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Synthesis of β -enamino malonates through caesium carbonate-promoted reaction of nitro-substituted donor–acceptor cyclopropanes†

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A caesium carbonate-promoted reaction of nitro-substituted donor–acceptor cyclopropanes (DACs) with primary aromatic amines in water provides a convenient access to β -enamino malonates under mild reaction conditions. The transformation takes place through the formation of allene intermediates from the DACs followed by the conjugate addition of various primary aromatic amines to the intermediates. The reaction proceeds more efficiently in water as compared with organic solvents and the products were isolated in good yields by filtering through a silica gel column without any prior extraction procedure.

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Introduction

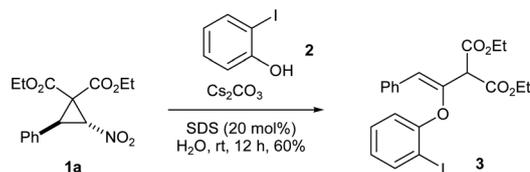
Donor–Acceptor Cyclopropanes (DACs) are one of the types of readily available and easily manipulable building blocks that give access to different classes of organic compounds.¹ Simple reagents are often enough to trigger their characteristic reactions such as ring-opening,² annulation³ and rearrangement.⁴ DACs having an extra aryl or nitro group (apart from the regular donor–acceptor groups) usually display distinct reactivity and afford products that are difficult to obtain by other methods.⁵ In this context, nitro-substituted DACs are renowned for their unique reactivity and they preferentially undergo ring-opening reactions rather than annulation reactions.⁶ When treated with Lewis acids, nitro-substituted DACs form arylmethylidene malonates as products or intermediates, which serve as versatile building blocks for a handful of heterocyclic and acyclic compounds.^{6c,7} On the other hand, when treated with bases, they form aryloxyethylenes or allenes as intermediates, which too serve as potential precursors for various compounds.⁸

Recently, we reported that nitro-substituted DACs when reacted with salicylaldehydes in the presence of caesium carbonate and a surfactant in water furnished a series of chromane derivatives through allene intermediates.⁹ During the course of the study, we observed that nitro-substituted DAC **1a** reacts with 2-iodophenol (**2**) under the same reaction conditions to give the respective Michael adduct **3** (Scheme 1, eqn (1)). The observation prompted us to investigate the reaction of nitro-

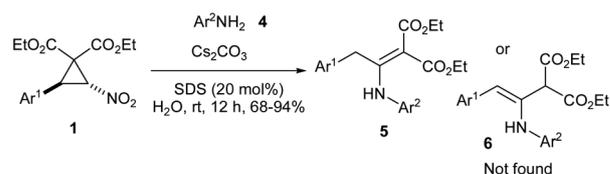
substituted DACs **1** with amines **4** for the synthesis of β -enamino malonates **5** (or **6**) (Scheme 1, eqn (2)).

It may be noted that enamines and their derivatives are versatile synthetic intermediates and are usually synthesized by the condensation of amines with carbonyl compounds,¹⁰ hydroamination of alkynes¹¹ or cross-coupling reaction between

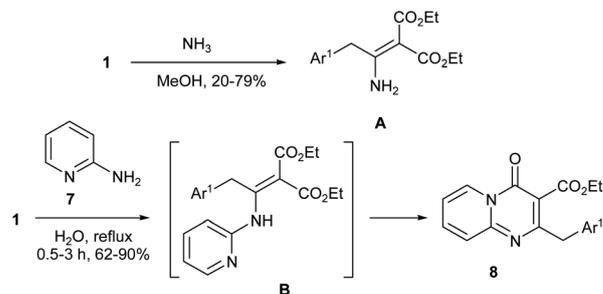
Our previous work (eqn. 1):



Present work (eqn. 2):



Comparison with literature works (eqns. 3 and 4)



Scheme 1 Comparison of the present work with literature works.

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† Electronic supplementary information (ESI) available: Copies of ¹H and ¹³C NMR spectra of all products. See DOI: <https://doi.org/10.1039/d4ra05619a>



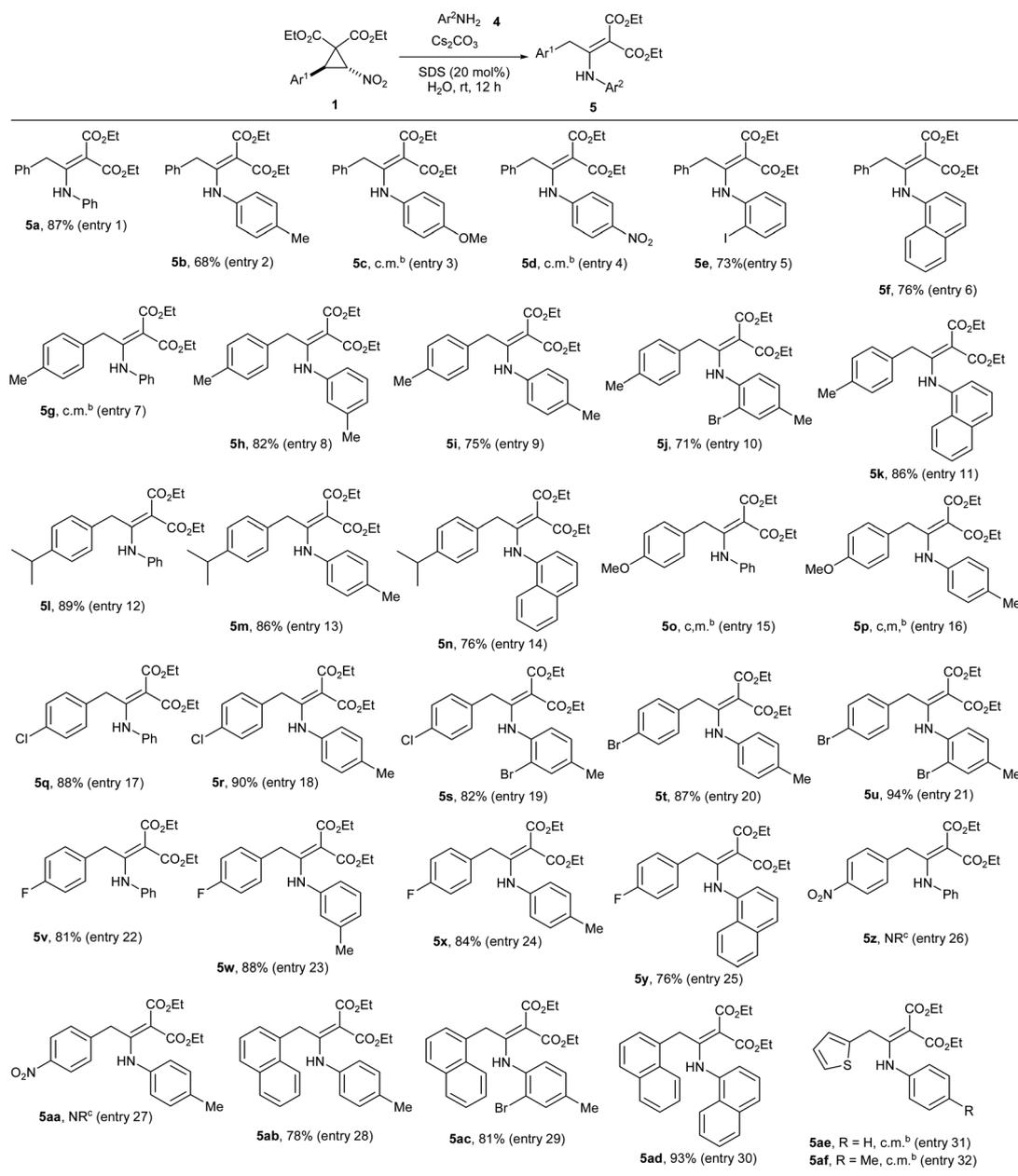
amines and vinyl halides or triflates.¹² Although, a handful of methods are available for the synthesis of enamino esters such as β -enamino malonates,¹³ DACs have been rarely used as starting materials for their synthesis. Sopova and coworkers have used nitro-substituted DACs **1** for the access of enamino malonates **A** using ammonia in methanol (Scheme 1, eqn (3)).¹⁴ We record that our previous work involving synthesis of pyridopyrimidinones **7** from nitro-substituted DACs **1** and 2-aminopyridine (**6**) in water should have also taken place through the formation of the respective enamino malonate intermediates **B** (Scheme 1, eqn (4)).^{8b} In this context, the present work

represents a convenient green strategy for the access of β -enamino malonates from amines and nitro-substituted DACs using water as solvent. It is interesting to note that water acts as a better solvent than organic solvents for certain reactions of nitro-substituted DACs, likely due to the involvement of polar intermediates.

Results and discussion

We began the study by reacting nitro-substituted DAC **1a** with various primary aromatic amines **4a-f** (Table 1, entries 1–6).

Table 1 The scope of the transformation^a

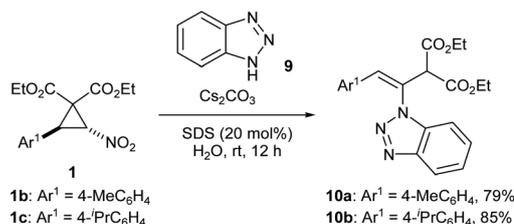


^a Isolated yield. ^b Complicated mixture of products. ^c No reaction.

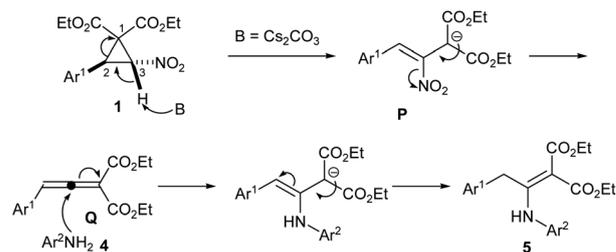


Owing to the greenness of the reaction conditions reported in the previous work [caesium carbonate, sodium dodecylsulphate (20 mol%), water, rt],⁹ we adapted the same reaction conditions for the present transformation. Accordingly, we reacted DAC **1a** with aniline **4a** under the above reaction conditions for 12 h. Then, the crude reaction mixture (without extraction) was made into slurry by mixing with a little silica gel and charged on a silica gel column. After eluting the column with 10% EtOAc in hexane (filtration), the expected enamino malonate **5a** was obtained in 87% yield (Table 1, entry 1). Out of curiosity, we also tested the suitability of organic solvents such as MeOH, EtOH, DCM, 1,2-DCE, THF, acetone, MeCN, DMF, DMSO and toluene for the transformation. Though the reaction takes place in MeOH and EtOH (the yields of **5a** were 28% and 23%, respectively, in these solvents), it did not take place in other organic solvents. Next, we investigated the reaction of **1a** with anilines having different electron donating, halogen and electron withdrawing substituents. With *p*-toluidine, the respective product enamino malonate **5b** was obtained in 68% yield by adapting the same procedure (entry 2). The presence of strong electron donating or withdrawing groups on aniline was not tolerated in the transformation. Thus, the reaction of **1a** with 4-methoxyaniline (**4c**) or *p*-nitroaniline (**4d**) led to a complicated mixture of products (entries 3 and 4). The reaction proceeded smoothly with *o*-iodoaniline (**4e**) and 1-naphthylamine (**4f**) and the respective enamino malonates **5e** and **5f** were obtained in 73% and 76% yields, respectively (entries 5 and 6). Next, we investigated the scope of the transformation for nitro-substituted DACs **1b–j** having different aryl groups with various primary aromatic amines (Table 1, entries 7–32). The presence of moderately electron donating methyl and isopropyl groups and also halogens on the aryl ring of DACs (**1b**, **1c** and **1e–g**) was well tolerated in the transformation and the respective enamino malonates were obtained in 71–94% yields (entries 7–14 and 17–25). At the same time, DACs having a good electron donating group such as methoxy on the aryl ring (**1d**) as well as an electron-rich aryl ring such as 2-thienyl (**1j**) were not compatible in the transformation and they formed complex mixtures of products, possibly due to the enhanced reactivity of the aryl rings (entries 15, 16, 31 and 32). Similarly, DAC **1h** having a strong electron withdrawing nitro group also did not undergo the expected reaction owing to the destabilizing effect of the aryl ring on the 1,3-zwitterionic intermediate that would be formed from the cyclopropane during the course of the reaction (see the mechanism).^{6c,7a} We also reacted DAC **1i** having a 1-naphthyl group with different anilines and the corresponding enamino malonates **5ab–5ad** were formed in 78–93% yields (entries 28–30).

Next, we focused our attention on the reaction of DAC **1b** with aromatic secondary amines such as *N*-methylaniline and indoline and aliphatic amines such as benzylamine, diisopropylamine, pyrrolidine and morpholine. Unfortunately, none of them gave the expected enamino malonates. During the investigation of the scope of the transformation with different amines, surprisingly, we observed that when DACs **1b** and **1c** were reacted with benzotriazole (**9**), they afforded the isomeric



Scheme 2 Reaction of DACs **1b** and **1c** with benzotriazole (**9**).



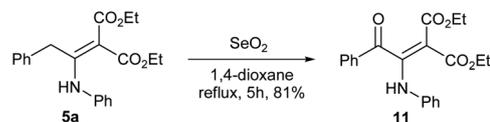
Scheme 3 Plausible mechanism of the transformation.

enamines **10a** and **10b** in 79 and 85% yields, respectively (Scheme 2). However, the transformation did not work with benzimidazole.

We propose a mechanism outlined in Scheme 3 for the formation of β -enamino malonates from DACs **1** and aromatic amines. Caesium carbonate removes the acidic proton at C-3 of the DAC, which opens the cyclopropane ring to produce intermediate **P**. The intermediate **P** may lose the nitro group to form the allene intermediate **Q**.^{8c,9} The aza-Michael addition of amine **4** to **Q** followed by migration of double bond to a conjugate position may afford enamino malonate **5**. In case of benzotriazole, the final double bond migration is not taking place.

We have also performed a gram scale synthesis of β -enamino malonate **5a** as a model substrate in order to evaluate various green chemistry metrics for the transformation (Table 2). Pleasingly, the transformation has a low *E*-factor (0.3648 kg waste per kg product) and high atom economy (88%), atom efficiency (73%), carbon efficiency (100%) and reaction mass efficiency (73%), indicating the greenness of the methodology.

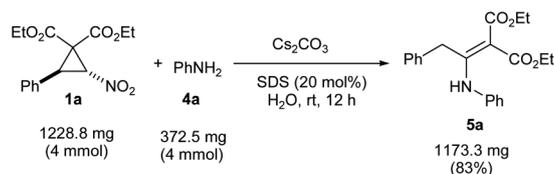
In order to prove the synthetic utility of the products made in the present study, we subjected enamino malonate **5a** to oxidation using SeO₂ in 1,4-dioxane under reflux conditions. Pleasingly, the reaction afforded the aroylmethylidene malonate derivative **11** in 81% yield (Scheme 4).



Scheme 4 Synthetic transformation of **5a** into aroylmethylidene malonate **11**.



Table 2 Evaluation of green chemistry metrics for the gram-scale synthesis of 5a



Entry	Chemicals	Molecular weight (g mol ⁻¹)	Weight (mg)
Substrate 1a	Diethyl 2-nitro-3-phenylcyclopropane-1,1-dicarboxylate	307.3020 (C ₁₅ H ₁₇ NO ₆)	1228.8
Substrate 4a	Aniline	93.13 (C ₆ H ₇ N)	372.52
Product 5a	Diethyl 2-[2-phenyl-1-(phenylamino)ethylidene]malonate	353.4116 (C ₂₁ H ₂₃ NO ₄)	1173.3
Base	Caesium carbonate	325.82 (Cs ₂ CO ₃)	1433.61
Surfactant	Sodium dodecyl sulphate	288.38 (C ₁₂ H ₂₅ NaO ₄ S)	230.70
Solvent	Water		
Product yield = 83%			
E-factor = [(1228.8 + 372.52) - 1173.3] ÷ 1173.3 = 0.3648 kg waste per kg product			
Atom economy = 353.4116 ÷ (307.3020 + 93.13) × 100 = 88%			
Atom efficiency = (83 × 88) ÷ 100 = 73%			
Carbon efficiency = 21 ÷ 21 = 100%			
Reaction mass efficiency = [1173.3 ÷ (1228.8 + 372.2)] × 100 = 73%			

Conclusions

In summary, we have developed a green procedure for the synthesis of β-enamino malonates from nitro-substituted DACs and primary aromatic amines. Water was found to be an efficient medium for the transformation and the products were isolated in good yields simply by passing the crude reaction mixture through a silica gel column by bypassing the extraction step. The reaction proceeds through caesium carbonate promoted ring-opening of the cyclopropane to form allene intermediates followed by the addition of amines. The operational simplicity, the use of water as medium, mild reaction conditions, simple purification procedure and reasonably wide substrate scope are some of the green aspects of the methodology.

Experimental section

General remarks

Melting points were determined by the open capillary tube method and are uncorrected. The ¹H and ¹³C NMR spectra were recorded on a 400 MHz NMR spectrometer. High-resolution mass spectra (ESI) were recorded on a Q-TOF mass spectrometer. X-ray crystallographic data were collected on a CCD diffractometer using graphite-monochromated Mo Kα radiation. Thin layer chromatography (TLC) was performed on pre-coated alumina sheets and detected under UV light. Silica gel (200–400 mesh) was used for column chromatography. Cyclopropanes 1a–j were prepared as per our reported procedure^{6c} and all are known compounds.^{6c,8a,15}

General procedure for the synthesis of β-enamino malonates 5a–af and 10a–b

To a suspension of nitrocyclopropane dicarboxylates 1 (1.0 mmol) in water (2 mL) were added aromatic primary amine 4

(1.0 mmol), sodium dodecyl sulfate (58 mg, 0.2 mmol), and caesium carbonate (358 mg, 1.1 mmol) and stirred at room temperature for 12 h. Next, the reaction mixture was mixed with silica gel to make slurry, charged on a silica gel column and eluted using ethyl acetate/hexane (1 : 9 v/v) to obtain the pure product.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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