Synthetic return of the Meldrum's acid. 2,2-dimethyl-1,3-dioxane- 4,6-dione assisted formation of tetrahydroquinolin-2-one derivatives. Short synthetic pathway to the biologically useful scaffold

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Abstract

A new method for the preparation of tetrahydroquinolin-2-one derivatives has been described. The two-step reaction between enaminone and acylating agent followed by electrophilic cyclization can be performed in a single synthesis procedure, without isolation of intermediates. The whole process is facilitated by the use of acyl Meldrum's acids which not only shortens the preparation time of the substrates but also easily extends the range of substituents used. Method scope and limitation were verified on various combinations of reagents and revealed general applicability of the method to the synthesis of tetrahydroquinolin-2-one core. Some exceptions to the regular course of the reaction were observed when a strongly EDG was introduced via acyl Meldrum's acids, and the mechanism of this process was elucidated during the investigation.

Introduction

The pyridone motif is frequently present in a wide range of biologically active compounds including pharmaceuticals. The main attention is paid to the drug-like activity of pyridones derivatives. Thus, the broad scope of biological targets could be found for pyridone molecules (Fig. 1); for instance: agonists of cannabinoid CB2R receptor **1**[1,2], analgesic agents with 4-pyridone moiety **2**[3, 4]kinase inhibitors **3** with anaplastic anticancer properties[5] or topoisomerase inhibitor camptothecin **4**. Also, other anticancer activity, as well as antiproliferative activity, is observed for 2-pirydone compounds reported by Li and coworkers **5**[6]. Whereas polycyclic pyridones **6** exhibit antifungal activity against *Candida albicans*[7]. Obviously, among pyridone derivatives also could be found a lot of commercially available drugs i.e. antifungal and antibacterial ciclopirox **7** or antisarcoma drug tazemetostat **8**.

On the other hand, pyridone application as biologically active agent possesses one additional advantage connected with fast biodegradation[8, 9].

Recently we focused our synthetic efforts on the preparation of 2-pyridone moiety fused with a saturated ring, as well as on the preparation of a permanently aromatic similar system isosteric with pyridone scaffold[10, 11]. According to our anticipation and molecular docking results, the referred compounds have exhibited anticancer activity however the convenience of synthesis was far from perfect. A significant number of synthetic methods could be found in chemical literature for the preparation of 2-pyridone moiety. Thus, among the most popular methods we can distinguish two main approaches[12], first with the transformation of existing heterocyclic ring into 2-pyridone and second based on the formation of the heterocyclic ring *de novo*. According to the first approach, pyrones could be easily transformed into pyridone ring by heating in boiling acetic acid in the presence of ammonium acetate[13, 14] (Fig. 2). Pyridine N-oxides may be transformed to pyridone under heating with carboxylic acids anhydrides[15].

The second approach assumes the formation of a ring from non-cyclic starting materials, frequently based on the condensation of the nitrogen-bearing component with 1,3-dicarbonyl compounds. The reaction of cyanoacetamide with ethyl 2,4-dioxovalerate is an example[16, 17]. Also, nitrile could be a source

of nitrogen in the case of the reaction with highly reactive malonyl chloride[18, 19]. A specific and interesting type of condensation to form 2-pyridones involves reactions where the nitrogen component is in the form of an enamine which reacts with 1,3 dicarboyl derivatives. Sheibani and co-workers published a paper where enamine conjugated with carbonyl reacts with (chlorocarbonyl)phenyl ketene[20]. Somewhat similar in approach were procedures used by Guillemont and co-workers. They published the formation of 2-pyridone scaffold in the reaction of conjugated enamine with activated malonic derivative[21].

Previously used in our laboratory method for the synthesis of tetrahydroquinolin-2-one scaffold[10, 11] was a compilation and adaptation of a procedure described by several research groups[22–24]. Due to the problem with direct procedure with the use of benzoylacetate ammonium acetate and cyclohexanone, where in situ formation of amide should take place followed by the subsequent reaction with cyclohexanone. We synthesized amide in a separate process, isolated it and in the next step, we condense 1,3-dicarbonyl amide with cyclohexanone to obtain desired 2-pyridone fused with a six-membered ring. This method however successful, in practice was tedious and time-consuming, thus we were looking for an improved method for the preparation of 2-pyridone scaffold.

Results and discussion

In the current paper, taking into consideration our experience with the synthesis of pyridones together with our knowledge about the application of Meldrum's acid[25–30] in synthesis and considering of available literature we would like to present a new approach for preparation of 2-pyridones.

Taking into consideration our previous experience, we considered as a key step to be obtaining a 1,3-dicarbonyl amide with an already attached fragment allowing for cyclization and obtaining a 2-pyridone with a fused hexagonal ring, i.e. tetrahydroquinolin-2-one. The following enamide **11** on Fig. 3 would meet these requirements. We also assumed at this stage that such an enamide would undergo further desired cyclization in acidic conditions.

Theoretically, having the enaminone and the acylating reagent, obtaining the appropriate enamide should not be a problem, however, the use of acyl-acetate esters is not recommended due to too low reactivity with the amino group and side reactions with the ketone fragment. However, the use of strong acylating reagents such as chlorides, anhydrides, or ketenes, as in the cited works[18–21], implies problems with their preparation or storage. Therefore, we proposed an idea to exploit acylating properties of Meldrum's acid derivatives, which allow to introduce 1,3-dicarbonyl moiety together with a possibility to introduce broad scope of side chains. It should be stressed that used acyl derivatives of Meldrum's acid are stable compounds, easily prepared and purified from commercially available starting materials.

First, we run a few experiments between 4 eq of 5-(hydroxy(phenyl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**9a**) with 1 Eq. 3-amino-5,5-dimethylcyclohex-2-enone **10a** in various conditions to optimize the method. As a result, we observed the formation of desired conjugated enamide with yield varying from

moderate 30% in case of reaction performed in boiling DCE without molecular sieves up to quantitive yield 97% with the presence of molecular sieves and at 55°C in DCE (Fig. 3).

Thus, isolated and purified enamide **11aa** was subjected to cyclization toward the formation of 7,7-dimethyl-4-phenyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (**12aa**). Our first attempts were focused on the application of mild Lewis acids as transition metals triflates, especially scandium triflate. However, this approach was unsuccessful regardless to condition applied (Fig. 4).

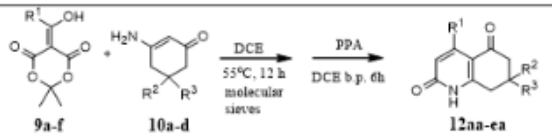
This failure prompted us to search for an effective catalyst for the preparation of 7,7-dimethyl-4-phenyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (**12aa**). We focused on protic acid catalysts especially on PPA as a moderately acidic agent with a well-known ability to catalyst similar reactions including Knorr-type cyclization[31–37].

We run two experiments with the cyclization of enamide **11aa** in the presence of PPA. First in boiling dichlorobenzene DCB with a reaction time of 2h allowed to the formation of 7,7-dimethyl-4-phenyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (**12aa**) with 37% yield, whereas the second was performed in boiling dichloroethane DCE within 6h with yield 34% (Fig. 5).

With these results, we put the question if those two processes, inter and intramolecular, could undergo subsequently without isolation of enamide intermediate in a kind of “one-pot” reaction. To evaluate our hypothesis we again carried out the condensation of a fourfold excess of benzoyl Meldrum’s acid **9a** with an enaminone **10a**. After completion of the enamide formation and disappearance of benzoyl Meldrum acid revealed with TLC analysis, PPA was added to the reaction, and the whole mixture was heated to boiling point for 6 hours. As a result, we obtained the 7,7-dimethyl-4-phenyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (**12aa**) with 32% yield (Fig. 6). As an alternative for the usage of PPA we tested TsOH in toluene however with a weaker result since the yield after cumulating two steps was only 15%.

Encouraged by these results, we decided to perform a series of reactions using various derivatives of Meldrum's acid and enaminones to evaluate the scope and limitations of the newly developed method. With our new method, we were able to prepare a wide range of compounds with 7,8-dihydroquinoline-2,5(1H,6H)-dione scaffold quickly in one laboratory step with moderate yields (Table 1).

Table 1. Synthesis of 7,8-dihydroquinoline-2,5(1H,6H)-dione derivatives from acyl Meldrum's acids and enaminones.



9a-f 10a-d 12aa-ea

Run	R^1	R^2	R^3	Product	Yield [%]
1	Ph	CH_3	CH_3	12aa	32
2	3-$CF_3C_6H_4$	CH_3	CH_3	12ba	29
3	4-$CH_3OC_6H_4$	CH_3	CH_3	13ca[a]	24[a]
4	CH_3	CH_3	CH_3	12da	33
5	Et	CH_3	CH_3	12ea	31
6	Ph	H	H	12ab	37
7	Ph	H	CH_3	12ac	20
8	Ph	H	Ph	12ad	22
9	(1-Naph)-CH_2	CH_3	CH_3	-[b]	-

a) Structurally different product was obtained with 24% yield

b) Decomposition of the initially formed enamide **11fa**

In the case of 5-(1-hydroxy-2-(naphthalen-1-yl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione used as a Meldrum's acid (Table 1, Run 9) formation of enamide was observed but further condensation using PPA failed. An identical situation was observed when 3-aminocyclopent-2-enone was applied. Surprisingly in the case of 5-(hydroxy(4-methoxyphenyl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**9c**) as a Meldrum's component (Table 1, Run 3) significantly different product compared to the rest of the results was isolated from the reaction mixture. The first problem was the elucidation of a structure of a new unexpected product. It was substantial for us during the analysis that this compound had a double fragment coming from the Meldrum derivative and only one coming from the enaminone. Based on data from NMR ad MS we proposed the following structure, which could be in equilibrium with its keto form (Fig. 7).

Thus, we decided to elucidate the reaction mechanism behind this particular reaction. First, we decided to check which step of the process is responsible for the formation of unusual product. As was mentioned unexpected product contain an "excess" of moieties originating from acyl Meldrum's acid, so it would suggest that the excess of 5-(hydroxy(4-methoxyphenyl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**9c**) used in "one step" process causes such an untypical reaction course. Therefore, we prepared

enamide **11ca** according to the stepwise procedure, isolated and purified it. In the next step, an attempt to cyclize purified **11ca** using PPA was performed. In this reaction, we gained again compound **13ca** with a yield of 21% (Fig. 8).

The result confirmed that the excess of acyl Meldrum's acid used in "one pot" wasn't responsible for the unusual course of the reaction. Compound **13ca** must be formed by the interaction of two molecules of enamide **11ca**. To explain the formation of product **13ca** we proposed a tentative reaction mechanism presented in Fig. 9.

Obviously, we paid attention to the fact that only the reaction of *p*-metoxy derivatives of Meldrum's acid with dimedone enamineone gave us an unexpected product. Thus, to explain this phenomenon we put the hypothesis that EDG causes a decrease in the electrophilicity of the keto carbonyl carbon in enamide **11ca**. Thereby inhibiting the privileged process of intramolecular cyclization which would lead to the usual product **12ca**, simultaneously causes that an entropically more difficult intermolecular process could be observed. To validate our hypothesis, we decided to obtain and purified enamide **11ga** with furyl substituent possessing a strong M + effect (Fig. 10a), and then once again carry out the intramolecular condensation with PPA. As a result, we obtained compound **13ga** which confirmed that EDG indeed affects the course of the reaction (Fig. 10b).

In the case of intermolecular (Fig. 9) and intramolecular (Fig. 5) reactions the role of the nucleophile is played by the enaminone fragment having the largest contribution to the HOMO orbital of the molecule. The discussed intermolecular condensation can theoretically occur in two directions – attack of a nucleophile on a keto-carbonyl (not shown on Fig. 9) or on amide carbonyl carbon atom. Considering the factors affecting the transition of reaction (presence of ED group) from intramolecular to intermolecular, it's likely that the enamineone nucleophile initiates the reaction with the amide carbonyl. Otherwise, we would be dealing with intramolecular cyclization.

Moreover in searching for the most basic position of the molecule, we estimated with the "Chemaxon pKa calculator"[38] pKa values for the conjugate acids of the enamide **11ca** and its enol form **11ca'** which are 1.0 and 0.4, respectively (Fig. 11).

In a reaction environment with an excess of PPA, these compounds will be largely in the protonated form. Obviously, the protonated forms are more electrophilic than the non-protonated. When considering the participation of these two forms in the actual course of the reaction, the position of the keto-enol equilibrium of protonated and deprotonated forms should be also taken into account. Considering the ^{1}H NMR spectra for EDG-substituted enamides in a non-polar solvent, the amount of the enol form is negligibly small. Thus the most electrophilic species in our reaction mixture have to be protonated enamide **11ca** (Fig. 11) which additionally supports our proposed mechanism.

Conclusion

In this paper, we presented the "one pot" reaction designed by us for the synthesis of 4-phenyltetrahydroquinolone cores. This reaction takes place with appropriate enamide as intermediate and then, its condensation with PPA. The proposed synthesis is much shorter and more economical compared to the procedures previously published by us, however, it has its limitations. The reaction proceeds towards intramolecular cyclization for enamides not substituted with strong EDG. For those with ED groups, we observed intermolecular condensations.

Methods

General

Commercially available reagents were purchased from Sigma Aldrich or Acros and used without further purification. Acyl Meldrum's acids **9a-f** and enaminones **10a-d** were prepared according to literature procedures; **9a**, **9b**, **9c**, **9f**[39], **9d**, **9e**[40], **10a-d**[41]. Analytical thin layer chromatography was performed on aluminum sheets of UV 254 Merck silica gel, and flash chromatography using SilicaFlash P60 silica gel (40 63 μm). 1 H and 13 C NMR spectra were recorded with Bruker Avance III HD 400 MHz or Varian Gemini 500 MHz and NMR chemic al shifts were reported in δ (ppm) using residual solvent peaks as standards, with the coupling constant J measured in Hz. High resolution mass spectra were recorded with an Agilent 6540 Q TOF system High resolution (HRMS) was recorded on Agilent 6540 QTOF.

General procedure for preparation of compounds **12aa-ea**, **13ga**

A solution of enaminone **10a-d** (0.5 mmol) in 5 ml of DCE and molecular sieves were placed in a round bottom flask with a stir bar and heated to 55°C. Then 2 mmol of acyl Meldrum's acid **9a-f** were added in 4 portions every 1 hour. The formation of enamide was monitored by TLC. When the spot of enaminone was no longer observed 0. 8 g of PPA was added. The reaction mixture was then heated to reflux, left for 6 h and after that DCE was evaporated. The residue was then suspended in water, cooled in the ice bath and neutralized with NaOH. Next, t h e resulting suspension was subjected to extraction with AcOEt and DCM. Organic layers were washed with brine and dried with anhydrous $MgSO_4$ The final product was isolated by flash column chromatography (C:M 200:1 and if needed A:H 2:1).

General procedure for preparation of compounds **11aa-ga**

A solution of dimedone enaminone **10a** (0.5 mmol) in 5 ml of DCE and molecular sieves were placed in a round bottom flask with a stir bar and heated to 55 o C. Then 2 mmol of acyl Meldrum's acid **9a-g** were added in 4 portions every 1 hour. The formation of enamide was monitored by TLC. When the spot of enaminone was no longer observed, DCE was evaporated. The final product was isolated by flash column chromatography C:M 120:1.

Declarations

Data Availability Statement

The datasets presented in the current study are available from the corresponding author on reasonable request.

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Author Contributions statement

M.R. conducted the experiments of compounds synthesis, analyzed data, and wrote the manuscript; A.T and A.H analyzed data, wrote the manuscript; S.M. conceived the experiments, conducted preliminary experiments, wrote the manuscript, and analyzed data,. All authors reviewed the manuscript. The manuscript was written through the contributions of all authors. All authors approved the final version of the manuscript.

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Figures

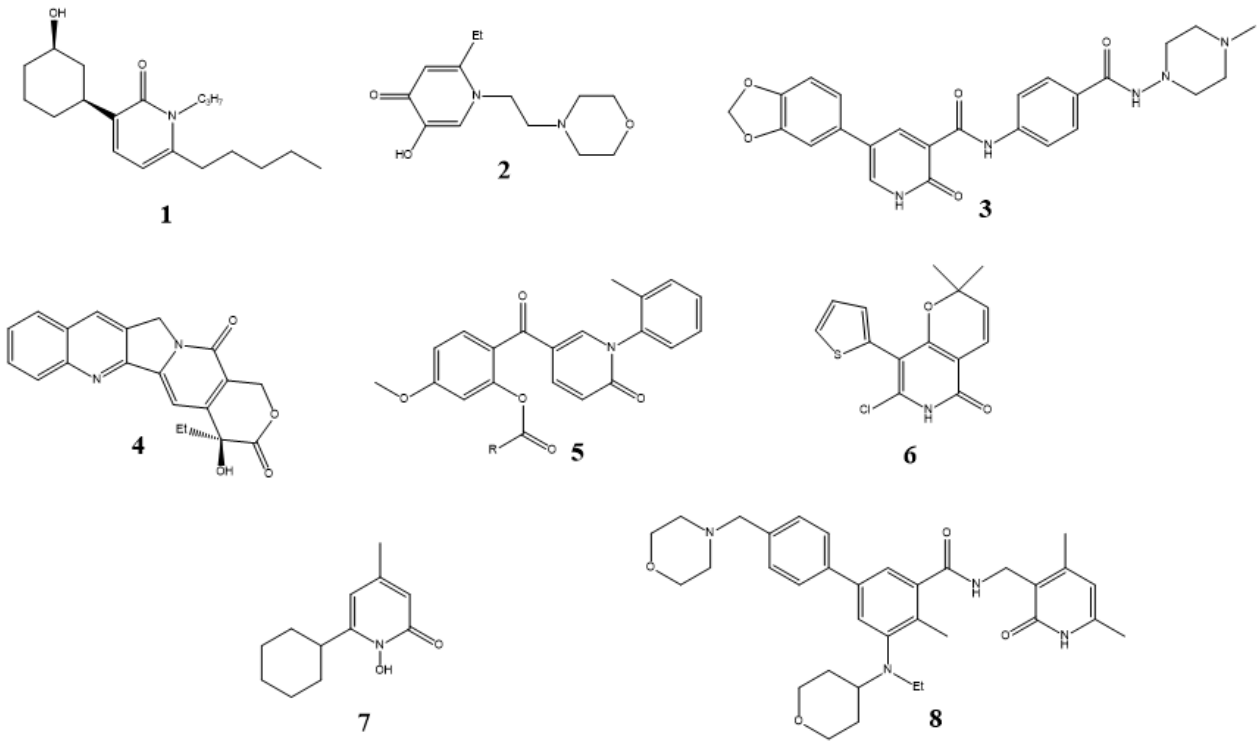

Figure 1

Examples of bioactive derivatives containing pyridone moiety.

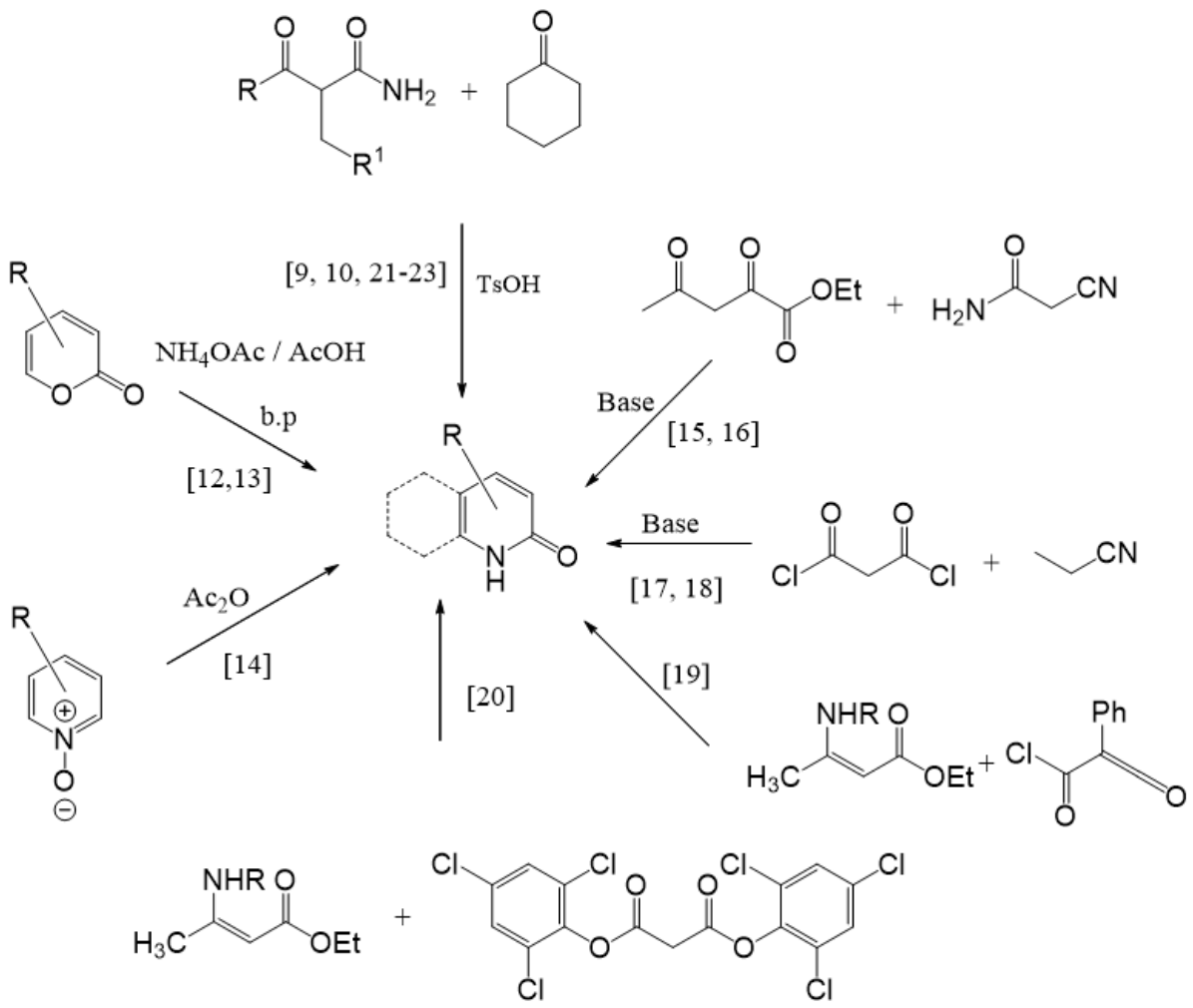

Figure 2

Selected examples of the synthesis routes of 2-pyridones

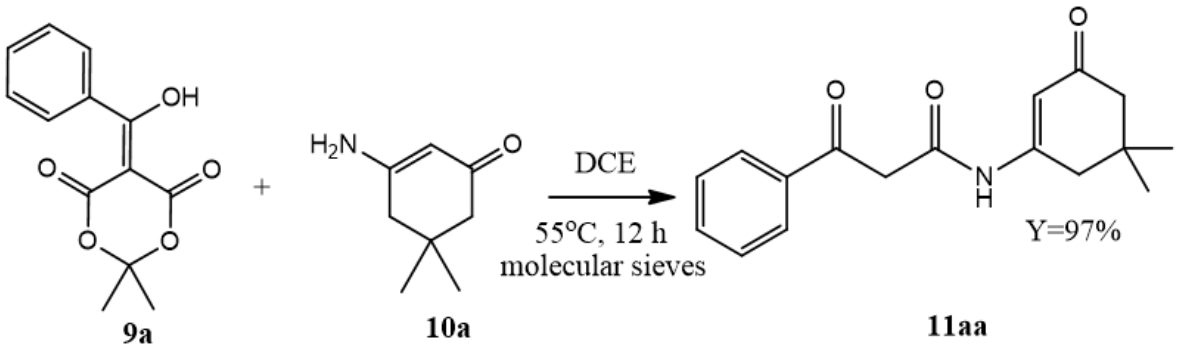

Figure 3

Preparation of enamide **11aa** with benzoyl Meldrum's acid **9a.**

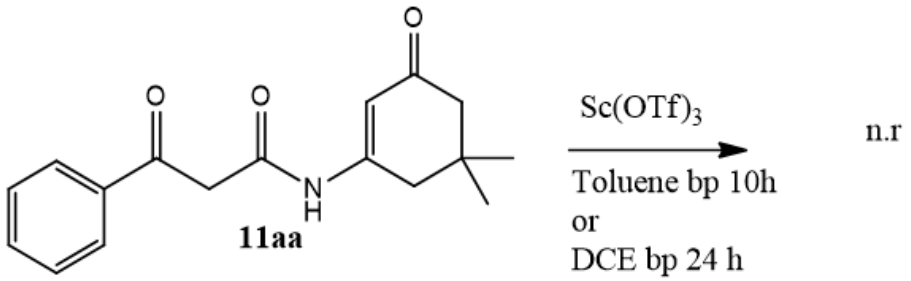

Figure 4

Attempts to cyclization of enamide with $Sc(OTf)_3$.

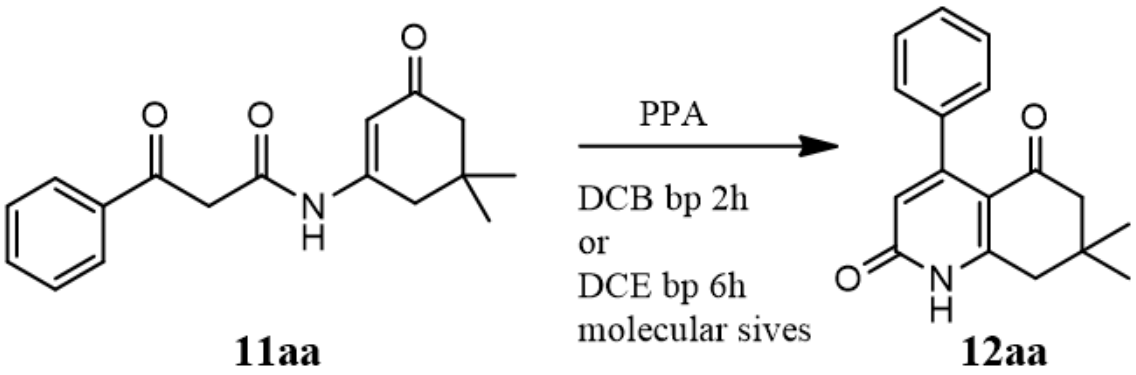

Figure 5

Formation of 7,7-dimethyl-4-phenyl-7,8-dihydroquinoline-2,5(1H,6H)-dione

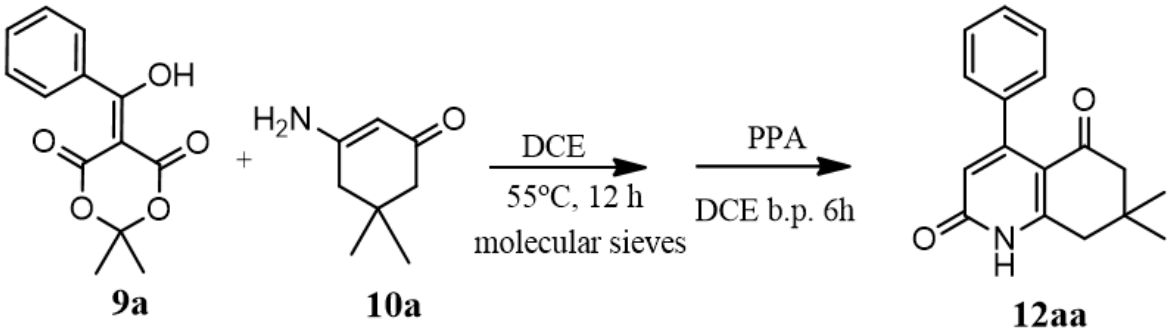

Figure 6

One pot process for synthesis of 7,7-dimethyl-4-phenyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (**12aa**)

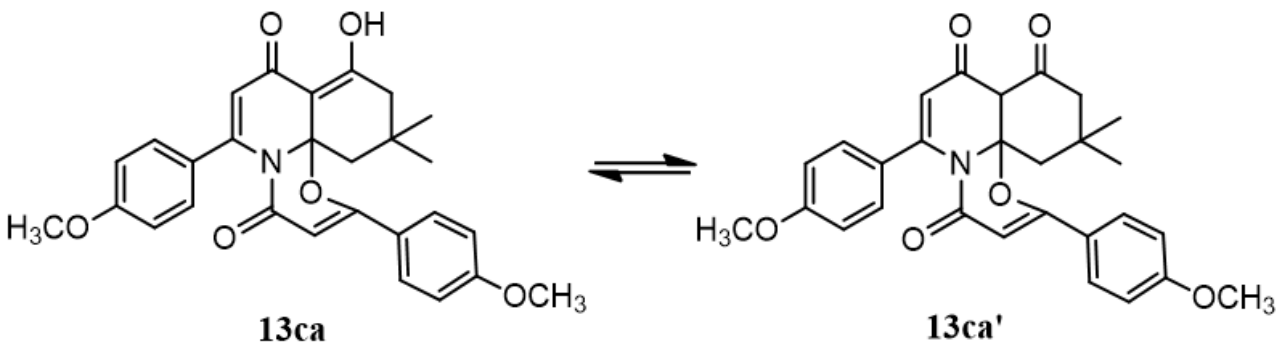

Figure 7

Proposed structure of unexpected cyclization product.

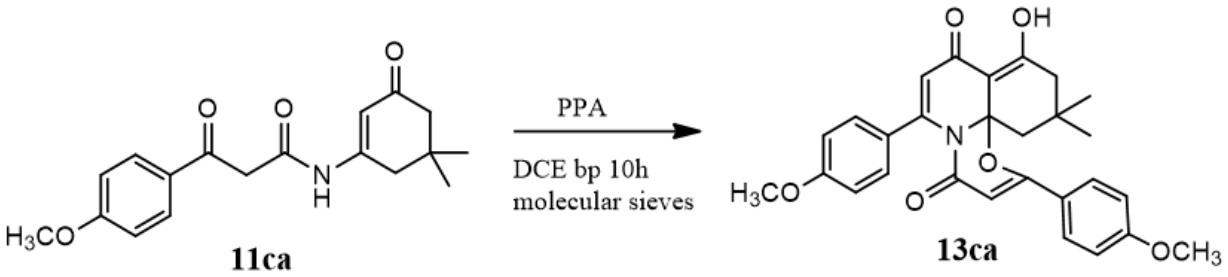

Figure 8

Formation of “unexpected” product during cyclization of enamide

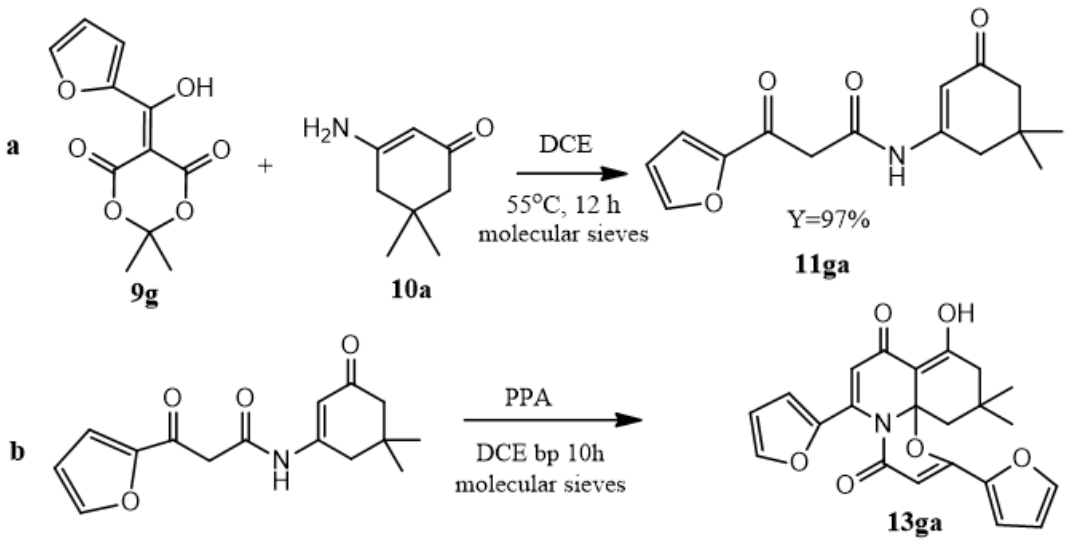

Figure 10

Reactions carried out to investigate the effect of the strong EDG on the course of condensation

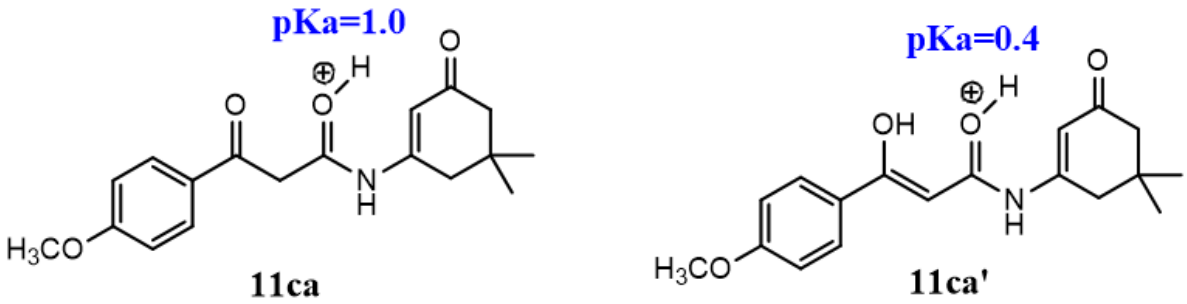

Figure 11

Conjugate acids to ketone and enol form of N-(5,5-dimethyl-3-oxo-cyclohexen-1-yl)-3-(4-methoxyphenyl)-3-oxo-propanamide

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupportingInformation.pdf