Unusual Coupling Reactions of Aldehydes and Alkynes: A Novel Preparation of Substituted Phthalic Acid Derivatives by Automated Synthesis

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Abstract: Based upon a highly versatile multicomponent methodology, a new one-pot synthesis of substituted phthalic acid derivatives from α,β-unsaturated aldehydes was developed. The reaction involves the intermediacy of an acetamidodiene species which undergoes Diels–Alder addition to diethyl acetylenedicarboxylate. The resultant acetamidocyclohexadiene is subject to elimination of acetamide under the reaction conditions to give rise to substituted diethyl phthalates in good yields. This domino condensation–cycloaddition–elimination sequence has been applied to a variety of α,β-unsaturated aldehydes. Furthermore, we demonstrated the exploitation of parallelized and automated synthesis technology for the rapid screening of reaction conditions and compositions. Detailed studies revealed the catalytic role of the employed acetamide and the occurrence of a stereoselective 1,4-*syn* elimination pathway under standard conditions.

Keywords: automated synthesis · Diels–Alder reaction · domino reaction · multicomponent reaction · organocatalysis

Introduction

In the realm of organic synthesis in which a premium is put on the rapid construction of highly substituted carbocyclic compounds, the venerable Diels–Alder reaction has emerged as one of the foremost synthetic tools by virtue of its versatility and stereocontrol.[1] Well known and extensively studied for many decades, the Diels–Alder reaction has also gained a strong foothold among time and cost effective multicomponent and domino reactions.[2] As combinatorial techniques have burst up on the scene of organic synthesis, the automated and parallelized screening of multitudes of reaction conditions and compositions has been perceived as a valuable means for the rapid investigation of chemical reactions.[3, 4]

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Recently, our group launched a program toward domino condensation-Diels–Alder reaction sequences for the direct synthesis of amino-functionalized carbo- and heterocyclic compounds from simple aldehydes and carboxamides. These multicomponent coupling reactions take advantage of the intermediacy of 1-(*N*-acylamino)-1,3-butadiene species (**I**)[5] which are subject to in situ trapping with electron-deficient dienophiles. Upon employment of various amide, aldehyde, and dienophile combinations, a library of functionalized aminocyclohexene derivatives was synthesized in good to excellent yields.[6] The underlying domino condensation-Diels–Alder reaction sequences constitutes the first example of multicomponent couplings of aldehydes, amides, and olefins (or alkynes). Up to four stereogenic centers arise from the formation of three carbon–carbon bonds and one carbon–nitrogen bond over the course of the reaction. Nevertheless, these multicomponent coupling reactions exhibited very high *endo* selectivity in most cases. It is also interesting to note that in no case hetero-Diels–Alder adducts have been observed (Scheme 1).

The structural diversity of the compound library significantly benefited from the employment of α,β-unsaturated aldehydes which allowed the synthesis of three-component adducts containing more diverse substitution patterns. As part of our studies of multicomponent coupling reactions with α,β-unsaturated aldehydes and amides,[7] we recently investigated reactions thereof in the presence of electron-deficient alkynes. Paralleling our experimentations with simple enoliz-

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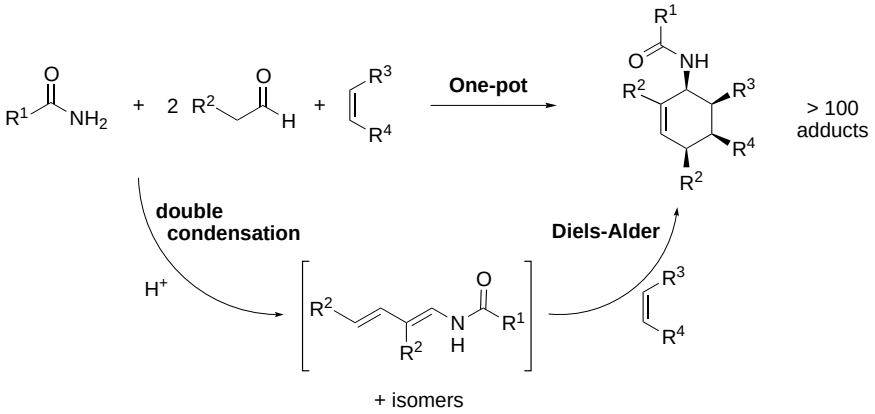


Scheme 1. Multicomponent coupling reaction of amide, aldehyde, and dienophile.

able aldehydes,[6a] we aimed at the one-pot synthesis of substituted aminodihydrophthalate derivatives. In order to secure the intermediacy of an 1-(*N*-acylamino)-1,3-butadiene species, the α,β-unsaturated aldehydes are required to contain an aliphatic chain of minimal four carbon atoms and a γ-hydrogen atom.

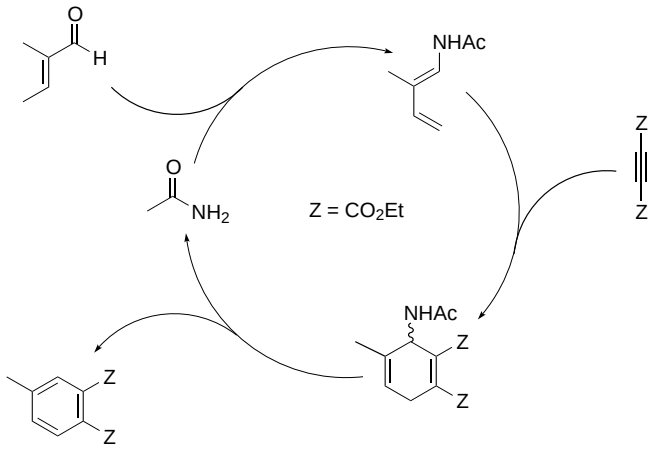
In order to enhance the efficiency of our screening experimentations, we considered automation a promising approach, as analogous reactions have been shown tolerant of moisture and air. Automated and parallel screenings of multitudes of reaction parameters have become a valuable means for the rapid investigation of chemical reactions. However, applications have largely been limited to pharmaceutical problems, and until now, a general usage in standard organic synthesis has not been demonstrated. In a joint collaboration between chemists and engineers, we raised the question whether automated synthesis can be exploited for the development of organic reactions. Here, we report on a new and fully automated synthesis of phthalic acid esters from α,β-unsaturated aldehydes. The potential of commercial automation technology for the synthesis and screening of reaction conditions and compositions as well as mechanistic details are discussed.

Results and Discussion

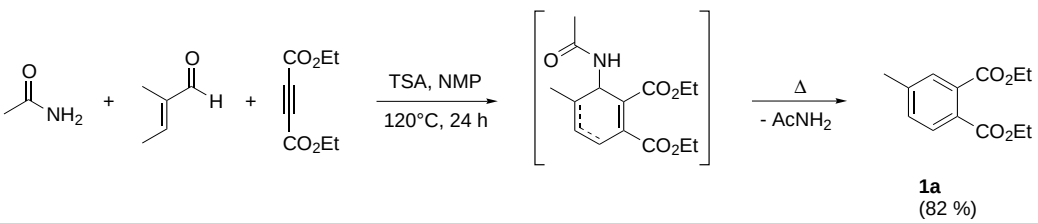
Initially, we performed model studies with the three-component system acetamide/tiglic aldehyde (2-methylcrotonaldehyde)/diethyl acetylenedicarboxylate. The mixture was confined to a threaded tube in the presence of catalytic amounts of *p*-toluenesulfonic acid monohydrate ($TSA \cdot H_2O$) in *N*-methylpyrrolidinone (NMP) and heated at 120 °C for 24 h. Contrary to our expectations, the targeted diethyl 3-(*N*-acetylamino)-4-methyl-*trans*-3,4-dihydrophthalate could not be detected in the reaction mixture. The unexpected high R_f values of the crude products in silica gel TLC were first indicators of a different reactivity pattern. The surprisingly liquid product turned out to lack any amide moiety but constitute an aromatic ring instead. NMR and MS analysis established the unexpected formation of diethyl 4-methylphthalate (**1a**) as the only product which was isolated in 82 % yield.

The net reaction for this one-pot synthesis of phthalic acid derivative **1a** is shown in Scheme 2. The reaction is assumed to proceed via the known 1-*N*-acetylamino-1,3-diene and *N*-acetylamino-cyclohexadiene intermediates with the latter undergoing facile elimination of acetamide under the reaction conditions. There are literature precedents of related syntheses of arenes via domino Diels – Alder elimination reactions.[8] However, these procedures involve several synthetic steps and largely rely upon rather special, expensive olefinic starting materials.

A closer look at the underlying reaction mechanism (Scheme 3) reveals the quasi catalytic role of the employed acetamide. The sequence commences with the consumption of acetamide in the synthesis of the aminodiene intermediate. Not only does this initial condensation step generate a highly



Scheme 3. Catalytic role of acetamide.



Scheme 2. One-pot synthesis of diethyl 4-methylphthalate (**1a**) from 2-methyl-2-butenal.

reactive electron-rich diene which facilitates the normal electron-demand Diels–Alder addition to the electron-deficient alkyne, but also cuts off potential side reactions of the highly reactive free aldehyde. According to previous results, the cycloaddition step involves the preferential consumption of the (1*E*,3*E*)-1-(*N*-acetylamino)-2-methyl-1,3-butadiene isomer and proceeds with extremely high *endo* selectivity. The employed acetamide is recovered by the terminating elimination of acetamide. Altogether, acetamide acts as a protective group and activator for the aldehyde. Interestingly, attachment and cleavage occur under the same reaction conditions with the latter being largely driven by the resultant aromatization of the six-membered ring. We thus wondered if it is possible to run the reaction also in the presence of sub-stoichiometric or catalytic amounts of acetamide. The organocatalytic aspect of this one-pot synthesis of phthalic acid derivatives seemed attractive to us, as organocatalysis, although known for some time, has emerged as a powerful catalytic tool. To the best of our knowledge, this principle has not been applied to the synthetic construction of aromatic rings.

Consequently, we set out to subject the synthesis of model compound **1a** to a wide screening of reaction conditions and compositions. The insensitivity towards air and moisture renders this reaction as ideally suitable for simple, automated handling and processing. Therefore, a cooperation with the Institute of Automation at the University Rostock was started up to ensure high-throughput screening experimentations in a fully automated, parallelized manner (Figure 1). Sample preparation (addition of reactant stock solutions), reaction processing (heating), and work-up (cooling, dilution, analysis) steps were performed by a Zymate Laboratory Automation System by Zymark (Hopkinton, MA, USA). It consists of a Zymate XP Robot mounted on a linear track which uses a variety of interchangeable hands to move consumables, liquids, vials, tubes, and containers of various sizes to the different stations and modules. We used a 60-well Syncore reactor (BÜCHI Labortechnik AG, Switzerland), different capping and uncapping stations, and several modules providing the liquid handling. A GC/MSD system (Agilent 5972 MSD with 5890 GC) has been integrated for online analysis. The reactions were run in 4 mL screw cap vials. As the integrated solid dispenser was not capable of dosing tiny amounts (< 150 mg), the solid reactants were employed as stock solutions in the solvent (NMP). The vials were placed onto a modified Syncore Reactor and were agitated and heated. Samples of the reaction mixture were taken by syringe, transferred to a GC vial, diluted with ethyl acetate, and subjected to auto sampled GC/MSD analysis.

These automated screening experiments significantly enhanced the acquisition of reaction data and gave detailed information on optimal reaction conditions and compositions. It is important to note that the reactions of automated runs generally exhibited lower yields (by 15–30%) than analogous reactions performed in a conventional solitary reaction vessel. We consider the miniaturization of the reaction stoichiometry, inaccuracies associated with the automated liquid handling, and a diminished heat transfer the major reasons for these discrepancies. However, the general tendencies could be unambiguously deduced from the vast amount of experiments that were performed in the aforementioned time effective parallel manner.

Figure 2 shows a typical series of automated screening experiments at 120 °C. Upon variation of the employed acetamide and acid amounts and the reaction time, detailed information on beneficial reaction conditions was obtained in one set of automated experiments. Generally, the reactions gave also good yields at sub-stoichiometric amounts of acetamide. Reactions in the presence of >50 mol% acetamide content were completed within 24 h. With regard to efficient organocatalysis (<50 mol% acetamide), extended

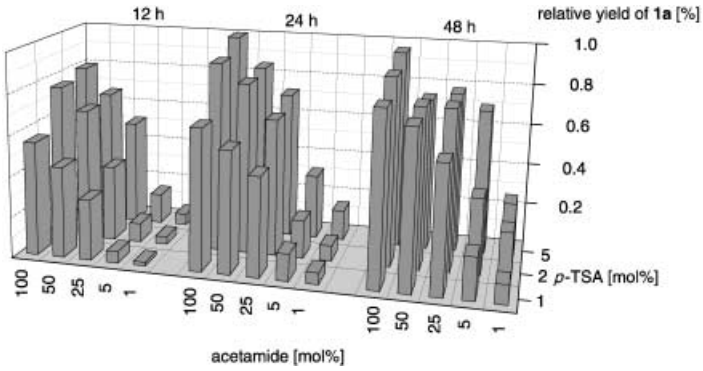


Figure 2. Initial automated screenings of reaction time and composition in the synthesis of **1a**.

Figure 1. Zymate laboratory automation system (left) and 60-well Syncore reactor station (right).

reaction times significantly increased the product yield. An analogous behaviour was found for the acid catalysis by *p*-toluenesulfonic acid monohydrate: the lower the amount of employed *p*-TSA, the longer the required reaction times.

Next, we used the optimized conditions for a detailed investigation of the organocatalytic aspect of this reaction. A series of reactions was performed with various understoichiometric amounts of acetamide at 120 and 160 °C (Figure 3). Below 50 mol % acetamide content, reactions at 120 °C gave the arene (**1a**) in yields that exceed the mol % value of the employed acetamide, thereby unambiguously establishing the catalytic role of acetamide. At 160 °C, the catalyst was shown to be more active giving 5–20 % higher yields. Upon further reduction of the catalyst loading, we still observed good to moderate conversion. Extended reaction times gave good to moderate yields in **1a** at 120 °C even in the presence of < 10 mol % acetamide catalyst. With 3 mol % acetamide, the turn over number (TON) of the catalyst amounts to 15. However, no investigations into the preparative recovery of the employed acetamide have been performed.

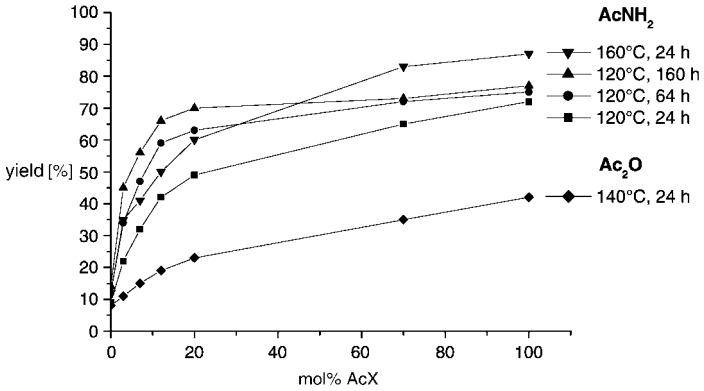


Figure 3. Catalytic performance of acetamide ($AcNH_2$) and acetic anhydride (Ac_2O).

Unlike nucleophilic acetamide, we also employed electrophilic acetic anhydride as an acylating agent to trap the intermediate dienol tautomer of the α,β-unsaturated aldehyde (Scheme 4). However, acetic anhydride required higher temperatures for reasonable conversion and proved a less active mediator in this reaction (Figure 3), presumably due to the highly acidic conditions associated with the formation of acetic acid as by-product.

As can be seen from Figure 3, the reaction also proceeds in the absence of acetamide, albeit with very low yields. Here, the α,β-unsaturated aldehyde is believed to tautomerize to give the corresponding 1,3-dienol. Subsequent cycloaromatization with the alkyne gives the phthalic acid ester upon elimination of water.

As a substitute for acetamide, we also tested the catalytic activity of other compounds in this reaction. Figure 4 compiles a series of experimentations in the presence of different amides and amines. Benzamide and acetamide were shown equivalent catalysts giving similar yields in phthalate **1a**. With more nucleophilic 1,1-dimethylurea (DMU), aniline (ANI), and piperidine (PIP), predominantly oligomers and only low yields (similar to reactions in the absence of any mediator) were obtained (< 25 %).

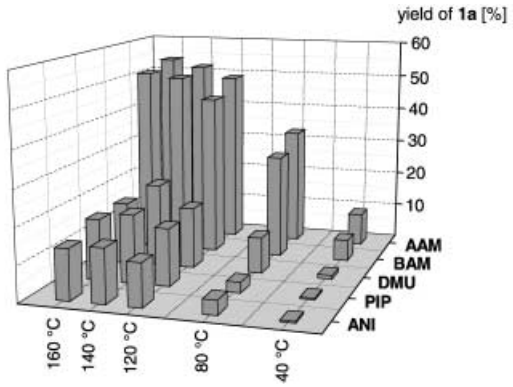
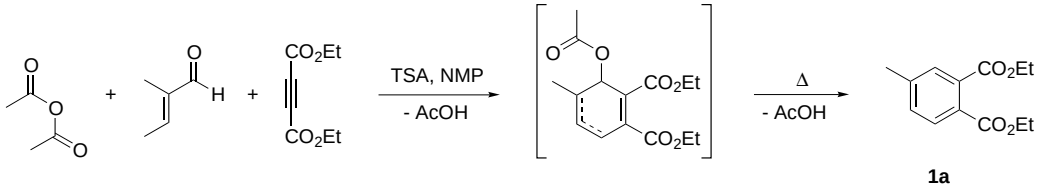


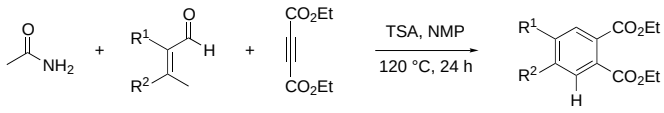
Figure 4. Yield-temperature plots for synthesis of **1a** under standard conditions (120 °C, 24 h) with 25 mol % of different amine sources.

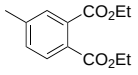
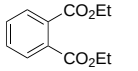
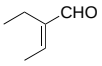
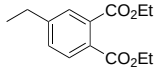
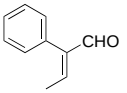
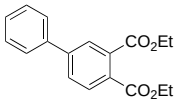
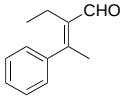
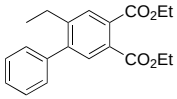
In order to extend the scope of this reaction and sound the generality of the method, we treated other α,β-unsaturated aldehydes with diethyl acetylenedicarboxylate at different reaction temperatures. Surprisingly at a reaction temperature of 120 °C the isolated products were dependent on the substitution pattern of the aldehyde employed. In the case of crotonaldehydes bearing solely α- and/or β-substituents, phthalic acid derivatives were formed. Table 1 compiles a series of five diethyl phthalates prepared in a one-pot procedure from the corresponding aldehydes. When employing crotonaldehydes (**1a–e**), the isolated yields were generally high (82–91 %). On account of the terminating acetamide elimination, employment of tiglic aldehyde (2-methylcrotonaldehyde) and prenal (3,3-dimethylacrolein) afforded a congruent product (**2**) in 82 and 91 % yield, respectively. Generally, substituted crotonaldehydes, which are in short commercial supply, can be accessed by standard procedures.[9] 2-Phenyl-3-ethylcrotonaldehyde (2-phenyl-3-methyl-2-butenal) was synthesized via Peterson olefination from acetophenone and butanal.[10] We assume that any conceivable diethyl phthalate can be synthesized in this manner, if the α,β-



Scheme 4. Acetanhydride-based reaction via cyclohexadienol species.

Table 1. One-pot reactions with crotonaldehydes containing no γ-substituents.

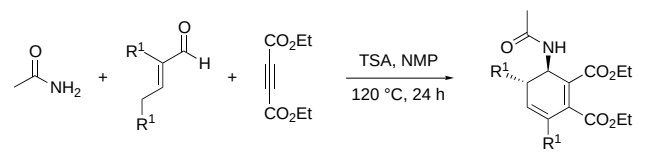


Entry	Aldehyde	Product		Yield [%]
1			**1a**	82
2				91
3			**1b**	90
4			**1c**	90
5			**1d**	91
6[10]			**1e**	66

unsaturated aldehyde is available and stable under the reaction conditions.

On the other hand, one-pot reactions employing crotonaldehyde derivatives that contain a substituent in γ-position gave different products using similar reaction conditions. Upon employment of these higher homologues of crotonaldehyde with elongated chain lengths, *N*-acetylamine-bearing cyclohexadienes were obtained, and elimination of acetamide was not observed. According to our studies with simple propanal and butanal, employment of their homo aldol condensation products 2-methyl-2-pentenal and 2-ethyl-2-hexenal also gave the dialkyl 3-*N*-acetylamino-4,6-dimethyl-*trans*-3,4-dihydrophthalates in good yields (**2a**,**b**, Table 2). The double bonds are subject to thermodynamic equilibration to give a conjugated π-bond system. The vicinal amino and alkyl moieties adopt a *trans* configuration.

Table 2. One-pot reactions with crotonaldehydes containing γ-substituents.



Entry	R^1	Product	Yield [%]
1	Me	**2a**	70
2	Et	**2b**	72

Interestingly, consumption of linear 2-pentenal in this reaction led to a cycloadduct with isolated double bonds (**2c**). Although double-bond migration to a conjugated position should be favored by the 6-methyl group (higher substitution at the double bond), X-ray crystallography (Figure 5) and NMR spectra clearly establish the presence of a 1,4-cyclohexadiene system (Scheme 5).

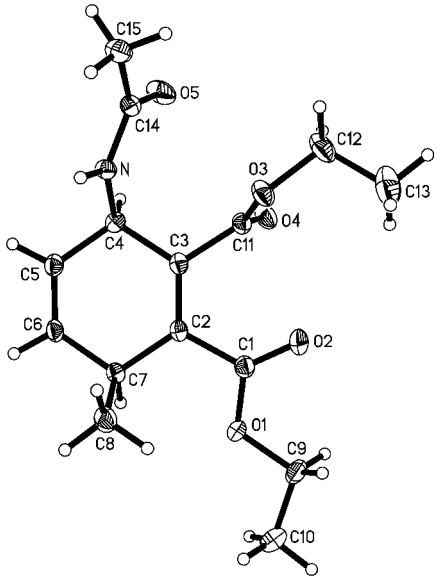
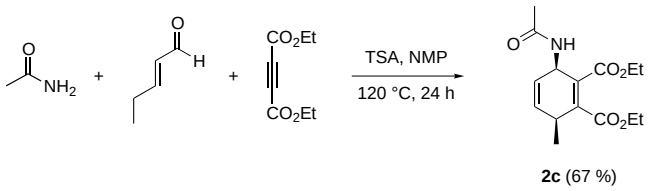


Figure 5. Crystal structure of diethyl 3-(*N*-acetylamino)-6-methyl-*cis*-3,6-dihydrophthalate (**2c**): The thermal ellipsoids correspond to 30% probability.



Scheme 5. Synthesis of diethyl 3-(*N*-acetylamino)-6-methyl-*cis*-3,6-dihydrophthalate (**2c**) from 2-pentenal.

The amino and methyl substituents in **2c** adopt a *syn* configuration as expected from an *endo* Diels–Alder reaction of (1*E*,3*E*)-1-(*N*-acetylamino)-1,3-pentadiene and diethyl acetylenedicarboxylate.[11]

In view of the apparently different products obtained by employment crotonaldehydes with and without γ-substituents, the mechanism of these domino reactions bears closer scrutiny. Under the premise of structurally equivalent [4 + 2] cycloaddition transition states in both cases, the terminating elimination step should account for the two differing products. It is interesting to note that substituents in the 4-position decrease the tendency towards elimination of acetamide. In principle, one might discuss 1,2- or 1,4-elimination[12] depending on the nature of the intermediate cyclohexadiene (conjugated or isolated diene system).

Obviously, a 1,2-elimination mechanism (E1 or E2) can be ruled out as the rather distant 4-substituent cannot explain the differing reactivities of cyclohexadiene intermediates with or

without 4-substitution. The same considerations disfavor 1,4-elimination in E1 manner which would proceed via a planar pentadienyl-cation intermediate, though the acidic reaction conditions might enhance protodeamination.

On the other hand, 4-substitution is likely to affect a concerted 1,4-pathway. Although intensive studies have been performed on 1,2-elimination,[13] little is known about 1,4-conjugate elimination of allylic leaving groups. The stereochemical course of bimolecular eliminations on non-cyclic polyenes has been discussed on the basis of the Woodward-Hoffmann rules for sigmatropic reactions.[14] Symmetry arguments show that bimolecular (E2) 1,4-*syn* eliminations are favored.[15] The process can be viewed as a thermally allowed $\sigma^2s\ \pi^2s\ \sigma^2s$ process. If elimination and addition are considered reverse processes that run through the same transition state, the symmetry of a thermally allowed process (according to Woodward–Hoffmann) can also be deduced from the frontier orbital overlap of a 1,4-*syn* addition involving the LUMO of the 1,3-diene (Figure 6).

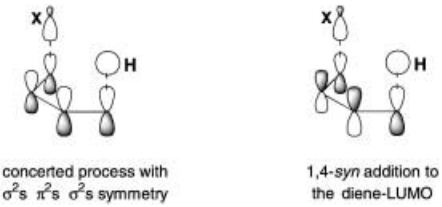


Figure 6. Symmetry of frontier orbitals in a concerted 1,4-addition of HX to a butadiene.

The inertness of cyclohexadienes **2a–c** toward elimination at 120 °C also supports the general preference for a stereospecific 1,4-*syn* elimination.[16] Although an identical stereochemical result would be the consequence of an initial suprafacial 3,3-sigmatropic rearrangement of the allylic ester followed by 1,2-*syn* elimination, the relatively low reaction temperature (120 °C) make the sigmatropic process unlikely.

The Woodward–Hoffmann selection rules deduced here apply only in those cases where orbital symmetry is the decisive criterion for the stereochemical course of the reaction. Moreover, alternative mechanisms of elimination might become competitive at higher temperatures. The acidic reaction conditions (1.5 mol% *p*-TSA) are likely to effect protonation of the acylamine substituent and thus facilitate elimination, though both 1,2- and 1,4-pathway are not dependent on protonation. Based upon the model reaction of 2-methyl-2-butenal with acetamide and diethyl acetylenedicarboxylate to give **1a**, we performed reactions with varied amounts of acid. As can be seen from Figure 7, the reaction is also amenable for acid-free conditions (67% yield). However, best results (> 87%) were obtained in the presence of 2–3 mol% *p*-toluenesulfonic acid monohydrate.

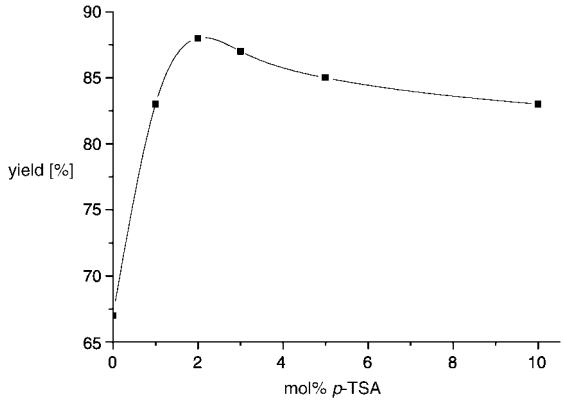


Figure 7. Yield of phthalate **1a** vs acid concentration (200 mol% $AcNH_2$, 120 °C, 12 h).

Given the high affinity of acetamide-bearing compounds toward O-protonation, elimination pathways other than a concerted 1,4-*syn* elimination, such as E1 (via a planar pentadienyl cation) and E2 (better leaving group), might also become competitive at higher temperatures. Indeed, isolated 4-substituted aminocyclohexadienes **2a–c** that withstood elimination at standard conditions (120 °C, 24 h) were cleanly converted to the corresponding phthalic acid esters in good yields after 48 h at 160 °C.

Consequently the feasibility of a one-pot procedure was tested. As expected the desired diethyl phthalates could be isolated in good to excellent yields (Table 4) from the reaction of 2-pentenal and other γ-substituted α,β-unsaturated aldehydes with acetamide and diethyl acetylenedicarboxylate at 160 °C.

Summary

The reaction of an α,β-unsaturated aldehyde and diethyl acetylenedicarboxylate in the presence of acetamide was shown to provide a new straightforward access to substituted phthalates. The substitution pattern of the intermediate three-component adduct is decisive to the outcome of the reaction under standard conditions, as rationalized from orbital symmetry analysis of the underlying 1,4-*syn* elimination

Table 3. High-temperature elimination of acetamide from aminocyclohexadienes **2a–c**.

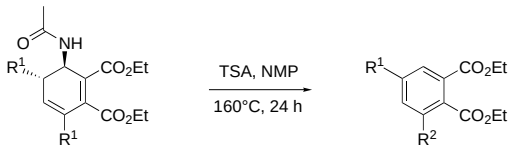
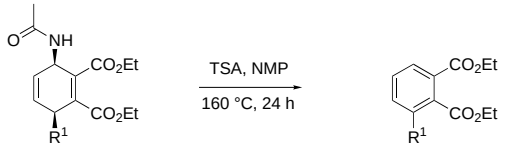
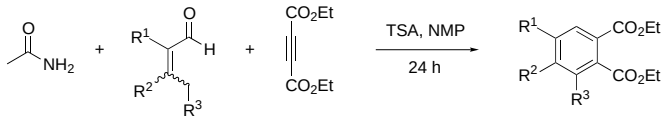
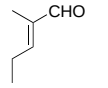
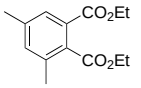
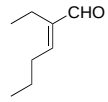
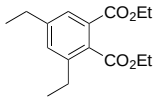
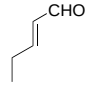
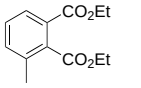
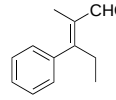
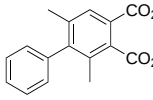
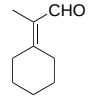
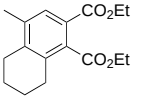
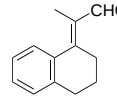
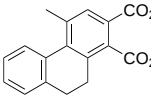
Entry	Reaction	R^1	Product	Yield [%]
1		Me	**3a**	91
2		Et	**3b**	89
3		Me	**3c**	83

Table 4. High-temperature one-pot synthesis of substituted diethyl phthalates.



Entry	Aldehyde	T [°C]	Product	Yield [%]
1		160		**3a** 86
2		160		**3b** 89
3		160		**3c** 69
4[10]		140		**3d** 50
5[10]		140		**3e** 88
6[10]		140		**3f** 52

pathway. Higher temperatures obviate these stereochemical restrictions and elimination occurs via other, unselective pathways. Mechanistic investigations revealed the catalytic role of the employed amide. We also demonstrated the applicability of parallelization and automation techniques to enhance the screening throughput, thereby speeding up the acquisition of synthetic and mechanistic information. We believe that a more general use of this type of equipment will be not only beneficial for the time effective optimization of reactions but also for the development of new reactions.

Experimental Section

General: Starting materials and solvent were used as received from commercial suppliers. Threaded ACE pressure tubes were used for preparative reactions. For automated runs, all reagents (amide, aldehyde, diethyl acetylenedicarboxylate, and *p*-TSA) were employed as *freshly* prepared 0.5 M stock solutions in NMP. Automated reactions were run on a Zymate Laboratory Automation System by Zymark Corp. (Hopkinton, MA, USA) at the Institute of Automation at the University of Rostock (http://www.iat.uni-rostock.de).

NMR spectra were recorded on a Bruker ARX400 and are reported in ppm. EI mass spectra were recorded on an AMD 402 spectrometer (70 eV). IR spectra were obtained from KBr pellets on a Nicolet Magna 550. Melting points are uncorrected.

General procedure for preparative one-pot syntheses starting from *α,β*-unsaturated aldehydes: Acetamide (287 mg, 5 mmol), *α,β*-unsaturated aldehyde (*cis* and/or *trans*, 2.5 mmol), diethyl acetylenedicarboxylate (853 mg, 5 mmol), and *p*-toluenesulfonic acid monohydrate (22 mg, 1.5 mol%) were combined in a threaded tube, and NMP (3 mL) was added. The reaction was stirred at elevated temperature (120–160 °C). After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum. Silica gel chromatography (heptane/ethyl acetate 2:1; R_f values in TLC indicated below) afforded the analytically pure products.

Diethyl 4-methyl phthalate (1a): 120 °C, 24 h; $R_f = 0.50$; Yield: 82%/91% from 2-methyl-2-butenal (210 mg, 2.5 mmol)/3,3-dimethylacrolein (210 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu} = 2983$ s, 2939 m, 2906 w, 1724 vs, 1610 m, 1575 m, 1465 m, 1447 m, 1367 s, 1287 vs, 1202 s, 1130 s, 1071 s, 1023 s, 839 m, 781 m, 703 m; MS-EI: *m/z* (%): 236 (21) $[M]^+$, 191 (73) $[M - OEt]^+$, 163 (100) $[M - CO_2Et]^+$, 119 (19) $[M - CO_2Et - OEt]^+$, 105 (14), 91 (15), 77 (24); HRMS: *m/z*: calcd for $C_{13}H_{16}O_4$: 236.10486; found: 236.10402; ^{1}H NMR ($CDCl_3$): $\delta = 7.47$ (d, $J = 7.8$ Hz, 1H, Ph), 7.27 (s, 1H, Ph), 7.11 (d, $J = 7.8$ Hz, 1H, Ph), 4.19–4.12 (2q, $J = 7.2/7.2$ Hz, 4H, $2CH_2$), 2.21 (s, 3H, Me), 1.18–1.14 (2t, $J = 7.1/7.1$ Hz, 6H, 2Me); ^{13}C{^{1}H}: $\delta = 168.1/167.2$ (2CO), 141.7/132.9 (2C), 131.1/129.1/129.0 (3CH), 128.6 (C), 61.4/61.3 ($2CH_2$), 21.2 (Me), 14.1/14.0 (2Me).

Diethyl phthalate (1b): 120 °C, 24 h; $R_f = 0.45$; Yield: 90% from crotonaldehyde (175 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu} = 3069$ w, 2983 s, 2939 w, 2906 w, 1724 vs, 1681 s, 1601 m, 1580 m, 1520 s, 1490 s, 1448 m, 1368 s, 1286 vs, 1125 s, 1074 s, 1041 s, 1019 s, 862 m, 745 s, 703 s; MS-EI: *m/z* (%): 222 (8) $[M]^+$, 177 (47) $[M - OEt]^+$, 149 (100) $[M - CO_2Et]^+$, 121 (17), 105 (34), 93 (18); HRMS: *m/z*: calcd for $C_{12}H_{14}O_4$: 222.08921; found: 222.09146; ^{1}H NMR ($CDCl_3$): $\delta = 7.53–7.50$ (dd, $J = 5.7/3.2$ Hz, 2H, Ph), 7.34–7.31 (dd, $J = 5.7/3.2$ Hz, 2H, Ph), 4.19–4.14 (q, $J = 7.0$ Hz, 4H, $2CH_2$), 1.19–1.15 (t, $J = 7.0$ Hz, 6H, 2Me); ^{13}C{^{1}H}: $\delta = 167.5$ (CO), 132.2 (C), 130.9/128.8 (CH), 61.5 (CH_2), 14.0 (Me).

Diethyl 4-ethylphthalate (1c): 120 °C, 24 h; $R_f = 0.60$; Yield: 90% from 2-ethyl-2-butenal (245 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu} = 2980$ s, 2938 m, 2905 w, 2876 w, 1724 vs, 1608 m, 1464 m, 1367 s, 1286 vs, 1197 s, 1130 s, 1072 s, 1023 s, 848 m, 791 m, 707 m; MS-EI: *m/z* (%): 250 (9) $[M]^+$, 205 (28) $[M - OEt]^+$, 177 (100) $[M - CO_2Et]^+$, 149 (11) $[M - CO_2Et - OEt]^+$, 133 (10), 125 (12), 115 (10), 77 (12), 53 (21); HRMS: *m/z*: calcd for $C_{14}H_{18}O_4$: 250.12051; found: 250.11942; ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.66$ (d, $J = 7.9$ Hz, 1H, Ph), 7.50 (d, $J = 1.6$ Hz, 1H, Ph), 7.47 (dd, $J = 7.9/1.6$ Hz, 1H, Ph), 4.28–4.22 (2q, $J = 7.0/7.0$ Hz, 4H, $2CH_2$), 2.68 (q, $J = 7.5$ Hz, 2H, CH_2), 1.28–1.24 (2t, $J = 7.0/7.0$ Hz, 6H, 2Me), 1.17 (t, $J = 7.5$ Hz, 3H, Me); ^{13}C{^{1}H}: $\delta = 167.3/166.6$ (2CO), 148.0/132.6 (2C), 130.4/129.0 (2CH), 128.5 (C), 127.7 (CH), 61.2/61.1 ($2CH_2$), 27.8 (CH_2), 15.1 (Me), 13.9/13.8 (2Me).

Diethyl 4-phenylphthalate (1d): 120 °C, 24 h; $R_f = 0.50$; Yield: 91% from 2-phenyl-2-butenal (370 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu} =$ 3033 w, 2983 s, 2938 m, 2904 w, 1724 vs, 1607 m, 1450 m, 1367 s, 1291 vs, 1132 s, 1074 s, 1016 m, 906 w, 849 w, 759 s, 699 s; MS-EI: *m/z* (%): 298 (38) $[M]^+$, 253 (22) $[M - OEt]^+$, 225 (100) $[M - CO_2Et]^+$, 152 (16) $[PhC_6H_3]^+$, 105 (28), 91 (14), 77 (15) $[Ph]^+$; HRMS: *m/z*: calcd for $C_{18}H_{18}O_4$: 298.12051; found: 298.12077; ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.94$ (s, 1H, Ph), 7.93 (dd, $J =$ 7.8/1.8 Hz, 1H, Ph), 7.83 (d, $J = 7.8$ Hz, 1H, Ph), 7.73 (d, $J = 7.1$ Hz, 2H, Ph), 7.50 (dd, $J = 7.4/7.1$ Hz, 2H, Ph), 7.43 (t, $J = 7.4$ Hz, 1H, Ph), 4.33–4.26 (2q, $J = 7.1/7.1$ Hz, 4H, $2CH_2$), 1.31–1.27 (2t, $J = 7.1/7.1$ Hz, 6H, 2Me); ^{13}C{^{1}H}: $\delta = 167.0/166.4$ (2CO), 143.2, 137.9, 133.1, 129.8 (4C), 129.6, 129.2, 129.1, 128.6, 127.0, 126.5 (6CH), 61.4/61.3 ($2CH_2$), 13.9/13.8 (2Me).

Diethyl 4-ethyl-5-phenylphthalate (1e): 120 °C, 24 h; $R_f = 0.50$; Yield: 66% from 2-ethyl-3-phenyl-2-butenal (437 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu} = 3057$ w, 3027 w, 2979 s, 2936 m, 2904 m, 2875 m, 2255 w, 1724 vs, 1609 m, 1556 m, 1464 s, 1447 s, 1367 s, 1306 vs, 1247 vs, 1175 s, 1136 s, 1071 s, 1030 s, 914 s, 855 m, 769 m, 733 s, 704 s; MS-EI: *m/z* (%): 326 (96) $[M]^+$, 281 (63) $[M - OEt]^+$, 253 (100), 225 (21), 209 (12), 181 (13), 165 (29); no other peaks of > 10%. HRMS: *m/z*: calcd for $C_{20}H_{22}O_4$: 326.15179; found: 326.15610; ^{1}H NMR ($CDCl_3$): $\delta = 7.54/7.50$ (2s, 2H, Ph), 7.34–7.27 (m, 3H, Ph), 7.18 (dm, $J = 6.5$ Hz, 2H, Ph), 4.30/4.24 (2q, $J = 7.1/7.1$ Hz, 4H, $2CH_2$), 2.54 (q, $J = 7.5$ Hz, 2H, CH_2), 1.31–1.23 (2t, $J = 7.1/7.1$ Hz, 6H, 2Me), 1.01 (t, $J = 7.5$ Hz, 3H, Me); ^{13}C{^{1}H}: $\delta = 167.9/167.3$ (2CO), 145.2, 144.1, 139.9, 131.4 (4CH), 130.5 (CH), 129.1 (C), 129.0 (CH), 128.8, 128.2, 127.5 (3CH), 61.5/61.4 ($2CH_2$), 26.0 (CH_2), 15.1 (Me), 14.0/13.9 (2Me).

Diethyl 3-(*N*-acetylamino)-4,6-dimethyl-*trans*-3,4-dihydrophthalate (2a): 120 °C, 24 h; $R_f = 0.10$; Yield: 69% from 2-methyl-2-pentenal (245 mg, 2.5 mmol), white solid. M.p. 79–83 °C; IR (cap.): $\tilde{\nu} = 3260$ s, 2985 s, 1734 vs, 1713 vs, 1640 vs, 1540 vs, 1449 s, 1378 s, 1307 s, 1264 vs, 1161 s, 1115 s, 1075 s, 1047 s; MS-EI: *m/z* (%): 309 (1) $[M]^+$, 263 (14) $[M - OEt]^+$, 248 (72) [*M* –

AcNH]$^+$, 204 (17) [M – OEt – AcNH]$^+$, 190 (24) [M – OEt – Me – AcNH]$^+$, 178 (100) [M – CO_2Et – AcNH]$^+$, 148 (30) [M – $(CO_2Et)_2$ – Me]$^+$, 43 (43) [Ac]$^+$, 29 (30) [Et]$^+$; no other peaks of > 15%; elemental analysis calcd (%) for $C_{16}H_{23}NO_5$: C 62.12, H 7.49, N 4.53; found: C 62.40, H 7.29, N 4.53; ^{1}H NMR ([D$_6$]DMSO): δ = 7.92 (d, J = 9.1 Hz, 1H, NH), 5.53 (d, J = 3.4 Hz, 1H, CH), 5.10 (dd, J = 4.8/9.1 Hz, 1H, CH), 4.13/4.05 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 3.01 (m, 1H, CH), 1.81 (s, 3H, Me), 1.60 (s, 3H, Me), 1.20 (d, J = 6.9 Hz, 3H, Me), 1.19/1.15 (2t, J = 7.1/7.1 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 168.9 (CON); 166.7/166.4 (2CO), 138.8, 132.8, 130.0 (3C), 127.1 (CH), 60.8/60.6 (2CH$_2$), 46.2 (CHN), 32.4 (CH), 22.3 (Me), 20.3 (Me), 19.4 (Me), 13.8 (2Me).

Diethyl 3-(*N*-acetylamino)-4,6-diethyl-*trans*-3,4-dihydrophthalate (2b): 120 °C, 24 h; R_f = 0.10; Yield: 84% from 2-ethyl-2-hexenal (315 mg, 2.5 mmol), white solid. M.p. 70–72 °C; IR (KBr): $\tilde{\nu}$ = 3324 s, 2974 s, 1728 vs, 1709 vs, 1647 vs, 1524 s, 1271 vs; MS-EI: m/z (%): 337 (1) [M]$^+$, 292 (3) [M – OEt]$^+$, 262 (83) [M – CO_2Et]$^+$, 232 (12) [M – CO_2Et – Et]$^+$, 218 (17) [M – CO_2Et – OEt]$^+$, 205 (15) [M – CO_2Et – AcNH]$^+$, 192 (100) [M – $(CO_2Et)_2$]$^+$, 176 (100) [M – CO_2Et – Ac – OEt]$^+$, 43 (40) [Ac]$^+$; no other peaks of > 10%; elemental analysis calcd (%) for $C_{18}H_{27}NO_5$: C 64.07, H 8.07, N 4.15; found: C 64.07, H 7.99, N 4.18; ^{1}H NMR ([D$_6$]DMSO): δ = 7.74 (d, J = 9.3 Hz, 1H, NH), 5.60 (d, J = 4.2 Hz, 1H, CH), 5.22 (dd, J = 5.1/9.3 Hz, CHN), 4.12/4.05 (2q, v7.1/7.1 Hz, 4H, 2CH$_2$), 2.96 (m, 1H, CH), 1.88–2.05 (br m, 2H, CH$_2$), 1.82 (s, 3H, Me), 1.71 (m, 1H of CH$_2$), 1.46 (m, 1H of CH$_2$), 1.18/1.14 (2t, J = 7.1/7.1 Hz, 6H, 2Me), 0.96 (t, J = 7.3 Hz, 3H, Me), 0.88 (t, J = 7.3 Hz, 3H, Me); ^{13}C{^{1}H}: δ = 168.9, 166.7, 166.3 (3CO), 138.1, 136.8, 133.4 (3C), 123.0 (CH), 60.8/60.5 (2CH$_2$), 44.7 (CHN), 38.1 (CH), 26.9 (CH$_2$), 25.4 (CH$_2$), 22.3, 13.7, 12.1, 10.9 (5Me).

Diethyl 3-(*N*-acetylamino)-6-methyl-*cis*-3,6-dihydrophthalate (2c): 120 °C, 24 h; R_f = 0.15; Yield: 67% from 2-pentenal (211 mg, 2.5 mmol), white solid. M.p. 77 °C; IR (KBr): $\tilde{\nu}$ = 3248 s, 3050 m, 2976 m, 2938 m, 2906 w, 1721 vs, 1642 vs, 1546 s, 1369 m, 1279 m, 1252 vs, 1182 s, 1097 m, 1059 s, 1030 m, 868 w, 779 w, 759 m, 644 w, 604 w; MS-EI: m/z (%): 295 (2) [M]$^+$, 249 (19) [M – OEt]$^+$, 234 (84), 191 (19), 178 (23), 164 (100), 134 (31), 106 (10), 43 (36) [Ac]$^+$; no other peaks of > 10%; HRMS: m/z: calcd for $C_{15}H_{21}NO_5$: 295.14197; found: 295.14200; ^{1}H NMR ([D$_6$]DMSO): δ = 8.08 (d, J = 8.7 Hz, 1H, NH), 5.82 (dd, J = 3.9/9.8 Hz, 1H, CH), 5.55 (dd, J = 3.9/9.9 Hz, 1H, CH), 5.18 (m, 1H, Me), 4.15, 4.07 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 3.08–3.00 (m, 1H, CH), 1.78 (s, 3H, Me), 1.21 (d, J = 7.1 Hz, 3H, Me), 1.20/1.15 (2t, J = 7.1/7.1 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 168.4, 166.6, 166.2 (3CO), 139.2/132.2 (2C), 131.2/123.2 (2CH), 60.8/60.6 (2CH$_2$), 42.8 (CHN), 31.7 (CH), 22.3, 20.1, 13.8, 13.7 (4Me).

Diethyl 3,5-dimethylphthalate (3a): 160 °C, 24 h; R_f = 0.55; Yield: 86% from 2-methyl-2-pentenal (245 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu}$ = 2982 s, 2935 m, 1724 vs, 1611 m, 1446 m, 1367 m, 1309 s, 1269 s, 1208 s, 1155 s, 1084 s, 1034 s, 870 m, 791 m, 765 m, 619 w; MS-EI: m/z (%): 250 (5) [M]$^+$, 204 (94) [M – OEt]$^+$, 177 (100), 148 (43) [M – CO_2Et – OEt]$^+$, 132 (37), 103 (15) [$C_6H_2(Me)_2$]$^+$, 91 (19), 77 (30); HRMS: m/z: calcd for $C_{14}H_{18}O_4$: 250.12051; found: 250.12422; ^{1}H NMR ($CDCl_3$): δ = 7.56 (s, 1H, Ph), 7.12 (s, 1H, Ph), 4.36–4.24 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 2.28, 2.26 (2s, 6H, 2Me), 1.30 (2t, J = 7.1/7.1 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 169.1/165.8 (2CO), 138.7/135.1 (2C), 134.6 (CH), 132.3/128.1 (2C), 127.6 (CH), 61.0/60.9 (2CH$_2$), 20.7/20.6 (2Me), 13.9/13.8 (2Me).

Diethyl 3,5-diethylphthalate (3b): 160 °C, 24 h; R_f = 0.55; Yield: 89% from 2-ethyl-2-hexenal (315 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu}$ = 3434 w, 2971 vs, 2937 s, 2904 w, 2876 m, 1732 vs, 1608 s, 1464 s, 1367 s, 1291 br vs, 1251 s, 1203 vs, 1154 vs, 1088 vs, 1027 s, 891 s, 865 m, 795 m; MS-EI: m/z (%): 278 (1) [M]$^+$, 232 (100) [M – OEt]$^+$, 205 (34), 176 (71), 160 (21), 133 (29), 117 (10); no other peaks of > 10%; HRMS: m/z: calcd for $C_{16}H_{22}O_4$: 278.15179; found: 278.15360; ^{1}H NMR ([D$_6$]DMSO): δ = 7.56 (d, J = 1.0 Hz, 1H, Ph), 7.40 (d, 1.0 Hz, 1H, Ph), 4.26/4.24 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 2.65/2.57 (2q, J = 7.5/7.5 Hz, 4H, 2CH$_2$), 1.26–1.25 (2t, J = 7.1/7.1 Hz, 6H, 2Me), 1.17/1.13 (2t, J = 7.5/7.5 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 168.1/165.7 (2CO), 145.5/141.5 (2C), 132.6 (CH), 131.5/128.4 (2C), 126.3 (CH), 61.1/60.8 (2CH$_2$), 27.7/25.7 (2CH$_2$), 15.7/15.2 (2Me), 13.9/13.8 (2Me).

Diethyl 3-methylphthalate (3c): 160 °C, 24 h; R_f = 0.65; Yield: 79% from 2-pentenal (211 mg, 2.5 mmol), colorless liquid. IR (cap.): $\tilde{\nu}$ = 3435 br w, 2983 vs, 2938 w, 2906 w, 1724 vs, 1595 m, 1463 s, 1446 s, 1390 m, 1367 s, 1281 br vs, 1184 vs, 1152 vs, 1113 vs, 1073 vs, 1030 s, 864 m, 753 s, 697 m; MS-EI: m/z (%): 236 (2) [M]$^+$, 190 (73) [M – OEt]$^+$, 163 (100), 134 (36), 89 (11), 77 (14); no other peaks of > 10%; HRMS: m/z: calcd for $C_{13}H_{16}O_4$: 236.10107; found: 236.10129; ^{1}H NMR ($CDCl_3$): δ = 7.82 (dm, J = 7.5 Hz, 1H, Ph), 7.39 (dm, J = 7.2 Hz, 1H, Ph), 7.34 (t*, J = 7.5 Hz, 1H, Ph), 4.42/4.34 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 2.36 (s, 3H, Me), 1.38/1.36 (2t, J = 7.1/7.1 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 169.2/165.8 (2CO), 135.3 (C), 134.2/128.8 (2CH), 128.1 (C), 127.4 (C, CH), 61.3 (2CH$_2$), 19.0 (Me), 14.1/14.0 (2Me).

Diethyl 3,5-dimethyl-4-phenylphthalate (3d): 140 °C, 24 h; R_f = 0.65; Yield: 50% from 2-methyl-3-ethylcinnamic aldehyde (436 mg, 2.5 mmol), colorless oil. MS-EI: m/z (%): 326 (15) [M]$^+$, 280 (100) [M – OEt]$^+$, 251 (87), 207 (22), 179 (17), 165 (31); no other peaks of > 10%; HRMS: m/z: calcd for $C_{20}H_{22}O_4$: 326.15179: found: 326.15150; ^{1}H NMR($CDCl_3$): δ = 7.69 (s, 1H), 7.36 (t*, J = 7.5 Hz, 2H, Ph), 7.28 (t, J = 7.5 Hz, 1H, Ph), 7.00 (dd, J = 1.5/7.5 Hz, 2H, Ph), 4.34/4.28 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 1.97/1.92 (2s, 6H, 2Me), 1.30 (2t, J = 7.2/7.2 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 169.8, 165.8, 146.7, 139.6, 137.4, 133.5, 133.4 (7C), 128.7, 128.6, 128.3, 127.2 (4CH), 126.5 (C), 61.3/61.2 (2CH$_2$), 20.9/17.5 (2Me), 14.2/14.0 (2Me).

Diethyl 4-methyl-5,6,7,8-tetrahydronaphthene-1,2-dicarboxylate (3e): 140 °C, 24 h; R_f = 0.55; Yield: 88% from 2-cyclohexylidenepropanal (347 mg, 2.5 mmol), colorless, pasty solid. M.p. 52 °C; IR (KBr): $\tilde{\nu}$ = 3438 br m, 2981 m, 2953 m, 2937 s, 2868 m, 1734 vs, 1714 vs, 1595 m, 1571 m, 1451 m, 1389 m, 1364 m, 1311 vs, 1274 vs, 1237 vs, 1186 vs, 1156 vs, 1113 m, 1051 s, 1029 s, 804 m, 785 s, 691 m; MS-EI: m/z (%): 290 (1) [M]$^+$, 244 (100) [M – OEt]$^+$, 216 (81), 188 (21), 172 (13), 143 (17), 129 (22), 115 (11); no other peaks of > 10%; HRMS: m/z: calcd for $C_{17}H_{22}O_4$: 290.15179; found: 290.15310; ^{1}H NMR ($CDCl_3$): δ = 7.63 (s, 1H, Ph), 4.40, 4.33 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 2.75, 2.60 (2t, J = 6.0/6.0 Hz, 4H, 2CH$_2$), 2.25 (s, 3H, Me), 1.85–1.75 (m, 4H, 2CH$_2$), 1.40–1.34 (2t, J = 7.1 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 169.8/166.0 (2CO), 141.3, 137.6, 134.0, 133.5 (4C), 128.2 (CH), 124.4 (C), 61.2/61.0 (2CH$_2$), 27.4/26.7 (2CH$_2$), 22.4/22.2 (2CH$_2$), 19.6 (Me), 14.2/14.1 (2Me).

Diethyl 4-methyl-9,10-dihydrophenanthrene-1,2-dicarboxylate (3f): 140 °C, 24 h; R_f = 0.60; Yield: 52% from 2-(3,4-dihydro-2*H*-naphthalen-1-ylidene)propanal (467 mg, 2.5 mmol), white solid. M.p. 103 °C; IR (cap.): $\tilde{\nu}$ = 3427 br w, 2979 w, 2948 w, 2901 w, 2838 w, 1722 vs, 1707 vs, 1446 m, 1365 m, 1302 s, 1226 s, 1200 m, 1174 m, 1148 m, 1065 s, 1028 m, 776 m, 750 m, 654 w; MS-EI: m/z (%): 338 (29) [M]$^+$, 292 (75) [M – OEt]$^+$, 263 (100) [M – CO_2Et]$^+$, 236 (14), 219 (16), 191 (33), 178 (25), 165 (18); no other peaks of > 10%; HRMS: m/z: calcd for $C_{21}H_{22}O_4$: 338.15179; found: 338.15280; ^{1}H NMR ($CDCl_3$): δ = 7.84 (s, 1H, Ph), 7.62 (dt, J = 6.5/1.6 Hz, 1H, Ph), 7.31–7.24 (m, 3H, Ph), 4.42, 4.36 (2q, J = 7.1/7.1 Hz, 4H, 2CH$_2$), 2.73 (br s, 4H, 2CH$_2$), 2.64 (s, 3H, Me), 1.40–1.35 (2t, J = 7.1/7.1 Hz, 6H, 2Me); ^{13}C{^{1}H}: δ = 169.5/165.7 (2CO), 139.9, 139.0, 137.0, 135.3, 133.2, 131.9 (6C), 131.7, 128.4, 128.0, 127.4, 125.9 (5CH), 125.5 (C), 61.4/61.2 (2CH$_2$), 29.0/26.9 (2CH$_2$), 22.9 (Me), 14.2/14.0 (2Me).

General procedure for high-temperature elimination of acetamide from 2a–c: Aminocyclohexene **2a–c** (2.5 mmol) and *p*-toluenesulfonic acid monohydrate (22 mg, 1.5 mol%) were combined in a threaded tube, and NMP (3 mL) was added. The reaction was stirred at elevated 160 °C. After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum. Silica gel chromatography (heptane/ethyl acetate 2:1) afforded the analytically pure products **3a–c**.

Diethyl 3,5-dimethylphthalate (3a): 160 °C, 24 h; R_f = 0.55; Yield: 91% from **2a** (245 mg, 2.5 mmol), colorless liquid. See section above for spectroscopic data.

Diethyl 3,5-diethylphthalate (3b): 160 °C, 24 h; R_f = 0.55; Yield: 89% from **2b** (315 mg, 2.5 mmol), colorless liquid. See section above for spectroscopic data.

Diethyl 3-methylphthalate (3c): 160 °C, 24 h; R_f = 0.65; Yield: 83% from **2c** (211 mg, 2.5 mmol), colorless liquid. See section above for spectroscopic data.

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[] CCDC-195184 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223–336–033; or e-mail: deposit@ccdc.cam.ac.uk).

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