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Facile solvent-free synthesis and structural elucidation of styrylcyclohex-2-enone derivatives

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Abstract A remarkably efficient procedure for the synthesis of styrylcyclohex-2-enone derivatives at room temperature is described using a mild reaction medium consisting of lithium perchlorate and *N*-(trimethylsilyl)diethylamine. Several compounds of this class are synthesized conveniently and rapidly. Spectroscopic and X-ray diffraction experiments confirm the proposed structures.

Keywords *Claisen-Schmidt* condensation; α,β-Unsaturated carbonyls; Solvent-free; Lithium perchlorate.

Introduction

α,β-Unsaturated carbonyl compounds are important intermediates in synthetic organic chemistry [1] and many methods for their synthesis have been reported so far [2]. The mixed aldol reaction, known as the *Claisen-Schmidt* condensation [3], is the most useful method extensively employed for the synthesis of α,β-unsaturated carbonyl systems *via* the reaction of aromatic aldehydes with α-acidic carbonyl moieties. In recent years several improvements have been made to widen the synthetic scope of this condensation reaction [4]. However, *Claisen-Schmidt* condensation of aldehydes with conjugated cyclic enones at their allylic position to produce pentadienone systems has not been comprehensively studied and in this regard only scattered data are reported in literature [5, 6]. In many of these reports, either no yields are provided or low quantities of products are obtained under strong basic conditions at elevated temperatures after long reaction times [5]. Thus, there is a demand for the investigation on synthetic methodology and structural elucidation of these products.

In recent years lithium perchlorate ($LiClO_4$) has emerged as a powerful *Lewis* acid to conveniently catalyze different organic transformations [7]. As a result, a dramatic improvement in many synthetic procedures is observed by the use of $LiClO_4$ in terms of rate acceleration, selectivity enhancement, and yield increase [8]. In continuation of our previous efforts on the use of $LiClO_4$ in synthetic organic chemistry [9, 10] and in the framework of our investigations on *Claisen-Schmidt* condensation of various cyclic ketones [11], we would like to introduce a facile procedure for the solvent-free condensation of **1** with various aldehydes under $LiClO_4$ and *N*-(trimethylsilyl)diethylamine (*TMS*N*Et*$_2$) catalysis at room-temperature (Scheme 1). Consequently, a rapid

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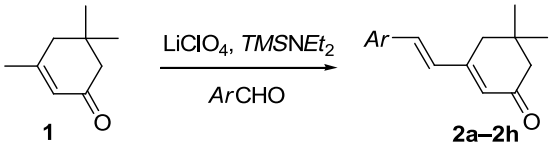

Scheme 1

access for the synthesis of the title compounds is offered along with full spectral characterization of the products and X-ray diffraction analysis of the phenyl derivative.

Results and discussion

A variety of aldehydes were subjected to condense with isophorone **1** at room-temperature using $LiClO_4$ and *TMS*N*Et*$_2$ in the presence of no additional solvent. The results are summarized in Table 1. When enone **1** was treated with benzaldehyde under these conditions, TLC monitoring of the reaction showed complete disappearance of the aldehyde and 85% formation of **2a** after 4 h (entry 1). Control experiments shed light on the role of the medium. Conduction of the reaction in the absence of $LiClO_4$ led to no formation of any product even after 24 h illustrating the promoting effect of the catalyst. Presence of *TMS*N*Et*$_2$ was also shown to be crucial for the reaction to proceed. When *TMS*N*Et*$_2$ was omitted from the mixture, less than 10% of **2a** formed after several hours. The use of alternative amines such as Et_3N and HN*Et*$_2$ prolonged the reaction time and the process did not reach complete conversion.

Structure of **2a** was confirmed with spectroscopic methods. Presence of a pair of vicinal olefinic hydrogen atoms with a coupling constant of about 16 Hz was a crucial indication for the condensation occurring at the allylic methyl group. In order to verify this structure, a single crystal of **2a** was prepared and subjected to an X-ray diffraction experiments. The outcome, as depicted in Fig. 1, clearly supports the proposed structure.

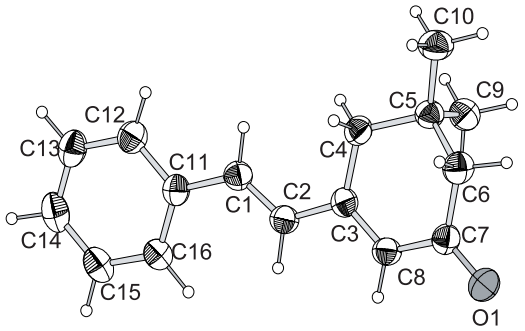

Fig. 1 Structure of **2a** at 193 K in the crystal. Displacement ellipsoids at 50% probability level

Table 1 $LiClO_4$ mediated condensation of **1** with various aromatic aldehydes

Entry	Aldehyde	Product **2**/*Ar*	Yield /%[a]	Ref.
1	Benzaldehyde	**2a**/*Ph*	85	[5c]
2	4-Methylbenzaldehyde	**2b**/4-*MePh*	83	–
3	4-Methoxybenzaldehyde	**2c**/4-*MeOPh*	88	[5c]
4	2,4,6-Trimethoxybenzaldehyde	**2d**/2,4,6-(*Me*O)$_3$*Ph*	89	–
5	4-Chlorobenzaldehyde	**2e**/4-Cl*Ph*	92	[5c]
6	4-Bromobenzaldehyde	**2f**/4-Br*Ph*	93	–
7	Thiophene-2-carbaldehyde	**2g**/2-thienyl	87	–
8	Furfural	**2h**/2-furyl	89	–

[a] Isolated yields

Similar products were prepared in the same manner by subjecting various aldehydes to the same-conditions. Therefore, when different aldehydes bearing various groups (entries 2–6) were mixed with **1**, *TMS*N*Et*$_2$, and $LiClO_4$, **2b**–**2f** were obtained in 83–93% within 3–4 h. Similarly, thiophene-2-carbaldehyde (entry 7) and furfural (entry 8) yielded **2g** and **2h**, respectively, within the same time period. All reactions proceeded efficiently and rapidly and formation of typical side products, which was reported previously [5], was not observed. Structures of **2b**–**2h** were similarly assigned based on their spectroscopic analysis by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy and their purity was confirmed by elemental analysis.

Based on these results, a mechanistic pathway can be offered for the reactions as depicted in Fig. 2. Reaction of **1** with *TMS*N*Et*$_2$ affords formation of **1a** and HN*Et*$_2$. *In situ* formation of the iminium salt **3**, as a result of the reaction of aldehydes with HN*Et*$_2$ in the presence of $LiClO_4$, has been postulated previously and is attributed to the *Lewis* acidity of the lithium ion and the high polarity of the reaction medium [10, 12]. Nucleophilic addition of **1a** to **3** followed by elimination of HN*Et*$_2$ yields products **2a**–**2h**.

In conclusion, we introduced a very simple procedure for the synthesis of the title compounds at room temperature and without the presence of additional

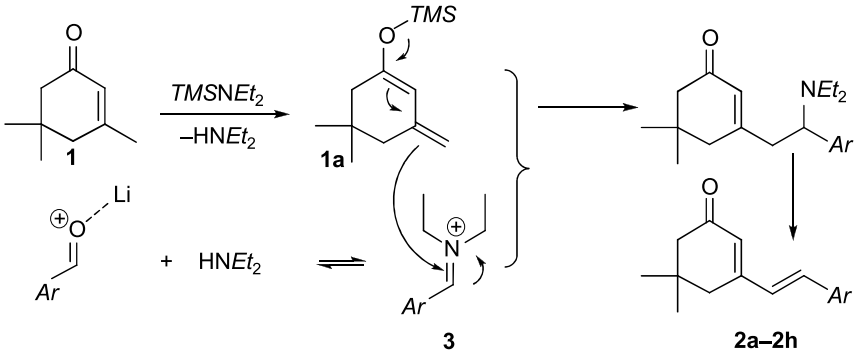

Fig. 2 Suggested mechanistic pathway for the reaction

solvent. In contrast to the few related existing reports [5] the medium used in our procedure is mild, reactions complete rapidly, formation of side products is not observed, and full spectroscopic characterization of the products is provided. The products are currently under investigation for the synthesis of decaline systems *via Diels-Alder* reactions.

Experimental

Reactions were monitored by TLC using silica gel coated plates and ethyl acetate/*n*-hexane solutions as mobile phase. Melting points were determined by a Büchi 530 melting point apparatus. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers. NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) instrument from $CDCl_3$ solutions and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at an ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument and results agreed favourably with calculated values. All reagents were purchased from commercial sources and were used after being purified by standard procedures.

General procedure

A solvent-free mixture of $LiClO_4$ (425 mg, 4 mmol) and $TMSNEt_2$ (852 mm^3, 4.5 mmol) was stirred at room temperature under inert atmosphere for 10 min. To this mixture was added the aldehyde (4 mmol) and stirring was continued for another 10 min. Enone **1** (580 mg, 4.2 mmol) was added to the reaction vessel. The course of the reaction was monitored until TLC and GC experiments showed complete disappearance of the starting aldehyde. The mixture was diluted by diethyl ether (10 cm^3), washed with 5% HCl (15 cm^3) solution, the organic phase was dried over Na_2SO_4, and the solvent was removed *in vacuo* by a rotary evaporator. The residue was recrystallized from hexane and the product was analyzed by physical and spectroscopic methods.

(E)-5,5-Dimethyl-3-styrylcyclohex-2-enone (**2a**, $C_{16}H_{18}O$)

Yellow crystals were obtained in 85% yield; mp 77–78°C (Ref. [5c] 76–78°C); IR (KBr): $\bar{\nu} = 3034, 1639, 1288\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$ (d, 2H, $J = 7.3$ Hz), 7.42–7.35 (m, 3H), 7.04 (d, 1H, $J = 16.2$ Hz), 6.95 (d, 1H, $J = 16.2$ Hz), 6.12 (s, 1H), 2.52 (s, 2H), 2.35 (s, 2H), 1.15 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6, 155.2, 136.4, 135.4, 130.0, 129.5, 129.3, 127.7, 127.6, 51.9, 39.5, 33.8, 28.9$ ppm; MS (70 eV): $m/z = 226$ (M^+), 193, 170, 141, 115.

(E)-5,5-Dimethyl-3-(2-p-tolylvinyl)cyclohex-2-enone (**2b**, $C_{17}H_{20}O$)

Yellow crystals were obtained in 83% yield; mp 102–103°C; IR (KBr): $\bar{\nu} = 3026, 1643, 1256\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43$ (d, 2H, $J = 8$ Hz), 7.22 (d, 2H, $J = 8$ Hz), 7.00 (d, 1H, $J = 16.2$ Hz), 6.91 (d, 1H, $J = 16.2$ Hz), 6.10 (s, 1H), 2.51 (s, 2H), 2.41 (s, 3H), 2.35 (s, 2H), 1.15 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6, 155.4, 139.8, 135.4, 133.7, 130.0, 129.0, 127.6, 127.1, 51.9, 39.5, 33.8, 28.9, 21.8$ ppm; MS (70 eV): $m/z = 240$ (M^+), 225, 169, 141, 115, 82.

(E)-3-[2-(4-Methoxyphenyl)vinyl]-5,5-dimethylcyclohex-2-enone (**2c**, $C_{17}H_{20}O_2$)

Yellow crystals were obtained in 88% yield; mp 61–62°C (Ref. [5c] 63–64°C); IR (KBr): $\bar{\nu} = 3025, 1644, 1254\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (d, 2H, $J = 8.7$ Hz), 6.98 (d, 1H, $J = 16.2$ Hz), 6.92 (d, 2H, $J = 8.7$ Hz), 6.81 (d, 1H, $J = 16.2$ Hz), 6.06 (s, 1H), 3.89 (s, 3H), 2.48 (s, 2H), 2.33 (s, 2H), 1.13 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6, 160.9, 155.6, 135.1, 129.2, 129.1, 127.8, 126.7, 114.8, 55.8, 51.9, 39.5, 33.7, 28.9$ ppm; MS (70 eV): $m/z = 256$ (M^+), 223, 172, 115.

(E)-5,5-Dimethyl-3-[2-(2,4,6-trimethoxyphenyl)vinyl]-cyclohex-2-enone (**2d**, $C_{19}H_{24}O_4$)

Dark yellow crystals were obtained in 89% yield; mp 151–152°C; IR (KBr): $\bar{\nu} = 3020, 1640, 1582\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.38$ (d, 1H, $J = 16.5$ Hz), 7.33 (d, 1H, $J = 16.5$ Hz), 6.17 (s, 2H), 6.06 (s, 1H), 3.92 (s, 6H), 3.88 (s, 3H), 2.53 (s, 2H), 2.33 (s, 2H), 1.14 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6, 162.1, 160.7, 158.1,$

130.6, 126.9, 125.7, 107.5, 91.1, 56.1, 55.7, 51.9, 39.2, 33.7, 29.0 ppm; MS (70 eV): $m/z = 316$ (M^+), 301, 285, 231, 207, 115.

(E)-3-[2-(4-Chlorophenyl)vinyl]-5,5-dimethyl-cyclohex-2-enone (**2e**, $C_{16}H_{17}ClO$)
Yellow crystals were obtained in 92% yield; mp 107–108°C (Ref. [5c] 111°C); IR (KBr): $\bar{\nu} = 3038$, 1646, 1379 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (d, 2H, $J = 8.5$ Hz), 7.38 (d, 2H, $J = 8.5$ Hz), 6.99 (d, 1H, $J = 16$ Hz), 6.90 (d, 1H, $J = 16$ Hz), 6.12 (s, 1H), 2.51 (s, 2H), 2.36 (s, 2H), 1.15 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.5$, 154.7, 135.2, 135.0, 133.9, 130.6, 129.5, 128.8, 127.9, 51.8, 39.5, 33.8, 28.9 ppm; MS (70 eV): $m/z = 260$ (M^+), 227, 169, 141, 115.

(E)-3-[2-(4-Bromophenyl)vinyl]-5,5-dimethylcyclohex-2-enone (**2f**, $C_{16}H_{17}BrO$)
Off white crystals were obtained in 93% yield; mp 120–121°C; IR (KBr): $\bar{\nu} = 3025$, 1643, 1379 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.52$ (d, 2H, $J = 8.1$ Hz), 7.38 (d, 2H, $J = 8.1$ Hz), 6.96 (d, 1H, $J = 16.4$ Hz), 6.91 (d, 1H, $J = 16.4$ Hz), 6.12 (s, 1H), 2.49 (s, 2H), 2.35 (s, 2H), 1.14 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6$, 154.7, 135.4, 134.0, 132.5, 130.7, 129.1, 128.0, 123.5, 51.8, 39.5, 33.8, 28.9 ppm; MS (70 eV): $m/z = 304$ (M^+), 288, 141, 115.

(E)-5,5-Dimethyl-3-(2-thiophen-2-ylvinyl)cyclohex-2-enone (**2g**, $C_{14}H_{16}OS$)
Yellow crystals were obtained in 87% yield; mp 84–85°C; IR (KBr): $\bar{\nu} = 2937$, 1656, 1294 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.34$ (d, 1H, $J = 5$ Hz), 7.18 (d, 1H, $J = 5$ Hz), 7.16 (d, 1H, $J = 15.9$ Hz), 7.06 (dd, 1H, $J = 5$, 5 Hz), 6.75 (d, 1H, $J = 15.9$ Hz), 6.07 (s, 1H), 2.46 (s, 2H), 2.34 (s, 2H), 1.14 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6$, 154.7, 142.1, 129.4, 128.9, 128.4, 128.3, 127.2, 127.1, 51.8, 39.4, 33.8, 28.9 ppm; MS (70 eV): $m/z = 232$ (M^+), 199, 176, 141, 115.

(E)-3-(2-Furan-2-ylvinyl)-5,5-dimethylcyclohex-2-enone (**2h**, $C_{14}H_{16}O_2$)
An oil was obtained in 89% yield; IR (KBr): $\bar{\nu} = 3125$, 1656, 1264 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.48$ (d, 1H, $J = 1.5$ Hz), 6.87 (d, 1H, $J = 16.1$ Hz), 6.81 (d, 1H, $J = 16.1$ Hz), 6.50 (d, 1H, $J = 3.5$ Hz), 6.48 (dd, 1H, $J = 1.5$, 3.4 Hz), 6.09 (s, 1H), 2.44 (s, 2H), 2.33 (s, 2H), 1.12 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6$, 154.9, 152.8, 144.2, 128.1, 127.3, 125.9, 112.6, 112.3, 51.8, 39.2, 33.7, 28.8 ppm; MS (70 eV): $m/z = 216$ (M^+), 188, 160, 131, 115.

X-Ray structure determination of ***2a***
A crystal of **2a**, grown from hexane, was investigated on an IPDS area detector system (Stoe) at −80°C using Mo Kα-radiation. $C_{16}H_{18}O$, $M_r = 226.31$, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 13.963(2)$ Å, $b = 5.896(1)$ Å, $c = 16.14(3)$ Å, $\beta = 103.05(1)°$, $V = 1294.4(4)$ Å^3, $d_c = 1.161$ mg/m^{-3}, $\mu = 0.070$ mm^{-1}. 7029 reflections to $\theta = 26.15°$, 2571 independent, $1362 > 4\sigma(F)$, $wR_2 = 0.066$, $R = 0.038$, ρ(min/max) $0.114/-0.116$ eÅ^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-629605. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. Code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk or *via* www.ccdc.cam.ac.uk/conts/retrieving.html].

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