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PAPER

Thiazolium-catalyzed intermolecular Stetter reaction of linear and cyclic alkyl α-diketones†

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An efficient method for the *N*-heterocyclic carbene (NHC)-catalyzed conjugate addition of acetyl anions to various α,β-unsaturated acceptors (Stetter reaction) has been optimized by using 2,3-butandione (biacetyl) as an alternative surrogate of acetaldehyde. The disclosed procedure proved to be compatible with microwave dielectric heating for reaction time reduction and with the use of different linear α-diketones as acyl anion donors (*e.g.* 3,4-hexanedione for propionyl anion additions). Moreover, the unprecedented *umpolung* reactivity of cyclic α-diketones in the atom economic nucleophilic acylation of chalcones is herein presented. Mechanistic aspects of the thiazolium-based catalysis involving linear and cyclic α-diketone substrates are also discussed.

Introduction

The formation of new carbon–carbon bonds by organocatalyzed reactions of carbonyl compounds is today a cornerstone of modern catalysis.[1] Surprisingly, however, the number of reports dealing with the use of α-diketones in organocatalytic approaches is quite scant in the literature,[2] despite the great potential of this class of substrates.[3] α-Diketones are, in fact, highly reactive compounds bearing a double carbonyl functionality, which allows them to behave either as an electrophile,[2a,b] a nucleophile,[2c] or both an electrophile and a nucleophile in domino reactions.[2d–f] The versatility of α-diketones in organocatalytic strategies is further demonstrated by their ability to undergo polarity reversal, or *umpolung*,[4] of the carbonyl functionality under *N*-heterocyclic carbene (NHC) catalysis,[5] and thus act as acyl anion precursors. This peculiar behavior of α-diketones was observed in the early fifties by Mizuhara and Handler, who established that the thiamine-promoted reaction of 2,3-butanedione (biacetyl) **1** and acetaldehyde involved scission of biacetyl into two moieties to form acetoin and acetate.[6] This finding, however, was almost ignored for the next six decades. Recently, we took advantage of Mizuhara and Handler's observation and reported the enzymatic[7a] and thiazolium-catalyzed[7b] synthesis of a number of chiral and achiral α-hydroxyketones by benzoin-type reactions of linear dialkyl α-diketones. In continuation of our ongoing research in this field, we present herein our results on the use of alkyl α-diketones as acyl anion equivalents in a mechanistically related nucleophilic acylation, that is, the Stetter reaction, which employs conjugate acceptors and produces valuable 1,4-dicarbonyl compounds.[8] Particular attention has been paid in this work to the conjugate addition of the acetyl anion ($MeCO^-$) due to the relevance of this simple nucleophile in organocatalytic strategies[5] and the continuous need for improving its generation.[9] In the case of the Stetter reaction, existing methods for the non-enzymatic,[10] NHC-catalyzed generation of acetyl anions comprise the use of acetaldehyde,[11] sodium pyruvate[12] or acetyldimethylphenylsilane[13] as its surrogates (Scheme 1).[14] Though operative in both racemic and asymmetric versions, the first method requires the utilization of a large excess (10 equiv.) of the volatile acetaldehyde. The second biomimetic strategy is effective under neutral aqueous conditions and it has been optimized for the particular class of unsaturated 2-acyl imidazoles as acceptors. The sila-Stetter reaction by Scheidt and co-workers is, perhaps, the most effective and versatile method for the conjugate addition of carbonyl anions, but in the case of the acetyl anion it requires the synthesis of its precursor acetyldimethylphenylsilane.[15] Herein, we present the commercially available, inexpensive (*ca.* € 4/1 g) biacetyl **1** as a bench stable (bp 88 °C), alternative acetyl anion equivalent for intermolecular Stetter reactions. The unprecedented *umpolung* reactivity of cyclic alkyl α-diketones in conjugate additions is also described to further demonstrate the potential of the proposed diketone-based carboligation methodology.

Results and discussion

The optimization study of the model reaction of biacetyl **1** with *trans*-chalcone started by applying the conditions previously disclosed for the benzoin-type reactions of **1**.[7b] Accordingly, a 1 : 2 mixture of **1** and **2a** was suspended in the eco-friendly polyethylene glycol (PEG_{400}) and treated at room temperature with a stoichiometric thiamine hydrochloride **3**–Et_3N couple (Table 1, entry 1). Disappointingly, the target adduct **7a** was isolated

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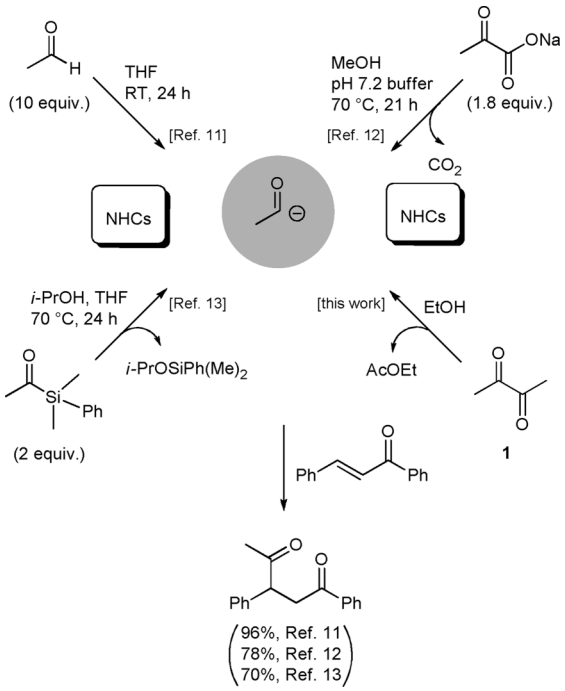
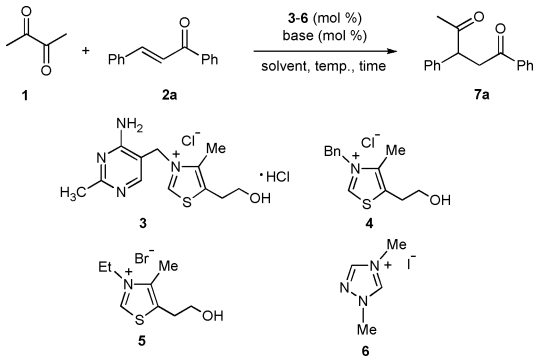


Scheme 1 Direct methods for acetyl anion generation in Stetter reactions (addition to *trans*-chalcone as the benchmark).

in poor yield (10%), very likely because of the heterogeneous reaction conditions. Indeed, the application of the above procedure to a homogeneous ethanolic reaction solution resulted in a higher yield of **7a** (55%, entry 2). Notably, formation of acetyl acetoin (**1** self-condensation product) and compounds arising from conjugate addition of either the nucleophilic thiazolium species or EtOH were not observed (GC-MS and ^{1}H NMR analyses) under these conditions. We next focused on developing a catalytic procedure; thiazolium **4** and **5**, and triazolium **6** pre-catalysts (20 mol%) were screened in combination with suitable bases (Et_3N, DBU, and Cs_2CO_3) in alcoholic (EtOH, *i*-PrOH, and *t*-BuOH) and aprotic (THF) solvents (entries 3–9; only diagnostic experiments are reported).[16] A higher product yield (58%) was achieved with a thiazolium **4**–Et_3N couple in EtOH (entry 3). The thiazolium derivative **5** was less effective than **4** (entry 4), while the triazolium **6** pre-catalyst failed to produce the desired product **7a** (entry 5), thus showing the strict dependence of process efficiency on the stereoelectronic features of the heteroazolium-derived carbene.[17] With regard to the effect of solvent, the results shown in Table 1 (entries 6–9) demonstrate that utilization of an amphiprotic solvent is crucial for a successful procedure, in full agreement with the proposed reaction mechanism (*vide infra*). For further optimization, the **1**/**2a** ratio and temperature were varied (entries 10–11) and the best yield (91%) was achieved with an excess of diketone **1** (2 equiv.) at 50 °C for 24 h (entry 11). Aiming at decreasing the reaction time, we finally considered the use of microwave (MW) dielectric heating[18] and found the optimal compromise between product yield (75%) and selectivity (formation of side-products was detected at temperatures higher than 70 °C) by irradiating the reaction mixture at 100 °C for 2 h (entry 12).

Under the optimized thermal and MW conditions (methods A and B, Table 2), the substrate scope of the proposed system

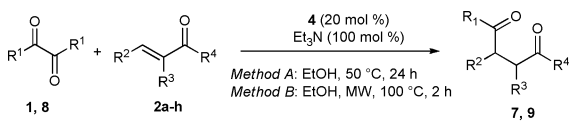
Table 1 Optimization of the Stetter reaction of biacetyl **1** with *trans*-chalcone[a]



Entry	Cat. (mol%)	Base (mol%)	Solv.	Temp. (°C)	Time (h)	Yield (%)[b]
1	**3** (100)	Et_3N (200)	PEG_{400}	25	5	10
2	**3** (100)	Et_3N (200)	EtOH	25	24	55
3	**4** (20)	Et_3N (100)	EtOH	25	24	58
4	**5** (20)	Et_3N (100)	EtOH	25	24	38
5	**6** (20)	DBU (20)	EtOH	25	24	< 5
6	**4** (20)	Et_3N (20)	THF	25	24	< 5
7	**5** (20)	Cs_2CO_3 (20)	THF	25	24	< 5
8	**4** (20)	Et_3N (100)	*i*-PrOH	25	24	20
9	**4** (20)	Et_3N (100)	*t*-BuOH	30	24	< 5
10[c]	**4** (20)	Et_3N (100)	EtOH	25	24	69
11[c]	**4** (20)	Et_3N (100)	EtOH	50	24	91
12[c,d]	**4** (20)	Et_3N (100)	EtOH	100	2	75

[a] Reactions performed with 1.00 mmol of **2a** (0.5 M) and 0.50 mmol of **1**. [b] Isolated yield. [c] Reactions performed with 0.50 mmol of **2a** and 1.00 mmol of **1** (0.5 M). [d] Microwave-assisted reaction performed with a single-mode cavity dedicated reactor (Biotage Initiator).

Table 2 Catalytic Stetter reactions of linear dialkyl α-diketones **1** and **8** with different α,β-unsaturated acceptors[a]



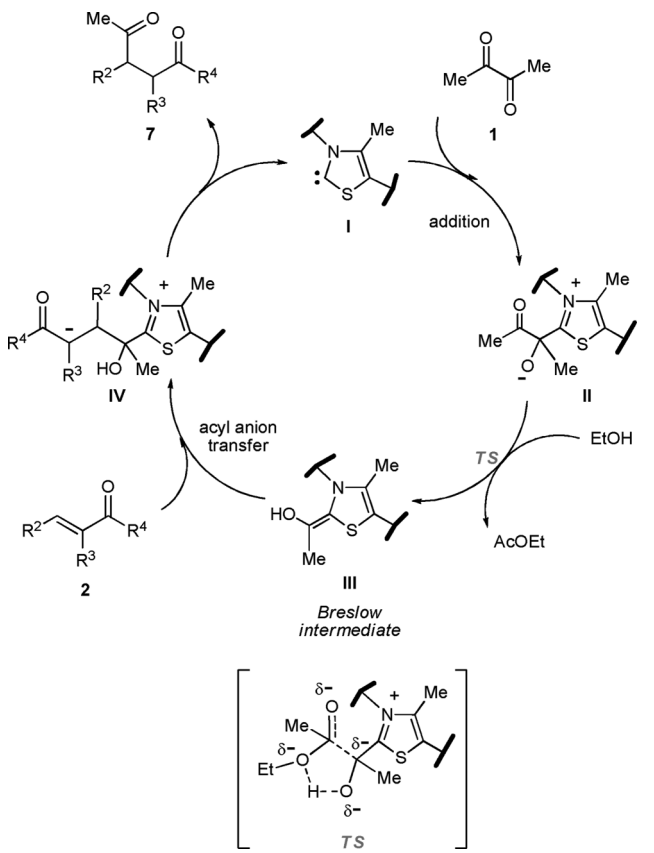
Entry	R^1	R^2	R^3	R^4	Prod.	Yield (%)[b]
1	Me	Ph	H	Ph	**7a**	91/75
2	Me	4-BrPh	H	Ph	**7b**	88/72
3	Me	4-MePh	H	Ph	**7c**	71/62
4	Me	Me	H	Ph	**7d**	82/65
5[c]	Me	H	H	Me	**7e**	80/—
6[c]	Me	Me	EtO_2C	OEt	**7f**	68/—
7[d,e]	Me	$-(CH_2)_3-$	H	[d]	**7g**	58/42
8	Et	Ph	H	Ph	**9a**	65/51
9	Et	4-BrPh	H	Ph	**9b**	62/50
10	Et	4-ClPh	H	Ph	**9h**	55/47

[a] Reactions performed with 1.00 mmol of α-diketone (0.5 M) and 0.50 mmol of **2**. [b] Isolated yields (method A/method B). [c] Reaction performed at 25 °C. [d] Structure of **2g**:  [e] Reaction performed with 4 equiv. of **1**.

was examined by reacting **1** with various α,β-unsaturated carbonyl electrophiles **2**. Chalcone derivatives having both electron-withdrawing and electron-donating substituents on the aromatic ring gave the corresponding adducts in comparable yields

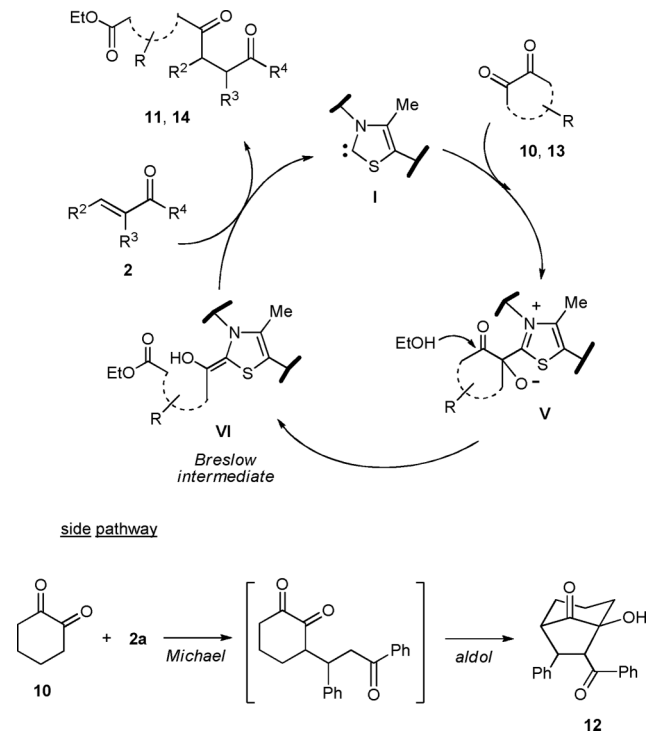
(88–71%) to those previously reported (entries 2–3).[11–13] Notably, the unprecedented addition to the less reactive alkyl chalcone **2d** resulted almost equally effective (82%, entry 4). Highly activated substrates such as methyl vinyl ketone **2e** and diethyl ethylidenemalonate **2f** could also be used in this transformation by reducing the reaction temperature (25 °C) to minimize the competitive EtOH addition (entries 5–6). Cyclohexenone **2g** was a competent coupling partner as well, but a higher excess of biacetyl **1** (4 equiv.) was required to reach a satisfactory reaction conversion (entry 7). To further validate the versatility of the proposed methodology, the bis-homologue of **1**, that is 3,4-hexanedione **8**, was tested as a propionyl anion equivalent in the nucleophilic acylation of chalcones **2a,b** and **2h**. Gratifyingly, the corresponding addition products **9a,b** and **9h** were recovered in similar yields (65–55%) to those obtained by using propionaldehyde as the acyl anion source.[19a]

Mechanistically we propose that the nucleophilic acylation of α,β-unsaturated acceptors **2** proceeds through the formation of the intermediate **II** resulting from the addition of the thiazolin-2-ylidene **I** to the α-diketone **1**, and its evolution to the Breslow intermediate **III** by attack of EtOH to the carbonyl of **II** with elimination of ethyl acetate (Scheme 2). Subsequent addition of the Breslow intermediate to the β-position of the conjugate acceptor **2** leads to the formation of product **7** and regeneration of the catalyst **I**. For the key step of the catalytic cycle (C–C bond breaking) we postulate an alkoxide-assisted nucleophilic attack of the amphiprotic solvent involving a proton transfer from EtOH to the alkoxide **II** as shown in the transition state ***TS***. In support of our hypothesis we found that the utilization of the bulkier and less acidic *t*-BuOH solvent in the model **1**/**2a** coupling resulted in no formation of the expected **7a** adduct (Table 1, entry 9).



Scheme 2 Proposed reaction pathway for the thiazolium-catalyzed Stetter reaction of linear α-diketones **1** and **8** (substrate **1** as representative example).

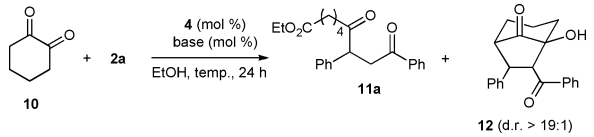
From the analysis of the proposed reaction mechanism involving linear α-diketones (Scheme 2), the interest of utilizing their cyclic counterparts in the Stetter reaction becomes apparent since both carbonyl functionalities of the α-diketone donor can be maintained. As depicted in Scheme 3, the nucleophilic attack of EtOH on thiazolium intermediate **V** would in fact result in the formation of the Breslow intermediate **VI** bearing an ester group ready for subsequent product elaboration.[20] Hence, the atom economic nucleophilic acylation of *trans*-chalcone with 1,2-cyclohexanedione **10** was next investigated (Table 3).



Scheme 3 Proposed reaction pathway for the thiazolium-catalyzed Stetter reaction of cyclic α-diketones and side tandem Michael–aldol reaction affording bicycle **12** by-product.

An initial experiment was performed with a 1 : 2 mixture of **10** and **2a** in EtOH at room temperature using the optimal catalytic **4**–Et_3N couple (entry 1). Under these conditions, the expected adduct **11a** was isolated in poor yield (10%) along with a major product (38%), which was identified as the diastereomeric bicyclo[3.2.1]octan-8-one derivative **12** (d.r. > 19 : 1).[21] We supposed that this compound was formed under the basic reaction conditions through a tandem sequence involving the initial Michael addition of **10** to chalcone **2a** followed by an intramolecular aldol reaction (Scheme 3).[22] Indeed, the above nucleophilic acylation conducted in the absence of pre-catalyst **4** afforded the bicycle **12** (88%) as the sole reaction product (entry 2).[21] After some experimentation (entries 3–6), we could almost suppress this side-reaction and obtain the target adduct **11a** in

Table 3 Optimization of the Stetter reaction of 1,2-cyclohexanedione **10** with *trans*-chalcone[a]



Entry	**10**/**2a**	**4** (mol%)	Base (mol%)	Temp. (°C)	**11a** + **12** (%)[b]
1	1 : 2	20	Et_3N (100)	25	10/38
2	1 : 2	0	Et_3N (100)	25	—/88
3	1 : 2	30	DBU (30)	25	12/39
4	1 : 2	20	Et_3N (50)	25	10/32
5	1 : 2	20	Et_3N (50)	50	67/5
6	2 : 1	20	Et_3N (50)	50	20/32
7[c]	1 : 2	100	Et_3N (50)	100	51/5

[a] Reactions performed with 1.00 mmol of **2a** (0.5 M). [b] Isolated yield. [c] Microwave-assisted reaction performed with Biotage Initiator (reaction time: 2 h).

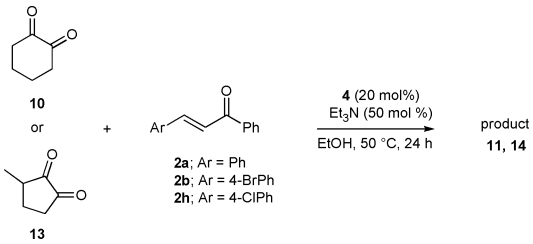
satisfactory 67% yield by warming (50 °C) for 24 h a 1 : 2 mixture of **10** and **2a** in the presence of catalytic **4** (20 mol%) and a diminished amount (50 mol%) of Et_3N (entry 5). As previously observed, the use of MW irradiation in the **10**/**2a** coupling shortened the reaction time (2 h) but slightly lowered the product yield (51%, entry 7).

Next, the scope and limitations of the Stetter reaction with cyclic alkyl α-diketones was briefly investigated (Table 4). Satisfactory yields were obtained under the optimized conditions for the reaction of 1,2-cyclohexanedione **10** with chalcones **2b** and **2h** (entries 2–3). 3-Methylcycopentane-1,2-dione **13** was also tested as acyl donor in the addition to chalcone **2a** (entry 4). Diketone **13** appeared to be less reactive than **10** as a satisfactory yield (48%) of the diastereomeric adduct **14a** (d.r. 1 : 1) could only be achieved by means of MW irradiation (100 °C, 2 h). It is worth noting, however, that the **13**/**2a** coupling proceeded regioselectively by a putative preferential attack of thiazolium **4**-derived carbene to the less hindered carbonyl of unsymmetrical diketone **13** (Scheme 3).

Conclusions

In summary, we have demonstrated that biacetyl **1** may be employed as an effective, bench-stable, inexpensive acetyl anion equivalent in thiazolium **4**-catalyzed Stetter reactions with different α,β-unsaturated acceptors. Detected yields of the corresponding adducts were comparable to those obtained for the same transformations by known NHC-based methods. In some cases, the application to our procedure of microwave dielectric heating significantly increased the chemical efficiency of the addition process in virtue of a substantial reduction of reaction time. The method optimized for biacetyl **1** proved to be successful for 3,4-hexanedione **8** as well, thus offering a novel strategy for propionyl anion conjugate additions. The unprecedented atom economic nucleophilic acylation of chalcones with cyclic α-diketones was finally optimized to furnish 1,4-diketone derivatives displaying a suitably spaced ester functionality in their structure. Investigations to disclose an asymmetric variant of the described carboligation reaction are currently underway in our laboratories.

Table 4 Intermolecular Stetter reactions of cyclic α-diketones **10** and **13** with chalcones[a]



Entry	Diketone	Chalcone	Product (%)[b]
1	**10**	**2a**	**11a** (67%)
2	**10**	**2b**	**11b** (61%)
3	**10**	**2h**	**11h** (69%)
4[c]	**13**	**2a**	**14a** (48%) (d.r. 1:1)

[a] Reactions performed with 1.00 mmol of **2** (0.5 M) and 0.50 mmol of diketone. [b] Isolated yield. [c] Microwave-assisted reaction performed with Biotage Initiator (100 °C, 2 h).

Experimental

Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Bulb-to-bulb distillation was performed with a Büchi Glass Oven B-580 apparatus. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ solutions at room temperature. Peaks assignments were aided by ^1H-^1H COSY and gradient-HMQC experiments. GC-MS spectra were recorded using a Varian 4000 GC-MS/MS system equipped with a fused capillary column Megadex 5 (25 m × 0.25 mm) containing dimethyl-*n*-pentyl-β-cyclodextrin on OV 1701. Analyses were carried out with a gradient of 1.5 °C min^{-1} (from 80 °C up to 200 °C). ESI-MS analyses were performed in positive ion mode with samples dissolved in 10 mM solution of ammonium formate in 1 : 1 MeCN/H_2O. Elemental analyses were performed with FLASH 2000 Series CHNS/O analyzer (ThermoFisher Scientific). Microwave-assisted reactions were carried out using a single-mode cavity dedicated reactor (Biotage Initiator™). Reactions were performed with temperature-controlled programs in glass vials (0.5–2 mL or 2–5 mL depending on the scale) sealed with a Teflon septum. Temperatures were measured externally by an IR sensor. The reaction time was counted when the reaction mixture

reached the stated temperature. Pressure was measured by a non-invasive sensor integrated into the cavity lid. α-Diketones **1**, **8**, **10**, and **13**, heteroazolium salts **3–6**, and unsaturated acceptors **2a** and **2d–g** are commercially available (Sigma-Aldrich). *trans*-Chalcones **2b–c** and **2h** were prepared according to a known procedure.[23] Spectroscopic data of compounds **7a**,[11–13] **7b**,[11] **7c**,[11] **7e**,[11,24] **7f**,[25] **7g**,[26] and **9a**[19] were identical to those reported in the literature.

Optimized procedures for the Stetter reaction of linear α-diketones 1 and 8 with conjugate acceptors 2a–h

Method A. To a vigorously stirred mixture of α-diketone **1** or **8** (1.00 mmol), α,β-unsaturated acceptor **2** (0.50 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **4** (54 mg, 0.20 mmol), in absolute EtOH (2 mL), was added Et_3N (139 μL, 1.00 mmol) in one portion. The mixture was warmed at 50 °C, stirred at that temperature for 24 h, and then cooled to room temperature and concentrated. The residue containing the target adduct **7** or **9** was purified by either flash chromatography or bulb-to-bulb distillation. When chalcones **2b** and **2h** were used as acceptors, the addition to the reaction mixture of a few drops of THF was required to obtain a fully homogeneous solution.

Method B. A 2.0–5.0 mL process vial was filled with α-diketone **1** or **8** (1.00 mmol), α,β-unsaturated acceptor **2** (0.50 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **4** (54 mg, 0.20 mmol), and absolute EtOH (2 mL). Then, Et_3N (139 μL, 1.00 mmol) was added in one portion. The vial was sealed with the Teflon septum and aluminium crimp by using an appropriate crimping tool. The vial was then placed in its correct position in the Biotage Initiator cavity where irradiation for 2 h at 100 °C was performed. After the full irradiation sequence was completed, the vial was cooled to room temperature and then opened. The mixture was concentrated and the residue containing the target adduct **7** or **9** was purified by either flash chromatography or bulb-to-bulb distillation. Product yields for Method B are reported in Table 2.

1,3-Diphenylpentane-1,4-dione (7a)

Column chromatography with 12 : 1 cyclohexane–AcOEt afforded **7a**[11] (229 mg, 91%; method A) as a pale yellow oil. ^{1}H NMR: δ = 7.99–7.92 (m, 2 H, Ar), 7.58–7.50 (m, 1 H, Ar), 7.49–7.45 (m, 2 H, Ar), 7.42–7.23 (m, 5 H, Ar), 4.42 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,3}$ = 10.0, Hz, H-3), 4.00 (dd, 1 H, $J_{2a,3}$ = 10.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2a), 3.16 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2b), 2.22 (s, 3 H, CH_3). ^{13}C NMR: δ = 207.6, 198.5, 138.3, 136.8, 133.6, 129.5, 128.9, 128.7, 128.4, 128.0, 54.2, 42.6, 29.5. ESI MS (252.1): 275.5 (M + Na^+). Found: C, 80.75; H, 6.22. $C_{17}H_{16}O_2$ requires C, 80.93; H, 6.39%.

3-(4-Bromophenyl)-1-phenylpentane-1,4-dione (7b)

Column chromatography with 12 : 1 cyclohexane–AcOEt afforded **7b**[11] (291 mg, 88%; method A) as a yellow amorphous solid. ^{1}H NMR: δ = 7.95–7.90 (m, 2 H, Ar), 7.60–7.51 (m, 1 H, Ar), 7.50–7.40 (m, 4 H, Ar), 7.20–7.15 (m, 2 H, Ar), 4.38 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,3}$ = 10.0, Hz, H-3), 3.95 (dd, 1 H, $J_{2a,3}$ = 10.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2a), 3.12 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2b), 2.20 (s, 3 H, CH_3). ^{13}C NMR: δ = 207.1, 198.1, 137.2, 136.5, 133.7, 132.6, 130.3, 128.9, 128.4, 122.0, 53.5, 42.5, 29.6. ESI MS (330.0): 353.9 (M + Na^+). Found: C, 61.78; H, 4.44. $C_{17}H_{15}BrO_2$ requires C, 61.65; H, 4.56%.

1-Phenyl-3-*p*-tolylpentane-1,4-dione (7c)

Column chromatography with 12 : 1 cyclohexane–AcOEt afforded **7c**[11] (189 mg, 71%; method A) as a white amorphous solid. ^{1}H NMR: δ = 8.00–7.90 (m, 2 H, Ar), 7.60–7.50 (m, 1 H, Ar), 7.45–7.40 (m, 2 H, Ar), 7.18 (s, 4 H, Ar), 4.36 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,3}$ = 10.0, Hz, H-3), 3.98 (dd, 1 H, $J_{2a,3}$ = 10.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2a), 3.12 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2b), 2.33 (s, 3 H, CH_3), 2.21 (s, 3 H, CH_3). ^{13}C NMR: δ = 207.8, 198.6, 137.7, 136.8, 135.2, 133.5, 130.1, 128.9, 128.5, 128.4, 53.8, 42.6, 29.5, 21.4. ESI MS (266.1): 305.4 (M + K^+). Found: C, 81.29; H, 6.63. $C_{17}H_{18}O_2$ requires C, 81.17; H, 6.81%.

3-Methyl-1-phenylpentane-1,4-dione (7d)

Column chromatography with 12 : 1 cyclohexane–AcOEt afforded **7d** (156 mg, 82%; method A) as a white foam. IR (film) ν_{max}: 2969, 1712, 1680, 1449, 1355, 1209, 1003, 689 cm^{-1}; ^{1}H NMR: δ = 8.00–7.95 (m, 2 H, Ar), 7.60–7.52 (m,1 H, Ar), 7.50–7.40 (m, 2 H, Ar), 3.54 (dd, 1 H, $J_{2a,3}$ = 8.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2a), 3.32–3.18 (m, 1 H, H-3), 2.94 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2b), 2.24 (s, 3 H, CH_3), 1.20 (d, 3 H, $J_{3,Me}$ = 5.5 Hz, CH_3). ^{13}C NMR: δ = 211.4, 198.5, 136.7, 133.1, 128.5, 128.0, 41.7, 41.6, 28.6, 16.7. ESI MS (190.0): 213.5 (M + Na^+). Found: C, 75.98; H, 6.43. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%.

Hexane-2,5-dione (7e)

The crude reaction mixture was bulb-to-bulb distilled (90 °C, 25 mmHg) to give **7e**[11,24] (91 mg, 80%) as a colorless liquid. Lit:[23] bp 88–89 °C (25 mmHg). IR (film) ν_{max}: 2915, 1715, 768 cm^{-1}; ^{1}H NMR: δ = 2.68 (s, 4 H, 2 H-2,2 H-3), 2.20 (s, 6 H, 2 CH_3). ^{13}C NMR: δ = 207.4, 37.0, 30.0.

Diethyl 2-(3-oxobutan-2-yl)malonate (7f)

The crude reaction mixture was bulb-to-bulb distilled (112 °C, 5 mmHg) to give **7f**[25] (156 mg, 68%) as a colorless liquid. Lit:[25] bp 110–120 °C (3 mmHg). IR (film) ν_{max}: 2930, 1745, 1720 cm^{-1}; ^{1}H NMR: δ = 4.20 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 4.15 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 3.74 (d, 1 H, $J_{2,2'}$ = 10.0 Hz, H-2), 3.28 (dq, 1 H, $J_{1'2'}$ = 7.0 Hz, $J_{2,2'}$ = 10.0 Hz, H-2′), 2.28 (s, 3 H, CH_3), 1.28 (t, 3 H, OCH_2CH_3), 1.25 (t, 3 H, OCH_2CH_3), 1.14 (d, 1 H, $J_{1'2'}$ = 7.0 Hz, CH_3). ^{13}C NMR: δ = 209.6, 168.5, 61.2, 54.4, 45.2, 28.4, 14.0, 13.9, 13.8.

3-Acetylcyclohexanone (7g)

The crude reaction mixture was bulb-to-bulb distilled (118 °C, 0.1 mmHg) to give **7g**[26] (81 mg, 58%) as a colorless liquid. Lit:[26] bp 130 °C (0.2 mmHg). IR (film) ν_{max}: 2850, 1710 cm^{-1}; ^{1}H NMR: δ = 2.94–2.80 (m, 1 H, H-3), 2.54–2.24 (m, 4 H, 2 H-2, 2 H-6), 2.19 (s, 3 H, CH_3), 2.14–2.04 and 1.80–1.60 (2 m, 4 H, 2 H-4, 2 H-5). ^{13}C NMR: δ = 209.8, 208.1, 50.5, 42.0, 40.5, 28.2, 27.1, 24.5.

1,3-Diphenylhexane-1,4-dione (9a)

Column chromatography with 15 : 1 cyclohexane–AcOEt afforded **9a**[19] (173 mg, 65%; method A) as a colorless oil. ^{1}H NMR: δ = 7.98–7.90 (m, 2 H, Ar), 7.58–7.50 (m, 1 H, Ar), 7.46–7.38 (m, 2 H, Ar), 7.35–7.30 (m, 2 H, Ar), 7.28–7.20 (m, 2 H, Ar), 4.43 (dd, 1 H, $J_{2b,3}$ = 3.5 Hz, $J_{2a,3}$ = 10.0 Hz, H-3), 4.05 (dd, 1 H, $J_{2a,3}$ = 10.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2a), 3.12 (dd, 1 H, $J_{2b,3}$ = 3.5 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2b), 2.78–2.60 and 2.58–2.42 (2 m, 2 H, 2 H-5); 1.02 (t, 1 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 210.2, 198.5, 138.6, 136.9, 133.0, 129.1, 129.0, 128.8, 128.5, 127.1, 53.2, 42.2, 35.0, 7.8. ESI MS (266.1): 289.4 (M + Na^+). Found: C, 81.02; H, 6.01. $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81%.

3-(4-Bromophenyl)-1-phenylhexane-1,4-dione (9b)

Column chromatography with 15 : 1 cyclohexane–AcOEt afforded **9b** (213 mg, 62%; method A) as a white foam. IR (film) ν_{max}: 2920, 1708, 1676, 1487, 1200, 1010, 747, 675 cm^{-1}; ^{1}H NMR: δ = 7.98–7.90 (m, 2 H, Ar), 7.60–7.40 (m, 5 H, Ar), 7.20–7.10 (m, 2 H, Ar), 4.40 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,3}$ = 10.0 Hz, H-3), 4.00 (dd, 1 H, $J_{2a,3}$ = 10.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2a), 3.13 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2b), 2.73–2.58 and 2.56–2.42 (2 m, 2 H, 2 H-5); 1.02 (t, 1 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 209.5, 197.9, 137.2, 136.3, 133.3, 132.2, 129.9, 128.5, 128.1, 122.6, 52.3, 42.4, 35.1, 7.8. ESI MS (344.0): 283.9 (M + K^+). Found: C, 62.85; H, 5.15. $C_{18}H_{17}BrO_2$ requires C, 62.62; H, 4.96%.

3-(4-Chlorophenyl)-1-phenylhexane-1,4-dione (9h)

Column chromatography with 15 : 1 cyclohexane–AcOEt afforded **9c** (165 mg, 55%; method A) as a white foam. IR (film) ν_{max}: 2978, 1708, 1676, 1490, 1201, 1015, 748, 661 cm^{-1}; ^{1}H NMR: δ = 7.98–7.90 (m, 2 H, Ar), 7.60–7.20 (m, 7 H, Ar), 4.41 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,3}$ = 10.0 Hz, H-3), 4.00 (dd, 1 H, $J_{2a,3}$ = 10.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2a), 3.14 (dd, 1 H, $J_{2b,3}$ = 4.0 Hz, $J_{2a,2b}$ = 18.0 Hz, H-2b), 2.74–2.58 and 2.57–2.42 (2 m, 2 H, 2 H-5); 1.00 (t, 1 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 209.6, 197.9, 136.7, 133.5, 133.3, 132.9, 130.8, 129.6, 129.2, 128.9, 128.6, 128.1, 52.3, 42.4, 35.1, 7.8. ESI MS (300.0): 223.6 (M + Na^+). Found: C, 71.59; H, 5.98. $C_{18}H_{17}ClO_2$ requires C, 71.88; H, 5.70%.

Optimized procedure for the Stetter reaction of cyclic α-diketone 10 with chalcones 2a,b and 2h

To a vigorously stirred mixture of α-diketone **10** (56 mg, 0.50 mmol), chalcone **2** (1.00 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **4** (27 mg, 0.10 mmol), in absolute EtOH (2 mL), was added Et_3N (35 µL, 0.25 mmol) in one portion. The mixture was warmed to 50 °C, stirred at that temperature for 24h, and then cooled to room temperature and concentrated. The residue containing the target adduct **11** was purified by flash chromatography. When chalcones **2b** and **2h** were used as acceptors, the addition to the reaction mixture of a few drops of THF was required to obtain a fully homogeneous solution.

Ethyl 6,9-dioxo-7,9-diphenylnonanoate (11a)

Column chromatography with 15 : 1 cyclohexane–AcOEt (containing 5% of dichloromethane) afforded **11a** (123 mg, 67%) as a white foam. IR (film) ν_{max}: 2931, 1748, 1672, 1447, 1227, 746, 661 cm^{-1}; ^{1}H NMR: δ = 7.96–7.90 (m, 2 H, Ar), 7.60–7.50 (m, 1 H, Ar), 7.47–7.40 (m, 2 H, Ar), 7.38–7.20 (m, 5 H, Ar), 4.40 (dd, 1 H, $J_{7,8b}$ = 3.5 Hz, $J_{7,8a}$ = 10.0 Hz, H-7), 4.08 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 4.03 (dd, 1 H, $J_{7,8a}$ = 10.0 Hz, $J_{8a,8b}$ = 18.0 Hz, H-8a), 3.13 (dd, 1 H, $J_{7,8b}$ = 3.5 Hz, $J_{8a,8b}$ = 18.0 Hz, H-8b), 2.70–2.60 and 2.54–2.44 (2 m, 2 H, 2 H-5), 2.25–2.17 (m, 2 H, 2 H-2), 1.65–1.45 (m, 4 H, 2 H-3, 2 H-4), 1.22 (t, 3 H, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR: δ = 208.8, 198.2, 173.4, 138.1, 135.6, 133.2, 129.1, 128.6, 128.3, 128.1, 127.6, 60.2, 53.3, 42.4, 41.3, 34.0, 24.3, 23.1, 14.2. ESI MS (366.1): 384.7 (M + NH_4^+). Found: C, 75.53; H, 7.39. $C_{23}H_{26}O_4$ requires C, 75.38; H, 7.15%.

Ethyl 7-(4-bromophenyl)-6,9-dioxo-9-phenylnonanoate (11b)

Column chromatography with 15 : 1 cyclohexane–AcOEt (containing 5% of dichloromethane) afforded **11b** (135 mg, 61%) as a white foam. IR (film) ν_{max}: 2932, 1729, 1710, 1682, 1486, 1178, 1010, 753, 685 cm^{-1}; ^{1}H NMR: δ = 7.96–7.90 (m, 2 H, Ar), 7.60–7.40 (m, 5 H, Ar), 7.20–7.10 (m, 2 H, Ar), 4.36 (dd, 1 H, $J_{7,8b}$ = 3.5 Hz, $J_{7,8a}$ = 10.0 Hz, H-7), 4.10 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 4.01 (dd, 1 H, $J_{7,8a}$ = 10.0 Hz, $J_{8a,8b}$ = 18.0 Hz, H-8a), 3.12 (dd, 1 H, $J_{7,8b}$ = 3.5 Hz, $J_{8a,8b}$ = 18.0 Hz, H-8b), 2.70–2.60 and 2.52–2.40 (2 m, 2 H, 2 H-5), 2.34–2.19 (m, 2 H, 2 H-2), 1.70–1.48 (m, 4 H, 2 H-3, 2 H-4), 1.24 (t, 3 H, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR: δ = 208.4, 197.8, 173.4, 137.0, 136.3, 133.4, 130.0, 19.4, 128.6, 128.4, 128.1, 60.2, 52.6, 42.3, 41.4, 34.0, 24.3, 23.0, 14.2. ESI MS (444.1): 462.4 (M + NH_4^+). Found: C, 62.29; H, 5.38. $C_{23}H_{25}BrO_4$ requires C, 62.03; H, 5.66%.

Ethyl 7-(4-chlorophenyl)-6,9-dioxo-9-phenylnonanoate (11h)

Column chromatography with 15 : 1 cyclohexane–AcOEt (containing 5% of dichloromethane) afforded **11h** (138 mg, 69%) as a white foam. IR (film) ν_{max}: 2939,1729,1716, 1682, 1489, 1179, 1014, 755, 685 cm^{-1}; ^{1}H NMR: δ = 7.98–7.90 (m, 2 H, Ar), 7.60–7.52 (m, 1 H, Ar), 7.50–7.40 (m, 2 H, Ar), 7.35–7.25 (m, 2 H, Ar), 7.22–7.15 (m, 2 H, Ar), 4.38 (dd, 1 H, $J_{7,8b}$ = 3.5 Hz, $J_{7,8a}$ = 10.0 Hz, H-7), 4.10 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 3.98 (dd, 1 H, $J_{7,8a}$ = 10.0 Hz, $J_{8a,8b}$ = 18.0 Hz, H-8a), 3.12 (dd, 1 H, $J_{7,8b}$ = 3.5 Hz, $J_{8a,8b}$ = 18.0 Hz, H-8b), 2.72–2.60 and 2.52–2.40 (2 m, 2 H, 2 H-5), 2.35–2.18 (m, 2 H, 2 H-2), 1.70–1.45 (m, 4 H, 2 H-3, 2 H-4), 1.23 (t, 3 H, J = 7.0 Hz, OCH_2CH_3). ^{13}C NMR: δ = 209.8, 199.1, 174.7, 137.8, 137.6, 134.9, 134.6, 130.9, 130.6, 129.9, 129.3, 61.5, 53.9, 43.6, 42.7, 35.2, 25.5, 24.2, 15.4. ESI MS (401.1): 419.8 (M + NH_4^+). Found: C, 68.77; H, 6.45. $C_{23}H_{25}ClO_4$ requires C, 68.91; H, 6.29%.

7-Benzoyl-1-hydroxy-6-phenylbicyclo[3.2.1]octan-8-one (12)

A mixture of α-diketone **10** (56 mg, 0.50 mmol), chalcone **2a** (208 mg, 1.00 mmol), Et_3N (70 µL, 0.50 mmol), and absolute EtOH (2 mL) was vigorously stirred at room temperature for 24 h and then concentrated. The resulting residue was eluted from a column of silica gel with 12 : 1 cyclohexane–AcOEt (containing 5% of dichloromethane) to give **12** (141 mg, 88%) as a single diastereoisomer. IR (film) ν_{max}: 2928, 1749, 1671, 1447, 1227, 1130, 747, 682 cm^{-1}; ^{1}H NMR: δ = 8.10–8.00 (m, 2 H, Ar), 7.60–7.50 (m, 1 H, Ar), 7.45–7.38 (m, 2 H, Ar), 7.35–7.15 (m, 5 H, Ar), 4.26 (d, 1 H, $J_{6,7}$ = 7.0 Hz, H-6), 3.77 (dd, 1 H, $J_{2a,7}$ = 1.5 Hz, $J_{6,7}$ = 7.0 Hz, H-7), 3.28 (s, 1 H, OH), 2.80–2.75 (m, 1 H, H-5), 2.45–2.30

(m, 2 H, H-3a, H-4a), 2.10–1.80 (m, 2 H, H-3b, H-4b), 1.78–1.45 (m, 2 H, 2 H-2). ^{13}C NMR: δ = 197.5, 133.5, 129.5, 129.0, 128.6, 128.3, 126.8, 126.7, 81.2, 59.8, 49.8, 40.8, 40.5, 35.9, 17.2. ESI MS (320.1): 343.8 (M + Na^+). Found: C, 78.49; H, 6.01. $C_{21}H_{20}O_3$ requires C, 78.73; H, 6.29%.

Ethyl 2-methyl-5,8-dioxo-6,8-diphenyloctanoate (14a)

A 2.0–5.0 mL process vial was filled with α-diketone **13** (56 mg, 0.50 mmol), chalcone **2a** (208 mg, 1.00 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **4** (27 mg, 0.10 mmol), and absolute EtOH (2 mL). Then, Et_3N (35 μL, 0.25 mmol) was added in one portion. The vial was sealed with the Teflon septum and aluminium crimp by using an appropriate crimping tool. The vial was then placed in its correct position in the Biotage Initiator cavity where irradiation for 2 h at 100 °C was performed. After the full irradiation sequence was completed, the vial was cooled to room temperature and then opened. The mixture was concentrated and the resulting residue was eluted from a column of silica gel with 15 : 1 cyclohexane–AcOEt (containing 5% of dichloromethane) to give **14a** (88 mg, 48%) as a 1 : 1 mixture of diastereoisomers. IR (film) ν_{max}: 2935, 1747, 1712, 1673, 1447, 1250, 689 cm^{-1}; ^{1}H NMR: δ = 7.98–7.90 (m, 2 H, Ar), 7.60–7.50 (m, 1 H, Ar), 7.48–7.40 (m, 2 H, Ar), 7.38–7.20 (m, 5 H, Ar), 4.40 (dd, 1 H, $J_{6,7b}$ = 3.5 Hz, $J_{6,7a}$ = 10.0 Hz, H-6), 4.15–3.95 (m, 3 H, H-7a, OCH_2CH_3), 3.14 (dd, 0.5 H, $J_{6,7b}$ = 3.5 Hz, $J_{7a,7b}$ = 18.0 Hz, H-7b(1)), 3.13 (dd, 0.5 H, $J_{6,7b}$ = 3.5 Hz, $J_{7a,7b}$ = 18.0 Hz, H-7b(2)), 2.72–2.60 and 2.57–2.44 (2 m, 2 H, 2 H-4), 2.40–2.30 (m, 1 H, H-2), 1.98–1.62 (m, 2 H, 2 H-3), 1.19 (t, 1.5 H, J = 7.0 Hz, OCH_2CH_3), 1.15 (t, 1.5 H, J = 7.0 Hz, OCH_2CH_3), 1.10 (d, 1.5 H, $J_{2,Me}$ = 7.0 Hz, CH_3), 1.04 (d, 1.5 H, $J_{2,Me}$ = 7.0 Hz, CH_3). ^{13}C NMR: δ = 208.6, 198.1, 176.2, 176.1, 137.9, 136.4, 133.2, 129.1, 128.6, 128.3, 128.1, 127.6, 127.7, 60.2, 60.1, 53.3, 53.2, 42.4, 39.2, 39.1, 38.6, 38.5, 27.9, 17.1, 16.8, 14.2. ESI MS (366.2): 384.5 (M + NH_4^+). Found: C, 75.45; H, 7.01. $C_{23}H_{26}O_4$ requires C, 75.38; H, 7.15%.

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