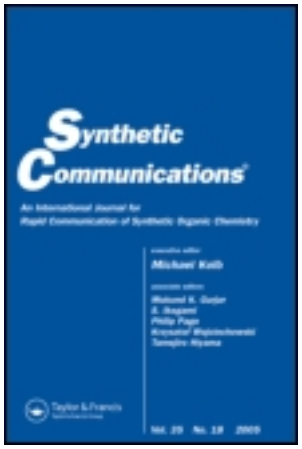

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Practical Synthesis of 4-Benzylidene-2-phenyl-5(4H)-oxazolones

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PRACTICAL SYNTHESIS OF 4-BENZYLIDENE-2-PHENYL-5(4*H*)-OXAZOLONES

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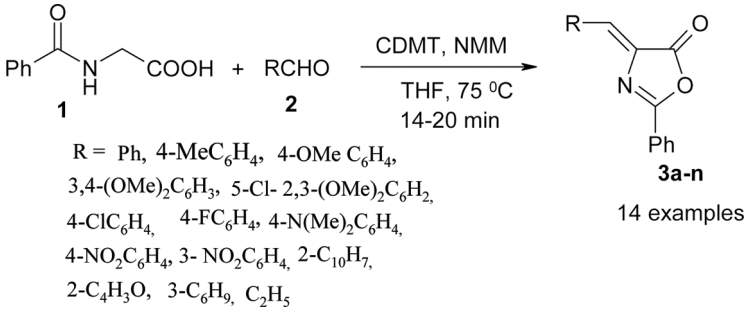
GRAPHICAL ABSTRACT



Abstract *A simple and alternative method has been developed for the synthesis of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones via reactions of hippuric acid with various aldehydes in the presence of 2-chloro-4,6-dimethoxy-1,3,5-triazine/*N*-methylmorpholine at 75°C.*

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Keywords 4-Benzylidene-2-phenyl-5(4*H*)-oxazolone; CDMT; cynuric chloride; hippuric acid; NMM

INTRODUCTION

4-Benzylidene-2-phenyl-5(4*H*)-oxazolones are important intermediates in the synthesis of several bioactive compounds that have analgesic,[1] anti-inflammatory,[2] antidepressant,[3] anticancer,[4] antimicrobial,[5] antidiabetic,[6] antiobesity,[7] antitumor,[8] and immunomodulatory[9] activities. They also act as precursors for the synthesis of important heterocyclic drugs, amino acids, and peptides.[10] 4-Benzylidene-2-phenyl-5(4*H*)-oxazolones have potential applications in photonics,

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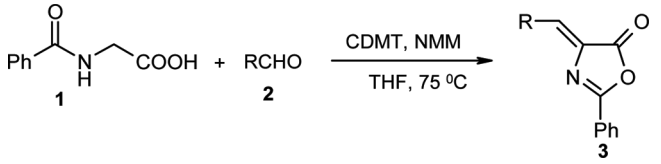


1 2 3

Scheme 1. Synthesis of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones.

electronics, and nonlinear optics.[11] Because of pharmacological and other diverse applications, synthesis of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones has interested organic chemists for a long time. Generally their preparation can be accomplished by the reaction of *N*-benzoylglycine (hippuric acid) with different araldehydes in the presence of acetic anhydride and various acetate salts in ethanol. In recent years, a number catalysts, such as $Pb(OAc)_2$,[12] Al_2O_3-H_3BO_3,[13] $Bi(OAc)_3$,[14] $ZnCl_2$,[15] ZnO,[16] and Montmorillonite K-10[17] have been reported in place of anhydrous sodium acetate in the Erlenmeyer azlactone synthesis. Microwave synthesis also has become an important tool, and there have been several reports describing syntheses of 4-arylidene-2-phenyl-5(4*H*)-oxazolones.[18] However, most of the methods reported use excess acetic anhydride and expensive acetate salts. Removal of the excess acetic anhydride from the reaction mixture is difficult and additional purification of the reaction product is often required. Therefore, a simple, efficient, and alternative method for the synthesis of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones is highly desirable.

Over the past few years, there has been considerable application of cyanuric chloride or its derivatives in organic synthesis.[19] 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) is commercially available, easily prepared from inexpensive cyanuric chloride, and has applications as a condensing reagent in peptide chemistry.[20] CDMT was used for the in situ activation of the carboxylic group in many organic transformations, such as the synthesis of carboxamides,[21] Weinreb amides,[22] monoacylated piperazines,[23] formyl amides,[24] aldehydes,[25] α-amino ketones,[26] and 2-oxazolines.[27] Thus in continuation of our work[28] on the development of efficient new synthetic methodologies for heterocyclic compounds and the use of cyanuric chloride derivatives in organic synthesis, herein we describe an efficient alternative approach using CDMT and *N*-methylmorpholine (NMM) at 75 °C, which avoids the usage of acetic anhydride and acetate salts in the synthesis of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones (Scheme 1).

RESULTS AND DISCUSSION

To optimize the reaction conditions, we investigated the reaction of hippuric acid (1.1 mmol) (**1**) with benzaldehyde (**2a**) (1.0 mmol) as a model reaction in the presence of CDMT (1.1 mmol) and NMM (1.5 mmol) in tetrahydrofuran (THF) at room temperature. It was found that the reaction led to the desired 4-(4-benzylidene)-2-phenyl-5(4*H*)-oxazolone with a yield of 65% after 3 h (Table 1, entry 1). Subsequently, we attempted to shorten the reaction time and increase the reaction yield. Thus, we investigated the effect of various aprotic solvents on the model reaction.

Table 1. Optimization of reaction conditions

			(CDMT/NMM)[a]		(Cy · Cl/NMM)[b]	
Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
1	THF	rt	180	65	600	32
2	CH_3CN	rt	180	60	600	30
3	CH_2Cl_2	rt	180	55	600	10
4	DMSO	rt	180	—	600	—
5	DMF	rt	180	10	600	Trace
6	THF	75	15	90	190	70
7	THF	80	15	90	190	70

[a]1.1/1.5 mmol.
[b]0.5/1.5 mmol.
[c]Isolated yield.

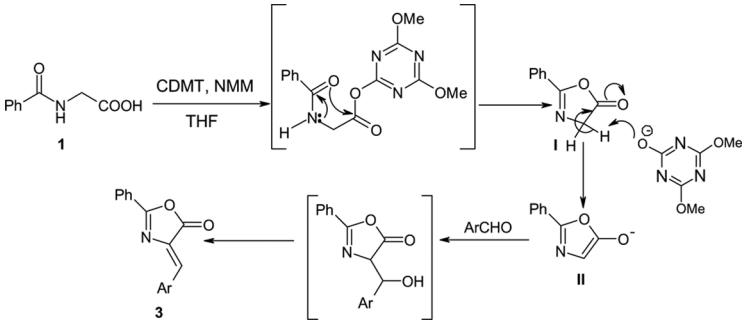
The progress of the reaction was monitored by thin-layer chromatography (TLC), and the results are summarized in Table 1. Among the studied solvents THF gave the best result. Acetonitrile and dichloromethane also afforded good yields of **3a**, but other solvents were not as efficient for this purpose (Table 1, entries 2–5). We then evaluated the effect of temperature on the reaction model. The reaction temperature had great influence on the reaction; thus, when the reaction temperature was increased from room temperature to 75 °C, the reaction was completed within 15 min and compound **3a** afforded in 90% yield (Table 1, entry 6).

With the optimized conditions in hand, the reactions of hippuric acid with a variety of aldehydes such as aromatic, heterocyclic, and aliphatic were investigated. As shown in Table 2, all the aromatic and heteroaromatic aldehydes gave the corresponding

Table 2. Synthesis of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones

Entry	R	Product	Method	Time (min)	Yield[a] (%)
1	C_6H_5	**3a**	**A**	15	90
			B	190	70
2	4-MeC_6H_4	**3b**	**A**	14	91
			B	195	72
3	4-OMe C_6H4	**3c**	**A**	14	92
4	3,4-$(OMe)_2C_6H_3$	**3d**	**A**	14	90
5	5-Cl- 2,3-$(OMe)_2C_6H_2$	**3e**	**A**	16	88
6	4-ClC_6H_4	**3f**	**A**	16	85
7	4-FC_6H_4	**3g**	**A**	17	84
8	4-$N(Me)_2C_6H_4$	**3h**	**A**	15	92
9	4-$NO_2C_6H_4$	**3i**	**A**	17	86
			B	210	66
10	3- $NO_2C_6H_4$	**3j**	**A**	18	84
11	2-$C_{10}H_7$	**3k**	**A**	15	89
12	2-C_4H_3O	**3l**	**A**	16	82
13	3-C_6H_9	**3m**	A	20	22
			B	220	—
14	C_2H_5	**3n**	A	20	25

[a]Isolated yields.



Scheme 2. Plausible mechanism for the formation of 4-benzylidene-2-phenyl-5(*4H*)-oxazolones.

products in good yields (Table 2, entries 1–13), whereas aliphatic aldehydes afforded the corresponding products in lower yields (Table 2, entries 14 and 15).

We have also synthesized 4-benzylidene-2-phenyl-5(4*H*)-oxazolones by using inexpensive commercially available cyanuric chloride (method B). In this method, reactions proceeded very slowly, probably owing to various salts present in the reaction mixture.

To explain the formation of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones, a suggested mechanism of method A using CDMT and NMM is shown in Scheme 2. This mechanism involves the initial activation of carboxylic group of hippuric acid (**1**) using CDMT and NMM, followed by cyclization to form **I**. This is then apparently deprotonated to form anion **II**, which adds to the aldehyde (**2**) to furnish the intermediate alcohol, which is dehydrated to form the final product (**3**).

EXPERIMENTAL

General Experimental Procedure for 4-Benzylidene-2-phenyl-5(4*H*)-oxazolone (3a): Method A

Hippuric acid (196 mg, 1.1 mmol) was added to a solution of CDMT (189 mg, 1.1 mmol) and NMM (151 mg, 1.5 mmol) in THF (10 mL) at room temperature under continuous stirring. A white precipitate was formed after 30 min, and then benzaldehyde (106 mg, 1.0 mmol) in the THF solution (5 mL) was added dropwise. The reaction mixture was stirred at 75 °C for 15 min. Solvent was then removed under reduced pressure. To the resulting residue, aqueous Na_2CO_3 solution (15 ml) was added and extracted with ethyl acetate (2×10 mL). The organic layer was separated, washed with water (2×50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was recrystallized in hot ethanol to give pure compound **3a.**

Yellow solid, yield 90%, mp: 169–171 °C (lit. mp 170 °C)[2]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (1H, s), 7.44–7.63 (m, 6H), 8.15–8.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 125.6$, 128.4, 128.9, 131.1, 131.7, 132.4, 133.3, 133.5, 163.6, 167.5; MS (ESI): $m/z = 250$ $[M + 1]^+$.

Method B

Cyanuric chloride (91 mg, 0.5 mmol) and NMM (151 mg, 1.5 mmol) were added to a solution of hippuric acid (179 mg, 1.0 mmol) in THF (25 mL) at room temperature. A white precipitate was immediately formed. After stirring for 1 h, the solid formed was filtered off on celite and the solution containing the activated ester was transferred into a flask containing benzaldehyde (106 mg, 1.0 mmol) in THF solution (5 mL). The reaction mixture was stirred for additional 190 min at 75 °C and then worked up as before to give **3a** (70%).

CONCLUSION

In conclusion, we have successfully developed a convenient and straightforward method for the synthesis of 4-benzylidene-2-phenyl-5(4*H*)-oxazolones. The method can be used as a valid alternative to reported methods, thereby avoiding the usage of acetic anhydride. Furthermore, this process is amenable to scaling up. The uses of inexpensive and easily available reagents are noteworthy advantages of this method.

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