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**Title:** Tandem Ring-Opening/Cyclization of trans-2-Aryl-3-nitro-cyclopropane -1,1-dicarboxylates with 2-Aminopyridines: Access to Pyrido[1,2-a]pyrimidin-4-one Derivatives

**Authors:** Selvi Subramani and Srinivasan Kannupal

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# Tandem Ring-Opening/Cyclization of *trans*-2-Aryl-3-nitro-cyclopropane -1,1-dicarboxylates with 2-Aminopyridines: Access to Pyrido[1,2-*a*]pyrimidin-4-one Derivatives

Subramani Selvi[a] and Kannupal Srinivasan*[a]

**Abstract:** A novel tandem ring-opening/cyclisation reaction of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates with 2-aminopyridines is described. The reaction does not require the assistance of any catalyst and proceeds more efficiently in water than in organic solvents. The strategy afforded pyrido[1,2-*a*]pyrimidin-4-one derivatives having a carboxylate group at C-3 in 62-90% yields.

## Introduction

The diverse reactivity of donor-acceptor (D-A) cyclopropanes has made them popular building blocks in organic synthesis.[1] They undergo a number of ring-opening,[2] ring-expansion[3] and formal cycloaddition[4] reactions thereby providing access to a wide variety of acyclic products, carbocycles, heterocycles and natural products. In the realm of D-A cyclopropane chemistry, the synthetic potential of nitro-substituted D-A cyclopropanes has been less explored as compared to others, despite their unique reactivity.[5] Yet, certain nitro-substituted D-A cyclopropanes have been subjected to nucleophilic ring-opening with amines[6] and phenols,[7] ring-expansion to isoxazoline-*N*-oxides[8] and formal cycloaddition reaction with nitrones.[9]

*trans*-2-Aryl-3-nitrocyclopropane-1,1-dicarboxylates are a kind of nitro-substituted D-A cyclopropanes which were first prepared by Sopova and co-workers in 1969.[10] Though the ring-opening reactions of these cyclopropanes with nucleophiles such as sodium malonate, sodium methoxide and ammonia were studied by the Sopova group,[11] no other reasonable synthetic applications of these cyclopropanes have been reported thereafter. Recently, we developed a convenient procedure for the synthesis of these cyclopropanes and explored their synthetic utility.[12] We found that these cyclopropanes upon treatment with Lewis acids give aroylmethylidene malonates, which could be synthetically manipulated for the access of important heterocycles such as imidazoles, quinoxalines, oxazoles and thiophenes.[12] He *et al.*, have recently reported the reaction of these cyclopropanes with Huisgen zwitterions for the access of pyrazolines.[13]

In continuation of our interest in exploring the synthetic potential of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates, we became interested in studying their ring-opening reaction with 2-aminopyridine and its derivatives. It may be noted that 2-aminopyridine is a versatile building block for the synthesis of biologically important pyrido-fused heterocycles.[14] Reissig *et al.*, have previously used 2-aminopyridine for the ring-opening of siloxycyclopropanedicarboxylates and obtained pyridoimidazole derivatives.[15] In the present study, we found that the tandem ring-opening/cyclisation of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates with 2-aminopyridines proceeds smoothly in water and affords a series of pyrido[1,2-*a*]pyrimidin-4-one derivatives. Although numerous simpler methods are available for the synthesis of pyrido[1,2-*a*]pyrimidin-4-ones,[16] the present method is unique as it provides the products with a carboxylate group at C-3, which could be used for either tuning the solubility or linking other auxo-pharmacophores. It is also worth noting that many pharmaceutically important pyrido[1,2-*a*]pyrimidin-4-one derivatives possess an attachment at C-3 (Figure 1).[17]

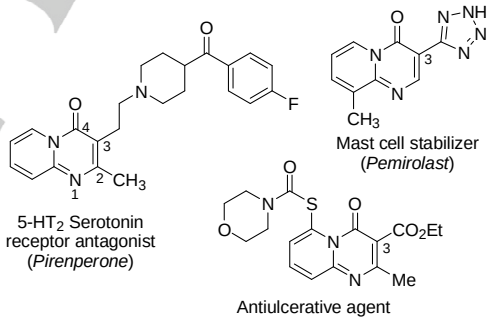


**Figure 1.** Pharmaceutically important pyrido[1,2-*a*]pyrimidin-4-ones.

## Results and Discussion

We began the study by reacting an equimolar amount of nitrocyclopropane dicarboxylate **1a** with 2-aminopyridine (**2a**) in different solvents (Table 1, entries 1-14). Pleasingly, the reaction gave pyrido[1,2-*a*]pyrimidin-4-one **3a** in 90% yield when carried out in water under reflux condition for 1 h (entry 4). The structure of **3a** was confirmed by NMR and MS spectra and further by X-ray analysis (Figure 2).[18] The reaction did not take place at room temperature and also gave inferior yields when performed at lower temperatures (for example, entry 5). In the initial stage of the reaction, **2a** was in solution while **1a** was practically 'on water'. As the reaction progressed, the reaction mixture became homogeneous and towards the end, the product started appearing 'on water'. Although the product could be isolated by simple filtration, it led to much loss of the product. Hence the product was extracted with dichloromethane and then purified.

[a] School of Chemistry
Bharathidasan University
Tiruchirappalli-620024, Tamil Nadu, India
E-mail: srinivasank@bdu.ac.in
http://www.bdu.ac.in/schools/chemistry/chemistry/dr_k_srinivasan.php

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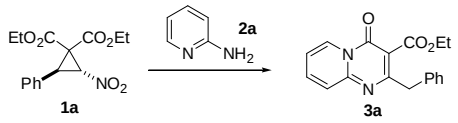
Among various solvents screened, only AcOH, dichloromethane and nitromethane gave **3a** in 50% or more yields (entries 3, 7 and 12). The reaction did not occur in 1,4-dioxane and DMF even after 24 h (entries 10 and 13). In all other cases [MeOH, EtOH, toluene, 1,2-dichloroethane (1,2- DCE), THF, acetonitrile and DMSO], the yield of **3a** ranged from 20-42% (entries 1, 2, 6, 8, 9, 11 and 14). Therefore, we selected heating the reaction mixture under reflux in water as the optimal condition for the transformation.

**Table 1.** Optimisation of reaction conditions




| Entry | Solvent and conditions[a] | Yield (%)[b] |
|---|---|---|
| 1 | MeOH, reflux, 5 h | 26 |
| 2 | EtOH, reflux, 3 h | 32 |
| 3 | AcOH, reflux, 3 h | 50 |
| 4 | $H_2O$, reflux, 1 h | 90 |
| 5 | $H_2O$, 60 °C, 48 h | 10[c] |
| 6 | Toluene, reflux, 3 h | 40 |
| 7 | $CH_2Cl_2$, reflux, 1 h | 68 |
| 8 | 1,2-DCE, reflux, 2 h | 20 |
| 9 | THF, reflux, 4 h | 28 |
| 10 | 1,4-Dioxane, reflux, 24 h | NR[d] |
| 11 | MeCN, reflux, 4 h | 25 |
| 12 | $MeNO_2$, reflux, 5 h | 55 |
| 13 | DMF, 80 °C, 24 h | NR[d] |
| 14 | DMSO, 120 °C, 4 h | 42 |

[a] No reaction occurs at room temperature in any of the solvents. [b] Isolated yield. [c] About 70% of the starting material was recovered. [d] No reaction.

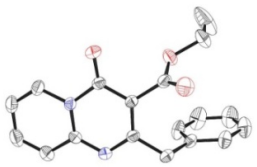
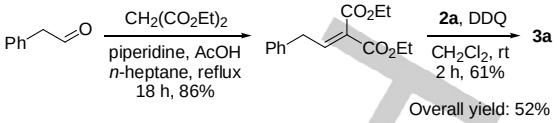


**Figure 2.** X-ray structure of **3a**.

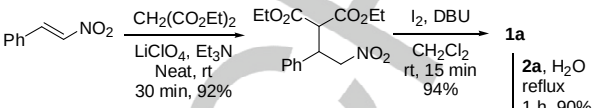
Before investigating the scope of the reaction for other substrates, we decided to evaluate the merits of the transformation by comparing it with a simpler alternative synthetic route to **3a**. As shown in Scheme 1, **3a** could be obtained in 52% overall yield over two steps (Knoevenagel condensation[19] and conjugate addition/cyclisation/aromatisation) from commercially available phenylacetaldehyde. On the other hand, the present transformation involves three steps from *trans*-$\beta$-nitrostyrene (conjugate addition,[20] cyclisation[12a] and ring-opening/cyclisation) and affords **3a** in 78% overall yield. Clearly, the present transformation, though involves an extra step, is superior to the alternative route in terms of overall yield and reaction time.

**A simpler alternative method:**




Overall yield: 52%

**Present method:**

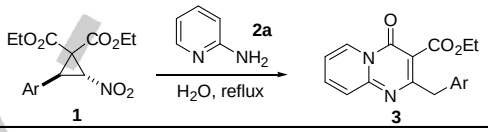


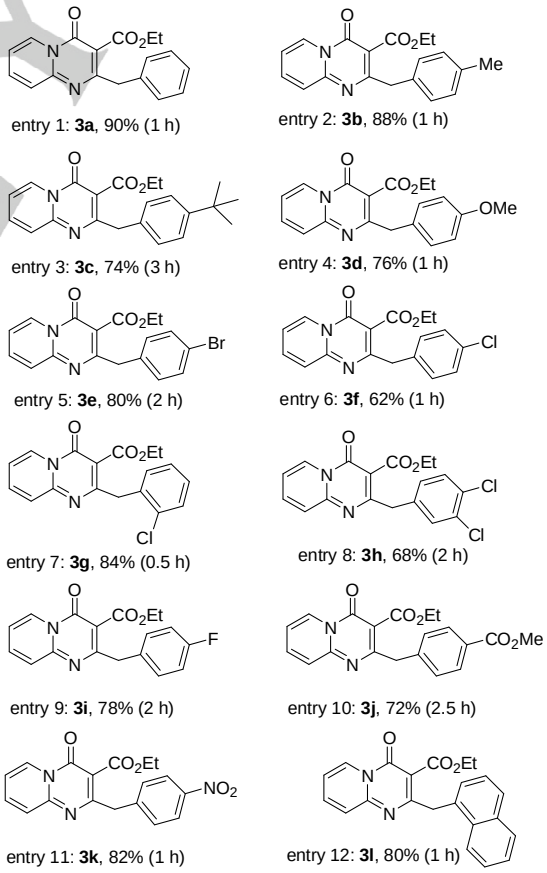

Overall yield: 78% **3a**

**Scheme 1.** Comparison of the present method with an alternative route.

Next, we investigated the scope of the reaction for various nitrocyclopropane dicarboxylates **1** with 2-aminopyridine (**2a**) and the results are summarized in Table 2. The transformation tolerated the presence of various electron donating, halogen and

**Table 2.** Scope of the reaction for various nitrocyclopropane dicarboxylates[a]




[a] Isolated yield.

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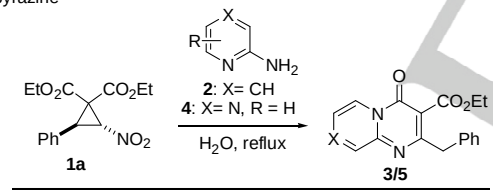
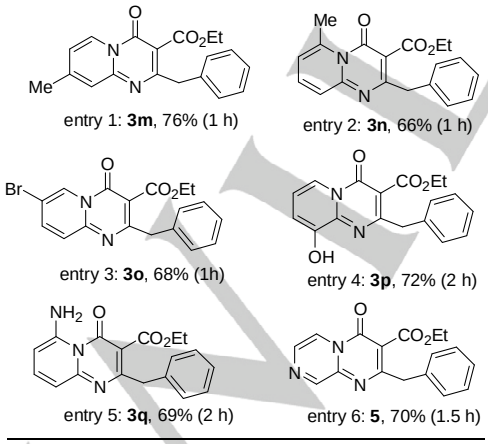
electron withdrawing substituents at different positions of the aryl ring of the cyclopropanes and the expected pyridopyrimidinones **3a-k** are produced in 62-90% yields (entries 1-11). Notably, the presence of ester group on the aryl ring of the cyclopropane did not interfere in the transformation (entry 10). The reaction also worked well when the aryl ring of the cyclopropane was 1-naphthyl and the respective pyridopyrimidinone **3l** was isolated in 80% yield (entry 12). However, when two or three electron donating methoxy groups were present on the aryl ring, the reaction led to a complicated mixture. For cyclopropanes having heteroaromatic 2-furyl and 2-thienyl rings, the reactions gave the respective pyridopyrimidinones only in trace amounts (detected by MS only).

We also explored the scope of the reaction for nitrocyclopropane dicarboxylate **1a** with various substituted 2-aminopyridines **2** and related compounds (Table 3). The reactions proceeded nicely with aminopyridines having 4-methyl, 6-methyl and 5-bromo substituents with the formation the corresponding pyridopyrimidinones **3m-o** in 66-76% yields (entries 1-3). Surprisingly, the presence of unprotected hydroxyl or amino group on the aminopyridine nucleus was also tolerated in the reaction and the respective pyridopyrimidinones **3p** and **3q** were obtained in good yields (entries 4 and 5). When 2-aminopyrazine (**4**) was used instead of 2-aminopyridines in the reaction, the expected pyrazinopyrimidinone **5** was produced in 70% yield (entry 6). However, the reaction did not take place with related compounds such as 2-aminopyrimidine, 2-aminothiazole, acetamidine, benzamidine and guanidine.

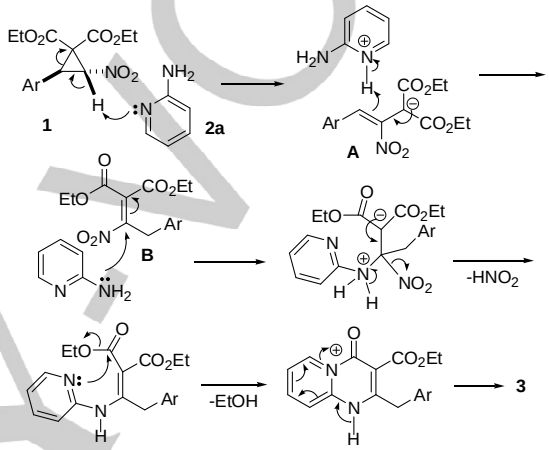
**Table 3.** Scope of the reaction for substituted 2-aminopyridines and 2-aminopyrazine[a]




[a] Isolated yield.

We propose a mechanism outlined in Scheme 2 for the formation of pyrido[1,2-*a*]pyrimidin-4-ones **3** from nitrocyclopropane dicarboxylates **1** and 2-aminopyridine (**2a**).[21] Accordingly, the abstraction of the acidic proton in **1** by **2a** triggers the ring-opening of **1** leading to the intermediate **B** *via* **A** (the intermediate **B** is different from the usual aroylmethylidene malonate intermediate, Ar−C(=O)−CH=C($CO_2Et$)$_2$ obtained by treatment of **1** with Lewis acids[12]). The nucleophilic substitution of nitro group in **B** by **2** (by addition elimination mechanism) and subsequent cyclization with the loss of ethanol afforded pyridopyrimidinones **3**. We envisage that the formation of the polar intermediate, **A** is more facilitated in water than in organic solvents and hence the reaction proceeded more efficiently in water.




**Scheme 2.** Mechanism for the formation of pyridopyrimidinones **3**.

Organic transformations are rarely performed in water owing to the insolubility of most organic substrates in water and also the deterioration of many reagents and catalysts in water. The present transformation is therefore a valuable addition to a handful of organic reactions that proceed more efficiently in water than in organic solvents.[22] It may also be noted that though water has been utilized as a nucleophile for the ring-opening of aryl-diester D-A cyclopropanes,[2f] it has not been previously used as solvent for carrying out any types of reactions of D-A cyclopropanes.

## Conclusions

We have studied tandem ring-opening/cyclization reactions of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates with aminopyridines and obtained several pyrido[1,2-*a*]pyrimidin-4-ones derivatives having a carboxylate group at C-3 in good yields. The reactions proceeded more efficiently in water than in organic media and did not require any other reagents or catalysts. The transformation takes place through the formation of nitroarylethylidene malonate intermediate from the cyclopropane, nucleophilic displacement of nitro group in the intermediate by aminopyridine and subsequent cyclization. Work is underway to explore further scope of the methodology.

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## Experimental Section

**General procedure for the synthesis of pyridopyrimidinones 3:** A mixture of nitrocyclopropane **1** (1 mmol) and 2-aminopyridine **2** (1 mmol) in water (5 mL) was heated under reflux for 0.5 to 2 h. After the reaction was complete, the reaction mixture was cooled to room temperature and extracted with dichloromethane. The organic layer was washed with water, dried (over anhydrous $Na_2SO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/hexane (3:2) to give pure pyridopyrimidinone **3**.

**Ethyl 2-(benzyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (3a):** Black solid. Yield: 277 mg (90%). M. p.: 106-108 °C. UV ($\lambda_{max}$, EtOAc): 354 nm ($\varepsilon$ = 4310 $M^{-1}cm^{-1}$). IR (Neat ): 1630, 1672, 1719 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 9.02 (d, *J* = 7.2 Hz, 1H), 7.76-7.72 (m, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.35-7.11 (m, 6H), 4.39-4.34 (m, 2H), 4.20 (s, 2H), 1.32 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.1, 165.7, 155.8, 150.6, 137.7, 137.6, 129.3, 128.6, 128.4, 127.7, 126.6, 126.4, 116.1, 109.7, 61.6, 42.4, 14.2 ppm. HRMS (ESI) calcd. for $C_{18}H_{16}N_2O_3$: 309.1234 [M + $H^+$], found: 309.1244. Anal. calcd. for $C_{18}H_{16}N_2O_3$: C 70.12, H 5.23, N 9.09; found: C 70.25, H 5.33, N 9.21.

**Supporting Information:** Experimental details, characterization data and copies of the $^1H$ and $^{13}C$ NMR spectra of all products.

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**Keywords** Donor acceptor cyclopropanes • Nitrogen heterocycles • Ring opening cyclisation • Synthetic methods • Water chemistry

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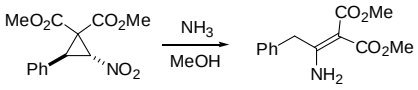


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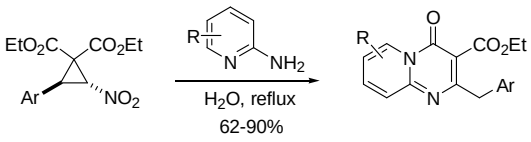


*trans*-2-Aryl-3-nitrocyclopropane-1,1-dicarboxylates underwent tandem ring-opening/cyclization with 2-aminopyridines in water to afford pyrido[1,2-*a*]pyrimidin-4-one derivatives.

**Donor-Acceptor Cyclopropanes**

*Subramani Selvi and Kannupal Srinivasan**

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**Tandem Ring-Opening/Cyclization of *trans*-2-Aryl-3-nitro-cyclopropane-1,1-dicarboxylates with 2-Aminopyridines: Access to Pyrido[1,2-*a*]pyrimidin-4-one Derivatives**

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