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Chromic(III) Sulfamate as a Versatile Catalyst for Organic Synthesis

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Chromic sulfamate was synthesized and used as catalyst for the first time in various organic reactions such as the transformation of aldehydes or ketones and indole to *bis*(indolyl)methanes, the transformation of aldehydes and acetic anhydride to 1,1-diacetates and Biginelli reaction. The advantages of the chromic sulfamate are ease of preparation, easy handling, simple work-up and versatility.

Key Words: Chromic sulfamate, *Bis*(indolyl)methanes, 1,1-Diacetates, 3,4-Dihydropyrimidin-2(1*H*)-ones.

INTRODUCTION

Acid catalysts are often being used in organic synthesis and industrial processes. For example, sulfuric acid, fluorohydric acids are used in alkylation, esterification and hydrolysis reactions, *etc.*[1-3]. However, these acid catalysts are toxic, corrosive and in addition, are difficult to remove from the reaction medium. The environmental care is one of the world wide increasing problems. It is well known that some metal sulfonates such as sulfates[4], methanesulfonates[5], *p*-toluenesulfonates[6], dodecyl sulfonates[7], triflates[8] have been reported as efficient catalysts. They have some properties such as low toxicity, moisture tolerance and reusability which make them attractive alternatives to conventional Lewis acids.

Meanwhile, metal sulfamates are also well-known to chemists. They have many advantages finding economically and environmentally attractive in both academic and industrial significance. For example, nickel sulfamate is widely used as electroplating metal[9,13a], cobalt sulfamate can be used as pigment, potassium sulfamate is the important material of synthesis of heterocyclic nitramines[10]. However, their application of catalyst has been neglected for a long time. Only zinc sulfamate and copper sulfamate have been used as catalyst in Biginelli reaction[11]. Therefore the study of catalysis of metal sulfamates is in demand. In our efforts to develop clean methods for organic transformations[12], we are especially interested in developing the potential use of simple, inexpensive Lewis acid catalyst. Chromic(III) sulfamate (CrSM)-catalyzed synthesis has not been previously reported to our knowledge, so we firstly report chromic(III) sulfamate is used as catalyst in various synthesis such as *bis*(indolyl)methanes (BIMs), 1,1-diacetates and 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs).

EXPERIMENTAL

Chromic(III) sulfamate was synthesized from sulfamic acid and chromic(III) oxide according to literature[13]. All reagents were purchased and used without further purification.

General procedure for synthesis of *bis*(indolyl)methanes: To a mixture of indole (20 mmol) and carbonyl compound (10 mmol), ethanol (5 mL), was added chromic(III) sulfamate (0.2 mmol) at room temperature under magnetic stirring. After completion of the reaction (monitored by GC), H_2O (10 mL) was added to the reaction mixture. Then, ethyl acetate (3 × 10 mL) was added and the upper organic phase was dried with Na_2SO_4 and evaporated under vacuum to give a crude product which was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:9 as the eluent) to furnish the product.

General procedure for the synthesis of 1, 1-diacetates: A mixture of aldehyde (20 mmol), Ac_2O (40 mmol), chromic(III) sulfamate (0.4 mmol) were put in a flask and stirred at room temperature for an appropriate time (monitored by GC). After the reaction, most of the mixture solidified gradually, 20 mL of CH_2Cl_2 was added to dissolve the solid product. The organic layer was washed twice with saturated Na_2CO_3 solution (20 mL), dried (Na_2SO_4) and evaporated to yield the almost pure product. The product was purified further by crystallization from cyclohexane or by column chromatography on silica gel (ethyl acetate/hexane, 1:9 as the eluent).

General procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones: A mixture of aldehyde (30 mmol), 1,3-dicarbonyl compound (36 mmol), urea or thiourea (45 mmol) and chromic(III) sulfamate (0.6 mmol) was heated to 90 ºC under solvent-free conditions for the required time in a

50 mL round-bottomed flask in water bath. After cooling, the reaction mixture was poured into crushed ice and stirred for 5-10 min. The solid was filtered under suction, washed with ice-cold water (2 × 30 mL) and then recrystallized from ethanol to afford pure product.

All products were identified by comparing their spectral and physical data with those for authentic samples.

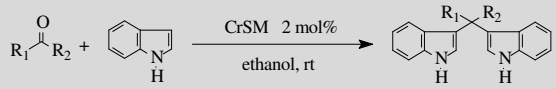
RESULTS AND DISCUSSION

Synthesis of *bis*(indolyl)methanes: *Bis*(indolyl) methanes, which contain two indole or substituted indole units in a molecule, feature widely in bioactive metabolites of terrestrial and marine origin. Recent studies have shown that *bis*(indolyl)methanes can act as highly selective fluorescent molecular sensors for Cu^{2+} cations and also as colon cancer cell and tumor growth inhibitors. Because of their versatile biological activities, in particular the pharmacological activity, various methods are mentioned for the preparation of *bis*(indolyl)methanes. The most common protocol involves the Lewis or protic acid-promoted electrophilic substitution reaction of indoles with carbonyl compounds[14]. Most of the previously reported methods suffer from several setbacks such as requirement of a stoichiometric amount of the Lewis acid, expensive catalyst, toxic solvent, long reaction time. Hence a more efficient and practical alternative using an inexpensive catalyst and environmentally friendly reagent is still warranted.

In this study, we successfully synthesized *bis*(indolyl)-methanes by electrophilic substitution reaction of indole with various aldehydes or ketones in the presence of chromic(III) sulfamate (Table-1). The methodology is found to be general as the reactions of a variety of substituted aromatic aldehydes, α,β-unsaturated aldehydes, as well as alicyclic and aromatic ketones. Good to excellent yields were obtained in very short reaction times in most cases. The nature and electronic properties of the substituents on the aromatic ring effect the reaction rate and aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table-1, entries 3-4, 8) reacted faster than electron-donating groups (Table-1, entries 6-7). It is important to note that heterocyclic aldehyde (Table-1, entry 2) and α,β-unsaturated aldehydes (Table-1, entries 9-10) underwent smoothly with indole giving excellent yields of the corresponding *bis*(indolyl)methanes. Furthermore, ketones required longer reaction times, which are most probably due to the electron-donating and steric effects of the methyl group (Table-1, entries 11-12).

Synthesis of 1,1-diacetates: 1,1-Diacetates are important precursors for the synthesis of acetoxy dienes and dihalo vinyl acetates. Due to the remarkable stability of acylals towards a variety of reaction conditions, they are also gaining importance in organic synthesis as an alternative to acetals for the protection of aldehydes[15]. Generally, the preparation of acylals has been achieved by the reaction of aldehydes with acetic anhydride under the catalysis of strong protic acids or Lewis acids. Although some improvements have been observed in reported methods[16], there still some limitations existed, such as the long reaction time, the highly corrosive and expensive catalysts. Hence, a practical and more efficient alternative using an inexpensive and environment friendly reagent is still of interest.

TABLE-1
SYNTHESIS OF *BIS*(INDOLYL)METHANES BY THE REACTION OF INDOLE WITH ALDEHYDES AND KETONES IN THE PRESENCE OF CrSM IN ETHANOL

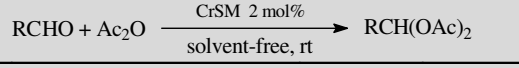


Entry	Carbonyl compound	Time (min)	Yield (%)*
1	Benzaldehyde	90	97.6
2	Furfural	120	96.9
3	2-Chlorobenzaldehyde	40	95.6
4	4-Methoxybenzaldehyde	60	96.1
5	Vanillin	30	93.8
6	Salicylaldehyde	120	90.5
7	4-Hydroxybenzaldehyde	75	94.1
8	2,4-Dichlorobenzaldehyde	50	96.0
9	Neral	30	97.2
10	Geranial	30	98.1
11	Cyclohexanone	120	89.5
12	Hypnone	150	90.3

*Isolated yields.

When aldehydes were treated with acetic anhydride in the presence of chromic(III) sulfamate, the corresponding 1,1-diacetates were obtained in good to high yields. According to the results aromatic aldehydes with an electron-withdrawing group were converted to their corresponding acylals under these conditions in high yields after a short time (Table-2, entries 2-5). On the other hand, furfural proceeded with difficulty. Furthermore, α,β-unsaturated aldehydes (Table-2, entries 7-8) reacted well without any decomposition or polymerization under the reaction conditions. The aromatic aldehydes with electron-donating group afforded the corresponding acylals in high yields and purity (Table-2, entry 9). Hydroxy groups were also acetylated to afford the corresponding triacetates (Table-2, entries 10-12).

TABLE-2
SYNTHESIS OF 1,1-DIACETATES IN PRESENCE OF CHROMIC(III) SULFAMATE



Entry	Aldehyde	Time (h)	Yield (%)*
1	Benzaldehyde	2.0	98.7
2	2-Chlorobenzaldehyde	1.0	93.5
3	4-Chlorobenzaldehyde	0.5	96.6
4	2, 4-Dichlorobenzaldehyde	1.0	90.1
5	3-Nitrobenzaldehyde	6.0	80.9
6	Furfural	1.0	87.2
7	Cinnamaldehyde	5.0	83.3
8	Crotonaldehyde	4.0	94.5
9	4-Methoxybenzaldehyde	2.0	96.4
10**	Salicylaldehyde	3.0	84.6
11**	4-Hydroxybenzaldehyde	5.5	92.0
12**	Vanillin	3.5	91.3

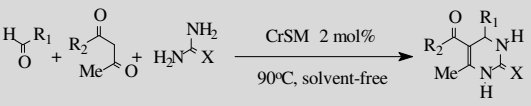
*Isolated yield. **4 equiv. of Ac_2O was used.

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones: 3,4-Dihydropyrimidine-2-(1*H*)-ones and their derivatives are pharmacologically important compounds because of the promising biological activities, including antiviral, antibacterial, antitumor, antihypertensive agents, α_{1a}-antagonists and neuropeptide Y antagonists. In addition, several alkaloids

recently isolated from marine sources with interesting biological activities also possess the dihydropyrimidinone core; most notable among these are the batzelladine alkaloids, which have been found to be potent HIV-gp-120-CD4 inhibitors. Therefore, the preparation of this heterocyclic core unit has attracted the attention of many organic chemists. In order to improve the efficiency of Biginelli reaction, a lot of catalysts have been developed[17]. Some drawbacks still remain, for example, some catalysts are expensive, complex or unavailable and organic solvents are always used. So, it is necessary to find a new catalyst for this important reaction.

According to the results we have obtained in Table-3, in all cases studied, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in satisfactory yields when chromic(III) sulfamate was used. It is worth mentioning that aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxy groups reacted efficiently and gave good to high yields (Table-3, entries 1-8). More importantly, furaldehyde which normally give low yield of products afforded the desired products in 86.7 % yield (Table-3, entry 2). Furthermore, the results showed that besides ethyl acetoacetate, acetylacetone could also be used as one of the substrates. The shorter reaction time and higher yields were observed because of its lower steric hindrance than that of ethyl acetoacetate (Table-3, entries 9-13). Under the same condition, also for thiourea, a slightly longer reaction time was required owing to its lower activity (Table-3, entries 14-15).

TABLE-3
SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES CATALYZED BY CHROMIC(III) SULFAMATE



Entry	R_1	R_2	X	Time (min)	Yield (%)*
1	C_6H_5	EtO	O	60	85.1
2	2-Furyl	EtO	O	60	86.7
3	2-ClC_6H_4	EtO	O	120	89.0
4	4-$CH_3OC_6H_4$	EtO	O	150	82.1
5	2-OHC_6H_4	EtO	O	100	93.1
6	4-OHC_6H_4	EtO	O	30	85.0
7	Vanillin	EtO	O	50	86.7
8	2, 4-$Cl_2C_6H_3$	EtO	O	60	81.6
9	C_6H_5	Me	O	15	95.0
10	2-Furyl	Me	O	20	92.1
11	2-ClC_6H_4	Me	O	15	98.2
12	4-$CH_3OC_6H_4$	Me	O	70	96.2
13	Vanillin	Me	O	30	98.5
14	C_6H_5	EtO	S	180	85.8
15	C_6H_5	Me	S	40	96.5

*Isolated yields.

Conclusion

Chromic sulfamate was found to catalyze efficiently a variety of organic synthesis and transformation reactions leading to the formation of various pharmacologically/biologically important molecules such as *bis*(indolyl)methanes, 3,4-dihydropyrimidin-2(1*H*)-ones and 1,1-diacetates. The ease of preparation, easy handling, simple work-up procedure makes all process more economical and industrially important.

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