



Sequential Michael addition/retro-Claisen condensation of 1,3-diarylpropan-1,3-diones with nitrostyrenes: one-step synthesis of 4-nitro-1,3-diarylbutan-1-ones

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Abstract. The sequential Michael addition/retro-Claisen condensation of 1,3-diarylpropan-1,3-diones with nitrostyrenes is described. 4-Nitro-1,3-diarylbutan-1-ones were efficiently synthesized in good to high yield under mild, transition-metal-free condition. This one-step method involving sequential carbon-carbon bond formation and cleavage provides a good alternative to the synthesis of various γ -nitro ketones.

Keywords. Michael addition; retro-Claisen condensation; γ -nitro ketone; carbon-carbon bond formation; carbon-carbon bond cleavage.

1. Introduction

The Michael addition is one of the most useful methods for the mild formation of carbon-carbon bonds.¹ Meanwhile, retro-Claisen condensation is an efficient method for the cleavage of carbon-carbon bonds.² The combination of Michael addition and retro-Claisen condensation will possibly produce a novel synthesis.

As one of the main classes of ketone compounds, γ -nitro ketones are widely used as intermediates for the synthesis of various functionalized carbocycles.^{3–8} The reported typical synthetically viable procedures for the construction of γ -nitro ketones include: i) the conjugate addition of nitromethane to chalcone;^{9–13} ii) the detri-fluoroacetylation Michael addition of 1-trifluoromethyl-1,3-diketones to conjugated nitroalkenes;¹⁴ iii) the amine-catalyzed Michael addition of ketones to nitrostyrene;^{15–25} iv) the nickel-catalyzed decarboxylative Michael addition of β -ketoacids to nitrostyrenes^{26,27} (Scheme 1). However, some drawbacks, such as low yield, limited diversity and expensive substrates, still remains in the existing methods. Therefore, the development of other synthetic methods for their direct preparation from readily accessible materials is required.

Here, we report a novel method to 4-nitro-1,3-diarylbutan-1-ones through the sequential Michael addition/retro-Claisen condensation reactions of 1,3-diarylpropan-1,3-diones with nitrostyrenes by using DBU as a catalyst and ethanol as a reagent and solvent under mild condition.

2. Experimental

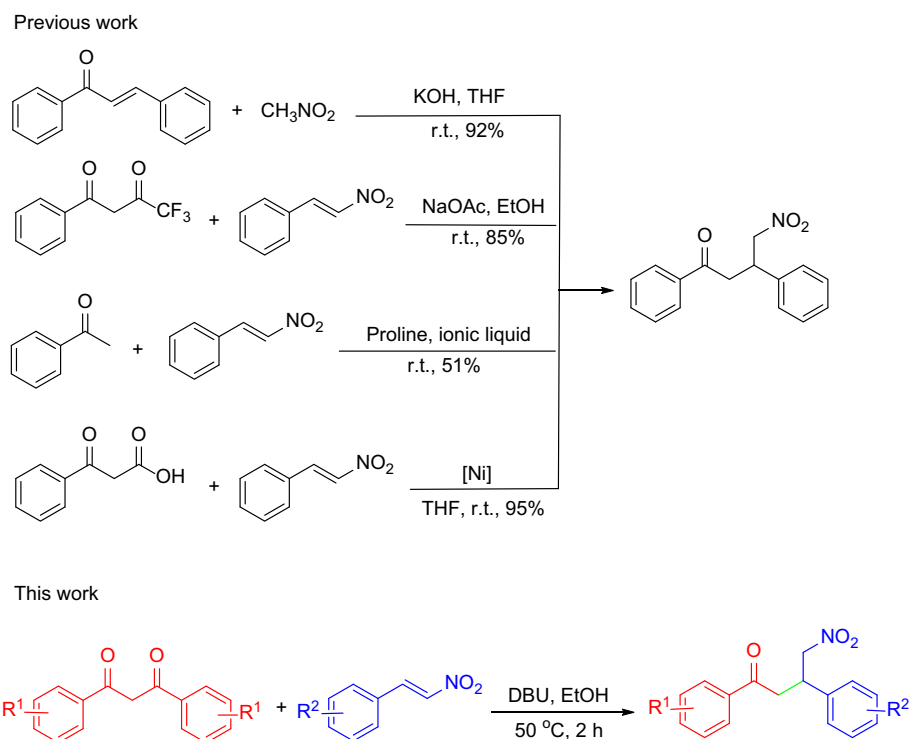
2.1 General information

¹H NMR and ¹³C NMR spectra were obtained with Mercury-400 BB or Mercury-600 BB instrument using CDCl₃ as solvent and Me₄Si as the internal standard. High-resolution mass spectra (HRMS) (ESI) were obtained with a Bruker Daltonics APEX II 47e and Orbitrap Elite mass spectrometer. 1,3-Diarylpropan-1,3-diones²⁸ and nitrostyrenes²⁹ were synthesized according to the literature procedure.

2.2 General procedure for the synthesis of 4-nitro-1,3-diarylbutan-1-ones (3a–3t)

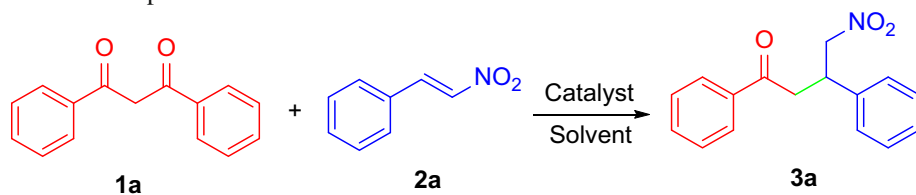
The mixture of 1,3-diarylpropan-1,3-diones **1** (0.5 mmol), nitrostyrenes **2** (0.5 mmol) and DBU (0.05 mmol) in EtOH

*For correspondence



Scheme 1. Preparation of 4-nitro-1,3-diarylbutan-1-ones.

Table 1. Optimization of the reaction conditions^a.



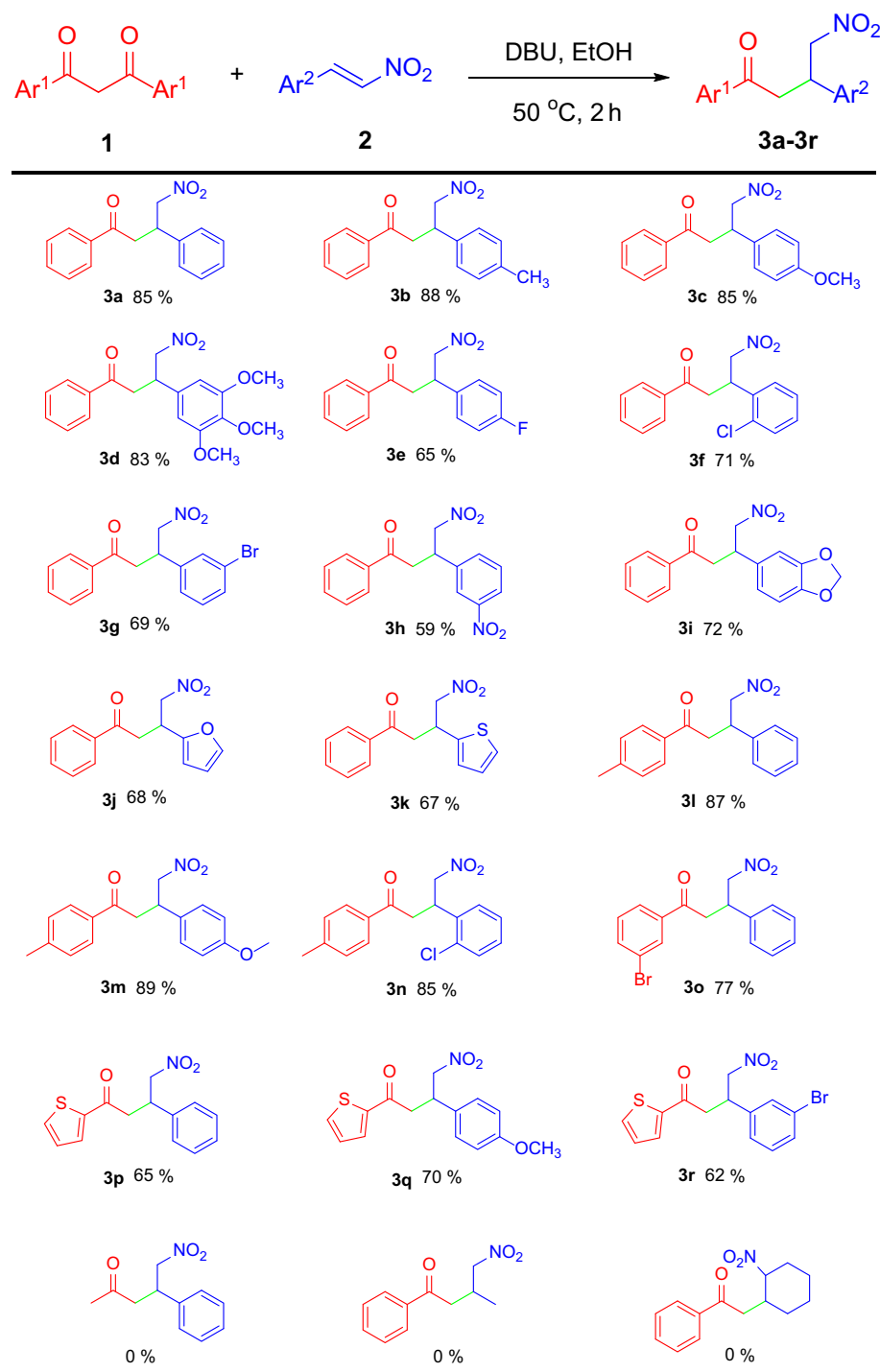
Entry	Catalyst	Solvent	Yield [%] ^b
1	-	EtOH	0
2	NaOH	EtOH	20
3	KOH	EtOH	9
4	NaHCO ₃	EtOH	33
5	K ₂ CO ₃	EtOH	40
6	Cs ₂ CO ₃	EtOH	50
7	DABCO	EtOH	65
8	DMAP	EtOH	76
9	Et ₃ N	EtOH	55
10	DBU	EtOH	85
11	DBU	MeOH	Trace
12	DBU	<i>i</i> -PrOH	23
13	DBU	<i>n</i> -BuOH	0

^aReaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (0.05 mmol) in alcohol (3 mL) was stirred at 50 °C for 2 h.

^bIsolated yield.

(3 mL) was stirred at 50 °C for 2 h. The reaction was monitored by TLC. After the completion of the reaction, the resulting mixture was concentrated under reduced pressure. The residue was isolated by column chromatography

using petroleum ether and ethyl acetate (v/v 8:1) as eluent to give the pure product. The analytical data for products are given in the Supplementary Information section.

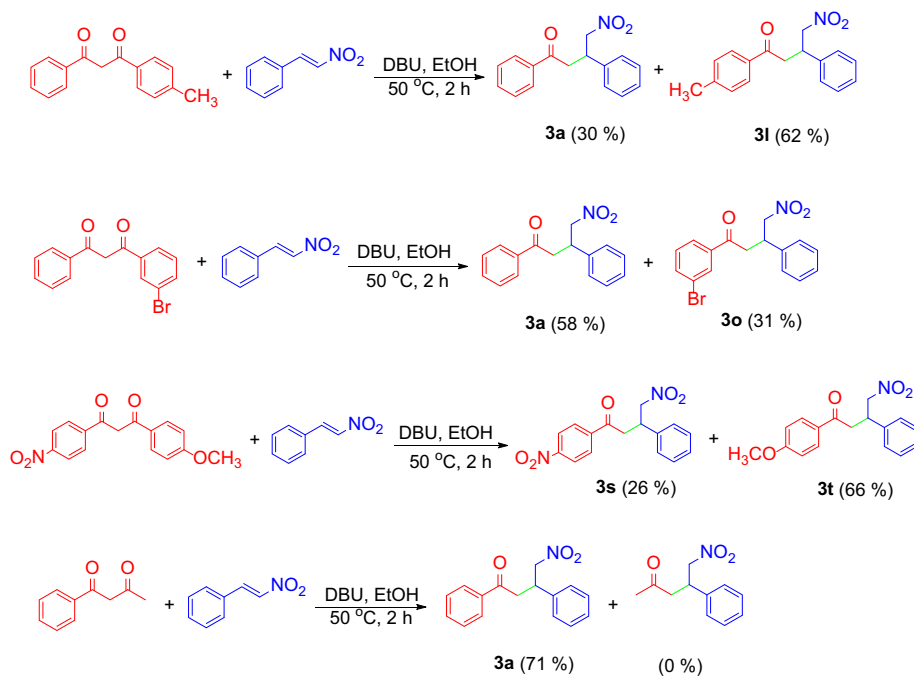
Table 2. Synthesis of 4-nitro-1,3-diarylbutan-1-ones from symmetrical 1,3-diarylpropan-1,3-diones and nitrostyrenes^a.

^aReaction conditions: 1,3-diarylpropan-1,3-diones (0.5 mmol), nitrostyrenes (0.5 mmol) and DBU (0.05 mmol) in EtOH (3 mL) was stirred at 50 °C for 2 h.

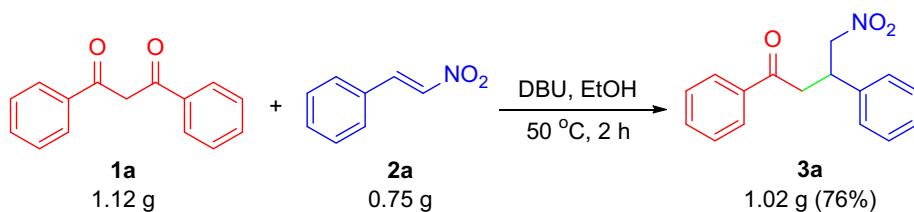
3. Results and Discussion

Initially, the reaction of 1,3-diphenylpropan-1,3-dione (**1a**) with nitrostyrene (**2a**) as a model reaction was

attempted to synthesize 4-nitro-1,3-diphenylbutan-1-one (**3a**) under a variety of conditions. It was found that the reaction of **1a** with **2a** in ethanol could not give any product in the absence of a base (Table 1, entry 1).



Scheme 2. Synthesis of 4-nitro-1,3-diarylbutan-1-ones from unsymmetrical 1,3-diarylpropan-1,3-diones and nitrostyrene.



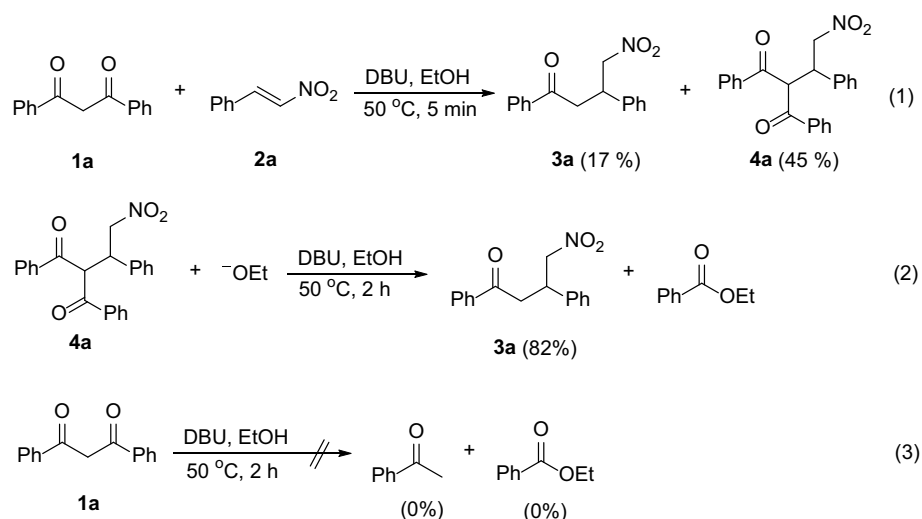
Scheme 3. Practical synthesis of **3a** on gram scale.

However, the reaction could afford **3a** in 20% yield in the presence of 0.1 equiv. of NaOH in ethanol at 50 °C (entry 2). In order to improve the yield of **3a**, other bases, such as KOH, NaHCO₃, K₂CO₃, Cs₂CO₃, DABCO, DMAP, Et₃N and DBU, as catalysts were examined (entries 3–10). All bases could catalyze the reaction to produce **3a** in low to high yield. The best yield of **3a** (85%) was obtained by using DBU as a catalyst (entry 10). Because ethanol in this reaction acted as a reactant and solvent, other alcohols, such as MeOH, *i*-PrOH and *n*-BuOH, were also attempted for the synthesis of **3a**. However, no better yield of **3a** was observed compared with ethanol (entries 11–13).

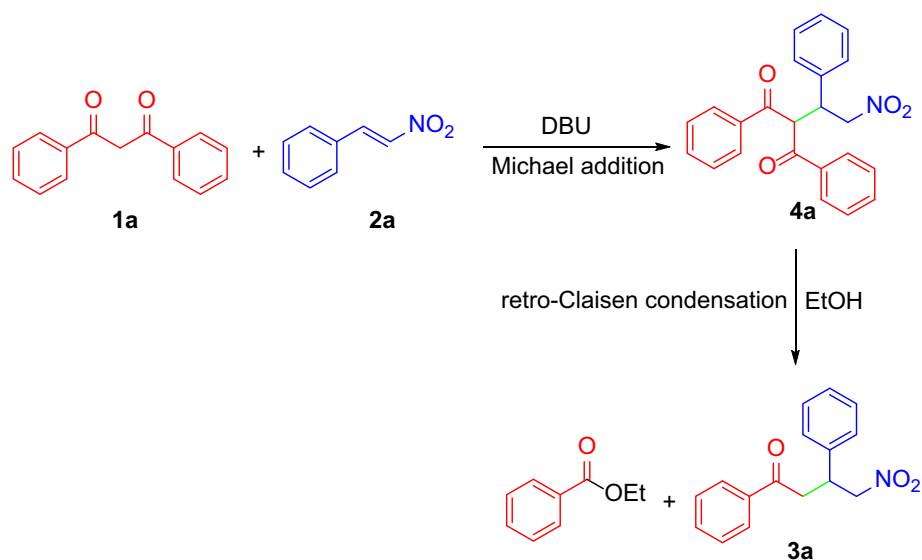
Under the optimized conditions, the synthesis of 4-nitro-1,3-diarylbutan-1-ones (**3a–3r**) were examined by reactions of symmetrical 1,3-diarylpropan-1,3-diones and various nitrostyrenes catalyzed by DBU in ethanol at 50 °C. The results are summarized in Table 2. It was found that various symmetrical 1,3-diarylpropan-1,3-diones and nitrostyrenes bearing aromatic rings and

heteroaromatic rings could afford the corresponding products in good to high yield. The substituents on aromatic rings including electron-donating (CH₃, CH₃O) and electron-withdrawing (F, Cl, Br, NO₂) groups did not show obvious effect on the yield. In contrast, the attempts for the reaction of pentan-2,4-dione with nitrostyrene (**2a**), the reaction of 1,3-diphenylpropan-1,3-dione (**1a**) with nitropropene, and **1a** with 1-nitrocyclohexene were not successful.

In addition, the reactions of unsymmetrical 1,3-diarylpropan-1,3-diones with nitrostyrenes under standard condition also proceeded smoothly. However, two kinds of 4-nitro-1,3-diarylbutan-1-ones were generally produced. For example, the reaction of 1-phenyl-3-(*p*-tolyl)propan-1,3-dione with nitrostyrene (**2a**) could give **3a** (30%) and **3l** (62%). The reaction of 1-(3-bromophenyl)-3-phenylpropan-1,3-dione with nitrostyrene (**2a**) could give **3a** (58%) and **3o** (31%). The reaction of 1-(4-nitrophenyl)-3-(4-methoxyphenyl)propan-1,3-dione with nitrostyrene (**2a**) could give



Scheme 4. Control experiments.

Scheme 5. Possible mechanism for the synthesis of **3a**.

3s (26%) and **3t** (66%) (Scheme 2). These results indicated that for the unsymmetrical 1,3-diarylpropan-1,3-diones, the reactions were more advantageous to the products including an electron-donating group on aromatic rings than the ones including an electron-withdrawing group. In addition, aryl-alkyl ketone, such as 1-phenylbutan-1,3-dione, as a substrate was also attempted for the reaction, but only one product **3a** (71%) was observed.

With the success over generality of the protocol, the reaction of 1,3-diphenylpropan-1,3-dione (**1a**) with nitrostyrene (**2a**) was also performed on a gram scale. The reaction of 1.12 g of **1a** with 0.75 g of **2a** in the presence of 76 mg of DBU in EtOH (12 mL) was performed under the optimized condition to give 1.02 g of **3a** in 76% isolated yield. This success of gram scale reaction

further showed the potency of optimized condition for the bulk processes (Scheme 3).

Control experiments were conducted as shown in Scheme 4. Treatment of 1,3-diphenylpropan-1,3-dione (**1a**) with nitrostyrene (**2a**) under the standard conditions for only 5 min gave a mixture of the desired product **3a** (17%) and a Michael addition product **4a** (45%), which could be isolated and identified by NMR spectra (Scheme 4, Eq. 1). Under the standard conditions, the isolated **4a** could react with a small concentration of ethoxide ion formed by DBU and EtOH in the system to produce **3a** in high yield through retro-Claisen condensation (Scheme 4, Eq. 2). This indicated that **4a** is the intermediate of the formation of product **3a**. In addition, the treatment of **1a** in the absence of nitrostyrene (**2a**) was also tested under standard conditions. However,

the possible product, acetophenone, was not observed (Scheme 4, Eq. 3). This implied that retro-Claisen condensation could not take place between substrate **1a** and EtOH.

Based on the above control experiments, a plausible mechanism is proposed for the synthesis of **3a** (Scheme 5). Firstly, the reaction of **1a** with **2a** catalyzed by DBU give a Michael addition product **4a** as an intermediate. Then retro-Claisen condensation is taken place through one carbonyl of **4a** attacked by ethanol and subsequent carbon-carbon bond cleavage to give the final product **3a**.

4. Conclusions

In conclusion, a simple and effective protocol for the synthesis of 4-nitro-1,3-diarylbutan-1-ones through tandem reaction of 1,3-diarylpropan-1,3-diones and nitrostyrenes in the presence of DBU has developed. Although the loss of one acyl group makes the reactions poorly atom economical, mild reaction conditions, shorter reaction time, high yield, good functional group tolerance and simplified procedures are the salient features of this method. A gram-scale reaction has been attempted to illustrate the potency of reported procedure towards the bulk synthesis.

Supporting Information (SI)

The experimental details, analytical data, ^1H NMR and ^{13}C NMR spectra for the products are available at www.ias.ac.in/chemsci.

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