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Highly diastereoselective Michael reaction under solvent-free conditions using microwaves: conjugate addition of flavanone to its chalcone precursor

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Abstract—Microwave-assisted reaction of 2′-hydroxychalcones in the presence of DBU resulted in the formation of hitherto unknown dimers by conjugate addition of the intermediate cyclic ketone to the starting enone. © 2001 Published by Elsevier Science Ltd.

Microwave (MW)-accelerated solvent-free organic syntheses are of great interest and importance in view of their simplicity, high and tunable selectivities, easy work-up and time- and energy-saving protocols. Recylability of the solid supports employed and the diminished amount of solvent usage also renders this technique truly, an environmental friendly procedure.[1] Numerous papers have been published on the MW-promoted deprotection, condensation, oxidation, reduction and rearrangements.[1f–h] With the exception of the preparation of heteroaromatic systems much less has been reported on the cyclizations, especially on the effect of MW on the stereoselectivity. During our project on the development of new MW-assisted, solvent-free methods for the stereoselective synthesis of heterocyclic compounds we decided to investigate the cyclization of 2′-hydroxychalcones **1**. Our earlier success in *MW-induced cyclization* of 2′-aminochalcones on montmorillonite K-10 clay leading to 2-aryl-1,2,3,4-tetrahydro-4-quinolones[2] prompted us to explore this approach.

Systematic studies on the MW-induced solvent-free cyclization of chalcones **1** on various supports (silica, K-10 clay, non-MW-absorbing materials such as Na_2SO_4 or $CaCO_3$) revealed that the reaction results in the formation of an equilibrium mixture of the corresponding flavanone **2**, and the starting material **1**. No significant difference was found between the equilibrium ratio, **2**:**1**, of MW-assisted or conventional thermal cyclization,[3] the only advantage of the former procedure was the much shorter reaction period. The

Table 1. Products from MW-assisted and thermal reaction of chalcones **1** in the presence DBU/Na_2SO_4

Entry	Starting material	Mode	T_{max} (°C)	Convn (%)	Isolated yields (%)			
					2	**3**	**4**	**5**
1	**1a**	MW	110	100	0	56	17	0
2	**1a**	Thermal	110	100	3.0	28	13	11
3	**1b**	MW	100	93	22	25	5.9	Trace
4	**1c**	MW	100	100	5.4	17	7	28
5	**1d**	MW	105	94	27	18	11	0
6	**1e**	MW	95	86	4.8	28	11	0

Keywords: addition reactions; chalcones; dimers; flavanones; microwave heating.

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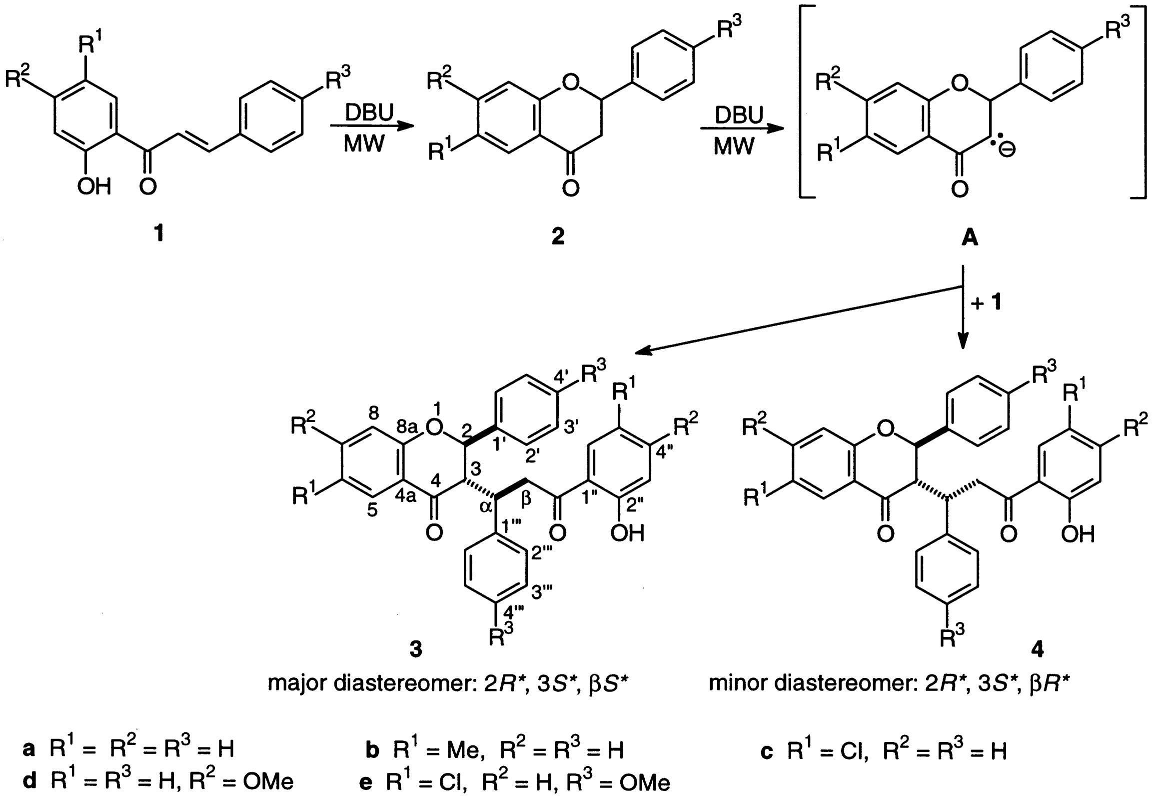
use of acidic or basic additives such as tartaric acid, *N*-benzyl-1-phenylethyl amine or DABCO did not change the **2**:**1** ratio.

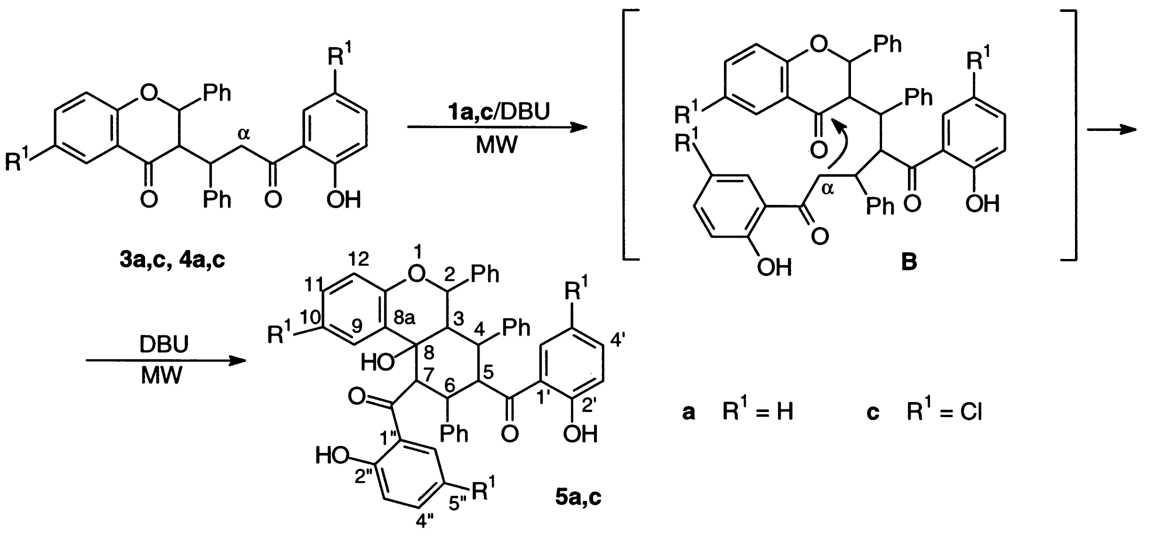
However, irradiation[4] of chalcones **1a**–**e** in the presence of Na_2SO_4 as a support and the strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as an additive resulted in the formation of diastereomeric dimers **3a**–**e** and **4a**–**e**[5] which obviously are originating via the conjugate addition of the carbanion **A** generated from primary product flavanone **2** to the α,β-enone **1** (Table 1, Scheme 1). The intermediacy of **2** was unequivocally proven by the kinetic curves determined by densitometrical analysis of TLC chromatograms of the reaction mixture. Electron-donating substituents such as methoxy and methyl slow down the cyclization and dimerization (Table 1, entries 3,5,6), this influence is more pronounced in the case of substitution in ring A. Dimers **3** and **4** have not been reported in the literature so far. In a previous paper[6] the formation of analogous but trimeric products, 3,3-disubstituted chromanones, from chromanone and α,β-unsaturated ketones and acid derivatives under basic conditions was published. In the light of the known[7] difficulties in the preparing of 3-alkylated chromanones and related derivatives from chromanone our MW-induced monosubstitution in position 3 has remarkable synthetic value.

The comparison of the MW-induced and conventional thermal heating (Table 1, entries 1 and 2) clearly show the advantageous effect of MW since in the latter case dimers **3a** and **4a** were obtained in lower yields beside considerable amount of trimer **5a**.[5] An alternative 3,3-disubstituted flavanone structure of **5a** could be unequivocally excluded on the basis of the lack of any flavanone C=O and the presence of six aliphatic methine unit and one aliphatic quaternary carbon in the ^{13}C and ^{1}H NMR spectra. The formation of **5a** could be rationalized in terms of a second conjugate addition of a α-carbanion formed from dimer **3** or **4** and a subsequent intramolecular addition in the intermediate **B**. (Scheme 2). An electron-withdrawing chloro substituent apparently increases the trimerisation (Table 1, entry 4).

The relative configuration of the major product **3a** was determined by X-ray analysis.[8] The crystal structure of **3a**, shown in Fig. 1, revealed an interesting and rare 2,3-*trans* diaxial arrangement of the substituents in the chromanone skeleton. $\{^1H\}$–$[^1H]$ NOE measurements provided that the same conformation exists in solution. Irradiation of H-2 resulted in 0.9 and 0.7% difference, respectively, on signals of H-3 and H_β but irradiation of H-3 resulted in 0.9% difference on signal H-2 only and no NOE was found with H_β. According to their ^1H NMR spectra the minor dimers **4** also should have 2,3-*trans* relative configuration but with two equatorial substituents ($J_{2,3}=9.6$–11.2 Hz). Thus, dimers **3** and **4** should differ in the stereochemistry of the β carbon of the dihydrochalcone unit. The dimerization occurred with remarkable diastereoselectivity; only two isomers of the possible four diastereomers formed with diastereomeric ratio between 62:38 and 81:19. The observed selectivity can be explained by the attack of carbanion **A** to the chalcone **1** from the less hindered side opposite to 2-phenyl group and the face selectivity of α,β-enone.



Scheme 1. Formation of dimers **3** and **4** from 2′-hydroxychalcones **1**.



Scheme 2. Formation of trimer **5**.

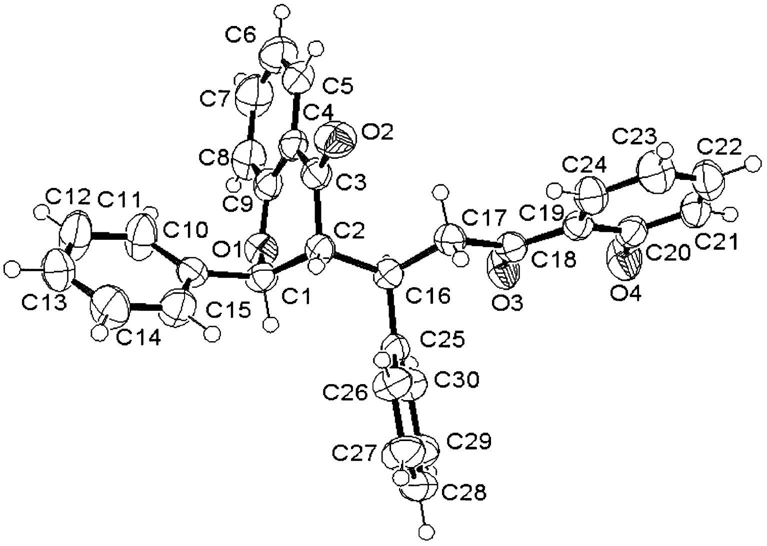


Figure 1. X-ray crystal structure of dimer **3a**.

Experiments to extend this MW-assisted protocol to the synthesis of various α-substituted benzo(hetera)-cyclanones are in progress.

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4. Typical procedure: A mixture of substituted 2′-hydroxy-chalcone (1 mmol), the corresponding support (5 g) and the additive (5 mg) in a pyrex tube was subjected to irradiation at 45 W for 20 min in a Maxidigest 350 Prolabo monomode, focused MW (2.45 GHz) reactor with

continuous rotation. The cooled mixture was washed with methylene chloride (2×10 mL) and concentrated in vacuo. The residue was purified by two subsequent column chromatography (silica gel) by using hexane–acetone (4:1, v/v) and toluene or toluene–ethyl methyl ketone (30:1, v/v) as eluent.

5. All isolated compounds were characterized by ^{1}H and ^{13}C NMR, MS and elemental analysis. Representative data are given as follows. **3a**: white crystals; mp 142–144°C (hexane–EtOAc). ^{1}H NMR (CDCl$_3$, 200 MHz): 3.31 (dd, J=10.5, 2.6 Hz, 1H, 3-H), 3.46 (dd, J=16.9, 5.0 Hz, 1H, α-H), 3.59 (dd, J=16.9, 8.9 Hz, 1H, α-H′), 3.97 (m, 1H, β-H), 5.29 (d, J=2.6 Hz, 1H, 2-H), 6.79–7.79 (m, 18H, Ar-H), 11.92 (s, 1H, 2″-OH). ^{13}C NMR (CDCl$_3$, 50 MHz): 39.5 (C_α), 41.8 (C_β), 79.0 (C-2), 118.2, 118.5, 118.9, 119.4, 120.8, 126.4, 127.2, 127.6, 128.1, 128.3, 128.7, 129.2, 129.8, 136.4, 136.9 (C-7, C-4″), 137.9, 141.4 (C-1′, C-1″), 159.6, 162.5 (C-8a, C-2″), 193.8 (C-4), 203.8 (C=O); MS (EI, 70 eV): 448 ($M^{+\bullet}$, 4), 431 (M-OH, 9), 357 (M-Bn, 14), 312 (24), 224 (*retro*-Michael fragment, 71), 191 (19), 147 (57), 121 (100), 120 (78), 105 (42), 92 (48).
   4a: white crystals; mp 155–156°C (hexane–EtOAc). ^{1}H NMR (CDCl$_3$, 200 MHz): 3.54–3.66 (overlapping m's, 2H, α-H, β-H), 3.79 (dd, J=10.2, 4.2 Hz, 1H, 3-H), 4.39 (dd, J=18.6, 9.6 Hz, 1H, α-H′), 5.26 (d, J=10.2 Hz, 1H, 2-H), 6.83–7.17, 7.43, 7.85 (m's, 18H, Ar-H), 12.16 (s, 1H, 2″-OH). ^{13}C NMR (CDCl$_3$, 50 MHz): 40.1 (C_β), 42.7 (C_α), 52.9 (C-3), 82.8 (C-2), 117.8, 118.4, 118.9, 119.5, 121.5, 121.9, 127.0, 127.1, 128.2, 128.3, 128.9, 129.2, 130.3, 136.1, 136.3 (C-7, C-4″), 137.0, 140.2 (C-1′, C-1″), 160.5, 162.4 (C-8a, C-2″), 194.4 (C-4), 204.9 (C=O); MS (EI, 70 eV): 312 (8), 223 (83), 147 (28), 121 (100), 120 (30), 104 (18), 92 (25), 77 (26).
   5a: white crystals; mp 253–255°C (hexane–EtOAc). ^{1}H NMR (CDCl$_3$, 200 MHz): 3.34 (dd, J=12.1, 11.6 Hz, 1H, 5-H), 3.41 (dd, J=11.8, 4.0 Hz, 1H, 3-H), 3.98 dd, J=12.1, 1.8 Hz, 1H, 6-H), 4.98 (d, J=4.0 Hz, 1H, 2-H), 5.28 (br s, 1H, 7-H), 5.45 (dd, J=11.8, 11.6 Hz, 1H, 4-H), 6.55–7.53 (m, 25H, Ar-H), 7.78 (dd, J=7.7, 1.5 Hz, 1H, 6′-H), 8.18 (br d, J∼6 Hz, 1H, 6″-H), 12.00, 12.54 (2×s, 2×1H, 2′-OH+2″-OH). ^{13}C NMR (CDCl$_3$, 50 MHz): 46.1, 46.7, 46.9, 49.2, 52.8 (C-3, C-4, C-5, C-6, C-7), 71.4 (C-8), 74.2 (C-2), 117.7, 118.4, 118.9, 120.6, 122.3, 123.1, 124.3, 125.0, 125.7, 127.3, 127.5, 127.6, 128.6, 129.2, 130.4, 130.7, 131.3, 136.1, 136.3, 138.8, 140.4, 141.1, 153.4 (C-12a), 162.2, 162.3 (C-2′, C-2″), 209.6, 209.7 (2×C=O).

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8. Colourless block crystals (0.9×0.72×0.55 mm) of $C_{30}H_{23}O_4$, M=447.48, monoclinic, a=11.0472(10) Å, b=15.6808(10) Å, c=13.0609(10) Å, β=93.73(1)°, V=2257.7(3) Å^3, Z=4, space group: $P2_1/n$, ρ_{calc}=1.316 g cm^{-3}. Data were collected at 293(1) K, Enraf Nonius MACH3 diffractometer, Mo Kα radiation λ=0.71073 Å, ω–2θ motion, $\theta_{\max}$=25.5°, 3535 reflections were measured of which 2761 reflections were unique with $I>2\sigma(I)$, decay: 1%. The structure was solved using the SIR-92 software and refined on F^2 using the SHELXL-97 program, R(F)=0.051 and $wR(F^2)$=0.141 for 3535 reflections, 307 parameters. Residual electron density: 0.403/–0.248 e Å^{-3}.