Highly Efficient Mechanochemical Reactions of 1,3-Dicarbonyl Compounds with Chalcones and Azachalcones Catalyzed by Potassium Carbonate

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Abstract: Under the high-speed vibration milling conditions, K_2CO_3 was found to be a very efficient catalyst for the solvent-free Michael reactions of 1,3-dicarbonyl compounds with chalcones and azachalcones. In most cases, conventional side reactions were avoided and thus excellent yields were achieved. The influences of other catalysts and the vibration frequency on the Michael reaction were investigated.

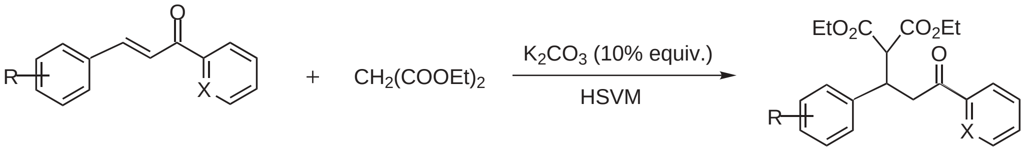
Key words: Michael addition, chalcone, azachalcone, potassium carbonate, mechanochemical reaction

The highly useful C–C bond formation through Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated ketones is frequently catalyzed by strong bases such as NaOH, KOH, $Ba(OH)_2$ and NaOEt. But these drastic conditions often cause some side reactions, including rearrangement, bis-addition, auto-condensation, subsequent condensation, retro Michael reaction and so on.[1] These undesirable side reactions decrease the yield and make the purification of the products very difficult. It has been pointed out that better results are obtained with weaker bases such as piperidine, tertiary amines, or quaternary ammonium hydroxides.[2] There have been reports on Michael reactions catalyzed by K_2CO_3 in organic solvent,[3] in water and in the presence of surfactant,[4] and under phase transfer catalysis conditions.[5] To some extent, these mild conditions can minimize the reversibility of the Michael addition reaction[6] and other side reactions, thus improved yields can be achieved. However, there were still some disadvantages due to long reaction time or tedious work-up in these methods. To circumvent the above problems, one of the best methods is to carry out this kind of reaction under solvent-free condition, which has the advantages of reduced pollution, low cost, and simplicity in process and handling.[6,7]

Recently a technique called 'high-speed vibration milling' (abbreviated as HSVM) has been successfully utilized to promote solvent-free mechanochemical reactions of fullerenes.[8–15] However, there has been no report on non-fullerene mechanochemical reaction under the HSVM conditions. Herein, we wish to report our study on the application of the HSVM technique to the solvent-free reactions of 1,3-dicarbonyl compounds with chalcones and azachalcones catalyzed by K_2CO_3. To the best of our knowledge, we are not aware of any report on solvent-free Michael reaction in the presence of catalytic amount of K_2CO_3 and without any other catalyst.

The Michael reactions of chalcones and azachalcones with diethyl malonate were first examined and were found to proceed efficiently in excellent yields at ambient temperature in short reaction time under our HSVM conditions (Scheme 1).

All solvent-free reactions were performed using a high-speed vibration mill that consists of a capsule and a milling ball made of stainless steel.[9b] The capsule containing the milling ball was fixed on a vibration arm of a home-built mill, and was vibrated vigorously at a rate of 3500 rounds per minute. The solvent-free mechanochemical reaction of chalcone **1** with equimolar amount of diethyl malonate **2** in the presence of K_2CO_3 under the HSVM conditions afforded essentially pure product **3** after



1 2 3

X= CH, N; R = H, 4-CH_3, 4-OCH_3, 4-NO_2, 3-NO_2, 4-CN, 4-Cl, 3,4-Cl, 3,4-(OCH_2O)-

Scheme 1

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washing the reaction mixture with water in most cases.[16] This protocol does not require the use of any organic solvent during the reaction process 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 diethyl malonate **2** to various chalcones and azachalcones **1** are summarized in Table 1.

Table 1 Michael Addition of Diethyl Malonate to Chalcones and Azachalcones Catalyzed by K_2CO_3 under the HSVM Conditions

1[a]			Product **3**[b]	Reaction time (min)[c]	Yield[d] (%)
	R	X			
1a	H	CH	**3a**	55	98
1b	4-CH_3	CH	**3b**	50	98
1c	4-OCH_3	CH	**3c**	60	91
1d	4-NO_2	CH	**3d**	35	99
1e	3-NO_2	CH	**3e**	10	99
1f	4-CN	CH	**3f**	15	99
1g	4-Cl	CH	**3g**	50	99
1h	3,4-Cl	CH	**3h**	30	99
1i	3,4-OCH_2O-	CH	**3i**	60	76
1j	4-NO_2	N	**3j**	25	99
1k	3-NO_2	N	**3k**	30	99
1l	4-CN	N	**3l**	30	99
1m	4-Cl	N	**3m**	60	92
1n	3,4-Cl	N	**3n**	30	99
1o	3,4-OCH_2O-	N	**3o**	25	98

[a] Prepared according to our recently reported method.[17]

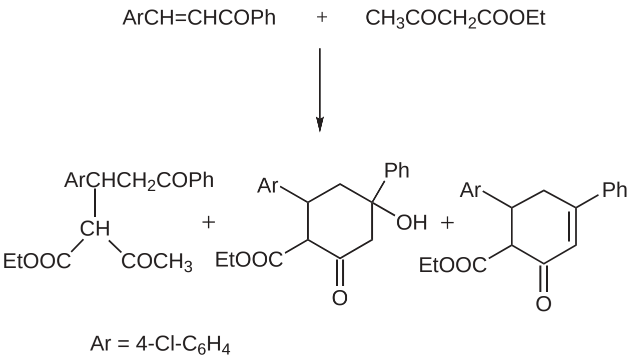
[b] Characterized by mp, IR, ^1H NMR, ^{13}C NMR and HRMS spectral data.

[c] Time needed for the reaction to complete and the maximum reaction time is limited to 1 h.

[d] Isolated yield from three runs.

As shown in Table 1, the Michael addition reactions generally gave products **3** in remarkably high yields, which are almost quantitative. This protocol can be extended to the Michael addition of other 1,3-dicarbonyl compounds such as ethyl acetoacetate to chalcones and azachalcones with quantitative yield in almost all cases. Compared with existing methods, the main advantages of the present procedure are milder condition, higher yield, shorter reaction time and occurrence of no side reactions. For example, compound **4** was previously prepared in 85% yield which was catalyzed by activated $Ba(OH)_2$ in EtOH at room temperature for 8 h,[1c] whereas under our solvent-free HSVM conditions, it was obtained in 99% yield at room temperature for 40 min. The reasons for the efficiency of the current solvent-free procedure may be due to an enhanced second-order reaction rate resulting from ultimately high concentrations of reactants with no use of solvent. Furthermore, in the HSVM technique, the high mechanical energy caused by local high pressure, friction, shear strain, etc. can greatly enforce the reaction.[14]

To investigate the effect of the applied base on this Michael reaction, we performed the reaction of 4-chlorochalcone (0.1 mmol) with ethyl acetoacetate (0.1 mmol) (Scheme 2) in the presence of several different catalysts. The results are summarized in Table 2.



4 **5** **6**

Scheme 2

Table 2 Michael Reaction of 4-Chlorochalcone with Ethyl Acetoacetate in the Presence of Different Catalysts under the HSVM Conditions

Entry	Catalyst (equiv)	Reaction time (min)	Product (yield[a])
1	None	40	**4** (28%)
2	K_2CO_3 (0.1)	40	**4** (99%)
3	Na_2CO_3 (0.1)	60	**4** (47%)
4	Na_2CO_3 (1.0)	60	**4** (68%)
5	KF/Al_2O_3[b] (0.1)	60	**4** (28%) + **5** (17%)
6	KF/Al_2O_3[b] (1.0)	60	**4** (46%) + **5** (24%)
7	NaOH (0.1)	60	**4** (26%) + **5** (44%) + **6** (23%)
8	NaOH (1.0)	60	**4** (trace) + **5** (57%) + **6** (32%)

[a] Isolated by column chromatography.

[b] 40 wt% KF, prepared according to reported method.[18]

From Table 3 we can see that, in this reaction system, basic catalyst is necessary to make it proceed practically. Weaker catalysts such as Na_2CO_3 and K_2CO_3 have higher product selectivity, affording only Michael adduct **4**. Between these two catalysts, K_2CO_3 promoted the reaction much more efficiently. When the Michael reaction was catalyzed by strong bases such as KF/Al_2O_3 and NaOH, further aldol condensation and subsequent dehydration occurred to afford compounds **5** and **6**. It is obvious that K_2CO_3 is the best catalyst for the Michael reaction under the HSVM conditions in term of yield and selectivity.

To further explore this reaction system, we have carried out the Michael reaction under different vibration frequencies. It was found that the vibration frequency of the applied vibration mill had a significant effect on the Michael reaction (Table 3).

Table 3 Michael Reaction of 4-Chlorochalcone with Ethyl Acetoacetate at Different Vibration Frequencies for 40 Minutes

Entry	Catalyst (equiv)	Vibration frequency (rpm)[a]	Yield[b] (%)
1	None	3500	28
2	None	1800	Trace
3	None	1200	No reaction
4	K_2CO_3 (0.1)	3500	99
5	K_2CO_3 (0.1)	1800	47
6	K_2CO_3 (0.1)	1200	19

[a] The reactions at 1800 rpm and 1200 rpm were run on a Retsch MM200 mixer mill.
[b] Isolated yield of **4** by column chromatography.

As shown in Table 3, higher vibration frequency of the vibration mill accelerated the reaction process greatly. It is easy to understand that the faster the mill vibrates the higher the mechanical energy, and therefore the local pressure, applied to the reaction system. Furthermore, when a mill vibrates at higher speed (or intensity of milling), the temperature of its capsule should reach a higher value, which may be advantageous for the diffusion process to promote homogenization and alloying in the powders and thus beneficial for the ongoing reaction.[19]

In conclusion, a powerful method is described for Michael reactions of 1,3-dicarbonyl compounds with chalcones and azachalcones in quantitative yields in most cases. All these mechanochemical reactions were conducted under the solvent-free and the HSVM conditions. The use of the HSVM technique and catalytic amount of K_2CO_3 gave very high product yield and selectivity. The advantages of mild condition, high yield, short reaction time together with a straightforward and easy work-up procedure make the present method convenient, effective and environmentally friendly, which could be a very efficient alternative to the classic methodology.

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(16) **General Procedure for the Synthesis of Compounds 3:**
A mixture of compound **1** (0.1 mmol), diethyl malonate **2** (15.2 μL, 0.1 mmol) and K_2CO_3 (1.4 mg, 0.01 mmol) was vigorously shaken by HSVM for a designated time. The reaction mixture was collected and washed with water to remove the small amount of K_2CO_3, and then dried to give the crude product **3**. The obtained product is essentially pure and can be further purified by crystallization from petroleum ether–EtOAc (10:1) at –20 °C. Products **3c**, **3i** and **3m** were purified by column chromatography on silica gel with petroleum ether–EtOAc (5:1) as an eluent.
Selected analytical data:
3f: Mp 93–94 °C. IR (KBr): 2224, 1752, 1731, 1686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.87$ (d, $J = 7.6$ Hz, 2 H), 7.54 (d, $J = 8.0$ Hz, 2 H), 7.53 (m, 1 H), 7.43 (d, $J = 7.6$ Hz, 2 H), 7.41 (d, $J = 8.0$ Hz, 2 H), 4.26–4.14 (m, 3 H), 3.98 (q, $J = 7.1$ Hz, 2 H), 3.81 (d, $J = 9.5$ Hz, 1 H), 3.57 (dd, $J = 17.3, 4.6$ Hz, 1 H), 3.48 (dd, $J = 17.3, 9.2$ Hz, 1 H), 1.23 (t, $J = 7.1$ Hz, 3 H), 1.04 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 196.90$, 167.92, 167.42, 146.41, 136.51, 133.50, 132.26 ($2 \times C$), 129.39 ($2 \times C$), 128.78 ($2 \times C$), 128.10 ($2 \times C$), 118.74, 111.15, 62.02, 61.74, 56.91, 42.08, 40.68, 14.10, 13.90. HRMS (EI–TOF): m/z [M^+] calcd for $C_{23}H_{23}NO_5$: 393.1576; found: 393.1577.

3h: Mp 114–115 °C. IR (KBr): 1743, 1721, 1684 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.90 (dd, J = 7.8, 1.3 Hz, 2 H), 7.56 (t, J = 7.3 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 2 H), 7.38 (d, J = 2.0 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 1 H), 7.16 (dd, J = 8.3, 2.0 Hz, 1 H), 4.26–4.11 (m, 3 H), 4.02 (q, J = 7.1 Hz, 2 H), 3.77 (d, J = 9.3 Hz, 1 H), 3.55 (dd, J = 17.2, 4.6 Hz, 1 H), 3.44 (dd, J = 17.2, 9.2 Hz, 1 H),1.25 (t, J = 7.1 Hz, 3 H), 1.09 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 197.04, 168.07, 167.55, 141.13, 136.62, 133.48, 132.47, 131.30, 130.45 (2 × C), 128.81 (2 C), 128.18 (2 × C), 128.06, 62.01, 61.79, 57.15, 42.18, 39.87, 14.15, 13.97. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{22}H_{22}O_5{}^{35}Cl_2$: 436.0844; found: 436.0847.

3i: Mp 58–60 °C. IR (KBr): 1748, 1728, 1682 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 7.90 (dd, J = 7.4, 1.2 Hz, 2 H), 7.54 (t, J = 7.3 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 6.76 (d, J = 1.1 Hz, 1 H), 6.71 (dd, J = 8.0, 1.1 Hz, 2 H), 6.66 (d, J = 8.0 Hz, 1 H), 5.88 (s, 2 H), 4.20 (qd, J = 7.1, 2.6 Hz, 2 H), 4.10 (td, J = 9.4, 4.7 Hz, 1 H), 4.01 (q, J = 7.1 Hz, 2 H), 3.75 (d, J = 9.8 Hz, 1 H), 3.50 (dd, J = 16.5, 4.6 Hz, 1 H), 3.39 (dd, J = 16.5, 9.3 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.08 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 197.70, 168.45, 167.83, 147.67, 146.65, 136.95, 134.32, 133.20, 128.71 (2 × C), 128.26 (2 × C), 121.65, 108.78, 108.27, 101.06, 61.81, 61.53, 57.90, 42.88, 40.75, 14.18, 14.01. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{23}H_{24}O_7$: 412.1522; found: 412.1527.

3j: Mp 66–67 °C. IR (KBr): 1749, 1730, 1699, 1521, 1348 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.64 (d, J = 4.2 Hz, 1 H), 8.11 (d, J = 8.6 Hz, 2 H), 7.90 (d, J = 7.8 Hz, 1 H), 7.78 (td, J = 7.6, 1.6 Hz, 1 H), 7.53 (d, J = 8.6 Hz, 2 H), 7.45 (dd, J = 7.0, 4.6 Hz, 1 H), 4.32 (td, J = 10.0, 4.0Hz, 1 H), 4.21 (qd, J = 7.1, 2.5 Hz, 2 H), 3.97 (q, J = 7.1 Hz, 2 H), 3.97 (dd, J = 18.2, 9.9 Hz, 1 H), 3.85 (d, J = 10.2 Hz, 1 H), 3.64 (dd, J = 18.2, 4.1 Hz, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.04 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 198.52, 167.80, 167.45, 152.88, 149.08, 148.93, 147.05, 137.13, 129.69 (2 × C), 127.62, 123.64 (2 × C), 121.96, 62.09, 61.76, 57.22, 41.67, 40.24, 14.17, 13.98. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{21}H_{22}N_2O_7$: 414.1427; found: 414.1424.

3k: Mp 72–74 °C. IR (KBr): 1748, 1729, 1691, 1531, 1352 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.65 (d, J = 4.3 Hz, 1 H), 8.22 (s, 1 H), 8.03 (dd, J = 7.7, 1.7 Hz, 1 H), 7.90 (d, J = 7.9 Hz, 1 H), 7.79 (dd, J = 7.4, 1.2 Hz, 1 H), 7.73 (d, J = 8.7 Hz, 1 H), 7.46 (d, J = 5.0 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 1 H), 4.3 2 (td, J = 9.8, 4.1 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.97 (dd, J = 18.2, 9.9 Hz, 1 H), 3.97 (q, J = 7.1 Hz, 2 H), 3.85 (d, J = 10.1 Hz, 1 H), 3.66 (dd, J = 18.2, 4.0 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 198.61, 167.84, 167.49, 152.92, 149.10, 148.28, 143.36, 137.07, 135.44, 129.29, 127.56, 123.43, 122.29, 121.91, 62.04, 61.71, 57.34, 41.61, 40.11, 14.15, 13.94. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{21}H_{22}N_2O_7$: 414.1427; found: 414.1428.

3l: Mp 42–44 °C. IR (KBr): 2228, 1750, 1732, 1700 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.64 (d, J = 4.6 Hz, 1 H), 7.91 (d, J = 7.8 Hz, 1 H), 7.78 (td, J = 7.6, 1.6 Hz, 1 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.47 (d, J = 8.3 Hz, 2 H), 7.46 (m, 1 H), 4.29–4.16 (m, 3 H), 3.96 (q, J = 7.1 Hz, 2 H), 3.96 (dd, J = 18.2, 9.9 Hz, 1 H), 3.82 (d, J = 10.3 Hz, 1 H), 3.62 (dd, J = 18.2, 4.0 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 198.57, 167.82, 167.47, 153.00, 149.04, 146.84, 137.06, 132.18 (2 × C), 129.59 (2 × C), 127.50, 121.91, 118.81, 111.07, 61.98, 61.64, 57.24, 41.56, 40.53, 14.13, 13.92. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{22}H_{22}N_2O_5$: 394.1529; found: 394.1528.

3m: Mp 50–52 °C. IR (KBr): 1750, 1730, 1697 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.64 (d, J = 4.4 Hz, 1 H), 7.91 (d, J = 7.7 Hz, 1 H), 7.77 (t, J = 7.6 Hz, 1 H), 7.44 (dd, J = 7.0, 5.2 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 2 H), 7.20 (d, J = 8.3 Hz, 2 H), 4.23–4.15 (m, 3 H), 3.95 (q, J = 7.1 Hz, 2 H), 3.90 (dd, J = 17.9, 9.8 Hz, 1 H), 3.78 (d, J = 10.3 Hz, 1 H), 3.57 (dd, J = 17.9, 4.0 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 198.84, 168.14, 167.73, 153.16, 148.99, 139.59, 137.01, 132.84, 130.02 (2 × C), 128.55 (2 × C), 127.37, 121.93, 61.84, 61.52, 57.73, 41.87, 39.92, 14.16, 13.93. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{21}H_{22}NO_5{}^{35}Cl$: 403.1187; found: 403.1184. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{21}H_{22}NO_5{}^{37}Cl$: 405.1157; found: 405.1147.

3n: Mp 72–73 °C. IR (KBr): 1755, 1731, 1695 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.65 (d, J = 4.4 Hz, 1 H), 7.93 (d, J = 7.4 Hz, 1 H), 7.79 (td, J = 7.6, 1.6 Hz, 1 H), 7.45 (m, 1 H), 7.43 (d, J = 2.0 Hz, 1 H), 7.30 (t, J = 8.3 Hz, 1 H), 7.20 (dd, J = 8.3, 2.0 Hz, 1 H), 4.25–4.13 (m, 3 H), 4.00 (q, J = 7.1 Hz, 1 H), 3.90 (dd, J = 18.2, 9.7 Hz, 1 H), 3.77 (d, J = 10.2 Hz, 1 H), 3.58 (dd, J = 18.2, 4.1 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.06 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 198.61, 167.92, 167.54, 152.98, 149.02, 141.43, 137.06, 132.31, 131.09, 130.66, 130.31, 128.19, 127.49, 121.94, 61.94, 61.66, 57.42, 41.62, 39.63, 14.14, 13.94. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{21}H_{21}NO_5{}^{35}Cl_2$: 437.0797; found: 437.0791. HRMS (EI–TOF): *m/z* [M$^+$] calcd $C_{21}H_{21}NO_5{}^{35}Cl{}^{37}Cl$: 439.0767; found: 439.0744.

3o: Mp 104–105 °C. IR (KBr): 1743, 1726, 1697 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.65 (d, J = 4.3 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.77 (td, J = 7.6, 1.4 Hz, 1 H), 7.42 (m, 1 H), 6.81 (d, J = 1.3 Hz, 1 H), 6.77 (dd, J = 7.9, 1.6 Hz, 1 H), 6.66 (d, J = 7.9 Hz, 1 H), 5.87 (s, 2 H), 4.23–4.10 (m, 3 H), 3.98 (q, J = 7.2 Hz, 2 H), 3.87 (dd, J = 17.7, 9.7 Hz, 1 H), 3.74 (d, J = 10.4 Hz, 1 H), 3.53 (dd, J = 17.7, 4.2 Hz, 1 H), 1.24 (t, J = 7.2 Hz, 1 H), 1.06 (t, J = 7.2 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 199.02, 168.31, 167.87, 153.27, 148.97, 147.53, 146.48, 136.96, 134.75, 127.27, 121.94, 121.82, 108.96, 108.17, 100.98, 61.74, 61.42, 58.16, 42.09, 40.25, 14.17, 14.00. HRMS (EI–TOF): *m/z* [M$^+$] calcd for $C_{22}H_{23}NO_7$: 413.1475; found: 413.1477.

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