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Alumina-promoted fast solid-phase Michael addition of enamines with conjugated enones under microwave irradiation

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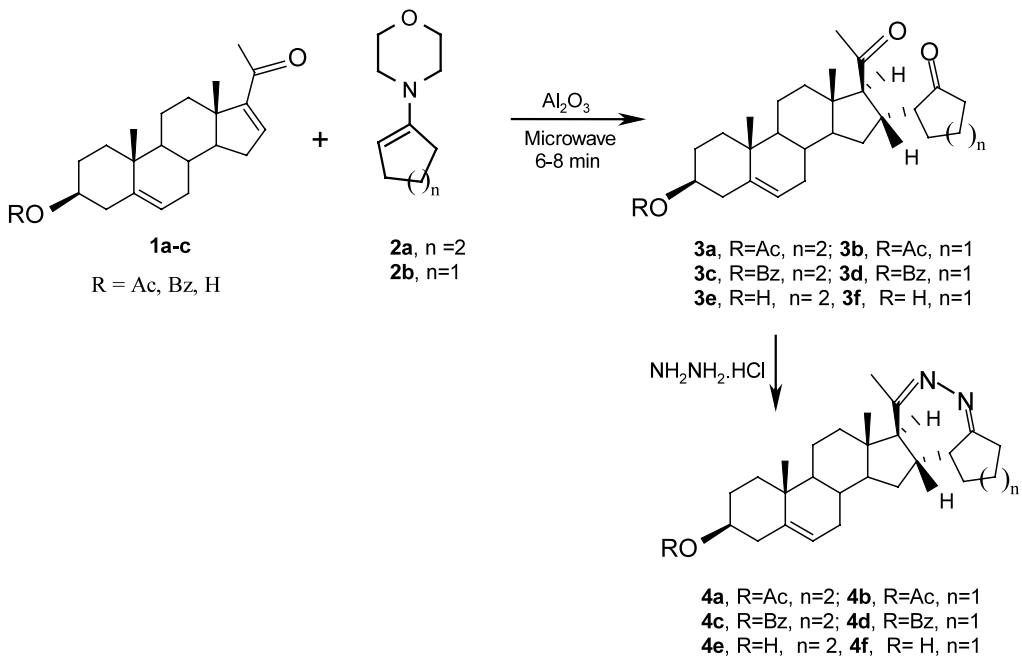
Abstract—A fast alumina-promoted solid-phase Michael addition of enamines to conjugated enones is described under microwave irradiation in high yields. The 1,5-diketo Michael adducts have been converted into a novel class of 1′,2′-diazepino(17,16-d′) steroids. © 2001 Elsevier Science Ltd. All rights reserved.

The Michael addition has attracted enormous attention as one of the most important carbon–carbon bond forming reactions in organic synthesis.[1] In general, Michael additions are conjugate additions of enolates to α,β-unsaturated carbonyl compounds affording 1,5-dioxo compounds and are generally carried out under strongly basic conditions.[2] However, such base-catalyzed methods are sometimes detrimental[3] to base sensitive functionalities and often lead to side reactions like auto-oxidation or retro-Michael type decompositions.[1a] In order to circumvent this problem considerable attention has been directed towards the search for more convenient methods.[4] On the other hand, enamines constitute an important class of Michael donors that



1a-c
R = Ac, Bz, H

2a, n =2
2b, n=1

3a, R=Ac, n=2; **3b**, R=Ac, n=1
3c, R=Bz, n=2; **3d**, R=Bz, n=1
3e, R=H, n= 2, **3f**, R= H, n=1

4a, R=Ac, n=2; **4b**, R=Ac, n=1
4c, R=Bz, n=2; **4d**, R=Bz, n=1
4e, R=H, n= 2, **4f**, R= H, n=1

Scheme 1.

Keywords: Michael addition; enamine; enone; microwave; alumina.

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have been utilized in complicated syntheses.[5] However, a literature survey revealed that in comparison to enolates, the use of enamines as Michael donors is significantly less common. The major disadvantage associated with enamines is their susceptibility to hydrolysis,[6] causing restrictions to their general use in Michael reactions. Consequently, the development of the use of enamines in Michael reactions that are efficient and offer operational advantages, remains a challenging problem to organic chemists.

Microwave energy is an unconventional energy source whose utility in synthetic organic chemistry has been increasingly recognized in recent years.[7] Microwave-promoted solid-phase heterogeneous reactions have attracted immense interest as environmentally benign reaction methodologies.[8] These methods are advantageous over conventional homogeneous reactions in the fact that they provide greater selectivity, enhanced reaction rates, cleaner products and manipulative simplicity.[9]

In continuation of our research on the chemistry of steroids,[10] we required an efficient preparation of 1,5-diketones as precursors to D-ring annelated heterosteroids.[11] As shown in Scheme 1, we considered readily available 16-dehydropregnenolone acetate (16-DPA) to be an ideal substrate as a Michael acceptor. Herein, we report our results on the alumina catalysed, fast, solid-phase Michael addition reaction of cyclic enamines with conjugated enones for carbon–carbon bond formation under microwave irradiation.[12]

When freshly prepared 1-morpholino-1-cyclohexene (**2a**, 1.5 mmol) was mixed thoroughly with 16-DPA (**1a**, 1.0 mmol) and basic alumina (1 g) and irradiated in the solid phase at 80% power for 6 min, the 3β-acetoxy-16-(2′-cyclohexanoyl)pregnenolone (**3a**) was isolated in 79% yield. The product was identified on the basis of analytical and spectroscopic data.[13] The ^{13}C NMR spectra (300 MHz) indicated the presence of the two characteristic carbonyl signals at δ 219.8 and 207.6 for the diketo adduct **3a**. In a similar manner, the corresponding Michael adducts **3b–f** were obtained from pregnenolones **1a–c** and enamines **2a–b** in high yields, under microwave irradiation (Table 1).

We have also examined the Michael addition of enamines (**2a–b**) with alicyclic conjugated enones (**1d–f**) in solid phase under microwave irradiation. The formation of the 1,5-diketo products **3g–l** could be achieved from **2a–b** and **1d–f** within 5–8 min, in 82–88% yields (Scheme 2).

However, it was observed that the reactions were sluggish in the absence of basic alumina, which indicated the catalytic role of alumina in this solid-phase reaction. In addition, the conventional thermal reactions of **1a–f** with **2a–b** failed to yield the expected products even on prolonged heating.

In order to investigate the scope of this reaction the adduct **3a** was reacted with hydrazine hydrochloride in refluxing ethanol for 4 h to afford 3β-acetoxy-3′-

Table 1. Alumina-promoted Michael addition of enamines to enones under microwave irradiation[a]

Entry	Enone			Enamine[b]	Product[c]				Yield[d] (%)	Reaction time (min)
		R	Ar			R	Ar	*n*		
1	**1a**	Ac	–	**2a**	**3a**	Ac	–	2	89	6
2	**1a**	Ac	–	**2b**	**3b**	Ac	–	1	86	5
3	**1b**	Bz	–	**2a**	**3c**	Bz	–	2	87	6
4	**1b**	Bz	–	**2b**	**3d**	Bz	–	1	85	7
5	**1c**	H	–	**2a**	**3e**	H	–	2	83	8
6	**1c**	H	–	**2b**	**3f**	H	–	1	81	8
7	**1d**	Me	Ph	**2a**	**3g**	Me	Ph	2	83	5
8	**1d**	Me	Ph	**2b**	**3h**	Me	Ph	1	80	6
9	**1e**	Me	*p*-ClPh	**2a**	**3i**	Me	*p*-ClPh	2	85	6
10	**1e**	Me	*p*-ClPh	**2b**	**3j**	Me	*p*-ClPh	1	82	6
11	**1f**	Ph	*p*-Tolyl	**2a**	**3k**	Ph	*p*-Tolyl	2	88	7
12	**1f**	Ph	*p*-Tolyl	**2b**	**3l**	Ph	*p*-Tolyl	1	86	8

[a] Reactions were carried using a Synthwave 402 Prolabo focussed microwave equipment at 80% power and temperature limitation of 250°C.
[b] Freshly prepared enamines.
[c] All products gave satisfactory spectroscopic and analytical data.
[d] Isolated yields after separation by column chromatography.

Scheme 2.

methyl-(6′,7′-cyclohexano)-1′,2′-diazepino(17,16-d′)androst-5-ene (**4a**) in 80% yield.[13] The heterosteroids **4b–f** were similarly prepared from **3b–f** in 77–86% yields.

In conclusion, we have reported an efficient solid-phase Michael reaction of enamines with enones promoted by alumina. The reaction is noteworthy, as it constitutes the first known example of the fast Michael addition of enamines using microwave irradiation. The method is advantageous over conventional methods because it avoids strongly basic or acidic conditions. Moreover, the easy work-up procedure and solvent-free conditions provides an environmentally friendly method. Further work on the generalization of this reaction is in progress.

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13. Selected analytical data for Michael adducts and heterosteroids.
    3β-Acetoxy-16-(2′-cyclohexanoyl)pregnenolone (**3a**): yield 79%; mp 178°C (hexane); $[\alpha]_D^{25}=+20.5$ (*c* 0.3%, $CHCl_3$); IR (KBr): ν_{max} 2950, 1740, 1710, 1460, 1440 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.37 (bs, 1H), 4.65 (bs, 1H), 2.17–3.00 (m, 4H), 2.15 (s, 3H), 2.06–2.14 (m, 7H), 2.02 (s, 3H), 1.02–2.01 (m, 17H), 1.01 (s, 3H), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 219.8, 207.6, 169.5, 138.8, 121.2, 72.8, 67.1, 54.4, 52.3, 48.9, 44.0, 37.7, 37.3, 37.0, 36.4, 36.0, 35.7, 30.8, 30.6, 30.1, 30.1, 27.9, 26.8, 20.5, 19.7, 19.3, 18.3, 13.2; MS (EI) *m*/*z* 394 (M^+–CH_3COOH). Anal. calcd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.65; H, 9.39.
    3β-Acetoxy-16-(2′-cyclopentanoyl)pregnenolone (**3b**): yield 79%, mp 175°C (hexane); $[\alpha]_D^{25}=+18.5$ (*c* 0.3%, $CHCl_3$); IR (KBr): ν_{max} 2910, 1725, 1710, 1690, 1650, 1460, 1440 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.32 (bs, 1H), 4.61 (bs, 1H), 2.00–3.05 (m, 4H), 2.16–2.10 (m, 5H), 2.15 (s, 3H), 2.03 (s, 3H), 2.01–1.02 (m, 17H), 1.01 (s, 3H), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 220.0, 207.9, 169.8, 139.1, 121.3, 73.0, 67.0, 54.6, 52.5, 49.2, 44.0, 38.2, 37.3, 36.7, 36.3, 35.9, 31.1, 31.0, 30.0, 29.8, 28.2, 27.0, 20.7, 20.2, 19.5, 18.6, 13.4; MS (EI) *m*/*z* 380 (M^+–CH_3COOH). Anal. calcd for $C_{28}H_{40}O_4$: C, 76.32; H, 9.15. Found: C, 76.35; H, 9.10.
    3β-Acetoxy-3′-methyl-(6′,7′-cyclohexano)-1′,2′-diazepino-(17,16-d′)androst-5-ene (**4a**): yield 80%; mp 181°C (dec.); IR (KBr): ν_{max} 2900, 1725, 1710, 1695, 1605, 1400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.25 (bs, 1H), 4.51 (m, 1H), 2.20–2.70 (m, 4H), 1.98 (s, 3H), 1.92 (s, 3H), 2.95–1.10 (m, 24H), 0.80 (s, 3H), 0.50 (s, 3H); MS (EI) *m*/*z* 390 (M^+–CH_3COOH). Anal. calcd for $C_{29}H_{42}O_2N_2$: C, 77.29; H, 9.39, N, 6.21. Found: C, 77.22; H, 9.35, N, 6.23.
    3β-Acetoxy-3′-methyl-(6′,7′-cyclopentano)-1′,2′-diazepino-(17,16-d′)androst-5-ene (**4b**): yield 78%; mp 176°C (dec.); IR (KBr): ν_{max} 2910, 1730, 1690, 1605, 1450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.20 (bs, 1H), 4.30 (m, 1H), 2.10–2.75 (m, 4H), 1.93 (s, 3H), 1.88 (s, 3H), 2.95–1.10 (m, 22H), 0.89 (s, 3H), 0.50 (s, 3H); MS (EI) *m*/*z* 376 (M^+–CH_3COOH). Anal. calcd for $C_{28}H_{40}O_2N_2$: C, 77.02; H, 9.23, N, 6.41. Found: C, 77.07; H, 9.27, N, 6.49.