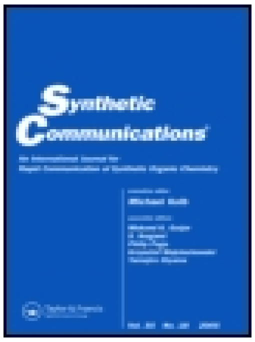

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$Sc(OTf)_3$ catalysed multicomponent synthesis of chromeno[2,3-*d*]pyrimidinetriones under solvent-free condition

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ABSTRACT
An efficient, simple, and environmentally friendly synthesis of a series of chromeno[2,3-*d*]pyrimidine-trione derivatives has been accomplished via the three-component reaction of a barbituric acid, dimedone/cyclohexane-1,3-dione, and aromatic aldehydes using $Sc(OTf)_3$ as a recyclable catalyst under solvent-free condition. This method exploits the use of $Sc(OTf)_3$ as a Lewis acid catalyst in organic synthesis and offers many rewards such as excellent product yield and easy work-up procedure. Harmless reaction conditions, as well as the absence of side-products, are another green aspects of this protocol.

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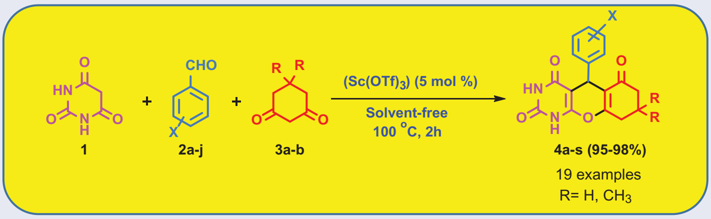
KEYWORDS
Scandium triflate; multicomponent reaction; barbituric acid; solvent-free; chromeno[2,3-*d*]pyrimidine-triones

GRAPHICAL ABSTRACT



Introduction

Green chemistry has become a contemporary research tool to design proficient and environmentally compatible synthetic methods.[1–3] The main objective of green chemistry is to pursue alternative reaction techniques to avoid the use of conventional organic solvents and with minimum waste generation.

Multi-component reactions (MCRs) are an important tool for gathering three or more starting material and converting them into a single product of higher molecular weight in a fast and efficient manner.[4–7] In recent years, MCRs by high merit of their junction, output, high yields, environmental friendliness, and simplicity of implementation have emerged

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as a powerful synthetic plan to make "drug-like" diverse structures of heterocyclic moieties.[8–11]

Transition metal catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions are the vital aspects of organic synthesis to give a biologically active organic molecular framework. Since catalysts play a central role in organic reactions thus they are widely applicable to provide energy efficient, selective, atom-economical solutions to many industrially important problems in organic chemistry synthesis.[12–15] The search for better and efficient catalysts for various organic reactions is always a challenge for organic chemists. Triflate salts have been widely used as a Lewis acid catalyst for organic synthesis since last decades. Among the triflate salts, $Sc(OTf)_3$ has come into view as a competent, mild, commercially available, economical, reusable water tolerant Lewis acidic catalyst in organic transformations.[16–18] Usually, most of the traditional Lewis acids immediately react with water rather than the substrate and are decomposed, while $Sc(OTf)_3$ is found to be stable in water and worked efficiently in a number of other organic solvents as a Lewis acid catalyst.[19] The smaller size of scandium (Sc^{3+}) than other ones is another factor which makes it a more efficient catalyst.[20,21] The use of scandium triflate as a catalyst for organic transformation has been increased promptly due to the above facts.

Chromenes are one of the important classes of organic compounds which have been found in several natural products like tocopherols, flavonoids, alkaloids, and anthocyanins,[22–26] in addition to biologically active molecules like an antibiotic rhodomyrtone[27] and cancer cell apoptosis inducer BENC-511[28] (Figure 1). The syntheses of chromene and their derivatives have garnered considerable awareness for their precious biological properties, such as anti-anaphylactic,[29] antitumor,[30] antimicrobial,[31] anticoagulant,[32] spasmolytic,[33] and diuretic activities.[34]

Pyrimidine derivatives and pyrimidine annelated heterocycles are also important biologically active compounds.[35,36] The combination of both moiety, i.e. chromene along with pyrimidine in a single molecular framework may result in the development of biologically and pharmaceutically important compounds. Due to their vital role in pharmacology, these compounds are utilized in many fields such as medicinal and pharmaceutical chemistry viz. in chemotherapy of cancer, against HIV and viral diseases, etc.[37,38]

Currently, a new approach for synthesizing heterocycles containing both pyrimidine as well as chromene moiety in a single molecule has attracted a great deal of interest.[39–41] Despite the available synthetic methods, there still exists a need for developing more efficient procedures, which allow the ready synthesis of polycyclic pyrimidine

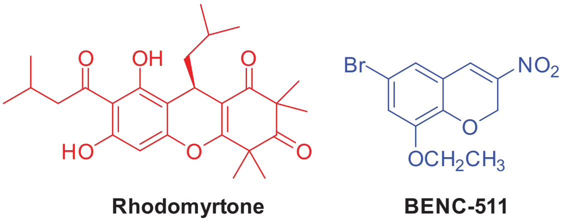


Figure 1. Naturally occurring chromene moieties.

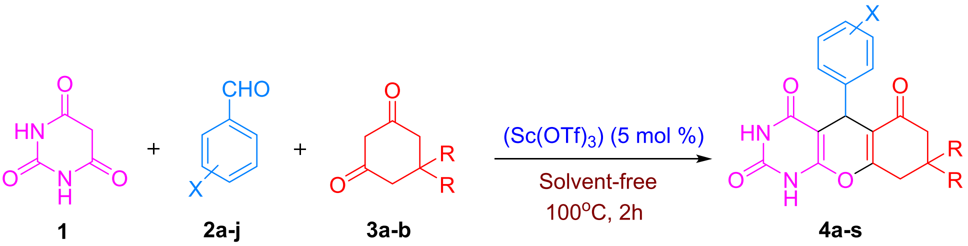
systems. However, to best of our knowledge, the synthesis of chromeno[2,3-*d*]pyrimidine-triones has not previously been reported through such an approach.

The previously reported methods have some limitations, such as the use of substoichiometric amount of catalyst (30% *p*-TSA, 20% P_2O_5, 10% $InCl_3$, 15% L-Proline), the low yield of product and side product.[42–44] Therefore, we are motivated for a better and greener approach for the synthesis of chromeno[2,3-*d*]pyrimidine-triones.

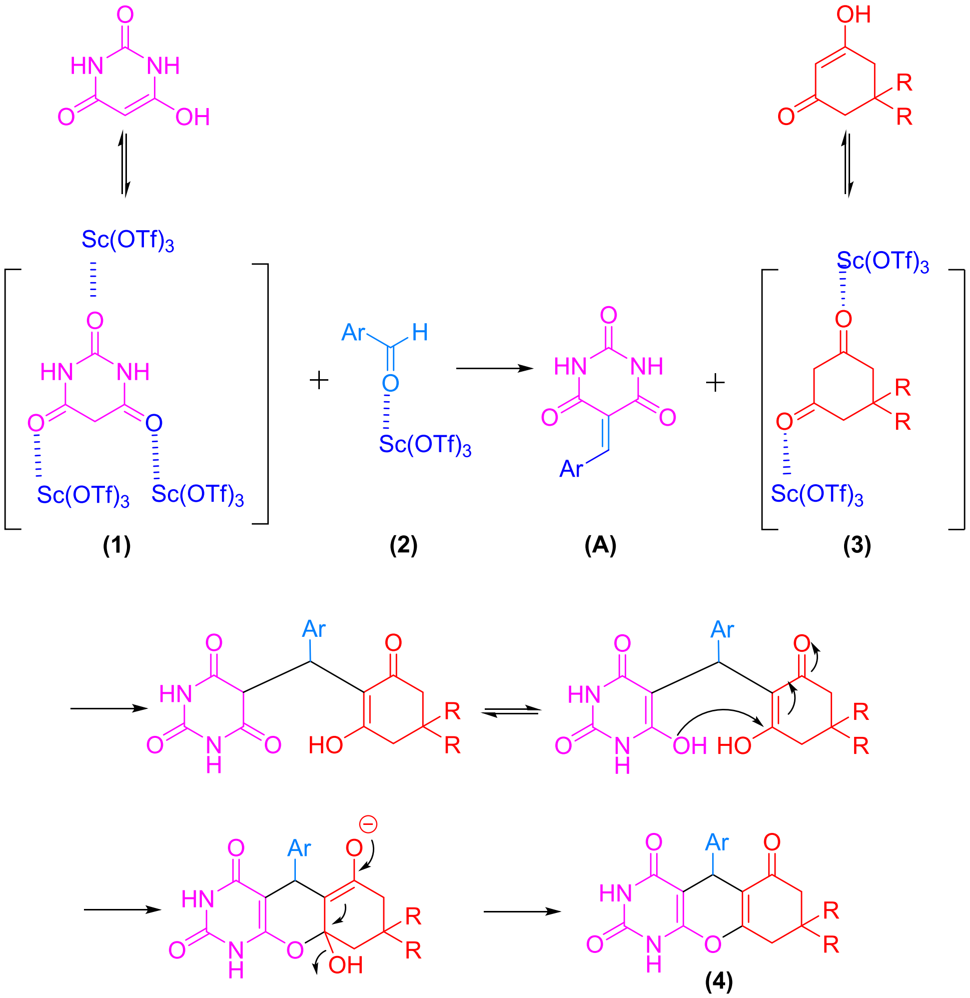
Results and discussion

In view of the above and as a part of our contemporary research on the design and construction of biologically active compounds we report herein the multicomponent reaction of barbituric acid(**1**) with substituted aromatic aldehydes (**2**) and 1,3-diketones(**3**) in the presence of catalytic amount of $Sc(OTf)_3$ under solvent-free condition at 100 °C to afford chromeno[2,3-*d*]pyrimidine-triones **(4a–s)** in excellent yields (Scheme 1).

Our study initiated by optimizing the reaction conditions by taking the multicomponent reaction of barbituric acid (**1**), 4-nitrobenzaldehyde (**2a**) and dimedone (**3a**) as a model reaction. The model reaction was examined under a variety of conditions, and the outcome is given in Table 1. First of all, we screened various catalysts such as, $AlCl_3$, LiCl, $ZnCl_2$, $Ni(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$ and $Sc(OTf)_3$ in ethanol at 100 °C because un-catalyzed reaction in ethanol at 100 °C proceeded lethargically, and gave only a trace amount of product **4a** after long reaction time (20 h) (Table 1, entry 2) while at room temperature no desired product was obtained. Out of various catalyst $ZnCl_2$, LiCl furnished only a trace amount of product while $AlCl_3$ promoted the reaction to some extent (Table 1, entry 3). This result encourages us to take Lewis acid catalyst for this reaction. Literature survey shows that metal triflates are better Lewis acid catalyst in aqueous as well as organic solvents. Due to this reason, various triflates like $Ni(OTf)_{2,}$ $Cu(OTf)_{2,}$ $Yb(OTf)_3$ and $Sc(OTf)_3$ were screened. The desired product **4a** was isolated in 60% yield with $Sc(OTf)_3$ (10 mol%) in ethanol at 100 °C without any observable side products (Table 1, entry 9). Subsequently, different solvents, such as toluene, hexane, $CHCl_3$, and water, were also examined. It was found that the polar solvents provided a better result than non-polar solvents. Surprisingly, 78% yield of product was obtained in absence of solvent with 10 mol% of $Sc(OTf)_3$ in the only 2 h (Table 1, entry 14). Consequently, the amount of $Sc(OTf)_3$ was also examined (Table 1, entry 14–17). The result showed that the product was isolated in 98% yield with 5% $Sc(OTf)_3$ at 100 °C (Table 1, entry 15) while only 29% yield of the product was obtained with 3 mol%



Scheme 1. $Sc(OTf)_3$ catalyzed synthesis of substituted chromeno[2,3-*d*]pyrimidine-triones (4a–s).



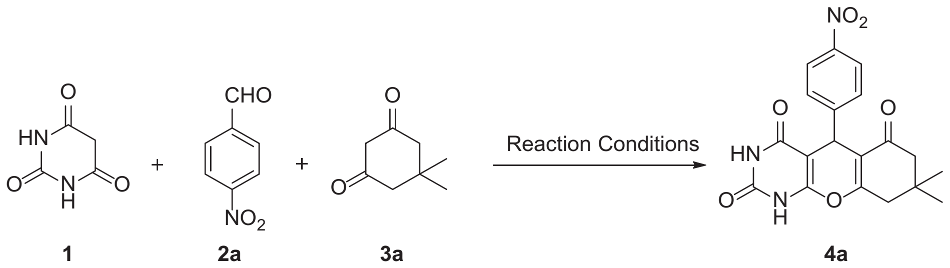
Scheme 2. A plausible mechanism for the formation of chromeno[2,3-*d*]pyrimidine-triones catalyzed by $Sc(OTf)_3$.

of $Sc(OTf)_3$ (Table 1, entry 16). The effect of temperature (80, 90, 100, 110, and 120 °C) was also studied for this reaction and it was concluded that 100 °C was the optimized temperature. The reaction was also carried out without a catalyst under the solvent-free condition at 100 °C for 2 h but no product was obtained (Table 1, entry 22). Even after 12 h, the reaction did not take place (Table 1, entry 23). The molar ratio of the reactant **1**, **2a**, and **3a** were also optimized and found to be 1:1:1.

To study the Scope and limitation of this multicomponent reaction, various aromatic aldehydes were allowed to undergo reaction with barbituric acid and cyclic 1,3-diketones under optimized reaction condition. Usually, this procedure was applicable for *ortho*-, *meta*-, and *para*-substituted aromatic aldehydes. The reaction proceeds efficiently with both electron-donating as well as -withdrawing groups and results are included in Table 2.

The structure of product **4l** was conclusively confirmed by single crystal X-ray determinations (Figure 2).[45]

Table 1. Optimization of reaction conditions for the synthesis of **4a.**[a]



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time(h)	% Yield[b]
1	–	EtOH	Room temp	20	0
2	–	EtOH	100	20	Trace
3	$AlCl_3$(10 mol%)	EtOH	100	5	35
4	LiCl(10 mol%)	EtOH	100	5	Trace
5	$ZnCl_2$(10 mol%)	EtOH	100	5	Trace
6	$Ni(OTf)_2$(10 mol%)	EtOH	100	5	38
7	$Cu(OTf)_2$(10 mol%)	EtOH	100	5	41
8	$Yb(OTf)_3$(10 mol%)	EtOH	100	5	45
9	$Sc(OTf)_3$(10 mol%)	EtOH	100	5	60
10	$Sc(OTf)_3$(10 mol%)	Toluene	100	12	0
11	$Sc(OTf)_3$(10 mol%)	Hexane	100	12	0
12	$Sc(OTf)_3$(10 mol%)	$CHCl_3$	100	8	Trace
13	$Sc(OTf)_3$(10 mol%)	H_2O	100	8	20
14	$Sc(OTf)_3$(10 mol%)	Solvent-free	100	2	78
15	**$Sc(OTf)_3$(5 mol%)**	**Solvent-free**	**100**	**2**	**98**[c]
16	$Sc(OTf)_3$(3 mol%)	Solvent-free	100	2	29
17	$Sc(OTf)_3$(15 mol%)	Solvent-free	100	2	81
18	$Sc(OTf)_3$(5 mol%)	Solvent-free	80	2	76
19	$Sc(OTf)_3$(5 mol%)	Solvent-free	90	2	80
20	$Sc(OTf)_3$(5 mol%)	Solvent-free	110	2	98
21	$Sc(OTf)_3$(5 mol%)	Solvent-free	120	2	82
22	–	Solvent-free	100	2	0
23	–	Solvent-free	100	12	0

[a] Barbituric acid-4-nitrobenzaldehyde-dimedone (1:1:1).
bIsolated yield.
[c] Optimized reaction condition.

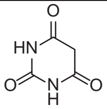
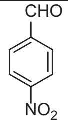
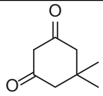
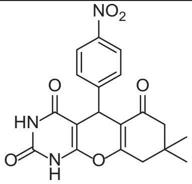
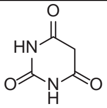
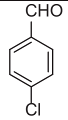
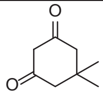
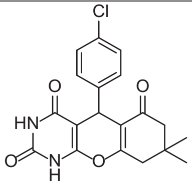
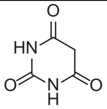
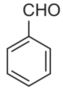
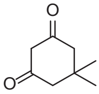
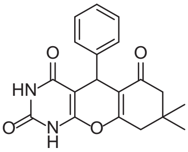
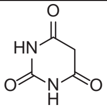
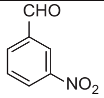
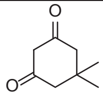
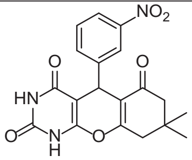
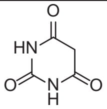
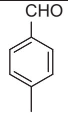
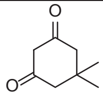
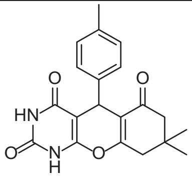
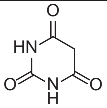
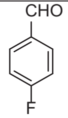
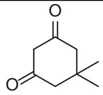
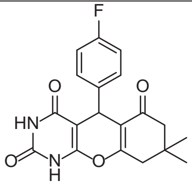
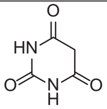
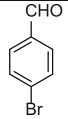
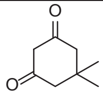
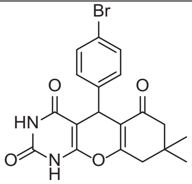
To investigate the reusability of the catalyst, recycling experiments were carried out on the model reaction of a barbituric acid, 4-nitrobenzaldehyde, and dimedone under the optimized conditions (Table 3). After completion of the reaction, the catalyst was recovered by concentrating the aqueous layer (filtrate) under reduced pressure, dried under vacuum, and reused for the second run. The catalytic activity remains fairly consistent up to fourth consecutive run without any significant decrease in the yield of the product (Figure 3) .

The reaction was initiated by the activation of carbonyl oxygen of barbituric acid (**1**) and aromatic aldehyde (**2**) through $Sc(OTf)_3$. Activated 1, 3-diketone attacks on **A** followed by the removal of water to give the final product **4** **(Scheme 2)**.

Conclusions

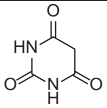
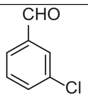
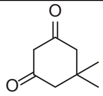
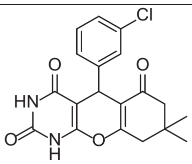
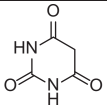
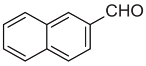
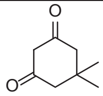
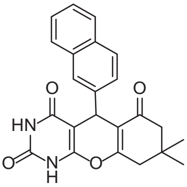
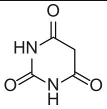
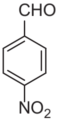
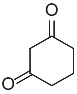
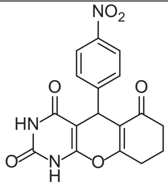
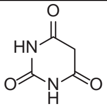
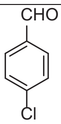
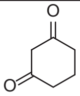
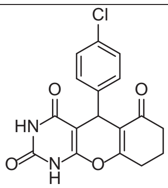
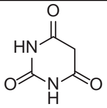
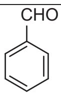
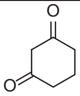
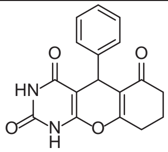
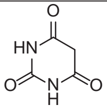
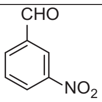
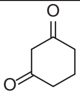
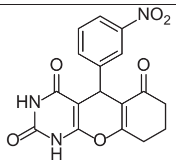
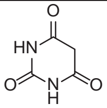
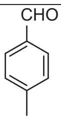
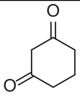
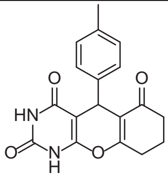
In conclusion, we have developed a new, facile, solvent-free, and efficient one-pot multicomponent synthesis of chromeno[2,3-*d*]pyrimidine-triones by using resourceful,

Table 2. Screening of substrates for the synthesis of chromeno[2,3-*d*]pyrimidine-triones.[a]

Entry	1	2	3	4[a]	Yield[b] (%)
4a		 **2a**	 **3a**		**98**
4b		 **2b**	 **3a**		**97**
4c		 **2c**	 **3a**		**95**
4d		 **2d**	 **3a**		**96**
4e		 **2e**	 **3a**		**98**
4f		 **2f**	 **3a**		**95**
4g		 **2g**	 **3a**		**96**

a

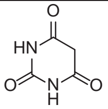
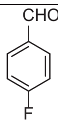
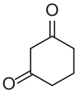
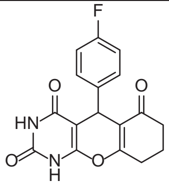
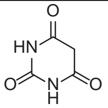
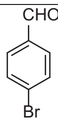
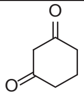
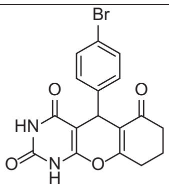
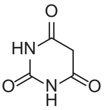
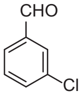
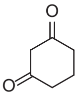
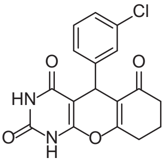
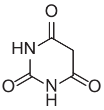
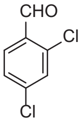
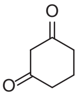
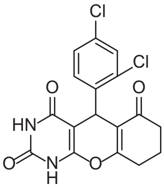
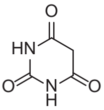
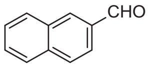
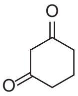
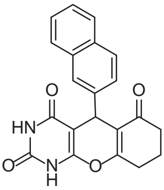
Table 2. (Continued)

4h		 **2h**	 **3a**		**97**
4i		 **2i**	 **3a**		**95**
4j		 **2a**	 **3b**		**95**
4k		 **2b**	 **3b**		**96**
4l		 **2c**	 **3b**		**98**
4m		 **2d**	 **3b**		**97**
4n		 **2e**	 **3b**		**95**

a

Table 2. (Continued)

a

4o		 **2f**	 **3b**		**98**
4p		 **2g**	 **3b**		**96**
4q		 **2h**	 **3b**		**97**
4r		 **2j**	 **3b**		**97**
4s		 **2i**	 **3b**		**95**

[a] Products were characterized by ^{1}H, ^{13}C NMR, and IR analysis.
[b] Isolated yield.

Sc(OTf)$_3$ catalyst and readily available starting materials. In this approach, the product can be isolated very easily without the use of column chromatography. This approach also offers low catalyst loading, high yield, easy work-up, and broad substrate scope.

Experimental

The barbituric acid, diketones, aromatic aldehydes, and Scandium triflate were purchased from Sigma–Aldrich Chemicals, USA, and E. Merck, Germany and were used as

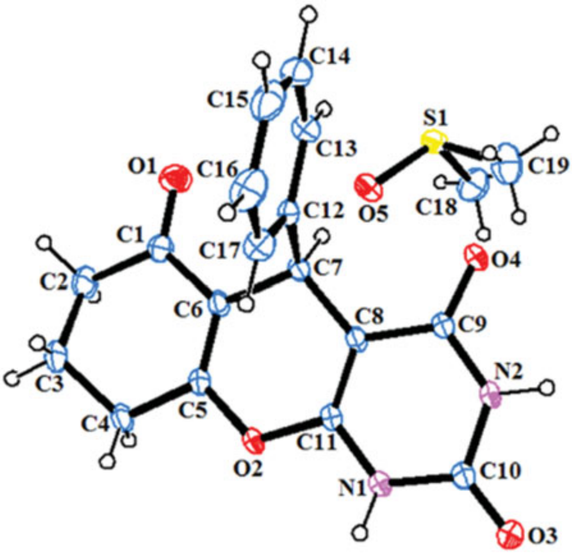


Figure 2. ORTEP image of **4l** (CCDC 1831617).

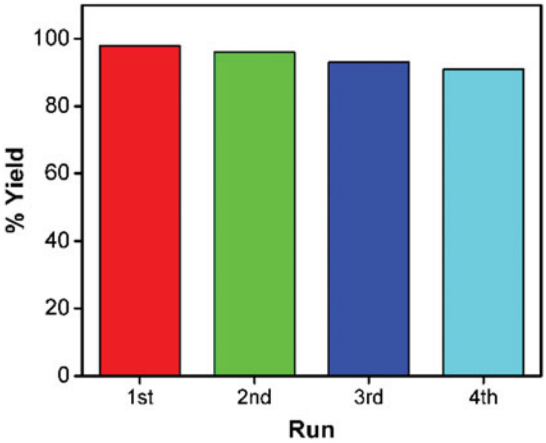


Figure 3. The reusability of the $Sc(OTf)_3$ catalyst for the multicomponent reaction of Barbituric acid, 4-nitrobenzaldehyde, and dimedone.

Table 3. Reusability and recyclability of $Sc(OTf)_3$ catalyst.[a]

Entry	Run	% Yield
1.	1st	98
2.	2nd	96[b]
3.	3rd	93[b]
4.	4th	91[b]

[a] Reaction condition: Barbituric Acid: 4-nitrobenzaldehyde: dimedone (1.0:1.0:1.0) and $Sc(OTf)_3$ (5 mol%) were heated at 100 °C for 2 h to produce solid product.

[b] The catalyst was recovered by concentrating the aqueous layer.

received. All the reactions were monitored by thin-layer chromatography (TLC) and visualized using UV light. Infra-Red (IR) spectra were recorded on a Perkin-Elmer FT–IR spectrometer. The melting points were determined by using Stuart Melting point apparatus SPM10. Elemental analysis (C, H, and N) were carried out using Perkin Elmer Microanalyser. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 500 MHz spectrometer in DMSO-d$_6$ and chemical shift were express as δ ppm, using TMS as an internal reference.

General procedure for the synthesis of Chromeno[2,3-*d*]pyrimidine-triones (4a–s): Barbituric acid (2 mmol), dimedone/cyclohexane-1,3-dione (2 mmol), aromatic aldehydes (2 mmol) and Scandium triflate (5 mol %) were heated at 100 °C for 2 h. After completion of the reaction (confirmed by TLC), the reaction mixture was diluted with water and filtered. The solid product was washed with water (3 × 5 mL). Then, crude product was recrystallized from ethanol to afford the pure product **(4a-s)**. By evaporation of the filtrate (water), Sc(OTf)$_3$ was recovered quantitatively and reused.

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[45] CCDC 1831617 for Compound 4l (crystal has been developed in Dimethyl sulfoxide) contains the Supplementary Crystallographic Data for This Paper. These Data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.