Cyclotrimerization of Enaminones: An Efficient Method for the Synthesis of 1,3,5-Triaroylbenzenes

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Abstract: An efficient method for the synthesis of 1,3,5-triaroylbenzenes **2a**–**f** by cyclotrimerization of enaminones **1a**–**f** in acetic acid/pyridine (4:1) is illustrated. The structures of the products have been delineated by spectroscopic methods.

Keywords: cyclotrimerization, enaminones, triaroylbenzenes, supramolecular chemistry, regioselectivity

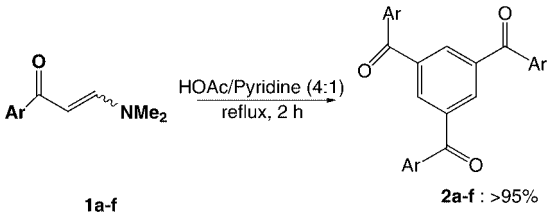
Recently, 1,3,5-triaroylbenzenes have attracted much attention for their intrinsic value as precursors in supramolecular assemblies.[1] Indeed, the level of architectural sophistication that can be achieved in such systems is closely tied to the availability of suitable starting materials.[2,3] 1,3,5-Triaroylbenzenes have been synthesized in low to moderate yield by limited routes which include oxidation of the corresponding secondary alcohol by CrO_3[4] or ethynylarylcarbinol by active MnO_2,[5] oxidative condensation of 1,3,5-triacylbenzene derivatives with bis-diquaternary ammonium salt of the conjugated dienes,[6] reaction of methyl benzoate with alkynes in the presence of quaternary ammonium salt,[7] acidic cyclotrimerization of ethylene epoxide derivatives[8] and aroylvinyl sulfonium salts.[9] Palladium-induced cyclotrimerization of β-aminoketones has also been reported to afford triaroylbenzenes but in low yield.[10] Balasubramanian has reported a convenient trimerization of aryl ethynyl ketones in refluxing DMF to give 1,3,5-triaroylbenzenes in good yield.[11]

Now I wish to report a simple and efficient trimerization of enaminones to give 1,3,5-triaroylbenzenes in synthetically quantitative yields.

Enaminones are versatile synthetic intermediates and widely used synthons in the synthesis of many heterocycles[12–14] and natural products[15] due to their regioselectivity and ability to function both as ambident nucleophiles and electrophiles.[14,16]

In the present work, when enaminones **1a**–**f** were heated at reflux for 2 hours in acetic acid/pyridine (4:1), 1,3,5-triaroylbenzene derivatives **2a**–**f** were obtained in quantitative yield (Scheme 1).

When the reaction was carried out in refluxing xylene, toluene, dioxane or DMF no trimerization was observed and the starting material was recovered unchanged. Moreover,



1, 2
a, Ar = C_6H_5
b, Ar = *p*-Me-C_6H_4
c, Ar = 1-naphthyl
d, Ar = *p*-diphenyl
e, Ar = *p*-Cl-C_6H_4
f, Ar = *p*-Br-C_6H_4

Scheme 1

when acetic acid was used as a solvent the trimerization occurred and the 1,3,5-triaroylbenzenes were obtained but in moderate yield (60%). However, when sodium acetate was used with acetic acid, the cyclotrimerization also took place and 1,3,5-triaroylbenzenes were obtained in good yield (75%). From these results, it is preliminarily observed that the cyclotrimerization is not a simple thermal transformation and an extremely solvent dependant process.

A rational explanation of the cyclotrimerization is depicted in Scheme 2. Thus, condensation of two molecules of enaminone **1** give intermediate diene **3** under the reaction conditions via removal of dimethylamine (Route 1). Then, subsequent [4+2] cycloaddition between foregoing diene **3** and enaminone **1**, which is present in excess in the reaction medium, affords cyclic intermediate **4** which in turn aromatized via removal of two molecules of dimethylamine to give 1,3,5-triaroylbenzene **2**. Alternatively, aryl ethynyl ketone[17] **5** could be formed from enaminone **1** via dimethylamine elimination (Route 2). Subsequently, the produced aryl ethynyl ketone **5** reacts with enaminone **1** to give zwitterionic intermediate **6**[11] which in turn either reacts with the enaminone **1** to give the above mentioned cyclic intermediate **4** proceeding to product **2** (Route 2A), or reacts with one molecule of compound **5** in the same manner than reported by Balasubramanian[12] to form intermediate **7** which undergoes aromatization via removal of dimethylamine to give **2** (Route 2B).

It is worth mentioning that none of the foregoing intermediates was detected in the reaction mixture by monitoring the reaction by either TLC or ^{1}H NMR spectroscopy.

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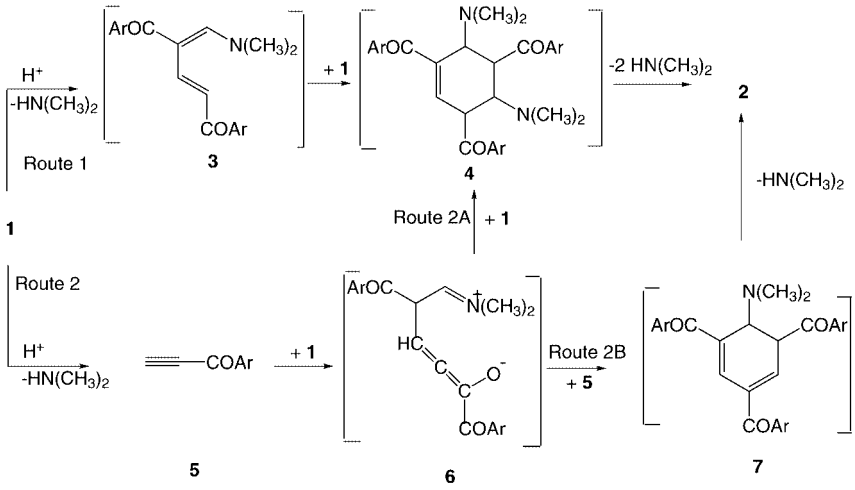
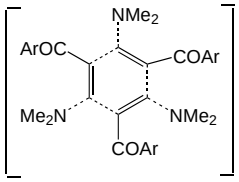


Scheme 2

Thus, a [2+2+2]-concerted cyclotrimerization of enaminone **1** via intermediate **8** (Figure 1) is also possible and can not be ruled out.



8

Figure 1

The structures of 1,3,5-triaroylbenzenes **2a–f** were confirmed by $^1H/^{13}C$ NMR, EI-MS and IR spectroscopy and also the UV/Vis spectra have been measured. Thus, in the ^1H NMR spectra of compounds **2a–f** a singlet signal was observed downfield at δ = 8.58–8.33 ppm assigned to three protons at positions 2, 4 and 6 in the benzene ring. ^{13}C NMR spectra revealed signals at δ = 195.7–193.4 ppm. Also, all the UV spectra of triaroylbenzenes **2a–f** revealed structured absorptions in the range 240–339 nm mainly dominated by $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions exhibited by the aryl and the carbonyl groups.

In summary, a new and efficient method for the synthesis of 1,3,5-triaroylbenzenes from enaminones has been described. The yield of the trimerization coupled with the availability of the precursors makes this method the most expeditious and efficient one among the previously reported methods for constructing 1,3,5-triaroylbenzenes.

NMR spectra were recorded on a Bruker 300 MHz spectrometers using TMS as internal standard and $CDCl_3$ as a solvent. IR spectra were obtained by using a Perkin-Elmer 983 spectrophotometer. UV/Vis spectra were recorded on Perkin-Elmer UV-spectrophotometer. Electron impact ionisation mass spectrometry (EI-MS) was performed on a Varian AMD 604 instrument using 70 eV ionization energy. Melting points (mp) are uncorrected. Enaminones **1a–f** have been prepared by reaction of dimethylformamide dimethyacetal (DMAC) with alkyl ketones.

1,3,5-Triaroylbenzenes (2a–f); General Procedure

A solution of enaminone **1** (10 mmol) in acetic acid/pyridine (4:1, 10 mL) was heated at reflux for 2 h. Then, the solvent was evaporated under vacuum, the resulting residue was washed with H_2O several times and recrystallized from an appropriate solvent.

1,3,5-Tribenzoylbenzene (2a)

Colorless crystals (from ethanol); mp 122 °C (lit.[17] 119 °C, Lit.[11] 120 °C).

IR (KBr): 1660 (C=O) cm^{-1}.

^1H NMR: δ = 8.45 (s, 3 H), 7.84 (m, 6 H), 7.65 (m, 9 H).

^{13}C NMR: δ = 194.8, 138.1, 136.3, 134.0, 133.2, 130.0, 128.6.

MS (EI): *m*/z (%) = 390 (M^+), 313, 105, 77.

UV/Vis (CH_3Cl): λ_{max} = 242, 244, 338 nm.

1,3.5-Tri-(*p*-methylbenzoyl)benzene (2b)

Colorless crystals (from ethanol); mp 156 °C (lit.[11] 156 °C).

IR (KBr): 1662 (C=O) cm^{-1}.

^1H NMR: δ = 8.32 (s, 3 H), 7.73 (m, 6 H), 7.28 (m, 6 H), 2.42 (s, 9 H).

^{13}C NMR: δ = 194.7, 144.2, 138.4, 133.8, 133.7, 130.3, 129.3, 21.7.

MS (EI): *m*/z (%) = 432 (M^+), 313, 119, 91.

UV/Vis (CH_3Cl): λ_{max} = 241, 269, 339 nm.

1,3,5-Tri-(1-naphthoyl)benzene (2c)

Colorless crystals (from ethanol); mp 205.3 °C (lit.[11] 196 °C).

IR (KBr): 1667 (C=O) cm^{-1}.

^1H NMR: δ = 8.58 (s, 3 H), 8.20 (m, 3 H), 7.95 (m, 6 H), 7.54 (m, 9 H), 7.21 (m, 3 H).

^{13}C NMR: δ = 195.9, 139.3, 135.4, 134.4, 133.8, 132.5, 130.8, 128.9, 127.7, 126.7, 125.4, 124.2.

MS (EI): *m*/z (%) = 540 (M^+), 155, 127.

UV/Vis (CH_3Cl): λ_{max} = 240, 290, 339 nm.

1,3,5-Tri-(*p*-phenylbenzoyl)benzene (2d)

Colorless crystals (from acetone); mp 185.5 °C.

IR (KBr): 1662 (C=O) cm^{-1}.

^{1}H NMR: δ = 8.45 (s, 3 H), 7.91 (m, 6 H), 7.55 (m, 6 H), 7.44 (m, 15 H).

^{13}C NMR: δ = 194.5, 138.4, 133.9, 130.8, 129.0, 128.9, 128.8, 128.4, 127.3, 127.2, 127.1.

MS (EI): *m*/z (%) = 618 (M^+), 181, 152.

UV/Vis (CH_3Cl): λ_{max} = 241, 300 nm.

1,3,5-Tri-(*p*-chlorobenzoyl)benzene (2e)
Colorless crystals (from ethanol): mp 180 °C (lit.[11] 179 °C).

IR (KBr): 1665 (C=O) cm^{-1}.

^{1}H NMR: δ = 8.33 (s, 3 H), 7.77 (m, 6 H), 7.5 (m, 6 H).

^{13}C NMR: δ = 193.4, 140.0, 138.0, 134.5, 133.8, 131.4, 129.1.

MS (EI): *m*/z (%) = 494 (M^+ + 1), 381, 139.

UV/Vis (CH_3Cl): λ_{max} = 241, 269, 339 nm.

1,3,5-Tri-(*p*-bromobenzoyl)benzene (2f)
Colorless crystals (from acetone); mp 210.5 °C.

IR (KBr): 1661 (C=O) cm^{-1}.

^{1}H NMR: δ = 8.39 (s, 3 H), 7.72 (m, 6 H), 7.65 (m, 6 H).

^{13}C NMR: δ = 193.5, 137.9, 134.9, 133.8, 132.0, 131.4, 128.0.

MS (EI): *m*/z (%) = 627 (M^+ + 3), 238, 182, 155.

UV/Vis (CH_3Cl): λ_{max} = 241, 272, 338 nm.

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