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Room temperature cyclization of arylpropiolic acid anhydride: Synthesis of naphtho[2,3-*c*]furan-1,3-dione derivatives

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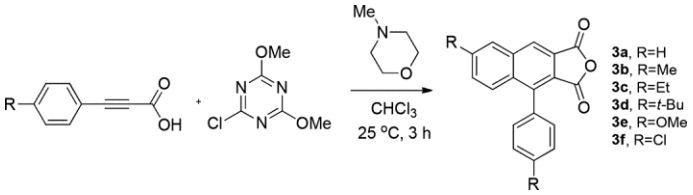
ABSTRACT

Cyclic anhydrides such as naphtho[2,3-*c*]furan-1,3-dione derivatives were synthesized from the reaction of arylpropiolic acids and 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in the presence of *N*-methylmorpholine (NMM) at room temperature. This mild condition provided the naphtho[2,3-*c*]furan-1,3-dione derivatives in good yields. Spectroscopic analysis suggested that the formation of arylpropiolate is the rate-determining step.

GRAPHICAL ABSTRACT



KEYWORDS:

Introduction

Cyclic anhydrides are useful building blocks and important intermediates in the synthesis of biologically active compounds and functional materials.[1] This group can be readily transformed into other functional groups such as lactones, imides, carboxylic acids, esters, and amides. As one of cyclic anhydride moieties, naphtho[2,3-*c*]furan-1,3-dione derivatives have received significant attention from pharmaceutical and material scientists owing to the fact that they have contributed to the synthesis of some very useful functional compounds such as helioxanthin,[2] fluorophores,[3] gas separation polyimides,[4] chiral ligands,[5] and lactone lignans.[6] Therefore, various synthetic methods have been developed for the preparation of naphtho[2,3-*c*]furan-1,3-dione derivatives. Haworth et al. have reported that the reaction of aryl propiolic acids with acetic anhydride provided the desired product.[7] Since it was reported, this method has been widely used and modified. The reaction with aryl propiolic acid at high

temperature gave low yields of the product because of thermal decarboxylation of propiolic acid. In order to address this issue, the reaction with aryl propioloylchloride and aryl propiolic acid was developed and found to provide the desired cyclic anhydride product.[8] However, the instability of the acyl chloride reduced the yields of the product. Recently, Kawano et al. have reported the microwave-assisted synthesis of naphtho[2,3-*c*]furan-1,3-dione derivatives and it was found that the reaction was complete in three minutes under these conditions.[9] Nevertheless, this reaction still requires a high reaction temperature. Another method involves the cyclization of benzylidene succinic anhydride, but it is limited to only one example.[10] Therefore, a more efficient synthetic method that can be performed under mild condition is required. In the study of the decarboxylative coupling reaction of phenylpropiolic acid, we found that the reaction with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) provided 4-phenylnaphtho[2,3-*c*]furan-1,3-dione at room temperature. It is known that CDMT is stable and inexpensive. This motivated us to develop a mild synthetic method of naphtho[2,3-c]furan-1,3-dione derivatives.

Results and Discussion

In order to optimize the reaction conditions, a variety of bases were tested. The results are summarized in **Table 1**. Use of Et_3N and pyridine furnished the desired product with 27% and 29% yields, respectively (entries 1 and 2). Bicyclic amine bases such as DBU and DBN provided only trace amounts of the product (entries 3 and 4). When the reaction was performed using *N*-methylmorpholine (NMM) was conducted, the desired product was formed in 82% yield (entry 5). Among the other reaction solvents that were tested, CH_2Cl_2 and Et_2O provided the desired product **3a** in 71% and 55% yields, respectively (entries 6 and 7). While THF showed 81% yield of product (entry 8), no product was found in DMSO as the solvent (entry 9). When the amount of the base

was decreased to 0.5 equivalents, the yield of the product also decreased to 54% (entry 10). In the absence of a base, the reaction did not take place (entry 11).

In order to evaluate this cyclization method at room temperature, several arylpropiolic acid derivatives were employed as starting materials and the desired cyclized products were isolated and characterized. The results are summarized in Scheme 1. As expected, phenylpropiolic acid afforded **3a** in 82% isolated yield. Arylpropiolic acids bearing alkyl groups such as methyl, ethyl, and tert-butyl at the *para*-position of the phenyl ring provided the corresponding products **3b**, **3c**, and **3d** in 74%, 77%, and 81% yields, respectively. 4-Methoxyphenylpropiolic acid afforded the desired product **3e** in 77% yield. In addition, 4-chloro-substituted arylpropiolic acid yielded **3f** in 65% yield.

The mechanism of the dehydro-Diels-Alder reaction of propiolic anhydride has been previously reported. Although Kishan et al. have proposed a concerted mechanism, it does not apply to the case of phenylpropiolic anhydride because their chosen model substrate was in the solid state.[11] Recently, Wessig et al. have reported a stepwise mechanism involving 1,4-biradicals.[12] Based on a previous report and our results, the reaction pathway shown in Scheme 1 has been proposed. It has been reported that CDMT reacted with NMM to provide 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM) which was used as an efficient condensing agent in the formation of esters and amides.[13] Phenylpropiolic acid reacted with DMTMM to give the corresponding ester as an intermediate **A**. Ester **A** then reacted with phenylpropiolic acid to afford the symmetric anhydride intermediate **B**, which further underwent a [4 + 2] cycloaddition reaction to give the cyclized anhydride intermediate **C**. The final product was formed via secondary hydrogen shift from the allenic intermediate **C**.

In order to find support for the proposed reaction pathway, the reaction was monitored by IR and ^{13}C NMR spectroscopies (**Figure 1** and **Figure 2**). Thus, phenylpropiolic acid, CDMT, and NMM were mixed at room temperature and their IR and ^{13}C NMR spectra were measured after 10 min, which are the points at the beginning of the reaction. In the IR spectrum, the five-membered ring anhydrides showed two weak bands at 1860 cm^{-1} and 1840 cm^{-1} and one strong band at 1780 cm^{-1}. The C-C triple bond stretching band of phenylpropiolic acid appeared at 2230 cm^{-1}. In ^{13}C NMR, a strong carbonyl carbon peak appeared at 172.5 ppm, which is assigned to the intermediate **A** and the two carbon peaks at 163.1 and 161.9 ppm are the chemical shifts of the anhydride carbon atoms of the product. It is worth noting that the symmetric anhydride **B** were not detected because the carbon peaks of the anhydride and alkyne groups in **B** were not present in the ^{13}C NMR spectrum. After 30 min, the bands and peaks of phenylpropiolic acid disappeared from both IR and ^{13}C NMR spectra. Based on these results, it is proposed that the formation of intermediate **A** is the rate determining step and intermediate **B** is too unstable to be detected. To the best of our knowledge, the symmetric anhydride **B** has never been isolated.

Conclusion

In summary, derivatives of naphtho[2,3-*c*]furan-1,3-dione were synthesized by reacting arylpropiolic acid with CDMT. The reaction proceeded with *N*-methylmorpholine at room temperature. Substituted arylpropiolic acid derivatives produced the corresponding cyclic anhydrides in moderate to good yields. Based on FT-IR and ^{13}C NMR spectroscopic analyses, it has been proposed that the formation of arylpropiolate is the rate-determining step.

Experimental Details

All reagents and solvents were purchased and used without further purification. Thin Layer Chromatography (TLC) on precoated plated of silicagel was performed on TLC silica gel 60 F_{254} with ethyl acetate/n-hexane (2:8) systems. Preparative flash chromatography were performed by elution from columns of silica gel (230–400 mesh size) using TLC plates were visualized by shortwave (254 nm) UV light. Melting points were determined on a capillary melting point apparatus and are uncorrected using electrothermal melting point apparatus. ^{1}H NMR (300 MHz and 600 MHz) and ^{13}C NMR (75 MHz and 151 MHz) spectra were recorded in $CDCl_3$ using VARIAN VnmrJ. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal reference and coupling constants (J-values) are in hertz (Hz). IR spectra were recorded on BRUKER EQIUINOX-55 spectrophotometer.

General procedure for the synthesis of cyclic anhydride derivatives

To a round bottom flask containing $CHCl_3$ (20 mL), aryl propiolic acid (2.0 mmol), CDMT (351 mg, 2.0 mmol), NMM (202 mg, 2 mmol) were added. The resulting mass was stirred vigorously for 3 h at room temperature (25^{o}C. After the reaction based on TLC, the reaction mass was filtered and removed the solvent using rotary evaporator. The crude mass was diluted with CH_2Cl_2, and washed with 10% citric acid, followed by 1N NaOH. The DCM layer was dried over sodium sulphate and concentrated which was further purified by flash column chromatography.

Selected product

4-Phenylnaphtho[2,3-c]furan-1,3-dione (3a)[14]

3-Phenylpropiolic acid (292 mg, 2.0 mmol) afforded 4-phenylnaphtho[2,3-c]furan-1,3-dione **(3a)** (225 mg, 0.82 mmol, 82%). M.p.: 261‑263^{o}C; lit[14]260‑262^{o}C; ^{1}H NMR ($CDCl_3$

500MHz): δ 8.57 (s, 1H), 8.18 (d, *J* = 8.2Hz , 1H), 7.92 (d, *J* = 8.7Hz , 1H), 7.82-7.78 (m, 1H), 7.73‑7.69 (m, 1H), 7.59‑7.58 (m, 3H), 7.43‑7.41 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 163.1, 161.9, 143.5, 136.2, 135.9, 133.2, 130.6, 130.3, 130.1, 129.8, 129.2, 128.9, 128.5, 127.2, 125.9, 122.3. Anal. Calcd for $C_{18}H_{10}O_3$: C, 78.82; H, 3.67. Found: C, 78.59; H, 3.71.

Supporting information

Supporting information for this article is available online at

Acknowledgment

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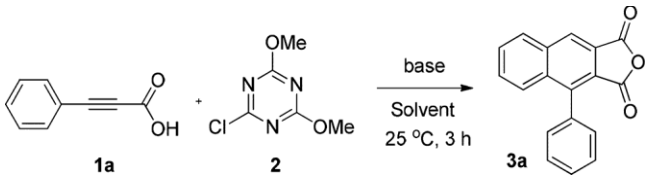
Table 1. Optimization of the synthesis of 4-phenylnaphtho[2,3-*c*]furan-1,3-dione (**3a**).[a]



Entry	Base	Solvent	Yield (%)
1	Et_3N	$CHCl_3$	27
2	Pyridine	$CHCl_3$	29
3	DBU	$CHCl_3$	3
4	DBN	$CHCl_3$	trace
5	NMM	$CHCl_3$	82
6	NMM	CH_2Cl_2	71
7	NMM	Et_2O	55
8	NMM	THF	81
9	NMM	DMSO	N.D.
10	NMM[c]	THF	54
11	–	THF	N.D.[d]

[a]Reaction conditions: **1** (0.4 mmol), **2** (0.4 mmol), and base (0.44 mmol) were reacted in different solvents (1.5mL) at 25°C for 3h. [b]Determined by ^{1}H NMR analysis. [c]0.2 mmol of NMM was used. [d]N.D. = not detected.

Figure 1. IR spectra of the reaction mixture of **1a**, CDMT, and NMM in $CHCl_3$ at 25°C. (a) Pure **1a**. (b) At the beginning of the reaction, (c) after 30 min, and (d) after 60 min. e) Pure **3a**.

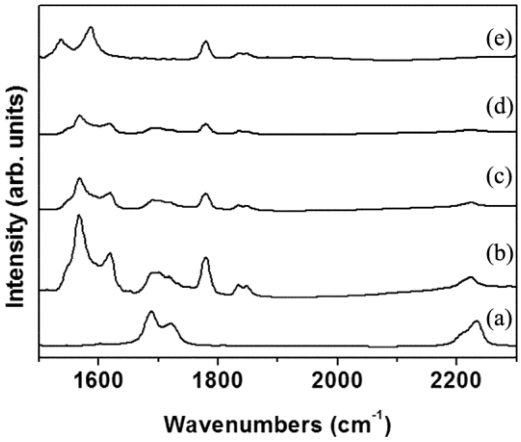
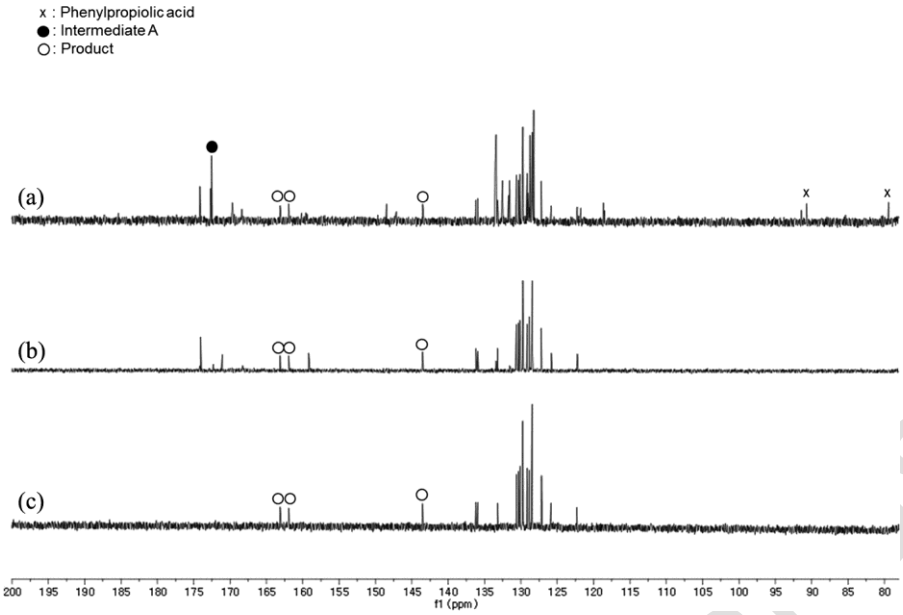
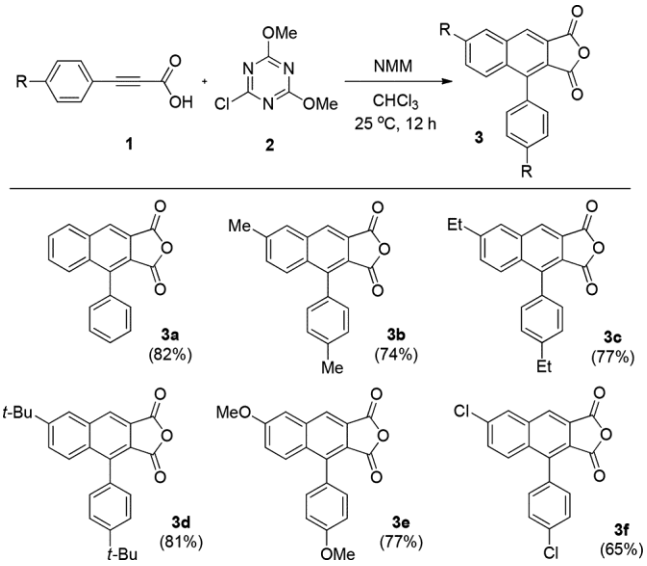


Figure 2. ^{13}C NMR spectra of the reaction mixture of **1a**, CDMT, and NMM in $CDCl_3$ at 25°C (a) at the beginning of the reaction and (b) after 30min . c) Pure **3a**.



Scheme 1. Synthesis of naphtho[2,3-c]furan-1,3-dione derivatives.[a], [a]Reaction conditions: **1** (2.0 mmol), **2** (2.0 mmol), and NMM (2.2 mmol) were reacted in $CHCl_3$ at 25°C for 3h. The values in parentheses are isolated yields.



Scheme 2. Proposed reaction pathway.[