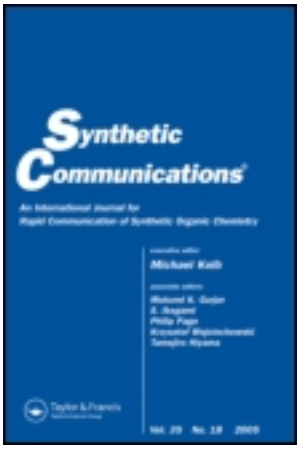

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 08 Aug 2012.Version of record first published: 06 Mar 2013.

To cite this article: Feng-Shou Liu , Xue-Hong Liu , Kang-Zhi Ye & Dong-Sheng Shen (2013): Facile Synthesis of 1,3,5-Triaroylbenzenes by Direct Cyclotrimerization of Ketone Enolates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:12, 1640-1645

To link to this article: http://dx.doi.org/10.1080/00397911.2012.658944

Synthetic Communications®, 43: 1640–1645, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.658944

FACILE SYNTHESIS OF 1,3,5-TRIAROYLBENZENES BY DIRECT CYCLOTRIMERIZATION OF KETONE ENOLATES

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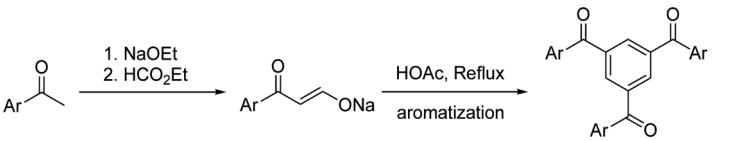
GRAPHICAL ABSTRACT



1a: Ar = Phenyl;
1b: Ar = 4-methylphenyl;
1c: Ar = 4-methyoxylphenyl;
1d: Ar = 4-chlorophenyl;
1e: Ar = 4-bromophenyl;

Abstract *Based on the improvement of the synthesis of 1,3,5-triaroylbenzenes, a convenient acid catalytic strategy was carried out and a series of 1,3,5-triaroylbenzenes were synthesized. The reaction temperature effect was investigated, and a mechanism of the cyclotrimerization has been proposed.*

Keywords Acid; cyclotrimerization; ketone enolate; 1,3,5-triaroylbenzene

INTRODUCTION

1,3,5-Triaroylbenzenes are an important class of compounds with a distinct structure, and they have attracted significant interest in recent years because of their numerous applications in medicine,[1] nonlinear optical materials,[2] supermolecular assemblies,[3] and the functional polymer materials.[4] Traditionally, 1,3,5-triaroylbenzene compounds have been synthesized through several routes, including the oxidation of secondary alcohols[3n] and ethynylarycarbinols,[3o] cyclotrimerization of ethylene epoxide,[3p] aroylvinyl sulfonium salts[3q] and aryl ethynyl ketones.[3r–v] Moreover, they also can be obtained by aromatic electrophilic substitution reactions such as Friedel–Crafts acylation,[5] cross-coupling reactions of acyl chlorides with

Received October 3, 2011.
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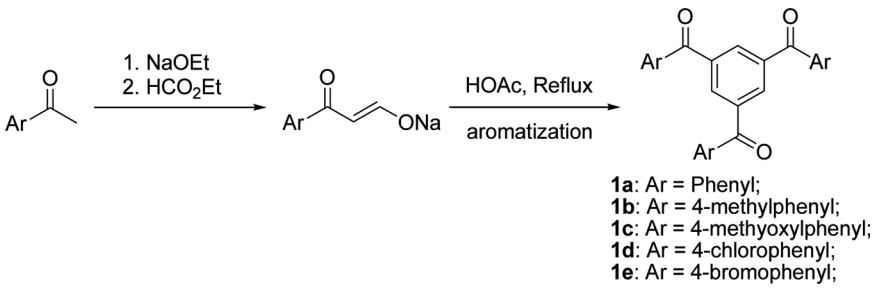
organometallic reagents,[6] and a variety of metal-mediated multistep coupling reactions.[7] Although the synthetic methods mentioned exhibit moderate to satisfactory yields, they suffer drawbacks either in the use of expensive staring materials, the need for relatively harsh conditions, or poor regioselectivity.

Recently, some new approaches have been developed to produce 1,3,5-triaroylbenezes. Elnagdi et al. synthesized a series of substituted enaminones, which were converted into 1,3,5-triaroylbenezes an acid mediated reaction.[8] Subsequently, Elghamry improved the reaction conditions by changing the solvent system and attained excellent yields.[9] Another synthetic method for preparing 1,3,5-triaroylbenezes, reported by Joseph et al., entails cyclotrimerization of β-aryl-β-haloacroleins in the presence of diethylamine.[10] In view of the proposed mechanism of the cyclotrimerization, both nucleophilic and electrophilic substituents on β-aryl-β-haloacroleins are required.

Notably, ketone enolates are easy to assess, and they have been used as precursors for the synthesis of enol thioethers, enaminones, enol ethers, α-formyl-α,β-unsaturated ketones, α-methylene ketones, and triacylbenzenes.[11] Moreover, Eiden and Haverland have described an example where α-formyl-α,β-unsaturated ketone (3-(2-methoxyphenyl)-3-oxopropanal) was used as starting material for the synthesis of triaroylbeneze in the presence of benzaldehyde and sodium hydroxide.[12] However, the mechanism of the reaction was not discussed and the spectrum of the desired product was not provided. In light of the [2 + 2 + 2] cyclotrimerization mentioned previously, we contemplated the cyclotrimerization of ketone enolates as a means of accessing the 1,3,5-triaroylbenezes that would demonstrate both atom economy and easy synthesis. As a demonstration of the advantages of this strategy, we report here a novel, one-step synthesis of triaroylbenzenes through the cyclotrimerization of ketone enolates.

RESULTS AND DISCUSSION

The ketone enolates utilized in this study were designed for their potential ability to undergo self-cyclotrimerization and generate triaroylbenzenes. The ketone enolate sodium salts were prepared from aryl ethyl ketones by classical Claisen condensation with sodium ethoxide and ethyl formate in a one-step reaction. Addition of acetic acid gave ketone enolates in situ and afforded triaroylbenzenes (**1a–e**) in a 78–88% overall yield (Scheme 1).



Scheme 1. Synthetic route to **1a–e**.

The reaction temperature played an important role in the cyclotrimerization reaction. At room temperature, the ketone enolate sodium salts were only converted into their corresponding ketone enolates, which is consistent with an earlier report.[11b] However, upon elevating the temperature to reflux, the product was obtained in satisfactory yield. Under these reaction conditions, the symmetric 1,3,5-triaroylbenzene was confirmed as the sole product in all cases except for 1,2,4-substituted analogs. As can be seen in Fig. 1, the ^{1}H NMR spectrum of **1a** revealed four kinds of protons. One singlet at $\delta = 8.40$ ppm can be ascribed to the signal of the arene backbone of **H1**, along with one doublet-doublet for **H2** and two multiplets for **H3** and **H4**, respectively.

In the light of the mechanism mentioned by Abdel-Khalik and Elnagdi,[8a] the regioselective reactions demand both nucleophilic and electrophilic substituents on the reactant. In the case of ketone enolates, nucleophiles can attack at the β-carbon of carbonyl groups, while electrophiles can attack at the α -carbon. Therefore, a rational explanation of the transformations that are responsible for the production of the triaroylbenzenes might be a series of Michael reactions. As depicted in Scheme 2, upon the addition of a proton, a ketone enolate (**3**) might be expected to form a new electrophile (**4**) and then added to a ketone enolate to yield the intermediates **5** and **6**. Subsequently, this reaction would repeat once again to generate intermediate **7**, which in turn could undergo an internal cyclization to give a six-membered ring (intermediate **8**) with the resultant elimination of three molecules of water to afford the desired triaroylbenzenes. Considering the requirement for the elimination of water in the reaction process, the greater reaction temperature is consistent with the proposed mechanism.

The yields of triaroylbenzenes obtained from cyclotrimerization of ketone enolates were comparable to the good yields obtained by cyclotrimerization of enaminones. Moreover, there are some noteworthy features of this cyclotrimerization process that merit further comment. For instance, the cyclotrimerization of

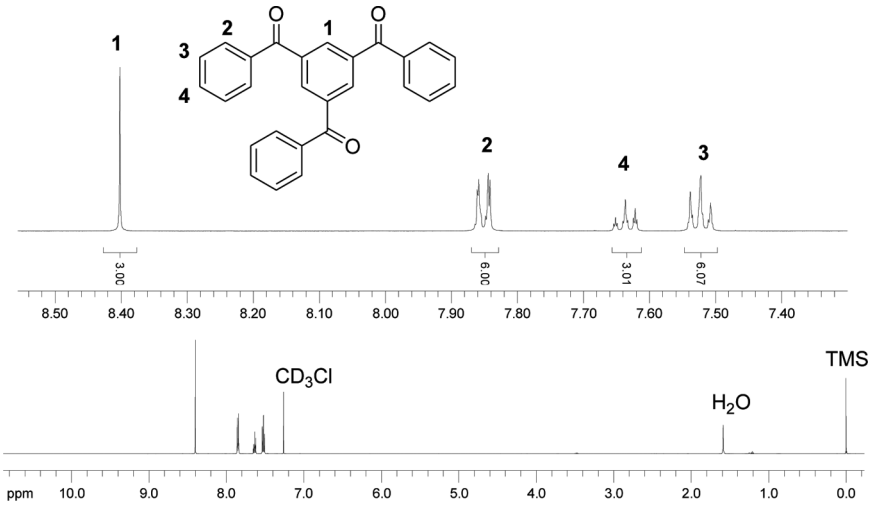
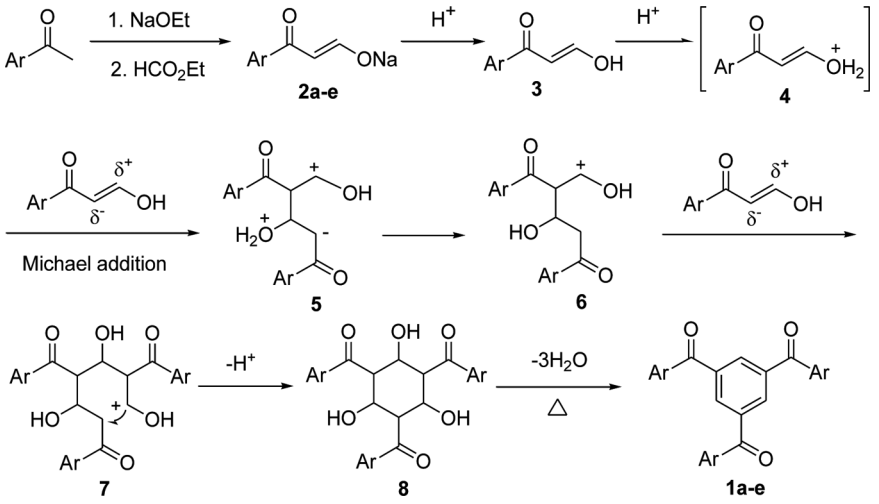


Figure 1. ^{1}H NMR spectrum of **1a**.



Scheme 2. Proposed mechanism of direct cyclotrimerization of ketone enolate.

ketone enolates demonstrates atom economy relative to the cyclotrimerization of enaminones. Also, the reaction is a direct cyclotrimerization of ketone enolates in the absence of dimethylamine. Moreover, the reaction proceeded with high regioselectivity wherein the 1,3,5-triaroylbenzene was obtained as the sole product.

CONCLUSION

In summary, we have developed a simple route for the synthesis of 1,3,5-triaroylbenzenes by the acid catalytic ketone enolates in a one-step strategy. It is crucial to increase the reaction temperature, which can promote the yield of products. Furthermore, a mechanism of the cyclotrimerization has been proposed.

EXPERIMENTAL

Toluene was purchased from Guangzhou Chemical Reagent Factory and was used after it was refluxed over metallic sodium for 8 h. Acetic acid, ethanol, and sodium ethoxide were purchased from Guangzhou Chemical Reagent Factory and used as recieved. Ethyl formate, acetophenone, 4-methylacetophenone, 4-methyoxylacetophenone, 4-chloroacetophenone, and 4-bromoacetophenone were purchased from Shanghai Chemical Reagent Factory and used as received. NMR spectra were recorded on a Varian Mercury-Plus 500-MHz NMR spectrometer and referenced versus tetramethylsilane (TMS) as standard. Elemental analyses were determined with a Vario EL series elemental analyzer from Elementar.

A solution of acetophenone (10 mmol) in ethyl formate (1.48 g, 20 mmol) was added dropwise to a stirred suspension of sodium ethoxide (0.68 g, 10 mmol) in anhydrous toluene (50 ml). After stirring for 4 h at room temperature, 25 ml acetic acid was added dropwise to the stirred suspended matter, and it was refluxed for another 2 h. Then, water (400 ml) was added, the organic phase was separated,

and the water phase was extracted with ether (2×40 ml). After combining with the organic phase and drying over anhydrous sodium sulfate, the solvent was removed on a rotary evaporator, and the residue was recrystallized in ethanol to afford the title compound.

ACKNOWLEDGMENTS

We acknowledge the National Natural Science Foundation of China (No. 21004014) and the Foundation for Distinguished Young Talents in Higher Education of Guangdong (No. LYM10091) for financial support.

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