]. The diterpenoids isolated from this plant have good pharmacological activities [16-20]. To improve the chemical and pharmacological properties of compounds 1, 2, 3, and 4, we have isolated already quoted from *Tetraclinis articulata* plant and then underwent an acetylation to give esters. The molecular structures of these compounds are illustrated in Scheme 1. Then, the second aim concerns theoretical studies using DFT methods, trying to obtain some information about the factors affecting reactivity and selectivity of these reactions.

RESULTS AND DISCUSSION

In order to optimize acetylation reaction of natural diterpenoids: totarolone 1, hinikione 2, totarol 3 and ferruginol 4, we have chosen as model substrates (Scheme 1). The reactions were conducted firstly using acetic anhydride (AC_2O) in pyridine at room temperature (RT) and in reflux in different reaction times (Table 1).



Scheme 1: Acetylation reactions of the diterpenes (totarolone, hinikione, totarol and ferruginol). AC_2O/Pyr/RT
To confirm the role of acetic anhydride, a blank reaction was carried out under similar reaction conditions with totarolone 1, hinikione 2, totarol 3 and ferruginol 4 as a substrate pyridine (Table 1)

Table 1: The yield of the diterpenes obtained after acetylation reaction (AC_2O/pyr)

Diterpenes	Acetic anhydride	Time/h	Yield % (RT)	Yield % (reflux)
1	0.5	3 h	(1a) 30	(1a) 50
2	1	6 h	(2a) 60	(2a) 95
3	1.5	9 h	(3a) 80	(3a) 100
4	2	12 h	(4a) 95	(4a) 100

As it can be seen in Table 1, the stoichiometry of the reaction is also a key point. Using 0.5 equivalent of acetic anhydride with diterpene 1, product 1a was obtained selectively in 30% yield after 3h at room temperature and in 50% yield at reflux. The replacement of 0.5 by one equivalent of acetic anhydride under similar reaction conditions gives the product 2a in only 60% yield after 6h at room temperature and in 95% yield at reflux. When it was used more than 1 equiv. of acetic anhydride, both acetate totarolone and acetate hinikione compounds 3a and 4a were obtained with a 100% yield at reflux.

When totarolone 1, hinikione 2, totarol 3 and ferruginol 4 were heated with a mixture of acetic anhydride and iodine under microwave irradiation, the acetylation reaction occurred easily. [21-29] (We use non-modified domestic microwave ovens as processes).

As shown in Table 2, the times and yield of the products increased with the increasing quantities of iodine, which is resulted by the fact that in the condition of a great excess of acetic anhydride, more acetic anhydride-iodine intermediates have been produced while increasing the amounts of iodine, and thus diterpenoids (1, 2, 3 and 4) were more easily acetylated. With an increment in the amount of iodine from 2 to 10 mol%, the yield of products increased up to 100%.

Table 2: The yield of the acetylated diterpenes obtained with different concentrations of iodine as a catalyst and different times

Products	% in mol. of (iodine I_2)	Time (min)	Yield % at microwave
1a	2	4	40
2a	5	8	80
3a	8	12	100
4a	10	16	100

MATERIALS AND METHODS

NMR studies were performed on a Bruker Avance 300 spectrometer in $CDCl_3$, chemical shifts are given in ppm relative to external TMS (tetramethylsilane) and coupling constant (*J*) in Hz. All the spectroscopic data of the known products were compared with those reported in the literature.

Synthesis of esters

- A solution of the diterpenoids 1, 2, 3 and 4 (60 mg, 0.2 mmol) in acetic anhydride 0.5, 1, 1.5 and 2 mmol respectively and pyridine (25 ml) was heated under reflux (or room temperature). After cooling the mixture was acidified with a solution of HCl (1N) and then extracted with CH_2Cl_2 (3 × 20 ml). The organic layer was washed with water, dried on anhydrous Na_2SO_4 and then evaporated under reduced pressure. The obtained residue was chromatographied on silica gel column using hexane and ethyl acetate (95/5) as eluent.
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Author methods for synthesis of esters

A series of different concentrations of iodine (2, 5, 8, and 10 mol%) was added to a mixture which contained 0.05 g of 1, 2, 3 and 4 and 15 mL of acetic anhydride in a 50 mL of three-necked flask fitted with a mechanical stirrer from sample 1 to sample 4. The mixtures were treated under the optimum conditions in which the diterpenoids samples were acetylated at 120 °C for different times (4min- 16min) under 400 W microwave powers. The mixture was washed with a solution of Na_2CO_3 (1N) then extracted with CH_2Cl_2 (3 × 20 ml). The organic layer was washed with water, dried on anhydrous Na_2SO_4 and then evaporated under reduced pressure. The obtained residue was chromatographied on silica gel column using hexane and ethyl acetate (95/5) as eluent.

(4bS,8aS)-1-isopropyl-4b,8,8-trimethyl-7-oxo-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-2-yl acetate (1a). Yield: 50%. ^{1}H NMR (300 MHz, CDC_{l3}) δ (ppm): 1.16 (s, 3H); 1.18 (s, 3H); 2.1 (s, 3H); 3.2 (m, 1H); 6.52 (d, J = 7 Hz, 1H); 6.95 (d, J = 7 Hz, 1H). ^{13}C NMR (75 MHz, CDC_{l3}) δ (ppm): 17.2, 19.1, 25 (4CH3); 170 (COC$_{H3}$); 141.1 (C1); 147.9 (C2); 118.1 (C3); 123.0 (C4); 143.1 (C4a); 134.5 (C10a); 218.5 (C7).

(4bS,8aS)-2-isopropyl-4b,8,8-trimethyl-7-oxo-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-3-yl acetate. (2a). Yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.48 (s, 3H); 2.1 (s, 3H); 3.1 (m, 1H); 6.7 (s, 1H); 6.9 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 17.0, 19.0, 25.1 (4CH3); 168 (COCH3); 126.1 (C1); 138.1 (C2); 147.7 (C3); 117.3 (C4); 144.7 (C4a); 132.8 (C10a); 215.7 (C7).

(4bS,8aS)-1-Isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthren-2-yl-acetate (3a). Yield: 100%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11 (s, 3H); 1.5 (s, 3H); 2.12 (s, 3H); 3.1 (m, 1H); 6.66 (d, J = 7.1 Hz, 1H); 6.9 (d, J =7.1Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 25.1, 25.3, 16.2 (4CH3); 169 (COCH3); 141.1 (C1); 147.6 (C2); 118.0 (C3); 124.1 (C4); 141.1 (C4a); 135.8 (C10a).

(4bS,8aS)-2-Isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthren-3-yl-acetate (4a). Yield: 100%.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11 (s, 3H); 1.44 (s, 3H); 2.08 (s, 3H); 3.12 (m, 1H); 6.85 (s, 1H); 6.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 17.0, 25.2, 25.4 (4CH3); 168.8 (COCH3); 126.21 (C1); 138.6 (C2); 147.8 (C3); 119.1 (C4); 142.1 (C4a); 134.1 (C10a).

DFT calculations.

An analysis of the DFT reactivity indices of the reagents is performed to understand the participation of these reagents in esterification reaction or aromatic substition [30], as well as in chemioselectivity [31]. The global DFT reactivity indices, namely electronic chemical potential, μ, chemical hardness, η, electrophilicity ω, and nucleophilicity N indices of diterpens **1, 2, 3, 4** and AC_2O are given in table 3.

Table 3: Electronic chemical potential, μ, chemical hardness, η, electrophilicity ω, and nucleophilicity N values, in eV, of diterpens 1, 2, 3, 4 and AC_2O

	η	μ	ω	N
Totarolone	5.11	-3.18	0.99	3.78
Hinikione	5.65	-2.72	0.65	3.97
Totarane	5.79	-2.92	0.73	3.70
Hinihane	5.78	-2.91	0.73	3.72
AC_2O	6.80	-4.28	1.34	1.85

*The index of the electrophilicity of AC_2O (1.34 eV) is higher than that four of diterpens **1, 2, 3, 4**. Therefore, in this reaction will behave as electrophilic when the products **1, 2, 3, 4** will behave as a nucleophiles.

*Δω < 1 eV. This shows that these reactions have no polar character.

* The electronic potential chemical of diterpens **1, 2, 3, 4** (-3.18, -2.72, -2.92, -2.91) is higher than that of the AC_2O -4.28 eV), which implies that the transfer of electrons will take place of diterpens towards the AC_2O.

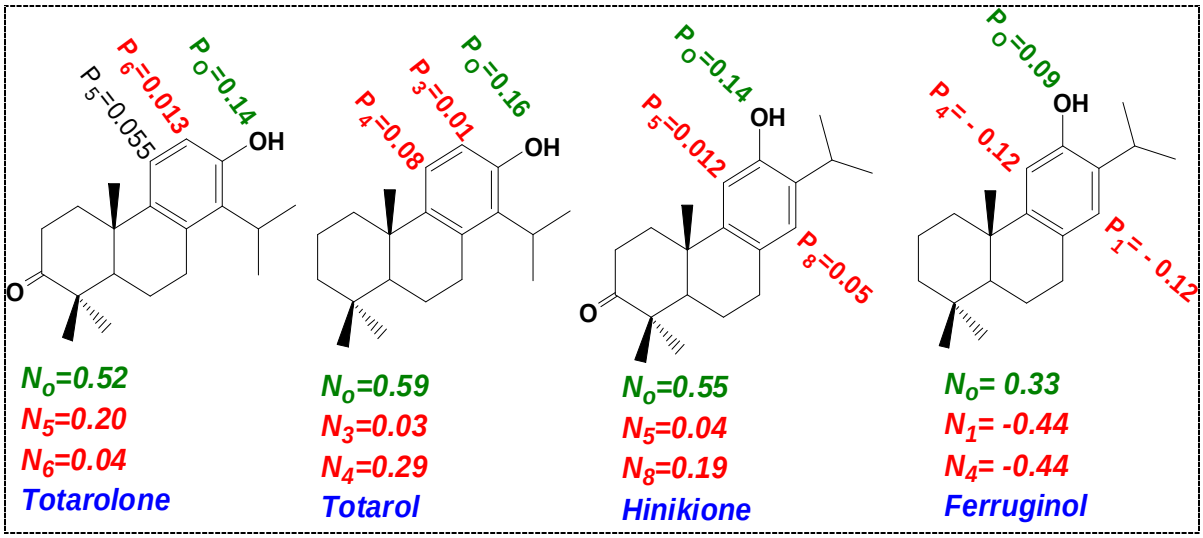
Analysis of the local descriptors.

Along a polar reaction involving the participation of asymmetric reagents, the most favorable reactive channel is the one involving the initial two-centre interaction between the most electrophilic centre of the electrophile and the most

nucleophilic centre of the nucleophile. Recently, we proposed the electrophilic P_k^+ and nucleophilic P_k^- Parr functions derived from the excess of spin electron density reached via the global electron density transfer (GEDT) process from the nucleophile to the electrophile, which are powerful tools in the study of the local reactivity in polar processes.

Accordingly, the nucleophilic P_k^- Parr functions for diterpene are analyzed (see Scheme 3).

The oxygen atom of the hydroxyl of diterpenes is the most nucleophilic centre of these molecules. The corresponding nucleophilic P_k^- Parr functions are 0.14, 0.16, 0.14 and 0.09. Note that the aromatics carbons for diterpenes present low nucleophilic activation. On the other hand, the C1, C4 carbons atom of both ferruginol are the most electrophilic centre of these molecules. This analysis is in complete agreement with the chemioselectivity observed in the reactions of these diterpenes



Scheme 3: values of the local nucleophilic Parr functions of the reagents

Computational methods

DFT computations were carried out using the B3LYP [32-33] exchange-correlation functional, together with the standard 6-31G(d) basis set [34]. The optimizations were carried out using the Berny analytical gradient optimization method [35-36]. All computations were carried out with the Gaussian 09 suite of programs [37].

The global electrophilicity index, **ω**, is given by the expression, $\boldsymbol{\omega} = \frac{\mu^2}{2\eta}$, in terms of the electronic chemical potential **μ** and the chemical hardness **η [38].** Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, as ε_{HOMO} and ε_{LUMO}, $\mu = \left(\frac{\varepsilon_{HOMO}+\varepsilon_{LUMO}}{2}\right)$ and $\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})$, respectively [39-40]. Recently, we introduced an empirical (relative) nucleophilicity index, N, based on the HOMO energies obtained within the Kohn–Sham scheme and defined as $\boldsymbol{N} = (\boldsymbol{E_{HOMO(Nu)}} - \boldsymbol{E_{HOMO(TCE)}})$ [4**1]**. The nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us to handle conveniently a nucleophilicity scale of positive values.

The P_k^+ electrophilic and P_k^- nucleophilic Parr functions [42-49], which allow for the characterization of the electrophilic and nucleophilic centers of a molecule, were obtained through the analysis of the Mulliken atomic spin density of the radical anion and the radical cation of the studied molecules, respectively.

CONCLUSION

The chemioselectivity of the reactions between some diterpenes with acetic anhydride was studied using DFT/B3LYP/6-31(d). Analysis of the global electrophilicity and nucleophilicity indices showed that diterpenes behave as a nucleophile, while acetic anhydride behaves as an electrophile. The chemioselectivity found experimentally was confirmed by local indices of nucleophilicity.

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