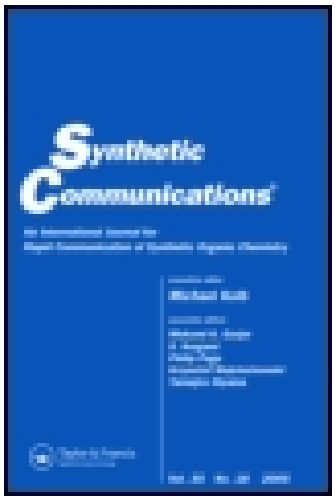

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$InCl_3$-Catalyzed, Three-Component Reactions for the Synthesis of Some Novel Functionalized/Annulated Barbituric Acids

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Abstract

Some novel 5-aminoalkylbarbituric acids and corresponding chromene derivatives were synthesized *via* one-pot three component Mannich reaction starting from 1,3-dimethylbarbituric acid, arylaldehydes and amines.

KEYWORDS: 5-aminoalkylbarbituric acids; Chromene; One pot three component reaction; Mannich reaction.

INTRODUCTION

6-Hydroxy-uracils (barbituric acids) represent a large number of compounds of biological importance which have wide application as drugs and pharmaceuticals. 5-Alkylated barbituric acids are one class of such compounds with diverse biological activity such as anti-convulsant,[1] sedative-hypnotic,[2] anticancer, HIV-1 and HIV-2 protease inhibitors[3] etc. Barbiturates, a class of 5-alkylatedbarbituric acids, are widely being used in the treatment of anxiety, insomnia, seizure disorders, migraine headaches and as anaesthetics.[4] Reports of barbituric acid derivatives which display anticancer, analeptic, anti-AIDS activity are also present.[6] Positive Allosteric Modulators (PAM, Fig I) has

anticonvulsant[5] properties, thiopentone (Fig I) shows intravenous anaesthetic[6] behaviour whereas bucolome (Fig I) acts as an analgesic.[6] Biologically viable list of substituted barbituric acid is very long and its applications have increased with time.[7]

Chromenes are an important class of naturally occurring compounds. They are found to have wide range of biological properties such as anticonvulsant,[8] antimicrobial,[9] antitumor,[10] diuretic, spasmolytic, and antinaphylactic activities.[11]Literature reports show using of harsh conditions for preparation of chromene derivatives.[12a,b] Recently, Marugan[12c] *et al.* have reported the synthesis as well as biological activity of molecules (I, II, Fig I)) as antagonists for neuropeptide S receptor (NPSR).

Awareness has emerged worldwide to use more of renewable resources and step economy protocol for organic synthesis.[13] One-pot multicomponent reactions (MCRs) is an efficient as well as environmentally benign synthetic methodology. It widely abides the needs for economy of steps, minimal usage of hazardous solvents, and reduction of waste and provides combinatorial libraries of medicinal scaffolds. Recently, imine based MCRs[14a] are being widely used due to its immense versatility. Mannich reaction falls under this category which results in the formation of β-amino carbonyl compounds which finds wide application as precursors in many pharmaceuticals.[14b]

In continuation of our interest on synthesizing diverse heterocyclic compounds of biological significance,[15] we report here the synthesis of some novel 5-aminoalkylbarbituric acids **4/** chromene derivatives **6** from an one-pot three component

Mannich reaction of 1,3-dimethyl barbituric acid **1,** aryl aldehyde **2** and amines **3** (Scheme I).

DISCUSSION

First, the reaction of 1,3-dimethyl barbituric acid **1,** benzaldehyde **2a** and pyrrolidine **3a** was carried out in absence of catalyst and solvent (Table I, entry 1), but no reaction occurred. Interestingly, when the reaction was carried out using ethanol as solvent (Table I, entry 2), it gave 50 % yield of the product **4a** in 6 h even in the absence of catalyst. But, addition of $InCl_3$ as catalyst in the reaction improved the yield of the product considerably and reduced the reaction time. 10 mol% of $InCl_3$ (Table I, entry 4) was found optimum to obtain the desired product in high yield, and increase or decrease in the amount of catalyst $InCl_3$ (Table I, entry 4-6) did not improve the yield of the product. The reaction did not occur when it was conducted using $InCl_3$ (10 mol %) as catalyst under solvent free conditions (Table I, entry 3). Subsequently, a range of catalysts were studied on their effectiveness but no such satisfactory results were obtained (Table I, entry 7-8).

Henceforth, the protocol with one-pot three component methodology using equimolar amounts of 1,3-dimethyl barbituric acid **1**, arylaldehydes **2** and amines **3** in presence of $InCl_3$ (10 mol%) was followed, which resulted in an excellent yield of desired 5-aminoalkylbarbituric acids. The experimental procedure is clean and simple:[16] equimolar mixture of 1,3-dimethyl barbituric acid **1**, benzaldehyde **2a** and pyrrolidine **3a** and $InCl_3$ (10 mol%) were fed in a round bottom flask and kept under stirring condition at room temperature for a time period of 2h in ethanol. After work up, we obtained an excellent

yield of 5-aminoalkylbarbituric acid **4a** by simple filtration and further recrystallized it from ethanol. The structure of the compound was confirmed as **4a** from the spectroscopic data and elemental analysis. The generality of the reaction scheme was performed by synthesizing a library of compounds **4b-k** (Table II) using different cyclic secondary amines *viz* pyrrolidine, piperidine and morpholine. Similar reaction with acyclic secondary and primary aliphatic amines gave us the desired product in moderate yield. In the same way, generality of the reaction scheme was done by synthesizing compounds **4l-o** (Table II). The synthesized compounds were characterized by spectroscopic data and elemental analysis. It was found that on conducting the reaction using 1.1 equivalent of amine, product obtained was identical with the one using equimolar amine. Also, using excess amine did not improve the yield of the desired product.

Notably, instead of benzaldehyde, when we performed the same reaction utilizing salicylaldehyde **5,** 1,3-dimethyl barbituric acid **1** and pyrrolidine **3a**, we obtained chromene derivative **6a** in excellent yields (Scheme I). Although it is obvious because of the presence of two suitably located OH groups which favoured the formation of pyran ring by eliminating water easily, but notable point is that cyclization occurred at very mild condition. However, the reaction did not occur in case of both primary as well as secondary aliphatic amines. Generalization of the reaction scheme was done by synthesizing a series of chromene derivatives **6a-c** (Table II).

Solvent optimization was done using various solvents namely acetonitrile, tetrahydrofuran, DMF and toluene, but no satisfactory results were obtained. Electronic

effects of the substituents in the aldehydes used were studied. The electron-donating group (EDG) at the para position of the benzaldehydes gave comparatively better yields of the product while stronger EWG-substituted ones gave evidently less yields. Moreover, halogenated benzaldehydes correspondingly gave very good yield as compared to other arylaldehydes. This methodology is not applicable to aliphatic aldehydes. However, primary aromatic amines were reluctant to the reaction and on performing the reaction, both in three as well as two component way, only resulted the condensed compound **8** with elimination of aniline **3f** (Scheme II).

The probable mechanism supporting the formation of **4a** and **6a** is presented in scheme **III**. Initialy, aldehyde **2a** and pyrrolidine **3a** reacts in presence of protic solvent ethanol to form the intermediate **[A]**, which thereafter undergoes nucleophilic attack by 1,3-dimethyl barbituric acid to generate the product **4a**. Similarly, salicylaldehyde **5** reacts with pyrrolidine **3a** to give intermediate **[B]** which then suffers nucleophilic attack by **1** and gives **[C]**. [**C]** on further elimination of water gives the desired product **6a**.

In conclusion, we have reported the efficient method for the synthesis of some novel 5-aminoalkylbarbituratic acids and corresponding chromene derivatives *via* simple one pot three component Mannich reaction at room temperature. The above said reaction protocol can be further utilized for synthesizing many more heterocyclic compounds.

EXPERIMENTAL

Representative Procedure For The Synthesis Of Compound 4

A mixture of aldehyde (0.105g, 1mmol), 1,3-dimethylbarbituric acid (0.155g, 1mmol) and pyrrolidine (0.07g, 1mmol) in presence of 10 mol% of $InCl_3$ were taken in a round bottomed flask. To this, ethanol (5 mL) added and stirred the reaction mixture vigorously at room temperature for 2h. After completion of reaction (monitored by TLC), solid compound appeared was filtered off and recrystallized from ethanol. The product **4a** was obtained in 82% (0.25 g) yield. The structure of the compound was ascertained from spectroscopic data and elemental analysis. Similarly compounds **4b-o** and **6a-d** were synthesized and characterized.

4a; Yield: 82%; Mp: 175.3˚C; IR ($CHCl_3$) ν_{max} = 1607, 1674, 3460 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$): δ 2.09 (br, 4H), 2.78 (br, 1H), 3.06 (br, 2H), 3.31(s, 6H), 3.63 (br, 1H), 5.17 (s, 1H), 7.11-7.90 (m, 5H), 9.73 (br, OH); ^{13}C NMR (75MHz, $CDCl_3$) δ 23.92, 24.37, 27.28, 28.56, 34.17, 45.25, 83.97, 126.50, 127.75, 127.84, 128.06, 128.92, 129.12, 130.08, 151.03, 152.97, 163.16; MS (ESI) 316.41 $(M+H)^+$; Anal. Calcd for $C_{17}H_{21}N_3O_3$: C,64.74; H, 6.71; N,13.32 %. Found: C, 64.81; H, 6.77; N, 13.43 %.

6a; Yield: 83%; Mp: 170.4˚C; IR ($CHCl_3$) ν_{max} = 1614, 1681, 3061 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (br, 4H), 3.03 (br, 2H), .3.30 (s, 6H), 3.64 (s, 6H), 5.64 (s, 1H), 6.81-7.56 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 23.42, 23.96, 24.92, 27.19, 45.55. 52.22, 54.60, 84.41, 117.58, 120.55, 124.51, 127.61, 130.09, 152.59, 154.75, 161.57,

163.90; MS (ESI) 314.22 $(M+H)^+$; Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.40 %. Found: C, 65.17; H, 6.17; N, 13.51 %.

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SUPPORTING INFORMATION

Full experimental detail, ^1H and ^{13}C NMR spectra of all compounds for this article can be accessed on the publisher's website.

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Table I. Catalyst and solvent screening for the synthesis of compound **4a**

Ent.	Catalyst (mol %)	Solvent	T.(h)	Yd.(%)
1	-	-	7	NR
2	-	EtOH	6	50
3	$InCl_3$ (10 mol %)	-	4	NR
4	$InCl_3$ (5 mol %)	EtOH	4	69
5	$InCl_3$ (10 mol %)	EtOH	2	82
6	$InCl_3$ (20 mol %)	EtOH	4	78
7	K_2CO_3 (10 mol %)	EtOH	4	69
8	L-Proline (10 mol %)	EtOH	5	60

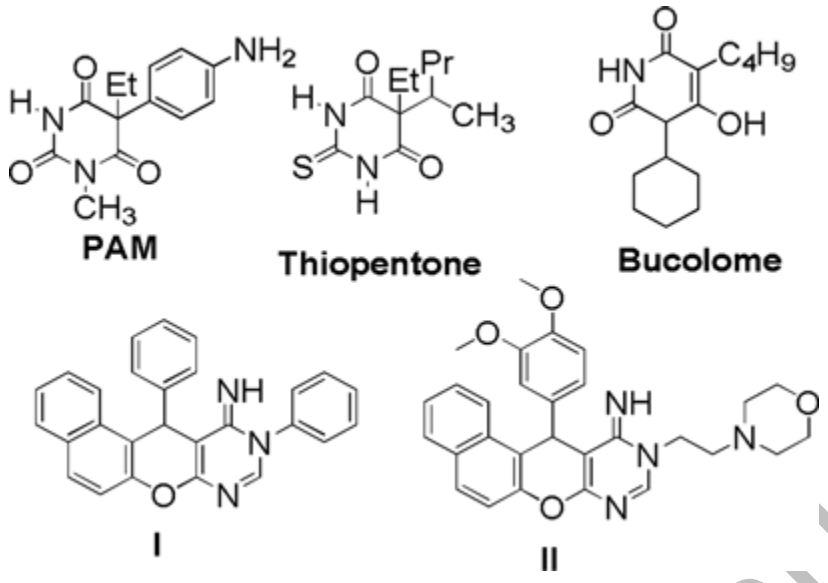
Yd. = Yield, Ent. = Entry, T. = Time, NR. = No Reaction

Table II. Synthesis of 5-aminoalkylbarbituric acids **4** and chromene **6**

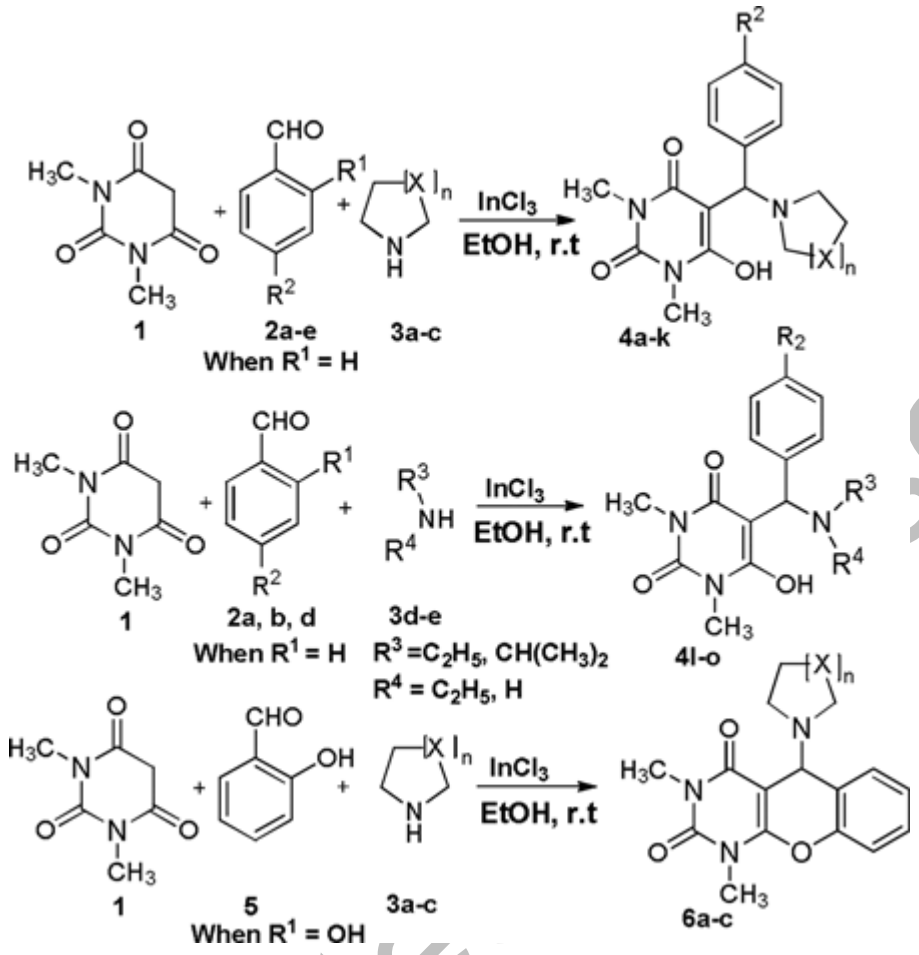
Ent	R^2	R^3	R^4	$[X]_n$	Pd.	Time (h)	Yd. (%)
1	H	-	-	$[CH_2]$	**4a**	2	82
2	CH_3	-	-	$[CH_2]$	**4b**	2	81
3	OCH_3	-	-	$[CH_2]$	**4c**	2	80
4	NO_2	-	-	$[CH_2]$	**4d**	2	77
5	Cl	-	-	$[CH_2]$	**4e**	2	83
6	H	-	-	$[CH_2]_2$	**4f**	2.5	80
7	CH_3	-	-	$[CH_2]_2$	**4g**	2.5	82
8	OCH_3	-	-	$[CH_2]_2$	**4h**	2.5	81
9	NO_2	-	-	$[CH_2]_2$	**4i**	2	76
10	Cl	-	-	$[CH_2]_2$	**4j**	2	83
11	H	-	-	$[CH_2O]$	**4k**	2.5	80
12	H	C_2H_5	C_2H_5	-	**4l**	3	81
13	H	$CH(CH_3)_2$	H	-	**4m**	3	80
14	CH_3	$CH(CH_3)_2$	H	-	**4n**	3	79
15	NO_2	$CH(CH_3)_2$	H	-	**4o**	2.5	75
16	H	-	-	$[CH_2]$	**6a**	3	83
17	H	-	-	$[CH_2]_2$	**6b**	2.5	82
18	H	-	-	$[CH_2O]$	**6c**	3	81

Ent. = Entry, Pd. = Product, Yd. = Yield

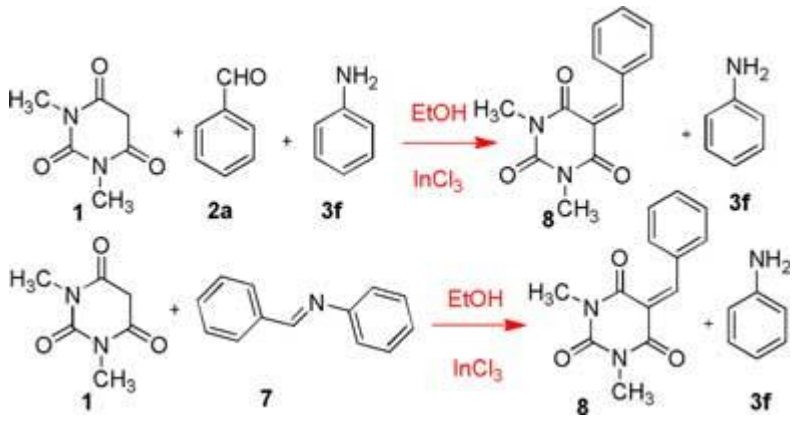
Figure I. Some bioactive molecules



Scheme I. Synthesis of 5-aminoalkylbarbituric acids **4** and chromene **6**



Scheme II.



Scheme III. Plausible mechanism for the formation of **4a** and **6a**