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Microwave induced selective enolization of steroidal ketones and efficient acetylation of sterols in semisolid state

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Abstract—Under microwave irradiation steroidal enones, more specifically, position three carbonyls were efficiently and selectively converted to the corresponding enol acetates in the presence of additional enolizable carbonyl functions at other positions, using acetic anhydride and a catalytic amount of toluene-*p*-sulfonic acid. Acetylation of hydroxyl groups of the sterols, including those at the hindered positions, was near quantitative. Strictly anhydrous conditions were not a pre-requisite for acetylation and the reaction system easily tolerated up to 10% (v/v) moisture.

1. Introduction

Selectivity in synthetic organic chemistry and especially in multi-step organic syntheses is a major asset, and is an integral part of a strategy for the synthesis of complex molecules such as steroids.[1] Steroid hormones serve many diverse purposes for the support and maintenance of life and hold a unique place among biologically and pharmaceutically important compounds.[2,3] The majority of steroids such as Δ^4- and Δ^5-androgens, corticosteroids, and their analogues contain acylable groups mainly hydroxyls, and enolizable carbonyls, and their synthesis requires a balanced and selective approach.[4,5]

Organic chemists have traditionally performed the enolization of carbonyl groups in the steroid molecules using acetic anhydride or isopropenyl acetate under the influence of an array of acidic and basic catalysts.[6–17] Acetylation of steroid carbonyls and hydroxyls using acetic anhydride catalyzed by toluene-*p*-sulfonic acid (*p*TSA) is of basic interest because of its low cost and simplicity of the reagents, and it still appears to be one of the best choices. Although the method has been in practice since 1940, practical success of the process has been relatively limited primarily because of the use of excessive quantities of acetylating reagent[6–17] and the catalyst;[6,11–15,18] (the use of equi-molar quantity of the catalyst is not unheard of), and secondarily due to the competing concomitant enol-acetylation[15,18] of one or more carbonyl groups present in the steroid molecule. Moreover, acidity created by the use of excessive amount of catalyst may be detrimental to acid sensitive substrates, and may often lead to undesired products.[19,20] Differentiating the relative reactivities of the carbonyl groups at positions 3, 11, 17 and 20, especially between positions 3, 17 and 20 in a steroid molecule, and the direction of enol acetate formation has been a subtle and critical task. Despite their importance from a pharmacological, industrial and synthetic point of view, comparatively few methods are aimed at developing a more selective approach for enolization of steroidal carbonyls. These modified procedures, which involve using small amount of catalyst,[9] performing reaction at ambient temperature,[16,17] or use of strong catalyst such as perchloric acid,[7,8] have both advantages and limitations. Perchloric acid catalyzed acetylation was first described by Barton et al.[7] who used carbon tetrachloride to obtain 17(20)-enol acetate. Subsequently, other workers employed this system for the enol acetylation of 3-keto steroids and related compounds.[21,22] Later, Edwards et al.[8] discovered the use of absolute ethyl acetate in perchloric acid catalyzed enol acetylation. The method of Edwards was selective but still required a large excess of acetic anhydride (~30 equiv.) under strictly anhydrous conditions. The use of strong acids such as perchloric acid[8] and hydrobromic acid[20] may invoke structural changes in the molecules as a result of rearrangement and/or dehydration. The 7-oxygenated-Δ^5 steroids are known to be particularly sensitive to strong acids.[23] Therefore, a considerable scope exists in developing efficient protocols for the acetylation of steroidal hydroxyl and carbonyl groups.

Recent years have witnessed[24–29] the advent of microwave dielectric heating as a superior, clean and fast growing technique over the conventional conduction, convection,

Keywords: steroids; microwave; selective enolization; acetylation.

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Table 1. Enol-acetylation of steroidal enones/ketones under microwave irradiation

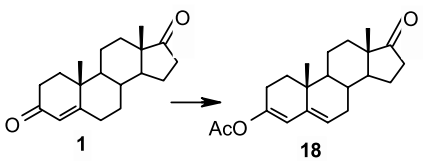
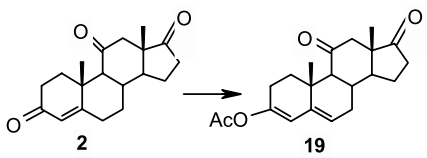
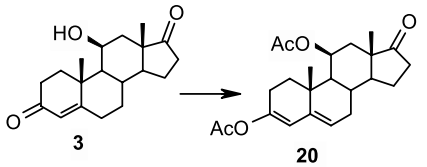
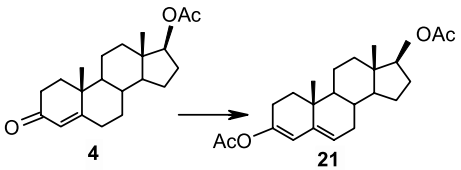
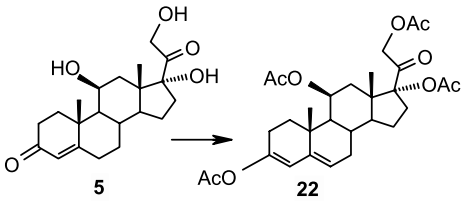
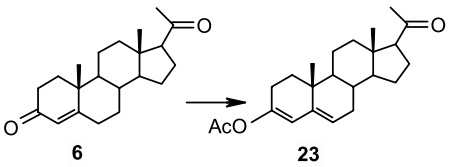
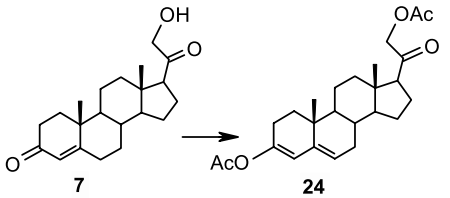
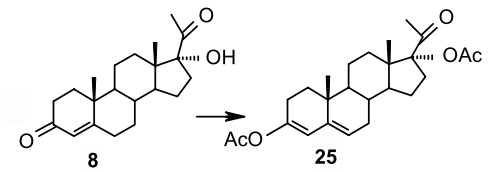
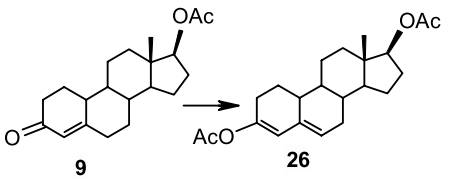
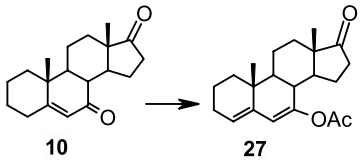
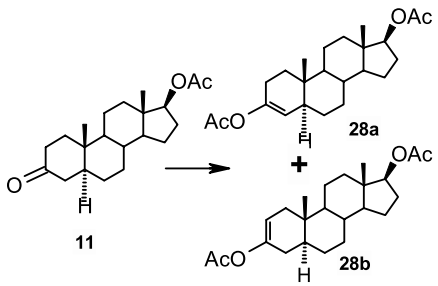
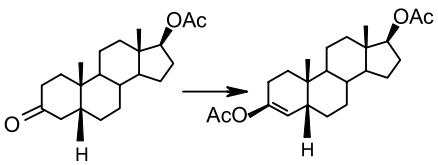
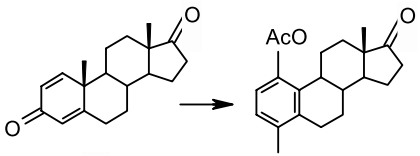
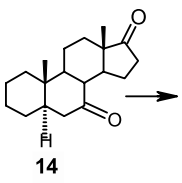
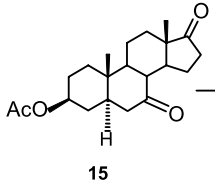
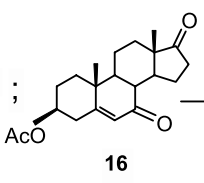
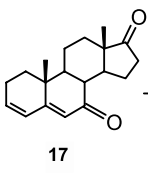
Steroids Enones/ketones	Product(s)	$Ac_2O/pTSA$[a]	Heating (min)[b]	Y/P[c] (%)	Analytical data[d] (product #/mp (°C)/LC/MS/^{1}H NMR[e]
		6/1	3	97/97	(**18**);[8,41] mp 133–135; λ_{max}=234; *m/z*: 351 (M+Na), 329 (+1), 287 (−42), 269 (−42, −18); ^{1}H NMR (200 MHz): δ 5.7 (d, *J*=2.2 Hz, 4-H), 5.43 (bm, 6-H), 2.14 (s,3-AcO), 1.03 (s,19-Me), 0.92 (s,18-Me)
		12/2	4	99/96	(**19**);[9,41] mp 189–191; λ_{max}=234; *m/z*: 365 (M+Na), 343 (+1), 301 (−42), 283 (−42, −18); ^{1}H NMR (200 MHz): δ 5.68 (d, *J*=1.7 Hz, 4-H), 5.4 (bm, 6-H), 2.14 (s,3-AcO), 1.21 (s,19-Me), 0.88 (s,18-Me)
		6/1	5	95/93	(**20**);[8,41] mp 159–161; λ_{max}=234; *m/z*: 409 (M+Na), 387 (+1), 345 (−42), 285 (−42, −60), 267 (−42, −60, −18); ^{1}H NMR (200 MHz): δ 5.66 (d, *J*=2.2 Hz, 4-H), 5.51 (bm, 6-H), 5.35 (t, *J*=3.67 Hz, 11a-H) 2.14, 2.05 (3, 11-AcO), 1.09 (s,19-Me), 1.04 (s,18-Me)
		6/1	3	94/92	(**21**);[8,41] mp 155–157; λ_{max}=234; *m/z*: 395 (M+Na), 373 (+1), 331 (−42), 271 (−42, −60); ^{1}H NMR (200 MHz): δ 5.68 (d, *J*=2.2 Hz, 4-H), 5.4 (bm, 6-H), 4.6 (dd, *J*=7.33, 9.03 Hz, 17a-H), 2.14 (s,3-AcO), 2.05 (s,17-Aco), 1.01 (s,19-Me), 0.83 (s,18-Me)
		12/1	5	92/88	(**22**);[42] mp 211–214; λ_{max}=234; *m/z*: 553 (M+Na), 531 (+1), 489 (−42), 471 (−60), 429 (−42, −60), 369 (−2×60, −42), 351 (−3×60), 309 (−3×60, −42), 291 (−3×60, −42, −18); ^{1}H NMR (200 MHz): δ 5.66 (d, *J*=1.7 Hz, 4-H), 5.5 (bm, 6-H), 5.3 (t, *J*=3.4 Hz, 11a-H)4.82, 4.64 (dd, *J*=16.6 Hz, 21-CH_2), 2.16, 2.14, 2.09, 2.03 (4×s, 3,11,17,21-AcO), 1.07 (s,19-Me), 0.87 (s,18-Me)
		12/1	5	97/92	(**23**);[8] mp. 136–138; λ_{max}=234; *m/z*: 379 (M+Na), 357 (+1), 315 (−42); ^{1}H NMR (400 MHz): δ 5.69 (d, *J*=1.59 Hz, 4-H), 5.39 (bd, *J*=2.79 Hz, 6-H), 2.13 (s, 6H, 3-AcO, 21-Me), 1.0 (s,19-Me), 0.6619-Me (s, 18-Me)

Table 1 (*continued*)

Steroids Enones/ketones	Product(s)	Ac_2O/*p*TSA[a]	Heating (min)[b]	Y/P[c] (%)	Analytical data[d] (product #/mp (°C)/LC/MS/^{1}H NMR[e]
 **7**	**24**	12/1	5	89/94	(**24**);[43] mp. 115–117; λ_{max}=234; *m/z*: 437 (M+Na), 415 (+1), 373 (−42), 313 (−42, −60); ^{1}H NMR (400 MHz): δ 5.69 (d, *J*=1.99 Hz, 4-H), 5.39 (bd, *J*=3.19 Hz, 6-H), 4.72 (d, J_{gem}=17.19 Hz, 21-H), 4.53 (d, J_{gem}=16.79 Hz, 21-H), 2.17, 2.13 (2×s, 3,21-AcO), 0.99 (s, 19-Me), 0.69 (s, 18-Me)
 **8**	**25**	12/1	5	97/79	(**25**);[8,41] mp. 205–207; λ_{max}=234; *m/z*: 437 (M+Na), 373 (−42), 313 (−42, −60), 295 (−42, −60, −18); ^{1}H NMR (400 MHz): δ 5.7 (d, *J*=1.99 Hz, 4-H), 5.4 (bd, *J*=3.59 Hz, 6-H), 2.14, 2.13 (2×s, 3,17-AcO), 2.05 (s, 21-CH_3) 1.0 (s, 19-Me), 0.67 (s, 18-Me)
 **9**	**26**	8/0.5	5	>90/75	(**26**);[8] mp 165–168; λ_{max}=236; *m/z*: 381 (M+Na), 359 (+1), 317 (−42), 257 (−42, −60), 299 (−60); ^{1}H NMR (200 MHz): δ 5.76 (d, *J*=1.2 Hz, 4-H), 5.49 (bm, 6-H), 4.62 (dd, *J*=7.57, 9.0 Hz, 17a-H), 2.13 (s, 3-AcO), 2.05 (s, 17-AcO), 0.82 (s, 18-Me)
 **10**	**27**	6/1	5	90/79	(**27**);[f] mp 94–95; λ_{max}=238; *m/z*: 351 (M+Na), 329 (+1), 311 (−18), 287 (−42), 269 (−42, −18); ^{1}H NMR (400): δ 5.7 (d, *J*=1.5 Hz, 6-H), 5.45 (t, *J*=3.4 Hz, 4-H), 2.15 (s, 7-AcO), 1.05 (s, 19-Me), 0.94 (s, 18-Me)
 **11**	**28a** + **28b**	12/2	5	98[g]/99	(**28a**); LCMS: *m/z*: 397 (M+Na), 375 (+1), 333 (−42), 315 (−42, −18), 273 (-42, −60), 255 (−42, −60, 18); ^{1}H NMR (400): δ 5.00 (s, 4-H), 4.6 (t, *J*=8.4 Hz, 17α-H), 2.1 (2×s, AcO), 0.99 (s, 19-Me), 0.835 (s, 18-Me)
					(**28b**);[8] ^{1}H NMR (400): δ 5.23 (dd, *J*=6 Hz, 2-H), 4.6 (t, *J*=8.4 Hz, 17α-H), 2.109, 2.035 (2×s, AcO), 0.99 (s, 19-Me), 0.79 (s, 18-Me)

(*continued on next page*)

Table 1 (*continued*)

Steroids Enones/ketones	Product(s)	$Ac_2O/pTSA$[a]	Heating (min)[b]	Y/P[c] (%)	Analytical data[d] (product #/mp (°C)/LC/MS/^{1}H NMR[e]
 **12**	**29**	12/2	5	98/99	(**29**);[8] mp 95–97; ^{1}H NMR (400): δ 5.04 (s, 4-H), 4.6 (t, J=8.4 Hz, 17α-H), 2.114, 2.029 (2×s, AcO), 0.978 (s, 19-Me), 0.782 (s, 18-Me)
 **13**	**30**	12/2	5	96/93[h]	(**30**);[32] mp 99–101; LCMS: m/z:349 (M+Na), 327 (+1), 309 (−18), 285 (−42), 267 (−42, −18); ^{1}H NMR (400 MHz): δ 7.0 (d, J=8.4 Hz, Ar-H), 6.73 (d, J=8.4 Hz, Ar-H), 2.26 (s, AcO), 2.21 (s, CH_3), 0.93 (s, 18-Me), ^{13}C NMR 220.7 (17-C), 169.6 (CO–AcO), 148.3, 135.5, 134.7, 131.7 (C–Ar), 128.4, 120.2 (CH–Ar), 50.5, 45.7, 39.7 (8,9,14-C), 35.9, 32.5, 29.1, 26.3, 25.1, 21.5 (CH_2), 21.8, 19.9, 14.6 (CH_3)
 **14**	**14**[f];  **15**	**15**[f];  **16**	**16**[g];  **17**		

For compounds **14** and **15**, starting steroid recovered, for % enolacetate (calculated based on ^{1}H NMR) see Table 2. Starting steroid (**16**, 97%) and androst-3,5-diene-7,17-dione (**17**, 3%) was isolated in 98% yield.

[a] mol equiv./mol%.

[b] Microwave (Panasonic) 900 MHz, at high power.

[c] Isolated product/purity based on LC of the isolated product (for product balance see Table 2).

[d] Isolated material used as such for analysis to determine exact composition.

[e] LCMS (Agilent 1100 series instrument) was used to determine product purity (Table 2), λ_{max}, m/z values; ^{1}H NMR (in $CDCl_3$) Bruker 200 and Varien ui 400 spectrometers were used.

[f] New compound, ^{13}C NMR (400 MHz): 220.4 (17-C=O), 169.9 ($OCOCH_3$), 148.4, 139.8 (5 and 7-C), 125.3, 119.2 (4 and 6-C), 52.4, 48.7, 38.3 (8,9,14-C), 35.9, 34.7, 31.7, 25.7, 24.1, 20.5, 18.6 (CH_2), 21.6, 18.5, 14.4 (CH_3), 49.16, 34.9 (10, 13-C).

[g] Contains a mixture of Δ^2 and Δ^3 compounds, structure is deduced from the mixture (6:4).

[h] Saponification gave 1-hydroxy-4-methyl-1,3,5(10)-estratriene-17-one, mp 248–49°C (lit.[32]), purity 95% (uncrystallized), m/z: 307 (M+Na), 285 (+1), 267 (−18), ^{1}H NMR (200 MHz): δ 6.86 (d, J=7.82 Hz, Ar-H), 6.48 (d, J=7.82 Hz, Ar-H), 2.16 (s, CH_3), 0.95 (s, 18-Me).

and radiation modes of heating. Organic synthesis through the intervention of microwave gave impetus to the development of solvent free procedures with rate enhancement.[30] During our ongoing search for new steroid analogues, required for our detailed biological and metabolic profiling[31] of steroids derived from dehydroepiandrosterone (DHEA, **31**), and with the aim to speed up the discovery process, we examined steroid syntheses using microwave irradiation. In spite of high affinity of polarizable carbonyl group for the catalyst, enol-acetylation of α,β-unsaturated ketones and specifically of the 3-keto steroids, was achieved in a few minutes with excellent selectivity. Moreover, the potential of the present reagent system (~0.025–2 mol% of *p*TSA·H_2O in acetic anhydride) was fully realized in rapidly acetylating, in semisolid state, free hydroxyl groups, including those at the hindered 11β and 17α-positions of the steroid molecules, in excellent yields.

2. Results and discussion

The hydroxyl(s) and carbonyl group(s) present in the steroid molecule lead to low solubility in aprotic solvents resulting in poor reactivity. In order to increase the reaction rate and the thermodynamic equilibrium towards acylated substrate, conventionally, large amounts of acylating agent and catalyst have been used. However, the present microwave driven acetylation of polar steroidal molecules, in semisolid state, constitutes a rapid, solvent free, selective and economical approach.

The microwave promoted enol-acetylation of carbonyl groups present in steroids catalyzed by toluene-*p*-sulfonic acid monohydrate (*p*TSA·H_2O) was performed at the high power output of the domestic multimode oven (925 W with five power settings) using commercial grade acetic anhydride as acetylating agent. An intimate mixture of steroid in a small amount of acetic anhydride (6–12 equiv.) and catalytic amount of *p*TSA·H_2O (1–2 mol%) was placed in an open glass tube, and irradiated in the microwave oven for a short period of time (3–5 min, Table 1). The results summarized in Tables 1 and 2 demonstrate the microwave promoted selectivity, consistently high rate of conversion, and high yields (90–99%, Table 1). The results were reproducible when reactions were carried out in an 1100 W microwave oven, but the higher wattage often necessitated use of lower power settings and/or shorter reaction times.

To test the efficiency of the *p*TSA·H_2O to catalyze the enolization, several steroids (**1**–**17**, Table 1) were reacted with as little as 1 mol% of the catalyst. The reagent mixture gave rapid enol acetylation of reactive α,β-unsaturated carbonyls (Δ^4-3-keto steroids **1**–**9** and Δ^5-7-keto steroid **10**) and of sterically unhindered position 3-keto steroids (**11** and **12**) under microwave irradiation. To demonstrate the chemoselectivity of this reagent, Δ^4-3-ketones (**1**–**9**) and Δ^5-7-ketone (**10**) having additional unconjugated carbonyl functionalities at different positions of the steroid molecule, were subjected to enolization, and the resulting heteroannular dienes; that is, 3,5-diene-3-acetate derivatives (**18**–**26**) and 7-acetoxyandrost-4,6-dien-17-one (**27**) were isolated in high yield and excellent selectivity (Table 2). However, conjugated Δ^5-7-ketone (**16**, Table 1), with an acetyl function at the homoallylic position 3, was not enolized at the position 7, and the starting steroid (**16**) was recovered unchanged. A trace amount (~3%) of androst-3,5-diene-7,17-dione (**17**), a deacetylated product, was detected in the LC-MS analysis of the isolated material. This difference is probably due to electronic and steric factors. Enol-acetylation of 3 carbonyl of 1,4-androstadiene-3,17-dione (**13**) with acetic anhydride containing either zinc chloride (Dreiding and Voltman[32]) or perchloric acid in absolute ethyl acetate (Edwards et al.[8]) has been reported to cause a dienol–phenol rearrangement leading to the formation of 1-hydroxy-4-methyl-1,3,5(10) estratriene-17-one as the end product. Under microwave irradiation we observed the identical rearrangement product from 1,4-androstadiene-3,17-dione (**13**) on treatment with 12 equiv. of acetic anhydride and 2 mol% of the catalyst, but reaction was completed in 5 min in contrast to the 24 h required by the method of Drieding and Voltman and 45 min by the procedure of Edwards et al. Saturated carbonyl functionalities at positions 11, 17 and 20 (**1**–**3**, **5**–**8**, Table 2) of Δ^4-3-keto and at position 17 of Δ^5-androstene-7,17-dione (**10**) and 1,4-androstadiene-3,17-dione (**13**), were inert to the reaction conditions.

Several other experiments were carried out in order to elaborate further the nature and selectivity of the reagent. Saturated steroids with unconjugated carbonyl functionality at positions 3, 7 and 17 (**11**,**12**,**14** and **15**, Table 1) were prepared by known standard procedures and characterized by NMR and LC-MS data. 17β-acetoxy-5α-androstan-3-one (**11**) exhibited enolization at position 3 and afforded a mixture (6:4) of Δ^3 and Δ^2-enolacetates as shown in structures **28a** and **28b** (Table 1), whereas, enolization of 17β-acetoxy-5β-androstan-3-one (**12**) afforded Δ^3-enolacetate only. In the case of androstane-5α-diones (**14** and **15**), the carbonyls at positions 7 and 17 were almost unenolizable and those steroids were recovered largely unchanged (Table 1). LC-MS analysis showed formation of trace quantities (1–3%) of compounds corresponding to the molecular weights of enolized products (Table 2). Thus, microwave induced enol-acetylation afforded selectivity seldom observed in conventional thermal heating methods. The Δ^5-7-keto-steroid (**10**) underwent enolization at position seven but its 3-acetoxy analogue (**16**) and the corresponding androstane derivatives (**14** and **15**) did not. The advantages of the present catalytic process are simple workup of the reaction and isolation of good quality product and minimal waste. Usually, on cooling, products happened to fall out, were stirred with ice water for the purpose of convenient filtration and collection, and were subjected to ^{1}H NMR and LC-MS analysis for correct product composition and structural assignment.

For comparison, we also studied the enol acetylation of several steroids by conventional heating. The reactions were performed in an oil bath preheated to 180°C. We observed enol acetylation of steroid molecules such as **1**, **3** and **6** in 5 min but percentage conversions were generally lower when compared to microwave heating methods. Extending the reaction time beyond 5 min in general resulted in discoloration of the reaction mixture, lower yields and poor selectivity. Polyoxygenated steroids like hydrocortisone (**5**)

Table 2. Regioselectivity/chemoselectivity in enol acetylation

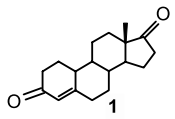
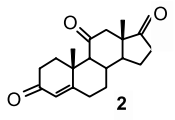
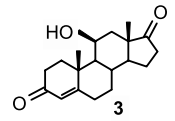
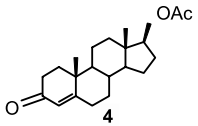
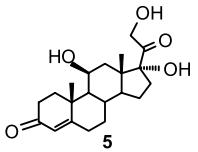
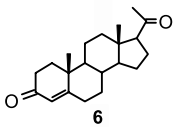
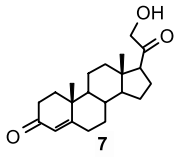
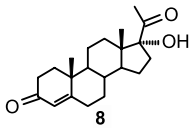
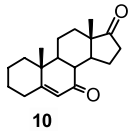
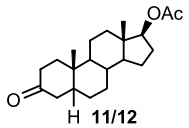
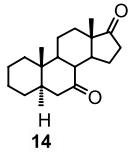
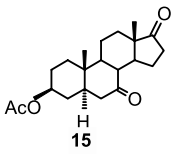
Starting steroids	% 3-Enol[a]	% 7-Enol[a]	%. 3,20-Dienol[a]	% Conversion	% Product balance[b]
	100	–	–	97	**1** (3%); λ_{max}=242; *m/z*: 309 (+Na), 287 (+1)
	100	–	–	96	**2** (3%); λ_{max}=242; *m/z*: 323 (+Na), 301 (+1)
	100	–	–	93	**3** (7%); as a 11-acetoxyandrst-4-en-3,17-dione; λ_{max}=242; *m/z*: 367 (+Na), 345 (+1), 285(−60)
	100	–	–	92	**4** (8%); λ_{max}=242; *m/z*: 353 (+Na), 331 (+1)
	100	–	–	88	**5** (12%); as a 11,17,21-TriAco-Δ^4 compd; λ_{max}=242; *m/z*: 511 (+Na), 489 (+1)
	96.8	–	3% λ_{max}=234; *m/z*: 421 (+Na)	95	**6** (5%); λ_{max}=242; *m/z*: 337 (+Na), 315 (+1)

Table 2 (*continued*)

Starting steroids	% 3-Enol[a]	% 7-Enol[a]	%. 3,20-Dienol[a]	% Conversion	% Product balance[b]
 **7**	100	–	–	94	**7** (6%); as 11-AcO compd; λ_{max}=242; *m/z*: 395 (+Na), 373 (+1)
 **8**	97.5	–	2.0, λ_{max}=236; *m/z*: 479 (+Na)	81	**8** (18.7%); as 17-AcO compd; λ_{max}=242; *m/z*: 395 (+Na), 373 (+1), 313 (−60)
 **10**	–	100		79	**10** (21%); λ_{max}=240; *m/z* 309 (+Na), 287 (+1)
 **11/12**	100		–	100	–
 **14**		3.4[c]	–	3.4[c]	**14** recovered (95%); λ_{max}=240; *m/z*: 311 (+Na), 289 (+1), 271 (−18); ^{1}H NMR: δ 1.07, 0.87 (2×s, 19,18-Me)

(*continued on next page*)

Table 2 (*continued*)

Starting steroids	% 3-Enol[a]	% 7-Enol[a]	%. 3,20-Dienol[a]	% Conversion	% Product balance[b]
 **15**	–	5.6[c]	–	5.6[c]	**15** recovered (94%); *m/z*: 369 (+Na), 347 (+1), 329 (−18), 287 (−18, −42); ^{1}H NMR: δ 4.68 (m, 3β-H), 2.03 (s, 3-OAc), 1.12 (s, 19-Me), 0.87 (s, 18-Me))

Reaction conditions as given in Table 1.

[a] Based on % conversion.

[b] Isolated product composition determined based on LCMS.

[c] Calculated based on height of 18-methyl signal in the ^{1}H NMR spectrum of the isolated product.

underwent rapid discoloration (within 5 min) under thermal heating giving a difficult to separate complex mixture of acetylated and enol-acetylated products, whereas under microwave heating, hydrocortisone (**5**) yielded 3-enol acetate (**22**) as major product (88%), the other product being 11,17,21-triacetate. Progesterone (**6**), under thermal heating underwent enolization at 3 and 20 carbonyl yielding a 2:1 mixture of mono and dienol acetates. Under microwave irradiation, it (**6**) gave 3-enol acetate (**23**) as major product (95% conversion). Steroids **14** and **16** were practically inert under microwave reaction conditions. However, under thermal heating, 5α-H compound (**14**) gave a complex mixture of 7- and 17-enol acetates. 5α-Androstane-3,17-dione (not shown in the tables) under thermal heating gave a mixture of 3 mono enol acetates in a ratio of 15:35:52. These mono enol acetates eluted closely in HPLC (relative retention times 1.000:1.004:1.008), and hence were very difficult to separate. Whereas, on microwave irradiation, enolization of only 3 carbonyl (92% conversion) was observed for this compound. These results showed that thermal heating did not differentiate between carbonyls present at 3, 7, 17 and 20 positions of steroid molecule. Acid sensitive 7-oxo steroid (**16**) was converted into a black tarry reaction mixture on thermal heating. LC-MS analysis indicated the presence of 3,5-dien-7-one product. The higher purity and quality of products often observed after microwave irradiation can probably largely be attributed to the homogeneous and smooth in situ heating.

It was noted that during enol acetylation of steroidal ketones the reagent combination acetylated free hydroxyl groups present in the steroid molecules, including those at the hindered 11β and 17α positions (**3**, **5**, **7** and **8**, Table 1 and **31**–**44**, Table 3). Further studies revealed that acetylation reactions that normally required 12–24 h under reflux conditions, could now be accomplished in less than 1 min in acetic anhydride using *p*TSA·H_2O as catalyst (as little as 0.5 mol%), in a microwave oven, affording dramatic saving in reaction time, from several hours to minutes or seconds and avoiding the use of a large excess of acetylating agent and catalyst.

Among a number of acetylation procedures known, condensation of acetic anhydride with sterols in pyridine has been routinely employed. This method has proved successful for the acetylation of primary and secondary hydroxyl group in the steroid molecule but sometimes fails to acetylate a tertiary hydroxyl group, specifically 17α-hydroxyl group, unless the conditions of the reaction are made more extreme. 17α-Hydroxy steroids have also been observed to be prone to D-ring homoannulation under a variety of forced reaction conditions.[33] Acetylation of 11β- and 17α-hydroxy derivatives, of which the naturally occurring adrenal cortical steroids are the most common examples, has been accomplished by using excessive amounts of acetic anhydride (50–60 mol equiv.) and more than 1 equiv. of *p*TSA, but still the reactions required 12–20 h to obtain good yields.[34–37] In addition to *p*TSA, Lewis acids, strong mineral acids[8,19,38] and heterogeneous catalysts such as vanadyl acetate[39] have been used to acetylate steroids. Recently, a non-catalytic method[40] has been reported for the acetylation of alcohols, amines and thiols using acetic anhydride under microwave irradiation. Each of these methods have their merits and demerits, but none of them is capable of acetylating steroidal hydroxyls in excellent yields and quality in as little as 40 s using minute amounts of *p*TSA·H_2O as catalyst (Table 3). Side reactions do not occur to any measurable extent and the products were isolated in quantitative yield as well as in excellent purity as determined by ^{1}H NMR and LC-MS analysis of the isolated products.

Sterically unhindered, equatorial 3β- and 17β-hydroxy groups on a variety of saturated and unsaturated steroids (Table 3, **31**–**33**, **35**–**37**) and phenolic 3-hydroxyl group of estradiol (**34**) were acetylated rapidly (40 s) requiring 0.5 mol% of the catalyst and the corresponding acetylated products were isolated in quantitative yields and excellent purity (LC-MS). Testosterone (**44**) was acetylated exclusively at the 17β-hydroxyl group by using only 0.025 mol% of *p*TSA·H_2O. The 3α-hydroxy group of 3α-hydroxy-5α-androstan-17-one (**40**, Table 3) and the 3β-hydroxyl group of pregnenolone (**39**, Table 3) required slightly more than 1 min (1.5 min) as compared to the shorter time required for acetylation of steroids **31**–**37** (0.67 min) under similar conditions (0.5 mol% of *p*TSA·H_2O) confirming that steric factors do influence the acetylation, and generally, an equatorial hydroxyl group was acetylated more readily than an axial group at the same position. However, the reactions could be completed in less than a minute by using slightly higher (1.0 mol%) concentration of *p*TSA·H_2O. Similarly, the 17α-hydroxy group of 20-keto-steroid (**42**, Table 3) was acetylated in 2 min but required a higher concentration of *p*TSA·H_2O in the mixture (2 mol%) and the product was isolated in 90% yield with a purity of 96% (LC-MS). Heating this compound at the reflux temperature failed to acetylate 17α-hydroxyl group to any appreciable extent and extending the reaction time (2 h) resulted in a black decomposed reaction mixture. LC-MS analysis showed presence of two mono acetylated products. Acid sensitive steroid (**41**) was also very sensitive to thermal heating and gave a highly discolored reaction mixture. Analysis showed presence of starting steroid and its acetylated and dehydrated products. Extended heating led to complete dehydration. Polyhydroxylated steroids (**5** and **43**) under microwave irradiation required about 5 min time for complete acetylation. Triol **43** under thermal heating gave a 1:1 mixture of di and tri acetates. Thermally stable unhindered steroids such as **31** could be acetylated under thermal heating. However, as discussed earlier, better yields and quality were obtained under microwave irradiation.

A series of acetylation experiments using DHEA (**31**, Table 1) were performed to study the effect of varying amounts of catalyst and acetic anhydride, and of power levels of the microwave oven on the course of the reaction. The results reveled that the extent of acetylation depended on the amount of *p*TSA·H_2O as well as power output of the microwave oven (Fig. 1). Both factors have positive influence on the rate of the reaction, but the amount of *p*TSA·H_2O had a limiting effect on the acetylation of the substrate. Increasing the mol% of *p*TSA·H_2O from 0.25 to 1.0% resulted in a dramatic increase in the yield (from 5 to 88%) at low power setting (1 on the scale of 1–5) of the

Table 3. Microwave induced acetylation of sterols

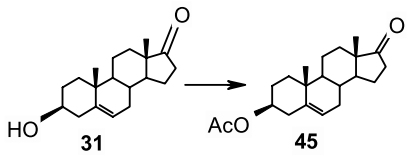
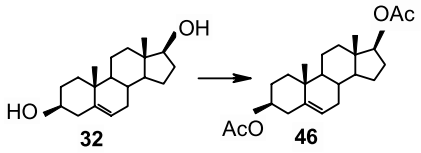
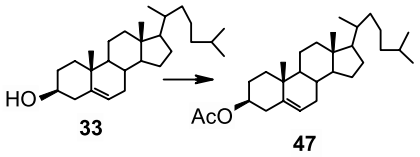
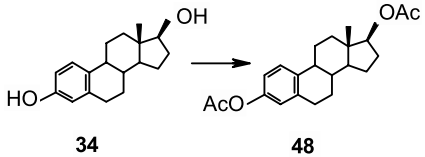
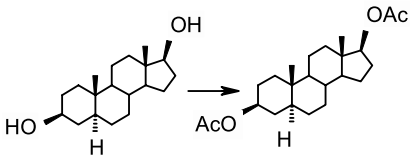
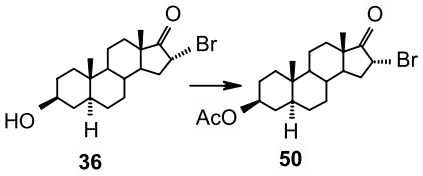
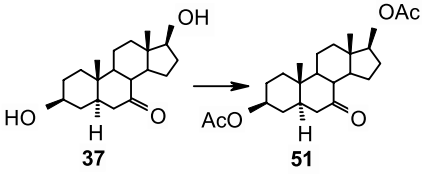
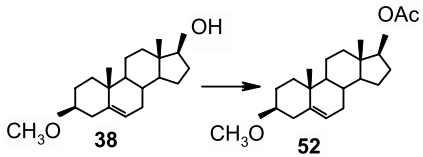
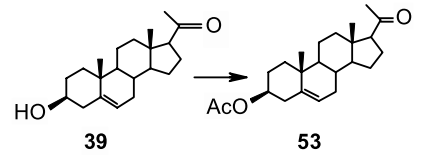
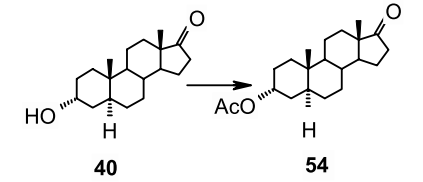
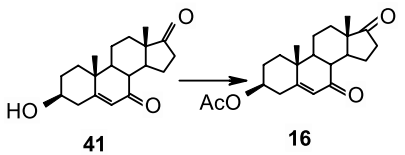
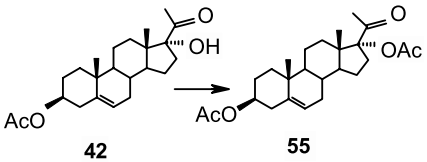
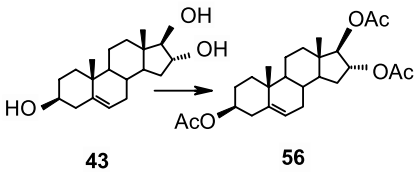
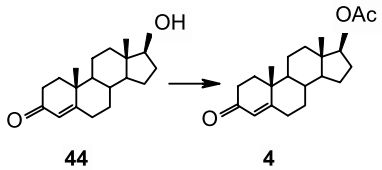
Steroids structures Sterols Sterol acetates	Ac_2O/pTSA[a]	Heating (min)[b]	Y/P[c] (%)	Analytical data[d] (product/mp (°C)./LC-MS/^{1}H NMR ($CDCl_3$)[e]
 **31** **45**	2.5/0.5	0.67[f]	100/100	(**45**);[41] mp 169–171; *m/z*: 353 (M+Na), 331 (+1), 271 (−60), 253 (−60, −18); ^{1}H NMR: δ 5.41 (d, *J*=4.64 Hz, 6-H), 4.61 (m, 3α-H), 2.04 (s, 3-AcO), 1.05 (19-Me), 0.89 (18-Me)
 **32** **46**	4/0.5	0.67	100/100	(**46**);[41] mp 161–163; *m/z*: 397 (M+Na), 375 (+1), 315 (−AcOH), 255 (−2×AcOH); ^{1}H NMR: δ 5.38 (d, *J*=4.88 Hz, 6-H), 4.59 (m, 3α-H), 4.59 (dd, *J*=7.3, 9.0 Hz, 17α-H) 2.05, 2.04 (2×s, 3,17-AcO), 1.03 (19-Me), 0.81 (18-Me)
 **33** **47**	2[g]/0.4	0.67	100/100	(**47**);[41] mp 114–116; ^{1}H NMR: δ 5.37 (d, *J*=4.89 Hz, 6-H), 4.62 (m, 3α-H), 2.04 (s, 3-AcO), 1.02 (s, 19-Me), 0.68 (s, 18-Me)
 **34** **48**	4/0.5	0.5	100/100	(**48**);[41] mp 97–98; *m/z*: 379 (M+Na), 357 (+1), 297 (−60), 255 (−60, −42); ^{1}H NMR: δ 7.26, 6.8 (ArH), 4.68 (dd, *J*=7.45, 9.0 Hz, 17α-H) 2.82 (s, 3-AcO), 2.06 (s, 17-AcO), 0.82 (18-Me)
 **35** **49**	6/0.5	0.67	100/100	(**49**);[41] mp 156–158; *m/z*: 399 (M+Na), 377 (+1), 317 (−60), 257 (−2×60); ^{1}H NMR: δ 4.68 (m, 3α-H), 4.58 (dd, *J*=7.57, 9.0 Hz, 17α-H) 2.03, 2.02 (2×s, 3, 17-AcO), 0.82 (19-Me), 0.76 (18-Me)

Table 3 (*continued*)

Steroids structures Sterols Sterol acetates	$Ac_2O/pTSA$[a]	Heating (min)[b]	Y/P[c] (%)	Analytical data[d] (product/mp (°C)./LC-MS/^{1}H NMR ($CDCl_3$)[e]
 **36** **50**	4/0.5	0.67	100/100	(**50**);[44] mp 175–177; ^{1}H NMR (400 MHz): δ 4.69 (m, 3α-H), 4.52 (d, J=6.39 Hz, 16β-H), 2.03 (s, 3-AcO), 0.89 (19-Me), 0.85 (18-Me)
 **37** **51**	6/0.5	0.67	100/100	(**51**);[41] mp 200–202; m/z: 413 (M+Na), 391 (+1), 331 (−60), 271 (−2×60), 253 (−2×60, −18); ^{1}H NMR: δ 4.68 (m, 3α-H), 4.58 (dd, J=7.57, 9.0 Hz, 17a-H) 2.03, 2.02 (2×s, 3,17-AcO), 0.82 (19-Me), 0.76 (18-Me)
 **38** **52**	3/0.5	1.0	100/100	(**52**);[45] mp 155–157; 154–156; m/z: 369 (M+Na), 327 (+1), 315 (−32), 287 (−60), 255 (−60, −32); ^{1}H NMR δ: 5.35 (d, J=4.64 Hz, 6-H), 3.06 (m,3α-H), 4.6 (dd, J=8.0, 9.0 Hz, 17α-H) 3.19 (s, OMe), 2.05 (s, 17-AcO), 1.0 (19-Me), 0.81 (18-Me)
 **39** **53**	4.0/0.5	1.5	98/100	(**53**);[41] mp 148–150; m/z: 381 (M+Na), 359 (+1), 299 (−60); ^{1}H NMR δ: 5.38 (d, J=5.13 Hz, 6-H), 4.06 (m, 3α-H) 2.13 (s, 20-Me), 2.04 (s, 3-AcO), 1.02 (s, 19-Me), 0.63 (s, 18 Me)
 **40** **54**	3.0/0.5	1.5	100/100	(**54**);[41] mp 166–168; m/z: 355 (M+Na), 333 (+1), 315 (−18), 273 (−60), 255 (−60, −18); ^{1}H NMR δ: 5.02 (bs, 3β-H), 2.06 (s, 3-AcO), 0.87 (s, 19-Me), 0.82 (s, 18-Me)

(*continued on next page*)

Table 3 (*continued*)

Steroids structures Sterols Sterol acetates	Ac_2O/pTSA[a]	Heating (min)[b]	Y/P[c] (%)	Analytical data[d] (product/mp (°C)./LC-MS/^{1}H NMR ($CDCl_3$)[e]
 **41** **16**	4.0/0.5	2.0	96/99	(**16**);[41] mp 185–187; λ_{max}=238; *m/z*: 367 (M+Na), 327 (−18), 285 (−60), 267 (−60, −18); ^{1}H NMR: δ 5.75 (d, *J*=1.71 Hz, 6-H), 4.73 (m, 3α-H), 2.06 (s, 3-AcO), 1.24 (s, 19-Me), 0.9 (s, 18-Me)
 **42** **55**	12.0/2.0	2.0	90/96	(**55**);[46] mp 173–176; *m/z*: 439 (M+Na), 417 (+1), 357 (−60), 297 (−2×60); ^{1}H NMR: δ 5.38 (d, *J*=4.64 Hz, 6-H), 4.6 (m, 3α-H), 2.12 (s, 20-Me), 2.04 (s, 3-AcO), 1.02 (s, 19-Me), 0.64 (s, 18-Me)
 **43** **56**	9.0/1.5	5.0	93/82[h]	(**56**);[41] mp 185–188; *m/z*: 455 (M+Na), 373 (−60), 313 (−2×60), 253 (−3×60); ^{1}H NMR: δ 5.36 (d, *J*=4.64 Hz, 6-H), 5.15 (m, 16β-H), 4.6 (m, 3α-H), 4.9 (d, *J*=5.62 Hz, 17α-H) 2.08, 2.05, 2.04 (3×s, 3,16, 17-AcO), 1.0, 0.83 (2×s, 19, 18-Me)
 **44** **4**	3/0.025	2	90/92[i]	(**4**);[41] mp 137–139; λ_{max}=242; *m/z*: 353 (M+Na), 331 (+1), 271 (−60); ^{1}H NMR: δ 5.73 (d, 6-H), 4.6 (dd, *J*=9.03, 7.57 Hz, 17α-H), 2.05 (s, 3-AcO), 1.2 (19-Me), 0.84 (18-Me)

[a] Eq. mol/mol%.
[b] Household microwave unit (Panasonic), 900 W, used at high power setting.
[c] Yield=based on % conversion, P=purity, area based on HPLC of the reaction mixture.
[d] Isolated crude material used as such for analysis to determine exact composition.
[e] An online LCMS was used to obtain λ_{max} and *m/z* values and for ^{1}H NMR Bruker 200 and Varien ui-400 spectrometers were used.
[f] 100 g batch size.
[g] To make a paste acetic acid was added.
[h] Contains 14% diacetate.
[i] 8% testosterone remained.

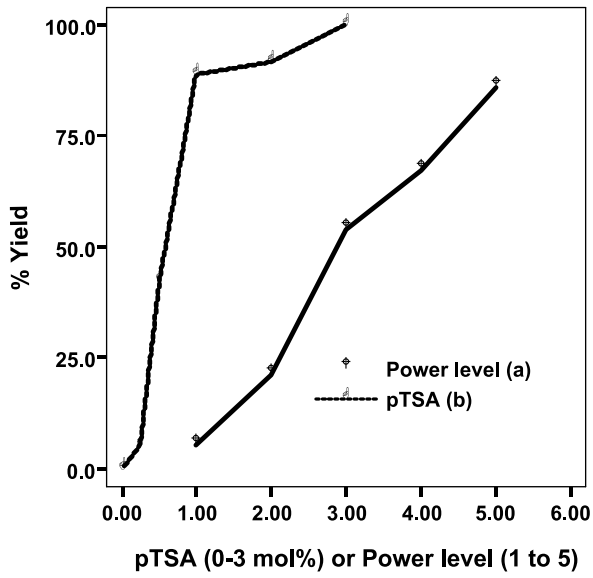


Figure 1. (a) Effect of power level (1–5) using 0.25 mol% of pTSA.H_2O; and (b) effect of catalyst *p*TSA·H_2O (0–3 mol%) at power level 1 on the course of the acetylation of DHEA; 3 mol equiv. acetic anhydride was used in both experiments.

microwave oven, but the increase from 1.0 to 2.0 mol% afforded only five percent increase (from 88 to 93%) in the yield of DHEA-3-acetate (**45**) at low power setting. Thus, the maximum rate enhancement at the low power level was observed at 0.5 to 1 mol% of the catalyst, and quantitative yield was obtained using these amounts of catalyst at higher power settings. The rate of the reaction increased linearly on augmenting the power output. Other factors being constant, the maximum conversion was obtained at the highest power level (Fig. 1). It may be noted that no reaction took place in the absence of *p*TSA·H_2O at the low power setting. These results clearly bring out that *p*TSA·H_2O has a definite role to play in the reaction. Increasing the mol equiv. of acetic anhydride (while keeping the *p*TSA·H_2O constant at 0.5 mol%) resulted in an initial increase in % conversion followed by a minimum as seen in Figure 2. It was followed

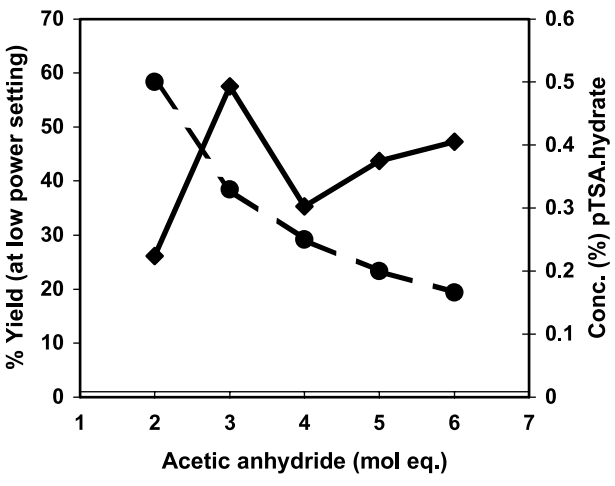


Figure 2. Effect of acetic anhydride (mol equiv.) and % concentration of *p*TSA·H_2O on the acetylation of DHEA at low (1) power level.

by a slow increase in % conversion achieved by increasing the volume of acetic anhydride. This seemingly unusual behavior can be attributed to the fall in the % concentration of *p*TSA·H_2O (Fig. 2) caused by the increase in the volume of the reaction mixture. The increase in the % conversion caused by the use of greater amounts of acetic anhydride was more than offset at that point by the decrease caused by the lowering of *p*TSA·H_2O concentration. This phenomenon once again demonstrated that a threshold concentration of *p*TSA·H_2O was required to carry out the reaction effectively.

Ideally, 1.0 mol equiv. of acetylating agent is all that is required to acetylate one hydroxyl group in the steroid molecule.[13] Since microwave induced acetylations were carried out in absence of a solvent, it was found that a minimum of 2.0 mol equiv. of acetic anhydride per hydroxyl group was needed for the conversion. For the smooth performance of the reaction, the amount of the acetylating agent should be sufficient to make a paste of the steroid. 2–3 mol equiv. of acetylating agent was usually enough to make a paste. If additional liquid is required, acetic acid serves well. In the case of DHEA (**31**), a minimum of 2.5–3.0 mol equivalent of acetic anhydride was required to make a paste and to effect complete acetylation. Furthermore, the real saving in time and profitability from this inexpensive procedure was gained during acetylation of a 100 g batch of DHEA (**31**), in just 40 s and the product, was isolated in quantitative yield, exhibited 100% purity in LC-MS analysis and was devoid of any discoloration.

3. Conclusion

We have demonstrated effective utilization of microwave energy to promote rapid and selective enolization of steroidal enones and position three steroidal ketones containing enolizable carbonyl functions at other positions. Although, reaction time and product compositions depend on the polar nature of the steroids, enolization reactions were completed in a maximum of five minutes with high yields and excellent selectivity. We have also shown the synthetic utility of this reaction during acetylation of steroidal hydroxyl groups, primary, secondary, tertiary or sterically hindered, to the corresponding acetyl derivatives in as little as 40 s. The acetylated steroids could be prepared rapidly, economically, and importantly, in large scale under mild condition and without inducing any structural changes in the molecule. We envisage that this solvent free procedure will find practical application in day-to-day organic syntheses as well.

4. Experimental

A domestic microwave oven (Panasonic, model # NN 6475A (1995), 925 W, with five power settings) was utilized at high power setting unless otherwise discussed. Acetic anhydride was used without further purification. Steroids were purchased either from Sterloids, New Port, USA or were synthesized in this laboratory by known procedures. Structures of the synthesized products were confirmed by

known references, melting point, nuclear magnetic resonance, ultraviolet and mass spectrometric data. Nuclear magnetic resonance (NMR) spectra were taken on Varien ^{unity}INNOVA-400 MHz or Brucker 200 MHz spectrometers. Spectra were measured in deuterated chloroform ($CDCl_3$) using tetramethylsilane (δ=0.0) as reference for ^{1}H NMR and $CHCl_3$ triplet (δ=77.0) for ^{13}C NMR. Abbreviations are s (singlet), d (doublet), t (triplet), dd (double doublet), q (quartet), m (multiplet). Agilent LC-MS, 1100 series was used for HPLC analysis. Diode array (DAD) UV detector and atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) mass detectors, were employed for simultaneous recording of UV and mass spectra of the compounds. Purity, % conversion and product composition were determined by LC-MS (Agilent-1100).

4.1. General procedure

A mixture of steroid (1 mmol), acetic anhydride (2.0–3.0 mmol per hydroxyl group to be acetylated, and 6–12 mmol for enol acetylation) and toluene-*p*-sulfonic acid mono hydrate (0.5–2 mol%, see Tables 1 and 3 for individual steroids) in a beaker or test tube was subjected to the continuous mode of microwave irradiation (925 W) at high power setting in a domestic type microwave oven. The desired parameter (microwave power and time) for enol acetylation of carbonyl group or complete acetylation of hydroxyl groups were set as reported in the respective tables. After completion of the reaction (checked by TLC), the contents were brought to room temperature, mixed with ice and water and stirred until product fell out. The solid was filtered under suction, washed with saturated sodium bicarbonate solution followed by water. The dried material was used as such for purity and composition analyses by LC-MS (see Table for details).

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