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A Facile and Efficient Protocol for the Construction of Oxime Esters from Carboxylic Acids and Evaluation of Their Antimicrobial Activities

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ABSTRACT

A facile and efficient protocol for the synthesis of various structurally and electronically divergent oxime esters from carboxylic acids and oximes in the presence of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and N-methylmorpholine (NMM) in 1,4-dioxane in high yields (90-97%). The synthesized compounds were assessed for their antimicrobial activities. Among the tested compounds 3d, 3j and 3p showed good antimicrobial activity.

Keywords: Oxime esters; Oximes; CDMT; NMM; Carboxylic acids

INTRODUCTION

Oxime esters and their derivatives have been shown to have favorable attracting attention from researchers, since compounds bearing oxime ester group are valued not only for their rich and varied chemistry, but also for many important biological properties. Oxime esters are one of the most important and versatile intermediates in organic synthesis. They are very attractive starting materials for the synthesis of various nitrogen and oxygen containing compounds including amine and its derivatives [1], nitriles [2], hetero aromatics such as indoles [3], pyrroles [4], pyridines [5], quinoline derivatives [6] etc.

The oxime ester moiety is a privileged group in chemistry due to its presence in a large number of medicinal scaffolds that exhibit a broad range of biological and pharmaceutical properties, such as antibacterial [7], anticonvulsant [8], insecticidal [9], antitumor [10], antiproliferative [11], herbicidal [12], antioxidant and antimicrobial [13], antifungal [14-16], anticancer [17,18] antiviral [19] activities. Some oxime esters have recently been reported to exhibit DNA-cleaving ability by using photolysis process [20,21]. Moreover, they can be used as intermediates for the synthesis of peptides [22] and fragrances [23] (Figures 1,2).

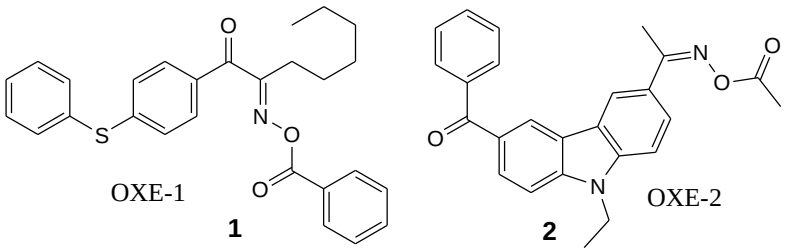


Figure 1: Photo active oximes

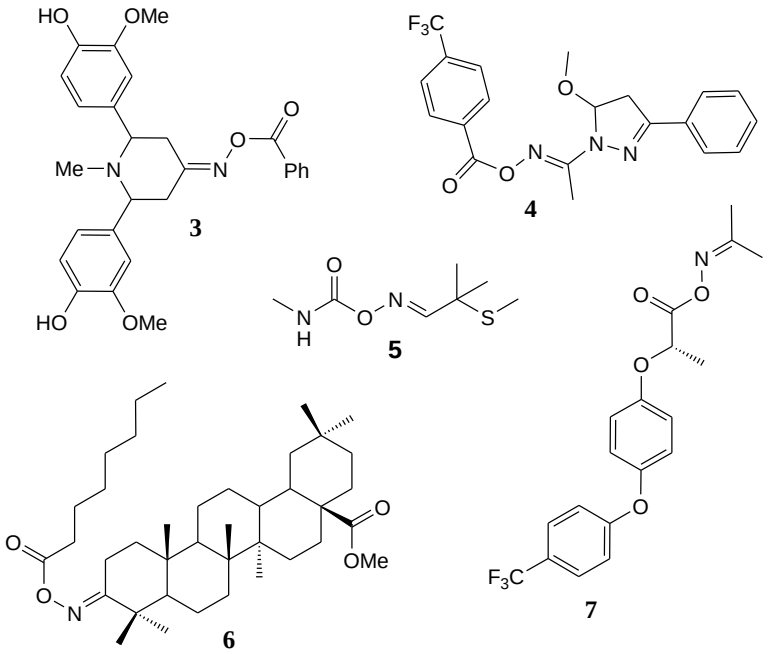
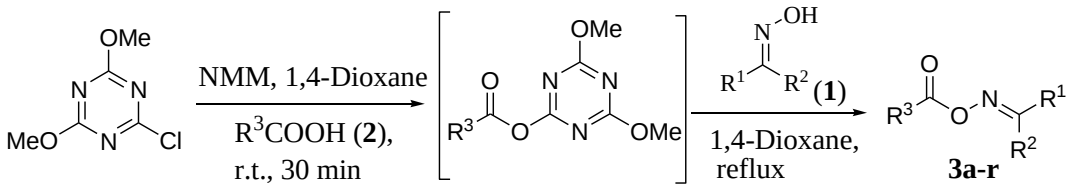


Figure 2: Examples of oxime esters containing antioxidant 3, antifungal 4, insecticide 5, antiinflammatory 6 and herbicide 7 activities

Owing to their important applications, various methods have been developed for the synthesis of oxime esters. Generally, oxime esters are synthesized by the reaction of oximes with activated carboxylic acids using basic or acidic conditions [24] or with carboxylic acids using coupling reagents like EDC [25]. Recently, benzoyl esters of alkyl and aryl substituted oximes have been prepared using benzoyl peroxide, [26] but it is applicable mainly to benzoyl esters of oximes. Very recently, oxime esters also prepared from α,β-unsaturated aldehydes and oximes using a N-heterocyclic carbine as a catalyst [27]. However, these methods have some drawbacks such as use of expensive catalysts and harsh reaction conditions. Therefore, developing a mild and more general procedure to access oxime esters is still highly desirable.

Cyanuric chloride or its derivatives have received considerable attention as easily available and inexpensive catalysts for various transformations [28]. 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) is commercially available, stable and can also be prepared from commercially available and inexpensive cyanuric chloride. It has been found to have applications as a condensing reagent in peptide chemistry [29] and used for the in situ activation of the carboxylic group in many transformations, such as the synthesis of N-methoxy-N-methyl amides, [30] aldehydes, ketones or α-amino ketones, [31] 2-oxazolines [32] and monoacylated piperazines [33]. Thus, in continuation of our work on the development of efficient new synthetic methodologies for heterocyclic compounds, herein, we describe an efficient method for the synthesis of oxime esters from carboxylic acids and oximes using CDMT and NMM in 1,4-dioxane at reflux conditions (Scheme 1).



Scheme 1: Construction of oxime esters from carboxylic acids and acetphenone oxime

RESULTS AND DISCUSSION

In the standard procedures, first the CDMT reacts with N-methylmorpholine (NMM) to form 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), and then the carboxylic acid is added to generate an active ester. This activated ester was further treated with oxime to afford the oxime esters. In a model study, benzoic acid (2a) was treated with CDMT and NMM in dichloromethane at room temperature. The corresponding activated ester was quantitatively formed after 30 min (monitored by TLC). This white suspension containing the activated ester was subsequently treated with acetphenone oxime (1a) at reflux conditions. We were delighted to observe the formation of the

desired product 3a, albeit in a low yield of 60% after 12 h (Table 1, entry 1). Then, we optimized the reaction conditions to increase the yield of the product and to reduce the reaction time. Thus, we investigated the effect of various solvents such as DCM, THF, 1,4-dioxane and CH_3CN on the model reaction (Table 1, entries 2-5). Among the tested solvents, 1,4-dioxane gave the best result. But, other solvents were not as sufficient for this purpose. Furthermore, the by-products formed were removed by a simple aqueous workup, and the desired oxime esters were purified by silica gel column chromatography and the compounds were characterized by advanced spectroscopic analysis 1H NMR, 13C NMR and MS (Tables 1,2).

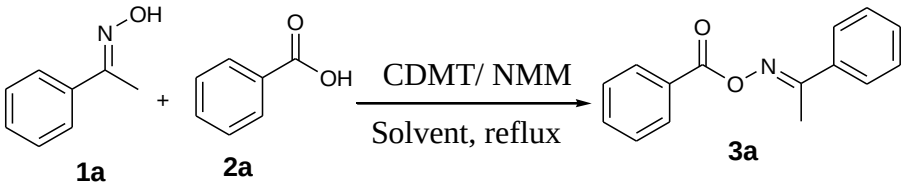
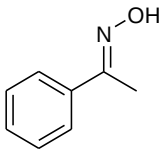
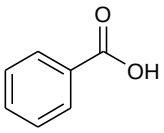
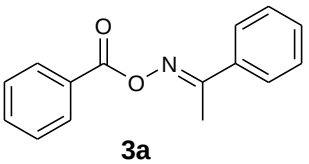
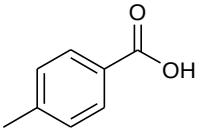
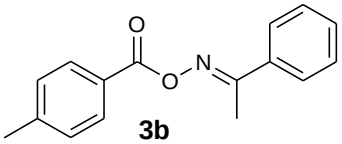
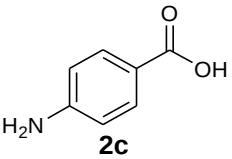
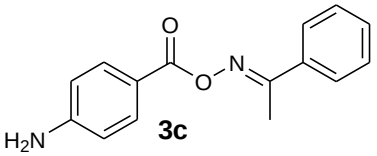
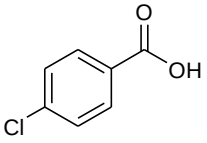
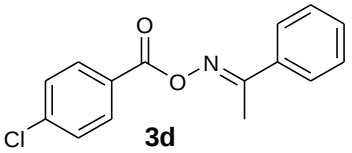
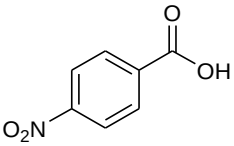
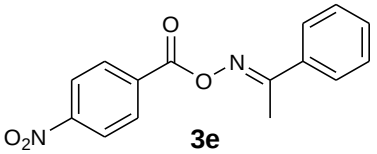
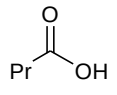
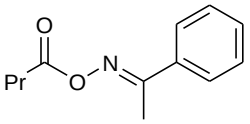
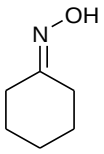
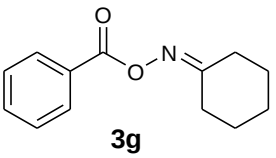
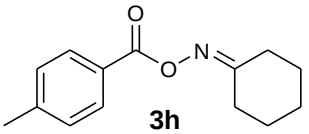
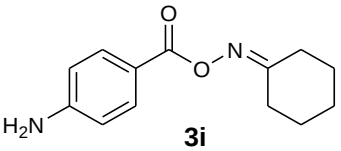
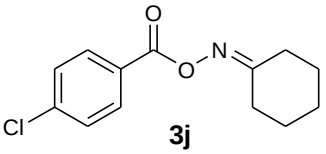
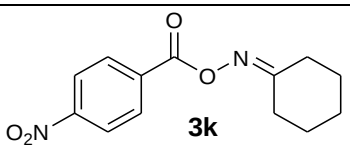
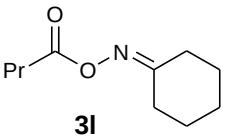
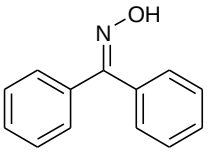
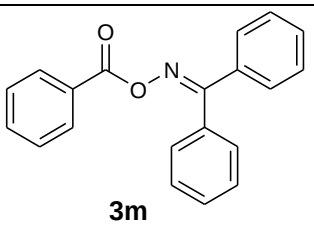
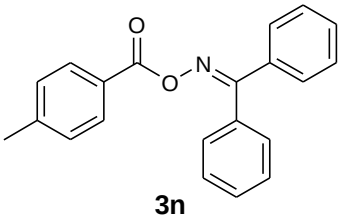
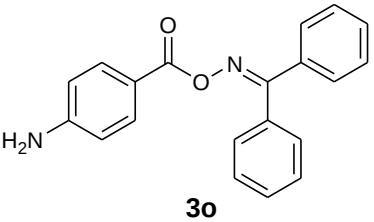


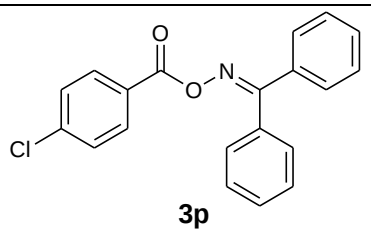
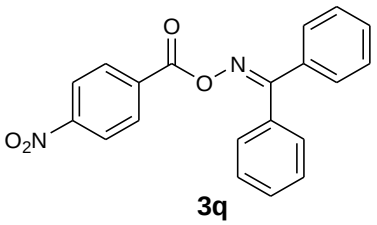
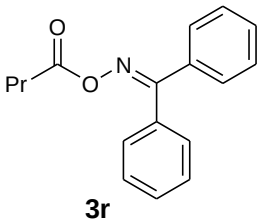
Table 1: Effect of various solvents in the synthesis of 3a[a].

Entry	Solvent	Time /h	Yield[b] / %
1	CH_2Cl_2	12	60
2	$CHCl_3$	14	55
3	THF	10	48
4	1,4- dioxane	6	95
5	CH_3CN	15	55

Table 2: Synthesis of alkyl and aryl oxime esters using CDMT/NMM in 1,4-dioxane at reflux conditions[a].

Entry	Oxime	Carboxylic acid	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	95
2	**1a**	 **2b**	 **3b**	91
3	**1a**	 **2c**	 **3c**	90
4	**1a**	 **2d**	 **3d**	93
5	**1a**	 **2e**	 **3e**	95

6	**1a**	 **2f**	 **3f**	93
7	 **1b**	**2a**	 **3g**	96
8	**1b**	**2b**	 **3h**	96
9	**1b**	**2c**	 **3i**	92
10	**1b**	**2d**	 **3j**	95
11	**1b**	**2e**	 **3k**	94
12	**1b**	**2f**	 **3l**	97
13	 **1c**	**2a**	 **3m**	92
14	**1c**	**2b**	 **3n**	95
15	**1c**	**2c**	 **3o**	91

16	**1c**	**2d**	 **3p**	93
17	**1c**	**2e**	 **3q**	94
18	**1c**	**2f**	 **3r**	97

[a]Reaction conditions: **1a** (0.5 equiv.), **2a** (1.0 equiv.), CDMT (1 equiv.), NMM (3 equiv.) 1,4-dioxane (5mL) at 50 °C, [b]Isolated yields.

With the optimized conditions in hand, the scope of the reaction substrates was investigated and the results are summarized in Table 2. From Table 2, it is clear that this method is highly efficient and useful for aromatic carboxylic acids with either electron-donating or electron-withdrawing substituents on the aryl residue. It is noteworthy that aliphatic carboxylic acid such as butyric acid was completely converted into the corresponding oxime ester in good yields (Table 2, entry 6). Next, different oximes were investigated as the reaction substrates (Table 2). As expected, the oximes such as phenyl acetophenone oxime, benzophenone oxime and cyclohexanone oxime reacted smoothly and produced the corresponding oxime esters in excellent yields (Table 2). All the compounds were characterized by advanced spectroscopic analysis (^{1}HNMR, ^{13}CNMR, and MS).

Biological activities

Antimicrobial activity

All the synthesized compounds **3a-3q** were evaluated for antibacterial activities against *Bacillus subtilis* (MTCC 8141), *Staphylococcus aureus* (MTCC 7443), *Escherichia coli* (MTCC 6365) and *Proteus vulgaris* (NCIM 2813). To carry out the antimicrobial activity (zone of inhibition), we used standard solution of 100 µg/ml. The results obtained as zone of inhibition (mm) are presented in **Table 3** and their minimum inhibitory concentration (MIC) values against these microorganisms were determined by serial dilution method and results are presented in **Table 4.** It is more attractive to speculate the observation that the result of the antimicrobial activity of the different derivatives of oxime esters appeared to be related to the nature of substituent on the phenyl unit. All the tested compounds found to be active against both gram positive and gram negative bacteria, they exhibited zone of inhibition ranging from 8.1 to 23 mm. Among the tested compounds, **3d**, **3j** and **3p** are more active against two bacterial strains; *Staphylococcus aureus* (MTCC 7443) and *Escherichia coli* (MTCC 6365) than all other, **3d**, **3j** and **3p** possessing chloro group at para position in phenyl moiety to ester ring. Compounds bearing nitro group exhibited slightly less antibacterial activity than standard. Compounds bearing methyl and amino groups were demonstrated to have moderate activity against all tested bacterial strains. The compounds **3a** and **3g** which are having no substitution on aryl ester moiety exhibited least antibacterial activity (Tables 3,4).

Table 3: Zone of inhibition (mm) against bacteria.

Compound No.	**Zone of inhibition (mm)**			
	B. subtilis	**S. *aureus***	**E. *coli***	***P. vulgaris***
3a	9.2	11.1	8.1	10.1
3b	15	17.8	16	12.5
3c	16	18	17.5	13.3
3d	18.3	23	21	17.8
3e	14	14.3	13	11.2

3g	8.5	9.3	8	9.2
3h	15	18	17.3	12
3i	14.5	15	13.8	12.5
3j	17.3	19.5	19.2	16
3k	15	16	15	11.1
3m	9.3	11.8	8.5	10.4
3n	14	16.2	14.9	12.3
3o	15	18	18	13.9
3p	18.4	20	17	16.7
3q	15.3	16.5	15.2	11.3
Amoxycillin	24.5	32.8	31.6	29.3
DMF	--	--	--	--

*Average of three readings
B. s = *Bacillus subtilis* (MTCC 8141); S. a = *Staphylococcus aureus* (MTCC 7443); E. c = *Escherichia coli* (MTCC 6365); P. v = *Proteus vulgaris* (NCIM 2813)

Table 4: Minimum Inhibitory Concentration (MIC) values of the tested compounds against various bacteria.

Compound No.	***MIC values in µg/ml**			
	B. s	**S. a**	**E. c**	**P. v**
3a	50	100	100	50
3b	50	100	100	50
3c	25	100	100	50
3d	50	100	100	50
3e	25	50	100	50
3g	50	100	100	50
3h	50	100	100	50
3i	50	25	100	100
3j	25	50	100	100
3k	25	50	100	50
3m	50	100	100	50
3n	50	100	100	50
3o	50	25	100	100
3p	25	50	100	100
3q	25	50	100	50
Amoxycillin	100	100	100	100
DMF	--	--	--	--

*Average of three readings
B. s = *Bacillus subtilis* (MTCC 8141); S. a = *Staphylococcus aureus* (MTCC 7443); E. c = *Escherichia coli* (MTCC 6365); P. v = *Proteus vulgaris* (NCIM 2813)

EXPERIMENTAL

General experimental procedure for the synthesis of alkyl and aryl oxime esters (3a-r)

To a stirred solution of CDMT (2.279 mmol) in 1, 4-dioxane (5 mL), NMM (6.837 mmol) was added drop wise and allowed to stir for 5 min. To the white suspension containing 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium solution of carboxylic acid (2.279 mmol) in 1,4-dioxane (5 mL) was added and stirred at room temperature for 30 min. Then a solution of oxime (1.025 mmol) in 1,4-dioxane added to the above reaction mixture and stirred at reflux. After the completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature, aq. 5% Na_2CO_3 solution was added and extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulphate and concentrated under vacuum to afford the crude compound. The crude compound was purified with silica gel column chromatography using hexane/EtOAc as eluents to afford the pure product.

The data for some oxime esters (Table 2, Entries 4, 10 and 16) is given below.

Acetophenone O-4-Chlorobenzoyl Oxime (3d)

White solid; Yield: 93%; Mp: 102-104 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, 2H), 7.82-7.80 (d, 2H), 7.46 (d, 5H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 162.9, 149.1, 139.8, 134.7, 131.0, 130.7, 128.9, 128.6, 127.1, 14.7; LC-MS: *m/z* = 296 $[M+Na]^+$; Anal. Calcd for $C_{15}H_{12}ClNO_2Na$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.79; H, 4.46; N, 5.09

Cyclohexanone O-4-Chlorobenzoyl Oxime (3j)

White solid; Yield: 95%; Mp: 108-110 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 2H), 7.34 (d, 2H), 2.38 (d, 4H), 1.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 163.4, 139.6, 130.9, 128.8, 127.8, 32.2, 29.7, 27.1, 25.4; LC-MS: *m/z* = 274 $[M+Na]^+$; Anal. Calcd for calcd for $C_{13}H_{14}ClNO_2Na$: C, 62.03; H, 5.61; N, 5.56. Found: C, 61.98; H, 5.67; N, 5.53

Benzophenone O-4-Chlorobenzoyl Oxime (3p)

White solid; Yield: 93%; Mp: 110-112 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73-7.68 (d, 2H), 7.60 (d, 2H), 7.52 (d, 2H), 7.48-7.46 (d, 2H), 7.41 (d, 3H) 7.40 (d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.85, 162.95, 139.74, 134.45, 132.75, 131.15, 130.98, 129.76, 129.13, 128.86, 128.72, 128.48, 128.33, 127.25; LC-MS: *m/z* = 358 $[M+Na]^+$; Anal. Calcd for $C_{20}H_{14}ClNO_2Na$: C, 71.54; H, 4.20; N, 4.17. Found: C, 71.50; H, 4.23; N, 4.11

CONCLUSION

In conclusion, we synthesized new one pot protocol for the convenient synthesis of alkyl and aryl oxime esters from the carboxylic acids and oximes in the presence of 2-chloro-4, 6-dimethoxy-1,3,5-triazine (CDMT) and N-methylmorpholine (NMM) in 1,4-dioxane in high yields (90-97%). The synthesized compounds were assessed for their antimicrobial activities. All the tested compounds found to be active against both gram positive and gram negative bacteria, they exhibited zone of inhibition ranging from 8.1 to 23 mm. Among the tested compounds 3d, 3j and 3p showed good antimicrobial activity. There for it is confirmed that the synthesized compounds are capable of rendering significant antimicrobial activities

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Supporting information

Full experimental details and ^1H, ^{13}C NMR and mass spectra can be accessed on the publisher's website.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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