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One-pot synthesis of cinnamic anhydrides from cinnamic acids and 6-chloro-2,4-dimethoxy-sec-triazine (CDMT) at room-temperature

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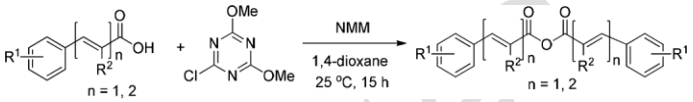
Full experimental detail, ^{1}H and ^{13}C NMR spectra have been provided in supporting information. This material can be found via the "Supplementary Content" section of this article's webpage.

ABSTRACT

Symmetric cinnamic anhydrides were prepared by the reactions of cinnamic acid substrates with 6-chloro-2,4-dimethoxy-sec-triazine (CDMT). The reactions were carried out at room temperature for 15 h. Diverse cinnamic acid substrates bearing electron-withdrawing or -donating groups worked well, providing the corresponding cinnamic anhydrides in moderate-to-good yields

GRAPHICAL ABSTRACT



KEYWORDS: 6-chloro-2,4-dimethoxy-sec-triazine, cinnamic acid, cinnamic anhydride, room temperature

Introduction

Acid anhydrides are useful reagents for the introduction of a carbonyl moiety into the target molecule.[1] Acid halides are the most common starting materials to synthesize acid anhydrides.[2] Although acid halides are highly active reagents, they have some drawbacks. To avoid the use of harmful and highly active acid halides, acid anhydrides have been widely used as acylating agents. Several methods have been developed for the synthesis of acid anhydrides. Among them, the

reactions with carboxylic acids and dehydrative coupling reagents are one of the most popular tools. This is because carboxylic acids are stable and readily accessible, and diverse dehydrative coupling reagents, such as thionyl chloride,[3] phosgene,[4] triphosgene,[5] phosphorus pentoxide,[6] dicyclohexylcarbodiimide,[7] isocyanate,[8] (trimethylsilyl)ethoxyacetylene,[9] Vilsmeier–Haack reagent,[10] $BrCCl_3$-PPh_3,[11] and Cl_3CCN-PPh_3,[12] have been reported. However, they have some drawbacks including toxic or unstable reagents, expensive or unavailable, tedious procedures, harsh reaction conditions, and low yields. Efficient, easily handled, commercially available, and stable reagents should be developed to solve these problems.

6-Chloro-2,4-dimethoxy-sec-triazine (CDMT) has been used to prepare esters and amides from carboxylic acids.[13] CDMT has also been used as a source of 2,4-dimethoxy-sec-triazine for the synthesis of 6-subsituted-2,4-dimethoxy-sec-triazine. CDMT can be used on kilogram scale and has also been used as an acylating agent low temperature (0-5˚C), but scope of substrates are limited to aromatic and aliphatic carboxylic acids, unsaturated acids were not studied.[14] During the development of various decarboxylative coupling reactions in our group, we found that the reaction of cinnamic acid with CDMT afforded a symmetric acid anhydride at room temperature. Hence it is clear that the reactivity of CDMT with saturated and unsaturated carboxylic acid is quite different. Cinnamic anhydride derivatives have been frequently used in the synthesis of natural products and bioactive materials.[15] Herein, we report a mild and simple preparation method for cinnamic acid derivatives from cinnamic acids and CDMT.

Results and Discussion

To optimize the reaction conditions, diverse bases were screened in the reaction of cinnamic acid with CDMT at 25 °C. N-methylmorpholine and triethylamine provided cinnamic

anhydride in 56% and 50% yields, respectively (entries 1 and 2). However, pyridine and DBU provided cinnamic anhydride in very low yields (entries 3 and 4). No anhydride was formed when morpholine, K_2CO_3, Na_2CO_3, DMAP or 1-methyl imidazole was used (entries 5–9). Next, solvents were screened. Toluene, Et_2O, and CH_2Cl_2 furnished the desired anhydride in 70%, 51%, and 50% yields, respectively (entries 8–10). The yield of the product increased to 95% in 1,4-dioxane (entry 11). Theoretically, 0.5 equiv of CDMT is needed to obtain the desired cinnamic acid anhydride. The equivalent of CDMT was examined. When the amount of CDMT was decreased to 0.5 and 0.7 equiv, the yields were 50% and 90%, respectively (entries 14 and 15). Reducing the reaction time and increasing the amount of base also decreased the yield to 81% and 65% respectively (entries 16 and 17).

With this optimized condition, diverse cinnamic acid substrates were tested for the synthesis of symmetric cinnamic anhydrides. As expected, cinnamic acid provided cinnamic anhydride (**2a**) in a good isolated yield. Cinnamic acid substrates bearing methyl, methoxy, and ethoxy substituents at the para position of the phenyl ring afforded the corresponding cinnamic anhydrides **2b**, **2c**, and **2d** in 75%, 81%, and 84% yields, respectively. 3-Methoxyphenyl and 3,5-dimethoxyphenyl acrylic acids gave **2e** and **2f** in good yields. 3-(Benzo[d][1,3]dioxol-5-yl)acrylic acid also provided the corresponding anhydride **2g**. Cinnamic acid substrates bearing halide groups such as bromide and fluoride produced **2h** and **2i** in 74% and 72% yields, respectively. Furan-2-ylacrylic acid afforded the product in a good yield. Interesting, an α-methyl substituted acid such as 2-methyl-3-phenylacrylic acid (**1k**) and a dienoic acid such as 5-phenylpenta-2,4-dienoic acid (**1l**) afforded the corresponding anhydrides **2k** and **2l** in 76% and 80% yields, respectively. 3-(4-cyanophenyl)acrylic acid and 3-(4-(methoxycarbonyl)phenyl)acrylic acid[16] were allowed to react with CDMT/NMM to afford the desired product **2m** and **2n** in 65% and 68% respectively.

However, 3-(4-nitrophenyl)acrylic acid did not afford the product because of its poor solubility in 1,4-dioxane and THF. 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)acrylic acid and 3-(4-(benzyloxy)phenyl)acrylic acid proceeded to form the product which was confirmed by TLC, but unable to isolate the product after column purification. Unfortunately, no anyhydride formation was observed in aliphatic acrylic acids and *N*-protected amino acids. Acid and base work-up did not affect the stability of the product during isolation in the case of cinnamic acid substrates whereas for aliphatic and aromatic acids, low temperature is needed to avoid the decomposition of the product.

To understand the selective formation of cinnamic anhydride from cinnamic acid and CDMT, several control reactions were investigated. It is known that CDMT reacts with NMM to give DMTMM.[17] When cinnamic acid was reacted with DMTMM, cinnamic anhydride was obtained in 87% yield (Scheme 3a). When benzoic acid was allowed to react under the optimized condition, the expected anhydride **5** was not obtained, and only benzoate **4** was formed in 81% yield (Scheme 3b).[18] Cinnamic acid did not react with benzoate **4** (Scheme 3c). When an equal amount of cinnamic acid and benzoic acid was reacted with CDMT and NMM, cinnamic anhydride was obtained in a higher yield than benzoate **4** (Scheme 3d). Cinnamic anhydride was the major product even under the condition of 5 equiv of CDMT and NMM; however, cinnamate **6** was obtained in 12% yield (Scheme 3e). When cinnamic acid **1c** with an electron-donating substituent and cinnamic acid **1i** with an electron-withdrawing substituent were reacted in the same vessel, symmetric anhydrides **2c** and **2i** were obtained in 32% and 27% yields, respectively, and unsymmetrical anhydride **7** was obtained in 26% yield (Scheme 3f). Anhydride **7** was identified by GCMS. These results indicate the following. 1) The reaction of CDMT with NMM afforded DMTMM, which worked as a coupling reagent. 2) Benzoic acid is not a suitable substrate for the

synthesis of an anhydride from CDMT. 3) Cinnamic acid reacts rapidly with CDMT, providing the corresponding cinnamate which further reacts with cinnamic acid to give the corresponding anhydride. 4) The reaction rate of cinnamate **6** with cinnamic acid might be faster than that of cinnamic acid with CDMT could be due to electronic nature of unsaturated carboxylic acids. 5) The electronic nature of the substituent on the aryl ring of cinnamic acid does not affect the yield of the product. 6) The reactivity of unsaturated carboxylic acid towards CDMT is different than the aromatic and aliphatic carboxylic acids; however the rate of the reactivity of carboxylic acids towards CDMT is can be defined as $sp > sp^2 > sp^3$ carboxylic acids for anhydride formation.[21] Aromatic and aliphatic acids required low temperature and sequential addition of reagents.[16b]

Conclusion

In summary, cinnamic anhydride derivatives were easily obtained from cinnamic acid substrates and CDMT in the presence of NMM. Diverse cinnamic acid substrates provided the corresponding cinnamic anhydrides in good yields at room temperature. The reaction conditions are mild, and the reaction showed a good functional group tolerance. Cinnamic acid showed a high reactivity towards CDMT, producing the corresponding cinnamate. The cinnamate was found to be more reactive than cinnamic acid, providing cinnamic anhydride.

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 F254 with ethyl acetate/n-hexane (2:8) systems. Preparative flash chromatography were performed by elution from columns of silica gel (230-400 mesh size). The TLC plates were visualized by shortwave (254nm) UV light. Melting points were determined on a capillary melting point

apparatus and are uncorrected using Electrothermal melting point apparatus. ^{1}H NMR (500MHz) and ^{13}C NMR (125MHz) 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).

General procedure for the SYNTHESIS of anhydride derivatives

To a round bottom flask, cinnamic acid substrates (3.0 mmol) and CDMT (3.0 mmol) in dioxane (10 mL) were added, followed by NMM (3.0 mmol) was added to the reaction mixture. The resulted solution was stirred at room temperature for 15 h. The resulting mixture was cooled and then filtered using a syringe filter. Then the mass concentrated and further diluted with diethyl ether. The organic layer was washed with 5% citric acid and followed by 5% sodium bicarbonate. The organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure, and the resulting crude product was purified by simple column chromatography (eluent = hexane/ethyl acetate).

Selected product

(E)-Cinnamic anhydride (2a)[19]

Cinnamic acid (444mg, 3.0 mmol) CDMT (527 mg, 3.0 mmol) and NMM (303 mg, 3.0 mmol) in dioxane afforded (*E*)-cinnamic anhydride (2a) as a white solid (355 mg, 85% yield); M.p.: 135.2–136.4 ºC; lit[20] 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 15.95 Hz, 2H), 7.63 – 7.56 (m, 4H), 7.49 – 7.40 (m, 6H), 6.54 (d, *J* = 15.95 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.48, 148.67, 133.71, 131.29, 129.08, 128.58, 116.73. MS (EI) *m*/*z*: 278. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07; Found: C, 77.77; H, 5.11.

Acknowledgment

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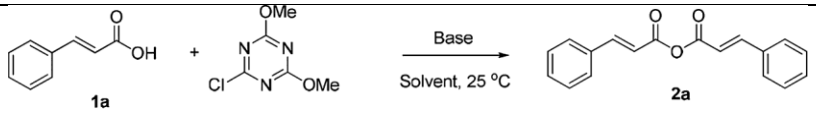
Table 1. Screening of bases, solvents, equivalent of CDMT, and reaction time for the synthesis of cinnamic anhydride.[a]

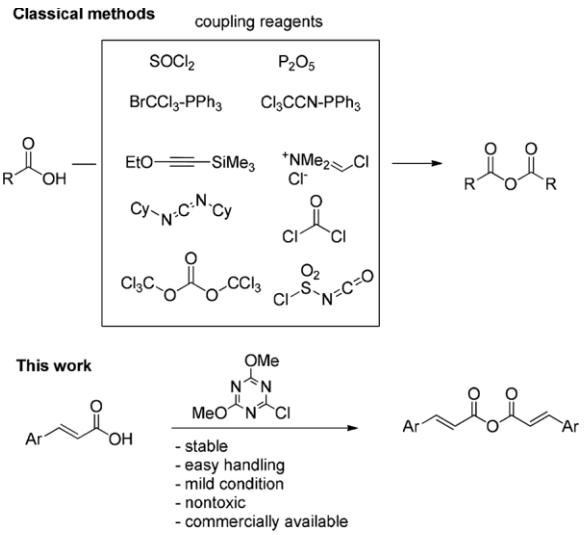


Entry	CDMT (equiv)	Base (1 equiv)	Solvent	Time, hrs	Yield (%)b
1	1.0	NMM	THF	15	56
2	1.0	Et_3N	THF	15	50
3	1.0	Pyridine	THF	15	4
4	1.0	DBU	THF	15	8
5	1.0	Morpholine	THF	15	0
6	1.0	K_2CO_3	THF	15	0
7	1.0	Na_2CO_3	THF	15	0
8	1.0	DMAP[c]	1,4-dioxane	15	0
9	1.0	1-Methyl imidazole	1,4-dioxane	15	0
10	1.0	NMM	Toluene	15	70
11	1.0	NMM	Et_2O	15	51
12	1.0	NMM	CH_2Cl_2	15	50
13	1.0	NMM	1,4-dioxane	15	95

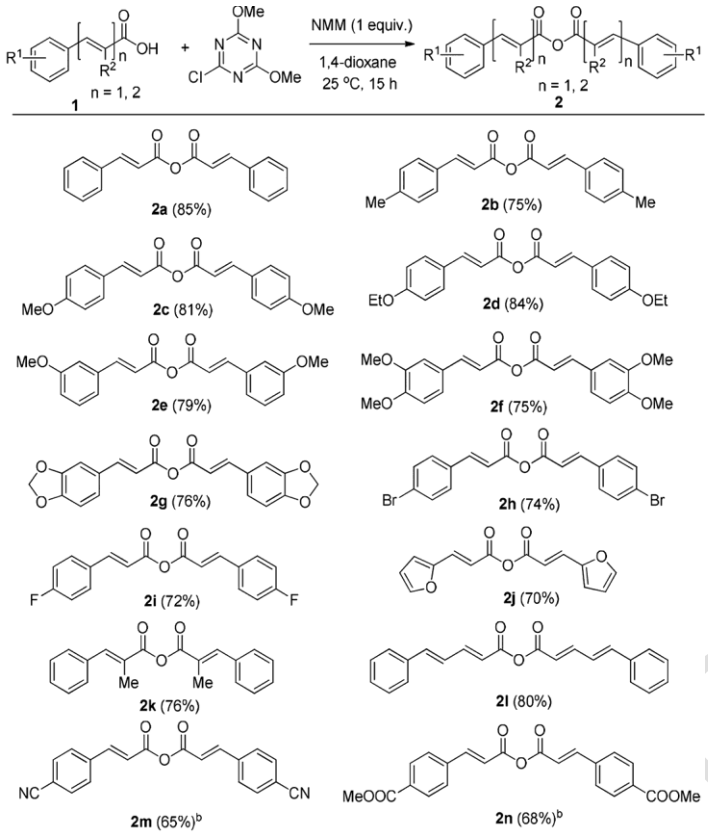
14	0.5	NMM	1,4-dioxane	15	50
15	0.7	NMM	1,4-dioxane	15	90
16	1.0	NMM	1,4-dioxane	3	81
17	1.0	NMM (2 equiv.)	1,4-dioxane	15	65

[a] Reaction conditions: **1a** (0.3 mmol), CDMT (0.3, 0.15, and 0.21 mmol), and base (0.3 mmol) reacted in a solvent (1 mL) at 25 °C. [b] Determined by gas chromatography using an internal standard naphthalene. [c] 4-Dimethylaminopyridine.

Scheme 1. Synthesis of anhydrides.

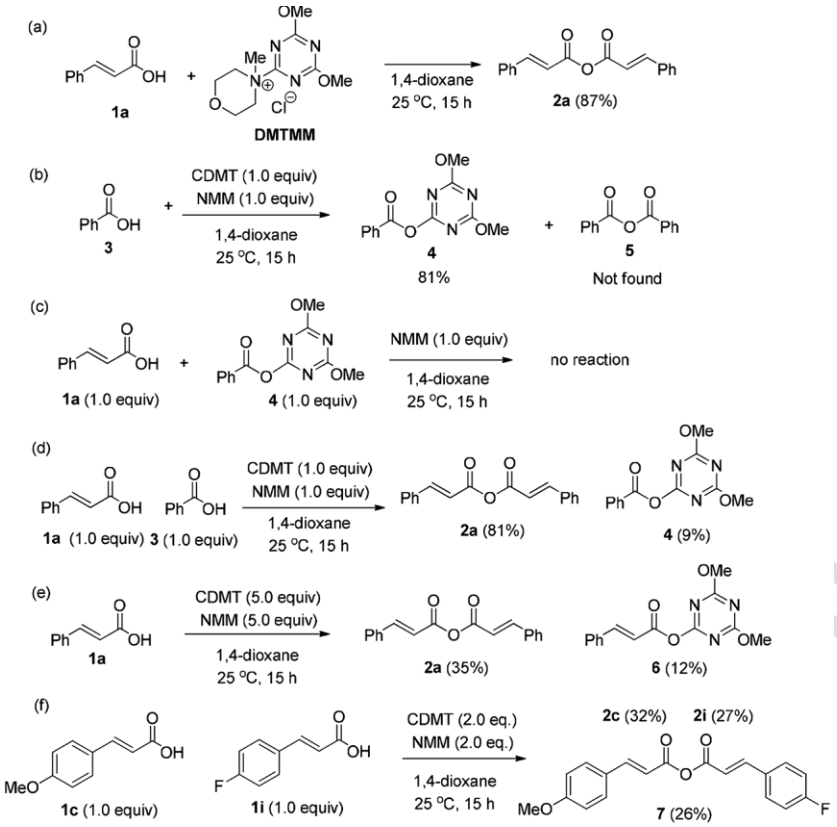


Scheme 2. Synthesis of Cinnamic Anhydride.[a]



[a] Reaction conditions: **1** (3 mmol), CDMT (3 mmol), and NMM (3 mmol) reacted in 1,4-dioxane (10 mL) at 25 °C for 15 h. The yields reported are isolated yields. [b]THF used as solvent.

Scheme 3. Reactivity of CDMT.



(a) Reaction conditions: **1a** (3 mmol), DMTMM (3 mmol) reacted in 1,4-dioxane (10 mL) at 25 °C for 15 h. (b) Reaction conditions: **3** (3 mmol), CDMT (3 mmol), and NMM (3 mmol) reacted in 1,4-dioxane (10 mL) at 25 °C for 15 h. (c) Reaction conditions: **1a** (3 mmol), **4** (3 mmol), and NMM (3 mmol) reacted in 1,4-dioxane (10 mL) at 25 °C for 15 h. (d) Reaction conditions: **1a** (3 mmol), **3** (3mmol), CDMT (3 mmol), and NMM (3 mmol) reacted in 1,4-dioxane (10 mL) at 25 °C for 15 h. (e) Reaction conditions: **1** (3 mmol), CDMT (15 mmol), and NMM (15 mmol) reacted in 1,4-dioxane (20 mL) at 25 °C for 15 h. (f) Reaction conditions: **1c** (3 mmol), **1i** (3mmol), CDMT (6 mmol), and NMM (6 mmol) reacted in 1,4-dioxane (10 mL) at 25 °C for 15 h. The yields were calculated by GC using naphthalene as an internal standard.