Mechanochemical Michael Reactions of Chalcones and Azachalcones with Ethyl Acetoacetate Catalyzed by K_2CO_3 under Solvent-Free Conditions

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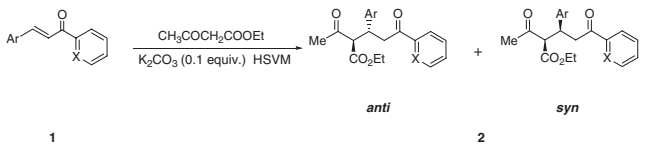
Michael addition reactions of chalcones and azachalcones with ethyl acetoacetate have been successfully performed in the presence of catalytic amount of K_2CO_3 (10 mol %) and under the high-speed vibration milling conditions. The reactions take place at ambient temperature without any solvent and full completion can be achieved in very short time (20–40 min). In most cases, conventional side reactions were avoided and thus high chemoselectivity and quantitative yields were achieved. The desired Michael adducts were exclusively obtained consisting of two diastereoisomers *anti* and *syn*, which were determined and assigned by ^{1}H NMR spectroscopy.

Mechanical alloying via high-energy ball-milling is a scalable experimental technique, which is broadly used for the preparation and modification of metals, metal hydrides, and other inorganic solids in materials science in recent years.[1–3] However, mechanochemistry is seldom attempted in organic synthesis. Even if attempted, mechanical processing of organic reactants is sometimes followed by additional treatment (usually heating),[4,5] or occasionally it is carried out in the presence of a solvent.[6] During the past two decades, solvent-free organic synthesis has received considerable attention owing to growing worldwide concerns over chemical wastes and future resources. From these points of view, we applied a recently developed mechanical and environmentally benign technique called 'high-speed vibration milling' (abbreviated as HSVM) to promote the Michael addition of chalcones and azachalcones with ethyl acetoacetate catalyzed by K_2CO_3 under the solvent-free condition. Traditionally, these reactions were performed in organic solvents and catalyzed by strong bases such as NaOH, KOH, $Ba(OH)_2$, and NaOEt. Under these drastic conditions, the transformation is sometimes complicated by side-reactions such as bis-additions, auto-condensations, rearrangements, subsequent condensation, retro Michael reaction, and so on.[7] These undesirable side reactions decrease the yield and make the purification of the products very tedious, and thus make it unsuitable for the synthesis of desired compounds. However, in our present protocol, the Michael addition reactions were found to proceed efficiently at ambient temperature in very short reaction time under the HSVM conditions (Scheme 1).

In a typical experimental procedure, a mixture of an unsaturated ketone, ethyl acetoacetate and K_2CO_3 in a molar ratio of 1:1:0.1 was introduced, together with a stainless-steel ball of 6.0-mm diameter, into a stainless-steel capsule (9.0 × 26.0 mm). The reaction capsule was fixed on the vibration arm of a home-built ball-milling apparatus, and was vibrated vigorously at a rate of 3500 rounds per minute at room temperature. The resulting powder was collected and washed with 10 mL of water to remove K_2CO_3 completely and then dried to afford the desired product **2**. This protocol does not require the use of any organic solvent and only 10% molar equivalent of K_2CO_3 is enough to promote the reaction efficiently. The yield and reaction time for the Michael addition of ethyl acetoacetate to various chalcones and azachalcones **1** are summarized in Table 1.



1 2

Scheme 1.

As can be seen from Table 1, the yields obtained were good to excellent. Compared with previous methodologies, the main advantages of the present procedure are milder reaction condition, higher yield, shorter reaction time and occurrence of no

Table 1. Michael addition of ethyl acetoacetate to chalcones and azachalcones catalyzed by 10 mol % K_2CO_3 under the HSVM conditions

	1[a]		2[b]	Reaction time /min	Yield /%[c] (*anti*:*syn*)[d]
	Ar	X			
1a	4-$NO_2C_6H_4$	CH	**2a**	30	98 (88:12)
1b	3-$NO_2C_6H_4$	CH	**2b**	40	96 (84:16)
1c	4-NCC_6H_4	CH	**2c**	35	99 (93:7)
1d	4-ClC_6H_4	CH	**2d**	40	99 (72:28)
1e	3,4-ClC_6H_4	CH	**2e**	40	99 (86:14)
1f	4-$NO_2C_6H_4$	N	**2f**	20	97 (88:12)
1g	3-$NO_2C_6H_4$	N	**2g**	25	92 (92:8)
1h	4-NCC_6H_4	N	**2h**	30	97 (83:17)
1i	3,4-ClC_6H_3	N	**2i**	40	94 (88:12)
1j	3,4-$CH_2O_2C_6H_3$	N	**2j**	40	86[e] (84:16)

[a]Prepared according to the recently reported method.[8] [b]Characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectral data.[9] [c]Isolated yield from three runs on a 0.1 mmol scale. [d]Based on ^{1}H NMR analysis. [e]Isolated by column chromatography (silica gel, petroleum ether:ethyl acetate, 5:1).

side reactions. For example, compound **2d** was previously prepared in 85% yield, which was catalyzed by activated $Ba(OH)_2$ in EtOH at room temperature for 8 h,[7c] whereas under our solvent-free HSVM conditions, it was obtained in 99% yield at room temperature for 40 min. The high efficiency of the current procedure may be ascribed to the increased reaction rate resulting from ultimately high concentrations of reactants with no use of solvent. Furthermore, common side reactions such as aldol cyclizations and ester solvolysis are avoided owing to the use of only catalytic amount of weak base K_2CO_3 and the solvent-free conditions, hence high chemoselectivity was achieved.

In all the examples listed in Table 1, each product consists of two diastereoisomers, *anti* and *syn* isomers. Interestingly, this diastereoselectivity has not been investigated in previous work,[7b–d,10] Herein, the *anti*/*syn* ratio was determined by ^{1}H NMR spectrscopy, in which the diastereoisomer with the singlet CH_3CO at lower field and the CH_3 in ethoxy group at higher field was assigned as *anti* isomer.[11] The *anti* isomer is the major one in all cases. For these two diastereoisomers, the average differential chemical shifts ($\Delta\delta$) for the CH_3CO and the CH_3 in ethoxy group are 0.26 and 0.24 ppm, respectively. They cannot be separated by column chromatography. Even after crystallization for several times, their ratio has no noticeable change. Probably the two diastereoisomers were in equilibrium via the corresponding enol form even under the present heterogeneous reaction conditions.[11]

In summary, Michael reactions of chalcones and azachalcones with ethyl acetoacetate mechanically induced under completely solvent-free and K_2CO_3-catalyzed conditions have been developed for the first time. The use of the HSVM technique and catalytic amount of K_2CO_3 can give very high chemoselectivity and thus high product yield. Furthermore, it is fast, clean and of low cost, and work-up procedure is very simple. These advantages indicate that solvent-free mechanochemistry has a potential to become an alternative to conventional organic synthesis.

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9 Selected spectral data for the *anti* isomer of product **2**. **2f**: IR (KBr) 1740, 1717, 1693, 1512, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, $J = 4.2$ Hz, 1H), 8.11 (d, $J = 8.3$ Hz, 2H), 7.90 (d, $J = 7.8$ Hz, 1H), 7.80 (t, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 8.3$ Hz, 2H), 7.45 (m, 1H), 4.34 (td, $J = 10.0$, 3.9 Hz, 1H), 4.04 (d, $J = 10.7$ Hz, 1H), 3.93 (q, $J = 7.0$ Hz, 2H), 3.81 (dd, $J = 18.0$, 9.5 Hz, 1H), 3.49 (dd, $J = 18.0$, 3.8 Hz, 1H), 2.33 (s, 3H), 1.01 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.09, 198.67, 167.63, 152.92, 149.06, 147.08, 137.13, 129.67 (2C), 127.60, 123.82, 123.62 (2C), 121.98, 65.22, 61.82, 41.77, 39.86, 29.64, 13.94; HRMS (EI–TOF) m/z calcd for $C_{20}H_{20}N_2O_6$ (M^+): 384.1321, found: 384.1317. **2g**: IR (KBr) 1734, 1714, 1695, 1532, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, $J = 4.5$ Hz, 1H), 8.19 (t, $J = 1.8$ Hz, 1H), 8.03 (dd, $J = 8.2$, 1.3 Hz, 1H), 7.90 (d, $J = 7.8$ Hz, 1H), 7.78 (td, $J = 7.7$, 1.7 Hz, 1H), 7.71 (d, $J = 7.7$ Hz, 1H), 7.45 (dd, $J = 7.6$, 1.1 Hz, 1H), 7.42 (t, $J = 7.9$ Hz, 1H), 4.33 (td, $J = 10.1$, 4.1 Hz, 1H), 4.04 (d, $J = 10.7$ Hz, 1H), 3.92 (q, $J = 7.2$ Hz, 2H), 3.82 (dd, $J = 17.9$, 9.5 Hz, 1H), 3.51 (dd, $J = 17.9$, 4.2 Hz, 1H), 2.33 (s, 3H), 1.00 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.15, 198.75, 167.66, 152.95, 149.08, 148.34, 143.59, 137.10, 135.46, 129.30, 127.57, 123.36, 122.24, 121.96, 65.34, 61.81, 41.80, 39.72, 29.72, 13.92; HRMS (EI–TOF) m/z calcd for $C_{20}H_{20}N_2O_6$ (M^+): 384.1321, found: 384.1338. **2h**: IR (KBr) 2229, 1740, 1716, 1694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (m, $J = 4.2$ Hz, 1H), 7.90 (dt, $J = 8.0$, 1.1 Hz, 1H), 7.79 (td, $J = 7.6$, 1.5 Hz, 1H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.46 (m, 1H), 7.44 (d, $J = 8.3$ Hz, 2H), 4.24 (m, 1H), 4.01 (dd, $J = 10.7$, 4.1 Hz, 1H), 3.92(q, $J = 7.2$ Hz, 2H), 3.78 (dd, $J = 18.1$, 9.5 Hz, 1H), 3.46 (dd, $J = 18.1$, 4.1 Hz, 1H), 2.32 (s, 3H), 1.00 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.19, 198.72, 167.69, 152.96, 149.04, 147.01, 137.11, 132.21 (2C), 129.59 (2C), 127.56, 121.97, 118.82, 111.06, 65.26, 61.76, 41.72, 40.12, 29.59, 13.91; HRMS (EI–TOF) m/z calcd for $C_{21}H_{20}N_2O_4$ (M^+): 364.1423, found: 364.1418. **2i**: IR (KBr) 1732, 1714, 1694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, $J = 3.5$ Hz, 1H), 7.92 (d, $J = 7.6$ Hz, 1H), 7.79 (td, $J = 7.7$, 1.4 Hz, 1H), 7.45 (m, 1H), 7.41 (d, $J = 2.1$ Hz, 1H), 7.30 (d, $J = 8.2$ Hz, 1H), 7.17 (dd, $J = 8.2$, 2.1 Hz, 1H), 4.17 (td, $J = 9.6$, 4.2 Hz, 1H), 3.96 (q, $J = 7.0$ Hz, 2H), 3.94 (d, $J = 10.7$ Hz, 1H), 3.73 (dd, $J = 17.5$, 9.5 Hz, 1H), 3.42 (dd, $J = 17.5$, 4.3 Hz, 1H), 2.31 (s, 3H), 1.04 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.45, 198.74, 167.73, 152.93, 149.01, 141.59, 137.11, 132.34, 131.07, 130.63, 130.34, 128.17, 127.55, 122.00, 65.50, 61.79, 41.81, 39.20, 29.65, 13.93; HRMS (EI–TOF) m/z calcd for $C_{20}H_{19}NO_4Cl_2$ (M^+): 407.0691, found: 407.0692. **2j**: IR (KBr) 1732, 1709, 1698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, $J = 4.2$ Hz, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.77 (td, $J = 7.7$, 1.3 Hz, 1H), 7.43 (m, 1H), 6.79 (d, $J = 1.4$ Hz, 1H), 6.75 (dd, $J = 8.0$, 1.8 Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.87 (s, 2H), 4.14 (td, $J = 9.6$, 4.0 Hz, 1H), 3.95 (q, $J = 7.2$ Hz, 2H), 3.91 (d, $J = 10.7$ Hz, 1H), 3.72 (dd, $J = 17.5$, 9.5 Hz, 1H), 3.38 (dd, $J = 17.5$, 4.3 Hz, 1H), 2.31 (s, 3H), 1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.30, 199.17, 168.12, 153.17, 148.96, 147.54, 146.46, 137.01, 134.83, 127.34, 121.99, 121.76, 108.93, 108.18, 101.00, 66.40, 61.50, 42.24, 39.99, 29.51, 13.98; HRMS (EI–TOF) m/z calcd for $C_{21}H_{21}NO_6$ (M^+): 383.1369, found: 383.1376.
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