Synthesis of 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones and coumarin-3-carboxylic acids via reaction of nitrones and Meldrum’s acid

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A variety of nitrones have been synthesized and reacted with Meldrum’s acid without the aid of any catalysts. Selectively, 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones have been obtained with excellent yields under environmentally benign reaction conditions. Whereas, nitrone of salisylaldehydes with Meldrum’s acid afford cyclized products i.e. coumarin-3-carboxylic acids.

Keywords: Nitrones, Meldrum’s acid, 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones, coumarin-3-carboxylic acids

From past half century, Meldrum’s acid and its derivatives have been a hot synthone for the synthesis of pharmacologically significant heterocyclics such as coumarins, indoles, benzothiophenes, pyridines and benzofuranes. Particularly, arylidene products of this molecule serve as Michael acceptors, along with acceptor of organometallic reagents and serves as dienophiles in cycloaddition reactions. In a domino fashion²⁻³. In addition, 2-oxo-2H-benzopyran-3-carboxylic acids (coumarin-3-carboxylic acids) are key precursor for the synthesis of coumarins, which act as vital building blocks for molecules/natural products exhibiting diverse pharmacological activities. Coumarin derivatives have extensive applications in the production of perfumes and cosmetics.³

For the synthesis of arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones and coumarin-3-carboxylic acid derivatives of Meldrum’s acid, Knoevenagel reaction has been a simplest way and to achieve this catalysts like sodium hydroxide, pyridine, piperidine, piperidinium acetate, triethyl ammonium formate, ionic liquid, surfactants, K₃PO₄, Zr(O₂PO₃K), ZnCl₂, light, nano-particles coupled with a variety of conditions such as thermal heating, grinding, microwave irradiation, and ultrasound irradiation are used.⁶⁻⁷.

Further, synthesis of arylidene derivatives require highly sophisticated reaction conditions to avoid subsequent Michael addition/formation of bis-adduct.⁸ Overall these already reported procedures are not very efficient, require expensive catalysts, volatile solvents, harsh reaction conditions, and leave harmful waste on aqueous work-up. Therefore, there is still scope for better development of green sustainable processes in view of environment concerns. Herein, is reported the first ever reaction of aldonitrone with Meldrum’s acid to afford arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones in facile a way.

Nitrones are well known 1,3-dipoles and are extensively explored for the synthesis of five membered heterocycles particularly, via [3+2] cycloaddition reaction⁹. Hamana et al. reported reactions of heterocyclic nitrones under acidic conditions and obtained only condensed products.¹⁰ In the present protocol is disclosed the first ever use of arlynitrones as aldehydes equivalents whereas some reports are there using reduced version for the selective synthesis of 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones and coumarin-3-carboxylic acids under environmentally benign reaction condition. The reaction proceeds via addition-elimination pathway and affords the desired products in very good to excellent yields.

Results and Discussion

For a pilot reaction, a mixture of freshly prepared N-phenyl-N-phenylmethylidenamine oxide (10 mmol) 1a and Meldrum’s acid (10 mmol) 2 was refluxed in different solvents without the use of any catalyst. Among solvents (such as water, MeOH, 1:1 THF, dichloromethane, acetonitrile) best yield (95%) of corresponding product 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione 3a in possibly reduced reaction time (15 min) was observed only in case of ethyl alcohol (Table 1). In the absence of solvent, reaction did not proceed significantly up to 5 hr. Under these reaction conditions, only arylidene products were obtained instead of bis-product 5 (Scheme 1).

Similarly, a variety of nitrones 1a-o obtained from aromatic aldehydes as well as heterocyclic aldehydes (3-formyl chromones) were reacted with Meldrum’s acid 2 under reflux in EtOH with similar success.
Nitrones bearing electron donating group \(1b-e, 1j\) and withdrawing \(1f-h, 1k-l\) on arylaldehyde part or chromone ring did not have significant effect either on rate of reaction or on yields of the 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones 3a-l (Table I).

Further, freshly prepared nitrone of salisylaldehyde 1m was reacted with Meldrum’s acid 2 under reflux in EtOH. Interestingly, neither 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione 3a nor bis-product 5 could be obtained (Scheme I), only cyclized product, i.e. coumarin-3-carboxylic acid 4a was obtained in very good yield (89%). Other nitrones based on ortho-hydroxy arylaldehydes 1n-o with Meldrum’s acid 2 afforded coumarin-3-carboxylic acids 4b,c in 10-15 min with high yields of 85-86% (Table I).

As far as mechanism is concerned, reaction proceeds via nucleophilic addition of 2 on 1a-l with subsequent elimination of amine part of 1a-l to afford 3a-l. In case of 1m-o, after addition-elimination, unstable arylidene product undergoes cyclization and subsequent dehydration leading to the formation of coumarin product.

### Experimental Section

Reagent-grade chemicals were purchased from a commercial source and used without further purification. Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. \(^1\)H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

### General procedure for the synthesis of 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (3a-l) and 2-oxo-2H-chromene-3-carboxylic acids (4a-c)

A mixture of nitrone (10 mmol) and Meldrum’s acid (10 mmol) was refluxed in ethanol (15 mL) for a

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**Table I — Synthesis of 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (3a-l) and 2-oxo-2H-chromene-3-carboxylic acids (4a-c)**

<table>
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<th>Entry</th>
<th>R Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>1a 3a</td>
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<tr>
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<td>1o 4c</td>
<td>10</td>
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*Reaction conditions: 1a-o (10 mmol) and 2 (10 mmol), were refluxed in 15 mL EtOH. The products were characterized by spectral techniques like IR, \(^1\)H NMR and mass spectroscopy. *Isolated yields after recrystallization.

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![Scheme I — Addition-elimination reaction of nitrones and Meldrum’s acid.](image-url)
given time (see Table 1). The progress of reaction was monitored via thin layer chromatography. After reaction completion, the reaction mass was cooled and excess solvent was removed under vacuum. Obtained crude product was washed with cold water (5 mL × 3). The solid product was filtered and dried. For further purification, products were recrystallized from EtOH. The products were characterized by comparison of their melting points and spectral (IR, 

\[ \text{H NMR (400 MHz, DMSO-d}_6\text{): } \delta \text{ 10.64 (br-s, 1H, OH), 8.28 (s, 1H), 8.16-6.89 (m, 4H, ArH), 1.77 (s, 6H, 2CH}_3\text{)}; MS: (m/z) 248 (M}^+\text{).} \]

\[ \text{5-(4-Hydroxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, 3c: IR (KBr): 3272, 3008, 2911, 2863, 1768, 1736, 1619, 1585, 1489, 1382, 1295 cm}^{-1}; \text{H NMR (400 MHz, DMSO-d}_6\text{): } \delta \text{ 10.64 (br-s, 1H, OH), 8.28 (s, 1H), 8.16-6.89 (m, 4H, ArH), 1.77 (s, 6H, 2CH}_3\text{)}; MS: (m/z) 266 (M}^+\text{).} \]

\[ \text{2,2-Dimethyl-5-((4-oxo-4H-chromen-3-yl)methylen)-1,3-dioxane-4,6-dione, 3g: IR (KBr): 3109, 3008, 2911, 2863, 1745, 1714, 1605, 1575, 1513, 1429, 1381, 1284 cm}^{-1}; \text{H NMR (400 MHz, DMSO-d}_6\text{): } \delta \text{ 8.73 (s, 1H), 7.81-7.37 (m, 4H, ArH), 8.05-7.47 (m, 4H, ArH), 1.81 (s, 6H, 2CH}_3\text{)}; MS: (m/z) 300 (M}^+\text{).} \]

\[ \text{1159} \]

Conclusion

In conclusion, a simple and rapid procedure for the synthesis of 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones and coumarin-3-carboxylic acids via simple addition-elimination has been developed. The present protocol has following synthetic features: in contrast to known methods, this procedure does not need any external catalyst, a variety of nitrones can be employed, Meldrum’s acid afforded the products by cascade Knoevenagel-Michael reaction and Coumarin products selectively without the formation of any other side-products/bis-products, this method produces good to excellent yields in shorter reaction time, and it seems that reaction is auto-catalyzed because eliminating-part of nitrone acts as catalyst.

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References


