Arabian Journal of Chemistry (2016) 9, S889–S892

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Esterification and etherification of steroid and terpene under Mitsunobu conditions

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Received 3 July 2011; accepted 10 September 2011
Available online 17 September 2011

KEYWORDS

Mitsunobu reaction;
Esterification;
Etherification;
Terpenes;
Steroids

Abstract The synthesis and study of steroids and terpenes continues to be a topic of widespread interest, the esterification and etherification under Mitsunobu conditions of primary alcohol such as geraniol prepared in 95% yield, and when a chiral secondary alcohol such as cholesterol or menthol is used, sufficient configurational inversion of alcohol with 65% yield, but the reaction of tertiary alcohols the α-terpeniol for example are rare.

1. Introduction

Steroids (Hanson, 2010) and terpenes (Gershenzon and Dudareva, 2007) constitute a large and structurally diverse family of natural products and are considered important scaffolds for the synthesis of molecules of pharmaceutical interest (Salvado et al., 2011).

The existence of steroids has been known for more than a century with the isolation of cholesterol from gall stones by Chevreul (1815) and the elucidation of its chemical structure by Windaus (1932), the steroids are among the most important secondary metabolites due to their high profile biological activity (Miguel et al., 2001).

Terpenes are a wide variety of 10-carbon skeletons formed from the coupling of two isoprene subunits. They are ubiquitous in nature as they are used as biosynthetic building blocks in many living organisms including plants and animals (Ruzicka, 1953). There are many different types of terpenes and they are classified by their structure.

The Mitsunobu reaction (Mitsunobu, 1981; Mitsunobu and Yamada, 1967) has been exploited in the chemistry of a wide range of naturally occurring compounds like carbohydrates (Sawada et al., 2003), peptides (Wisniewski et al., 1998), steroids (Jeffrey and Charles, 1996), terpenes (Racero et al., 2000) and others with formation of esters, ethers and new C–C bonds (Hughes, 1992). The nucleophilic substitution of an alcohol group mediated by the triaryl- or trialkyl-phosphine/dialkyl azodicarboxylate redox system is widely used to prepare biologically active compounds. Furthermore, the pK_a of the usable acid component must be below 13, preferably below 11, because the Mitsunobu reaction has demonstrated a very excellent reactive ability, efforts have been made toward widening the utilisation scope (Takashi, 1995).

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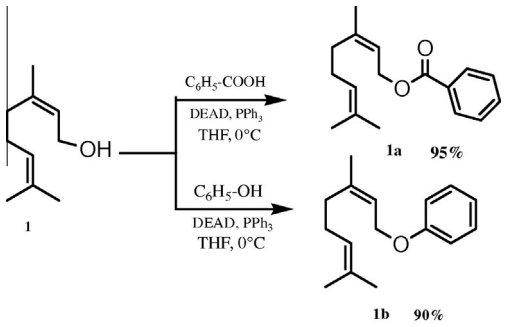
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2011.09.008



Scheme 1

This paper examines the nature of alcohol of steroid and terpene upon the yield of the Mitsunobu reaction in esterification and etherification reactions from carboxylic acid and phenol as nucleophilic. Specifically, when a chiral secondary alcohol is employed, the esterification and etherification undergo an SN_2 displacement with inversion of configuration with good yield, and the Mitsunobu reaction of tertiary alcohols have rarely been reported.

2. Results and discussions

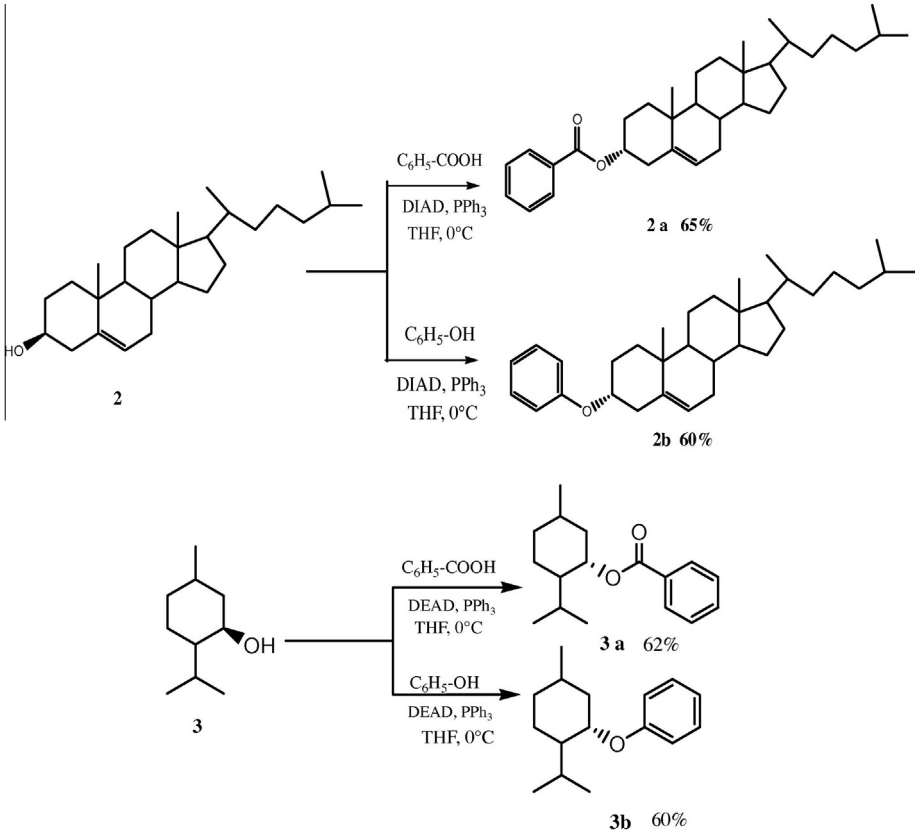
The hydroxy group is one of the most present functional groups in natural products. Diversely functionalized alcohols of steroid and terpene were esterified and etherified under Mitsunobu reaction with benzoic acid and phenol respectively, in the presence of 1.1 equiv of diethylazodicarbixylate and 1.1 equiv of triphenylphosphite in THF at 0 °C. These formations of ester and ether of geraniol gave in excellent yield (95%) (Scheme 1).

The Mitsunobu converts an alcohol **2, 3** to its inverted esters and ethers with participation of three stoichiometric components: an acidic pronucleophile (carboxylic acid and phenol respectively), a diethylazodicarboxylate (DEAD) and a phosphine (typically triphenylphosphine) in THF at 0 °C, The phosphine oxide and hydrazine byproducts are easily removed by recrystallisation in ether than filtration. Chromatographic separation provides the chiral secondary alcohol in overall yields of (65–60%) (Scheme 2).

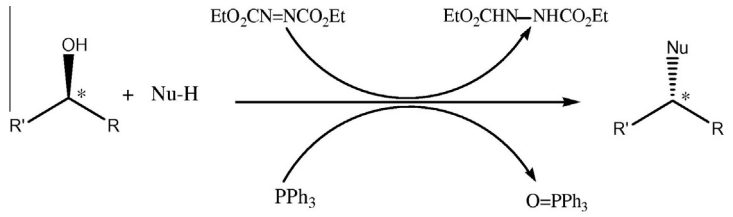
Overall, the stable C–O bond of an alcohol is broken, however, this energetically unfavourable process is offset by formation of very strong P═O and N–H bonds of byproducts, this is a result of the strong affinity for oxygen by triphenylphosphite and for hydrogen by DEAD (Scheme 3). Since the original C–O bond is broken in the Mitsunobu reaction *via* an SN_2 mechanism, inversion of configuration at that carbon centre occurs and indeed, this route has been employed to generate either esters or ethers with inversion of configuration.

However, there is a limitation on the acidity of Nu-H with a pK_a should be less than 11 for the reaction to proceed satisfactorily. The Mitsunobu reaction works by creating kinetic and thermodynamic incentive for inversion (Mitsunobu, 1981).

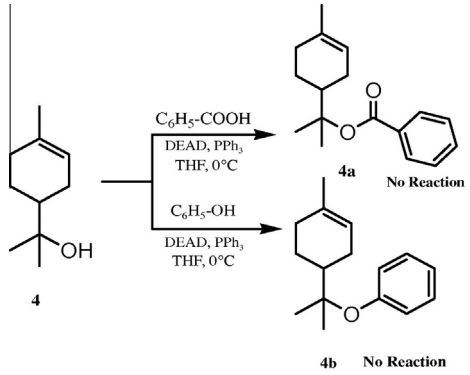
Reaction with tertiary alcohol α-terpeniol was made, but no results were given because of the steric hindrance which hinders the nucleophilic attack (Scheme 4).



Scheme 2



Scheme 3



Scheme 4

The reaction is sensitive to the steric bulk of the alcohol, whereas the carboxylic acid and phenol components are insensitive to both steric and electronic effects.

3. Experimental

3.1. General

All commercial chemicals and solvents were used as received. Melting points were determined in open capillary tubes on a Buchi apparatus and are uncorrected. 1H and 13C spectra were respectively recorded in a 250 MHz Bruker spectrometers. Chemical shifts are reported in δ units (ppm). All coupling constants J are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and combination of these signals. Optical rotations were measured in a 1-cm cell on a Perkin–Elmer polarimeter. All reactions were monitored by TLC on silica Merck h60 F254 (Art 5554) precoated aluminium plates and were developed by spraying with $KMnO_4$ solution. Column chromatographies were performed on Merck silica gel 60H (Art 9385).

3.2. General procedure for the Mitsunobu reaction

An alcohol (1.0 equiv) was added to a solution of acidic pronucleophile (1.1 equiv) and triphenylphosphine reagent (1.1 equiv) in anhydrous THF under a N_2 atmosphere at 0 °C. The resulting suspension/solution was treated with diethylazodicarboxylate (1.1 equiv) and the reaction mixture was continued stirring at room temperature up to completion of the reaction. The solvent was evaporated and the residue dissolved in ether, the triphenylphosphane oxide precipitated and was filtered off and then the filtrate evaporated under reduced pressure. The product was purified by column chromatography on silica gel to afford the pure products.

3.2.1. Esterification

*3.2.1.1. Geranyl benzoat (**1a**).* Pale yellow oil, yield (95%), TCL: R_f = 0.6 (*n*-hexane–ethyl acetate, 9:1, v/v), IR (CCl_4, σ cm^{-1}): 1625 (C=C), 1720 (C=O), ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.98 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.45 (m, 4H, $2CH_2$), 5.2 (d, J = 10 Hz, 2H, O-CH_2), 5.4 (m, 1H, CH), 5.82 (m, 1H, CH), 7.8–8.4 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 250 MHz): 167.5, 141.9, 132.5, 131.98, 130.95, 130.01, 129.98, 124.5, 119.5, 61.2, 40.00, 26.5, 26.6, 18.00, 17.95, MS (ESI$^+$) *m/z:* 259 $[M+H]^+$.

*3.2.1.2. 3β-Cholesteryl benzoat (**2a**).* White solid, yield (65%), TCL: R_f = 0.58 (*n*-hexane–ethyl acetate, 9:1, v/v), $[\alpha]_D = -15°$. (c = 2, CH_3Cl). IR (CCl_4, σ cm^{-1}): 1625 (C=C), 1720 (C=O), ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.65 (s, 3H, C13-CH_3), 0.85 (dd, 6H, J = 6.9 Hz, C25-$(CH_3)_2$), 0.95 (d, 3H, J = 7.12 Hz, C20-CH_3), 1.01 (s, 3H, C10-CH_3), 3.7 (m, 1H, C3β-H), 5.4 (d, 1H, J = 5.11 Hz, H6), 7.5–8.1 (m, 5H, H_{aroma}). ^{13}C NMR ($CDCl_3$, 250 MHz): 167.00, 140.00, 132.8, 129.30, 129.70, 128.40, 123.20, 74.90, 57.10, 56.50, 50.47, 42.70, 40.60, 39.94, 38.60, 37.57, 37.15, 36.60, 36.20, 32.35, 32.31, 29.96, 28.63, 28.43, 24.70, 42.20, 21.46, 23.22, 22.97, 19.20, 19.14, 12.25, MS (ESI$^+$) *m/z:* 513 $[M+Na]^+$.

*3.2.1.3. (2R-3S-5R)-Menthyl benzoat (**3a**).* White solid, yield (62%), TCL: R_f = 0.6 (*n*-hexane–ethyl acetate, 9:1, v/v), $[\alpha]_D = -64°$ (c = 2, CH_3Cl). IR (CCl_4, σ cm^{-1}): 1730 (C=O), ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.75 (d, J = 7.1 Hz, 3H, CH_3), 0.85(d, J = 7.3 Hz, 3H, CH_3), 0.93–0.98 (m, 4H, CH_2+ CH ipr+ *CH*-CH_3), 1.2 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), 1.54 (m, 3H, CH_2+CH), 2.1 (m, 1H, CH), 4.6 (m, 1H, O-CH), 7.6–8.2 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 250 MHz): 167.00, 133.00, 131.00, 129.70, 128.40, 69.10, 41.50, 36.50, 32.50, 24.60, 23.60, 21.15, 21.00, 20.90, 17.80, MS (ESI$^+$) *m/z:* 245 $[M+H]^+$.

3.2.2. Etherification

*3.2.2.1. Geranylphenyl ether (**1b**).* Pale yellow oil, yield (90%), TCL: R_f = 0.67 (*n*-hexane–ethyl acetate, 9.5:0.5, v/v). IR (CCl_4, σ cm^{-1}): 1220 (C–O), 1650 (C=C), ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.68 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.15 (m, 4H, $2CH_2$), 3.45 (d, J = 7.01 Hz, 2H, O-CH_2), 5.1 (m, 1H, CH), 5.5 (m, 1H, CH), 6.9–7.1 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 250 MHz): 162.00, 141.90, 132.70, 129.50, 123.50, 122.00, 121.00, 114.4, 68.80, 41.00, 26.80, 26.7, 18.00, 17.95, MS (ESI$^+$) *m/z:* 231 $[M+H]^+$.

*3.2.2.2. 3β-Cholesteryl phenyl ether (**2b**)*. White solid, yield (65%), TCL: R_f = 0.65 (*n*-hexane–ethyl acetate, 9:1, v/v), $[\alpha]_D = -19°$ ($c = 2$, CH_3Cl). IR (CCl_4, $\sigma\ cm^{-1}$): 1180 (C–O), 1650 (C═C),, ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.65 (s, 3H, C13-CH_3), 0.85 (dd, 6H, J = 5.6 Hz, C25-$(CH_3)_2$), 0.90 (d, 3H, J = 5.9 Hz, C20-CH_3), 1.00 (s, 3H, C10-CH_3), 3.60 (m, 1H, C3 *β-H), 5.3 (d,* 1H, J = 6.03 Hz, H6), 6.80–7.15 (m, 5H, H_{aroma}). ^{13}C NMR ($CDCl_3$, 250 MHz): 158.80, 140.00, 129.10, 123.20, 120.10, 77.50, 57.10, 56.50, 50.47, 42.70, 40.60, 39.5, 39.20, 37.6, 37.15, 36.60, 36.20, 32.35, 32.31, 31.5, 28.63, 28.43, 24.70, 42.20, 21.46, 23.22, 22.97, 19.20, 19.14, 12.25, MS (ESI^+) *m/z:* 475 $[M+H]^+$.

*3.2.2.3. (2R-3S-5R)-Menthyl phenyl ether (**3b**)*. White solid, yield (60%), TCL: R_f = 0.68 (*n*-hexane–ethyl acetate, 9.5:0.5, v/v), $[\alpha]_D = -56°$ ($c = 2$, CH_3Cl). IR (CCl_4, $\sigma\ cm^{-1}$): 1670 (C═C), ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.65(d, J = 6.20 Hz, 3H, CH_3), 0.76 (d, J = 6.051 Hz, 3H, CH_3), 0.85 (m, 4H, CH_2+ CH ipr+ *CH*-CH_3), 0.95 (m, 2H, CH_2), 1.00 (m, 2H, CH_2), 1.20 (m, 3H, CH_2+CH), 1.90 (m, 1H, CH), 3.98 (m, 1H, O-CH), 6.8–7.15 (m, 5H, H_{aroma}). ^{13}C NMR ($CDCl_3$, 250 MHz): 159.00, 129.20, 120.20, 114.50, 71.50, 42.20, 37.20, 32.5, 25.00, 23.5, 20.80, 20.62, 20.60, 20.20, MS (ESI^+) *m/z:* 245 $[M+H]^+$.

4. Conclusion

In conclusion, we applied the esterification and etherification of the Mitsunobu reactions on steroid and terpene compounds, The reactivity of primary alcohols was greater compared to secondary and tertiary alcohols, this reaction is an extremely versatile and mediation efficient conversion of secondary alcohols to ethers and esters, and with tertiary alcohol was also studied using α-terpeniol and others, but no reaction was observed. However, the procedure is highly dependent on steric factors.

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