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ORIGINAL ARTICLE

Lemon juice catalyzed C–C bond formation via C–H activation of methylarene: a sustainable synthesis of chromenopyrimidines

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Abstract

An economical and proficient approach has been developed for the synthesis of chromenopyrimidines via three-component reaction of thiobarbituric acid/barbituric acid, methylarenes and dimedone/1,3-cyclohexanedione by using lemon juice as a natural, biodegradable catalyst and TBHP as an oxidant. This transformation involves metal-free C–C bond formation via C–H activation of methylarenes under mild reaction conditions.

Graphical abstract

Keywords C–H activation · Multicomponent reaction · Chromenopyrimidine · TBHP · Lemon juice

Introduction

Recently, the direct C–H bond functionalization/C–C bond formation of hydrocarbons via C–H bond activation has attracted much attention in organic synthesis [1–6]. Especially, in view of the green perspective, selective and controlled functionalization without using metal catalyst has become a challenging area for organic chemists. As a characteristic C–H bond functionalization route, the direct benzylic oxidation of alkylarenes is a vital procedure to afford the parallel carbonyl compounds [7–10] which is used as a constituent in the construction of well-designed fine chemicals and pharmaceuticals [11–13]. Methylarenes are the most abundant and inexpensive naturally available surrogates for carbonyl compounds, which are obtained from crude oil as a by-product in the production of gasoline and coke. A number of methods have been reported for the direct benzylic oxidation of alkylarenes using heavy metal catalysts such as stoichiometric amount of $KMnO_4$ [14], Cr(VI) [15], excess amount of Fe [16], Ru [17], Mn [18], Bi [19], Co [20], Au [21], Rh [22], with an oxidant. These methods are non-selective, tiresome, environmentally unfavorable and operationally difficult. In view of the above, the direct selective oxidation of methylarenes to benzaldehydes is of crucial importance. Thus, there is a demand of operationally simple, high yielding, green, eco-friendly protocol using metal-free oxidants and high-atom economical pathway. The work on the controlled oxidation of methylarenes to benzaldehyde

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in good yield [23–25] provoked us to design a new process that utilizes methylarenes as a green, low-cost and readily accessible starting material for the *in situ* generation of benzaldehydes.

Chromenes are very important structural motif found in a variety of natural products like anthocyanins, tocopherols, alkaloids, flavonoids [26–31] and biologically active molecules like antibiotic rhodomyrtone [32] and cancer cell apoptosis inducer BENC-511 [33]. Chromenes also exhibit an extensive range of biological activities such as anti-anaphylactic [34], antimicrobial [35], antitumor [36], spasmolytic [37], anticoagulant [38] and diuretic activities [39]. Therefore, the development of synthetic procedures that facilitate the synthesis of these compounds has attracted considerable attention. Pyrimidine derivatives are of extensive curiosity due to their potential biological activity [40] and also their versatility as synthones in organic synthesis [41, 42].

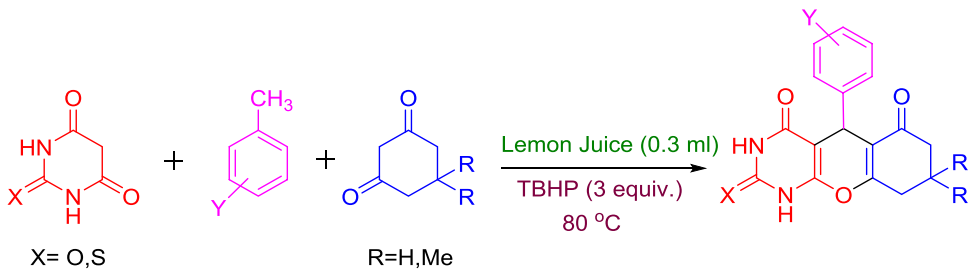
Recent developments in the utilization of benzylic C–H bonds inspired us to look into the C–H bond activation of easily available and inexpensive methylarenes to achieve the synthesis of biologically active chromenopyrimidines. In past decades, the use of a natural catalysts in organic synthesis has also attracted considerable attention due to their eco-friendly and environmentally acceptable nature. Lemon juice is a biodegradable and natural catalyst. The existence of citric and ascorbic acid makes the lemon juice as an acidic catalyst in organic synthesis [43–46].

Previously, chromenopyrimidines have been produced by multicomponent reaction of barbituric acid, 1,3-cyclohexanedione/dimedone and aromatic aldehyde using various catalysts [47–49]. In spite of these efforts, a metal-free and mild approach for the synthesis of chromenopyrimidine derivatives using accessible, inexpensive, naturally available and sustainable surrogates is still in high demand.

By considering all the above facts and as a part of our contemporary research on the design and construction of biologically active compounds [50], we herein report a lemon juice catalyzed, metal-free, one-pot synthesis of chromenopyrimidine derivatives via C–H activation of methylarenes by using tert-butyl hydroperoxide (TBHP, 70% in H_2O) as an oxidant (Scheme 1).

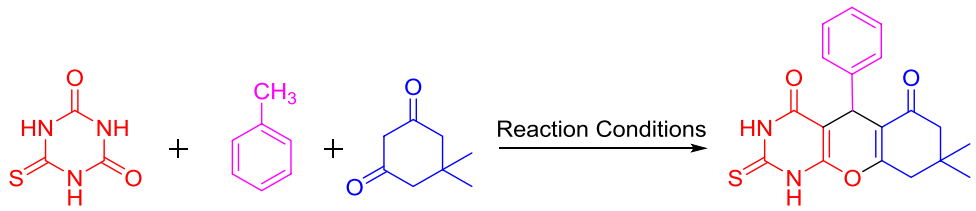
Results and discussion

The work initiated by taking thiobarbituric acid (1.0 mmol), toluene (2.0 mmol) and dimedone (1.0 mmol) as a model reaction. The desired product (**4h**) could not be obtained in sufficient yield when 10 mol% of sulfamic acid, benzoic acid, formic acid and acetic acid was used with 10 equiv. of TBHP (70% in H_2O) (Table 1, entry 1–4). When lemon juice was used with TBHP, 40% yield of the product was obtained (Table 1, entry 5). Subsequently, screening of various solvents like benzene, CCl_4, hexane, CH_2Cl_2, $CHCl_3$, H_2O (Table 1, entries 6–11) was done. Pleasingly, 67% yield was afforded with lemon juice (0.2 ml) and TBHP (4 equiv.) under solvent-free condition (Table 1, entry 14). Now, the amount of lemon juice and TBHP were optimized, and it was found that 0.3 ml of lemon juice with 3 equivalents of TBHP worked best, giving 85% yield of the product (Table 1, entry 17). Since lemon juice contains citric acid and ascorbic acid, their different amounts were tested under optimized condition (Table 1, entry 19–24) and it was found that lemon juice has better catalytic properties than citric acid followed by ascorbic acid. Better catalytic activity of citric acid than ascorbic acid can be attributed to the higher K_a (acid dissociation constant) value of citric acid. Encouraged by this, numerous oxidants like H_2O_2, oxone, $K_2S_2O_8$, meta-chloroperoxybenzoic acid (m-CPBA), peracetic acid (PAA), benzyl peroxide, benzoyl peroxide, tert-butyl peroxybenzoate (TBPB) and di-tert-butyl peroxide (DTBP) were tested with lemon juice, under solvent-free condition, but unfavorable results were obtained (Table 1, entry 25–33). In the further optimization, lemon juice without TBHP (Table 1, entry 34), TBHP without lemon juice (Table 1, entry 35) and reaction without lemon juice and TBHP (Table 1, entry 36) under solvent-free condition have been done, but they did not lead to the desired product. Combination of citric and ascorbic acid has been tested under optimized condition to investigate their effect in lemon juice catalyzed reactions, and results are summarized in Table 1 (entry 37–40). Combinations have been made on the basis of amount of citric and ascorbic acid present in lemon juice [51, 52].



Scheme 1 Lemon juice catalyzed one-pot synthesis of chromenopyrimidine derivatives

Table 1 Optimized reaction condition for the model reaction **4h**[a]



Entry	Catalyst	Oxidant (eq.)	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	Sulfamic acid (10 mol%)	TBHP(10)	–	80	10	15
2	Benzoic acid (10 mol%)	TBHP(10)	–	80	10	18
3	Formic acid (10 mol%)	TBHP(10)	–	80	10	10
4	Acetic acid (10 mol%)	TBHP(10)	–	80	10	12
5	Lemon juice (0.2 ml)	TBHP(10)	–	80	10	40
6	Lemon juice (0.2 ml)	TBHP(10)	Benzene	80	7	Trace
7	Lemon juice (0.2 ml)	TBHP(10)	CCl_4	80	7	Trace
8	Lemon juice (0.2 ml)	TBHP(10)	Hexane	80	7	28
9	Lemon juice (0.2 ml)	TBHP(10)	CH_2Cl_2	80	7	30
10	Lemon juice (0.2 ml)	TBHP(10)	$CHCl_3$	80	7	32
11	Lemon juice (0.2 ml)	TBHP(10)	H_2O	80	7	50
12	Lemon juice (0.2 ml)	TBHP(5)	H_2O	80	7	50
13	Lemon juice (0.2 ml)	TBHP(4)	H_2O	80	7	50
14	Lemon juice (0.2 ml)	TBHP(4)	–	80	3	67
15	Lemon juice (0.2 ml)	TBHP(3)	–	80	3	76
16	Lemon juice (0.2 ml)	TBHP(2)	–	80	3	65
17	Lemon juice (0.3 ml)	TBHP(3)	–	80	3	85
18	Lemon juice (0.4 ml)	TBHP(3)	–	80	3	75
19	Citric acid (1 mol%)	TBHP(3)	–	80	5	34
20	Citric acid (2 mol%)	TBHP(3)	–	80	5	40
21	Citric acid (3 mol%)	TBHP(3)	–	80	5	46
22	Citric acid (5 mol%)	TBHP(3)	–	80	5	58
23	Citric acid (10 mol%)	TBHP(3)	–	80	5	60
24	Ascorbic acid (10 mol%)	TBHP(3)	–	80	5	8
25	Lemon juice (0.3 ml)	H_2O_2(3)	–	80	3	n.d.
26	Lemon juice (0.3 ml)	Oxone(3)	–	80	3	n.d.
27	Lemon juice (0.3 ml)	$K_2S_2O_8$(3)	–	80	3	Trace
28	Lemon juice (0.3 ml)	m-CPBA(3)	–	80	3	n.d.
29	Lemon juice (0.3 ml)	PAA(3)	–	80	3	Trace
30	Lemon juice (0.3 ml)	Benzyl Peroxide(3)	–	80	3	n.d.
31	Lemon juice (0.3 ml)	Benzoyl Peroxide(3)	–	80	3	n.d.
32	Lemon juice (0.3 ml)	TBPB(3)	–	80	3	20
33	Lemon juice (0.3 ml)	DTBP(3)	–	80	3	30
34	Lemon juice (0.3 ml)	–	–	80	3	n.d.
35	–	TBHP(3)	–	80	3	n.d.
36	–	–	–	80	12	n.d.
37	Citric acid/ascorbic Acid (10:1)	TBHP(3)	–	80	3	45
38	Citric acid/ascorbic Acid (100:1)	TBHP(3)	–	80	3	50
39	Citric acid/ascorbic Acid (1000:1)	TBHP(3)	–	80	3	57
40	Citric acid/ascorbic Acid (10000:1)	TBHP(3)	–	80	3	67

[a]Reaction condition: thiobarbituric acid (1.0 mmol), toluene (2.0 mmol), dimedone (1.0 mmol)

[b]Isolated yield after column chromatography

n.d. not detected

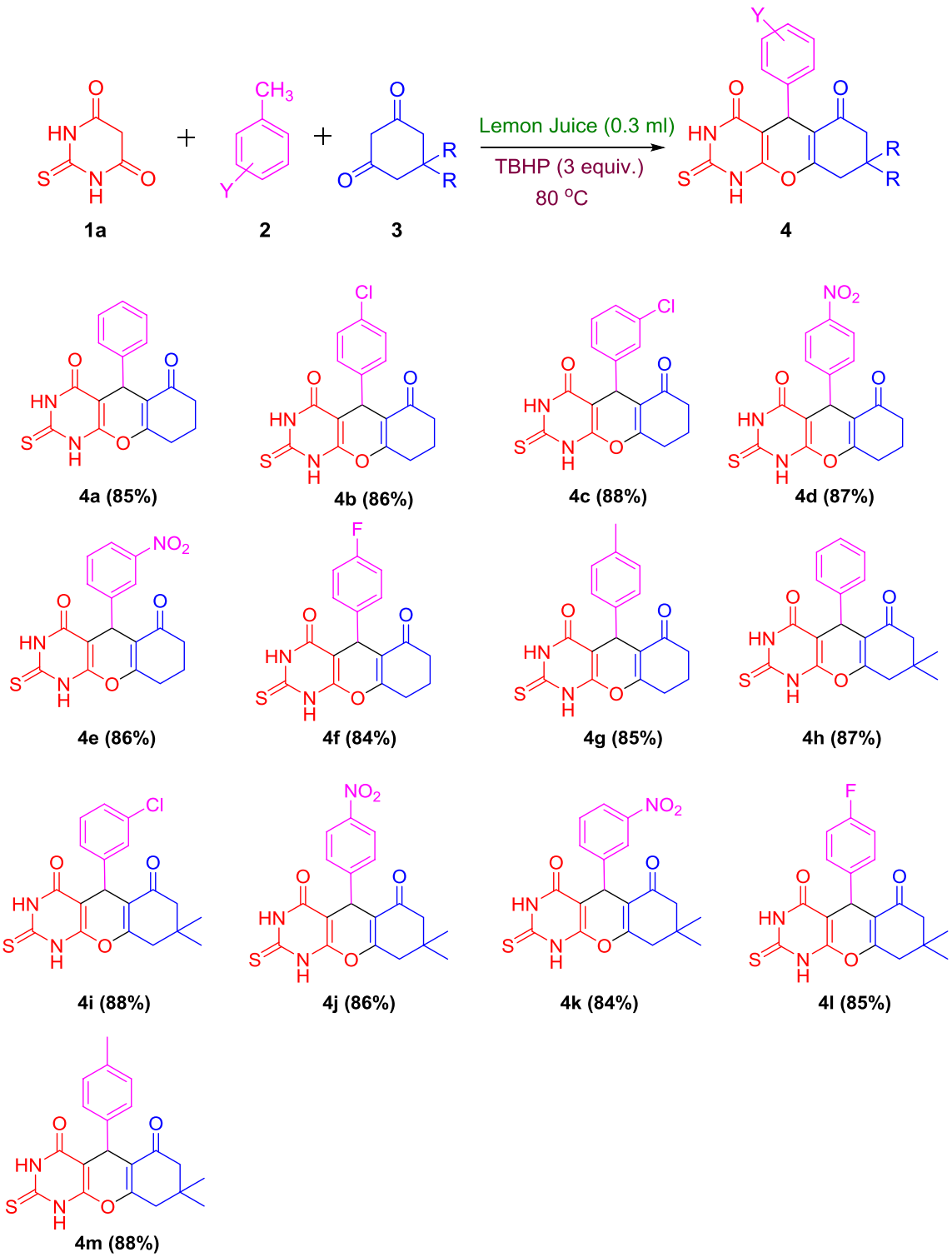


Fig. 1 Substrate Scope. Reaction condition: thiobarbituric acid (1.0 mmol), methylarenes (2.0 mmol), dimedone/1,3-cyclohexanedione (1.0 mmol), TBHP (3 equiv.), lemon juice (0.3 ml), 3 h. Isolated yields are shown

In order to extend the scope of this methodology, a wide range of methylarenes, i.e., both electron-donating and electron-withdrawing groups containing methylarenes, were investigated under optimal conditions. The substituted methylarenes worked efficiently with thiobarbituric/barbituric acid and dimedone/1,3-cyclohexanedione to afford the desired products in good yields (84–88%) (Figs. 1, 2).

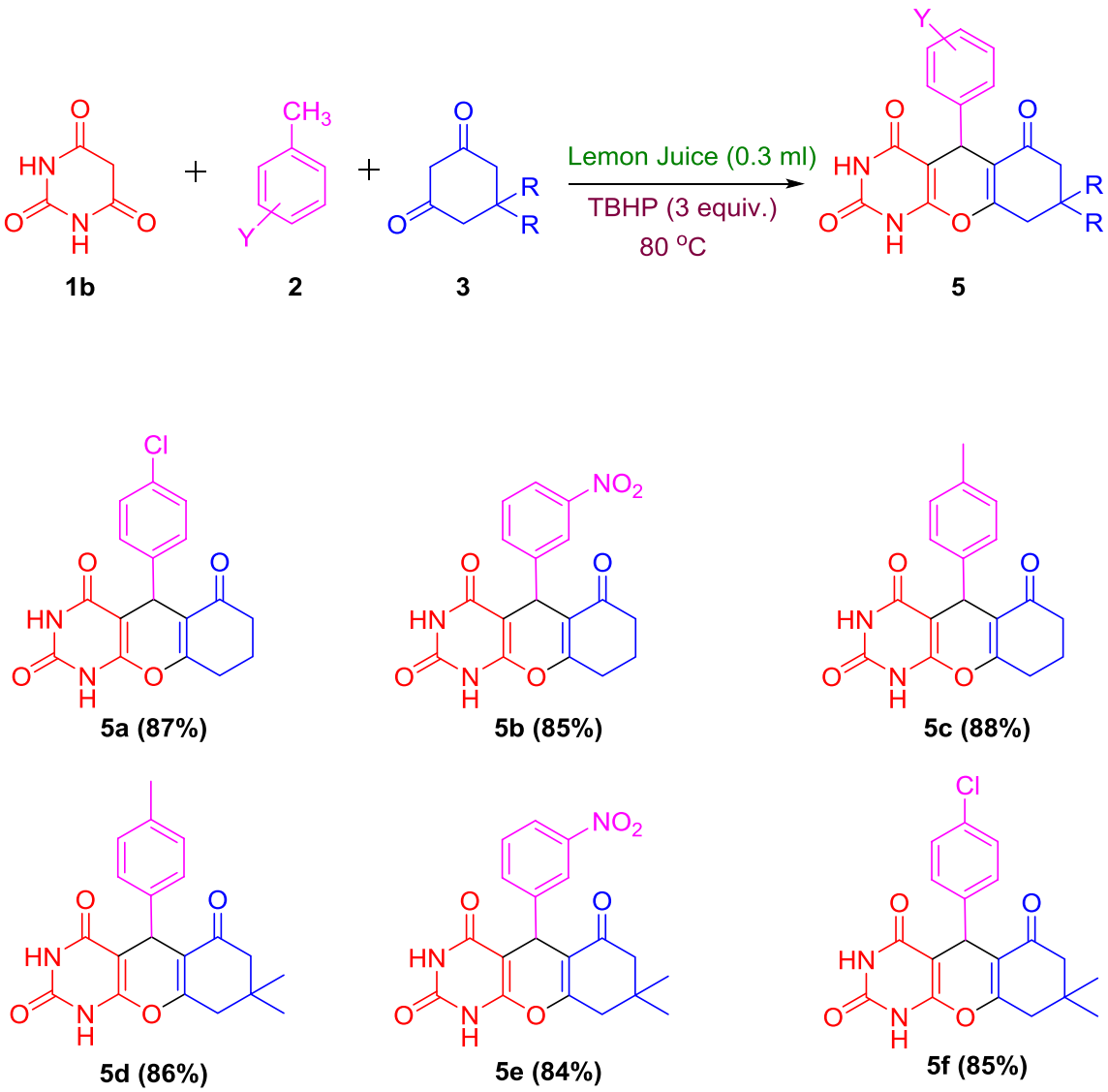
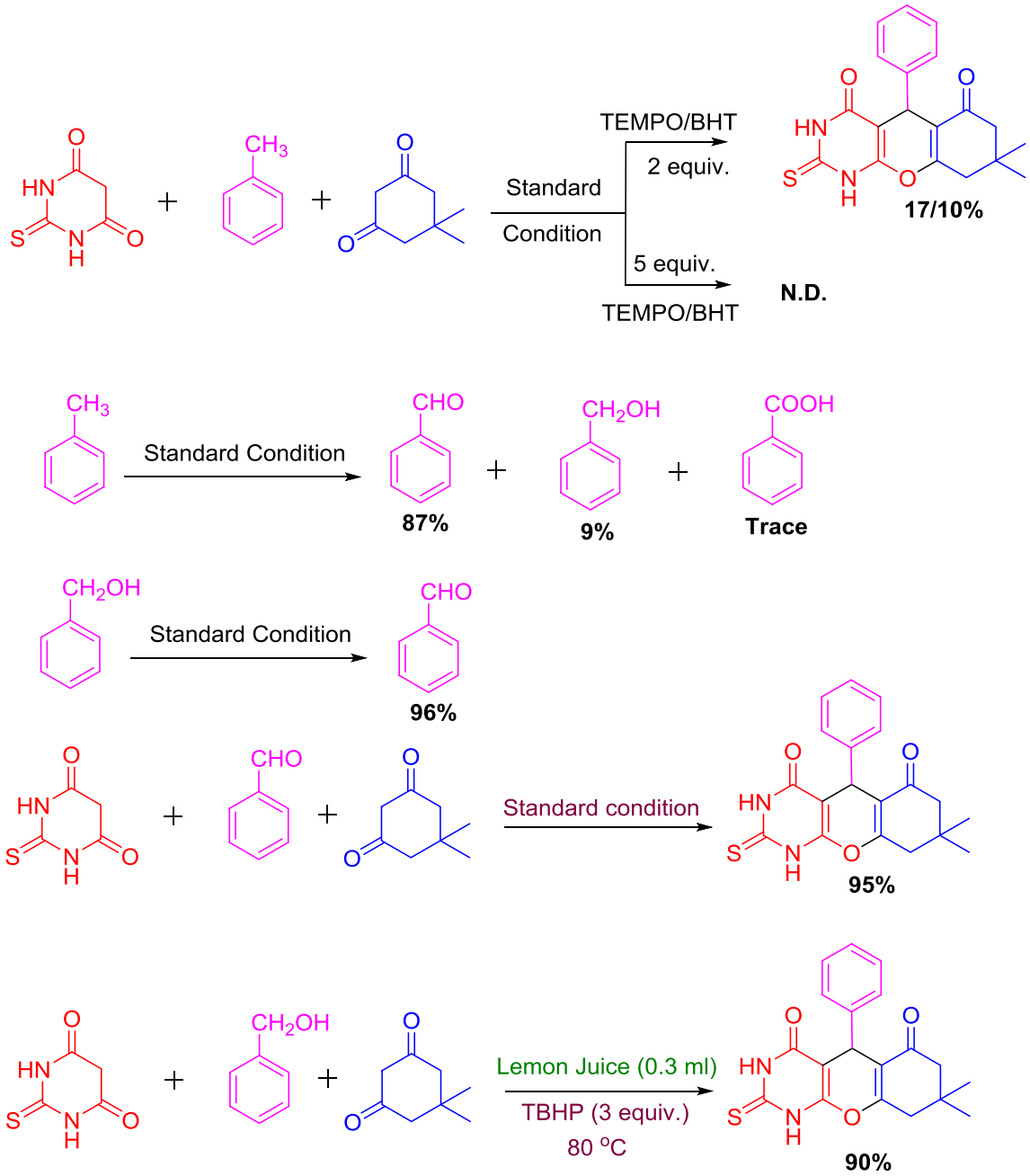


Fig. 2 Substrate Scope. Reaction condition: barbituric acid (1.0 mmol), methylarenes (2.0 mmol), dimedone/1,3-cyclohexanedione (1.0 mmol), TBHP (3 equiv.), lemon juice (0.3 ml), 3 h. Isolated yields are shown

Some control experiments were carried out to establish the reaction mechanism. By performing quenching experiment with radical scavengers like (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) and butylatedhydroxytoluene (BHT), the participation of free-radical species in the reaction was established. The model reaction gave the corresponding product **4h** in 17% and 10% yields in the presence of 2 equiv. of TEMPO and BHT, respectively, under standard conditions, whereas the product formation quenched completely with 5 equivalents. Thus, the involvement of radical intermediate was established by inhibitory action of TEMPO and BHT. A blank experiment was performed by taking toluene with TBHP which resulted in 87% of benzaldehyde, 9% of benzyl alcohol and trace amount of benzoic acid. The intermediacy of benzyl alcohol was confirmed by subjecting benzyl alcohol to standard conditions to deliver benzaldehyde in 96% yield. Further, the intermediacy of benzyl alcohol was confirmed by using it in the synthesis of **4h** under standard reaction conditions (Scheme 2).

The plausible reaction mechanism based on reported literature, isolated product and controlled experiment is given in Scheme 3. Oxidation of methylarenes (**2**) by TBHP leads to corresponding aromatic aldehyde (**2Y**) through radical pathway. Now Knoevenagel condensation takes place between (**1**) and (**2Y**) to produce (**A**). Ultimately, Michael addition between (**A**) and (**3**) followed by removal of H_2O produced the final product (**4/5**).



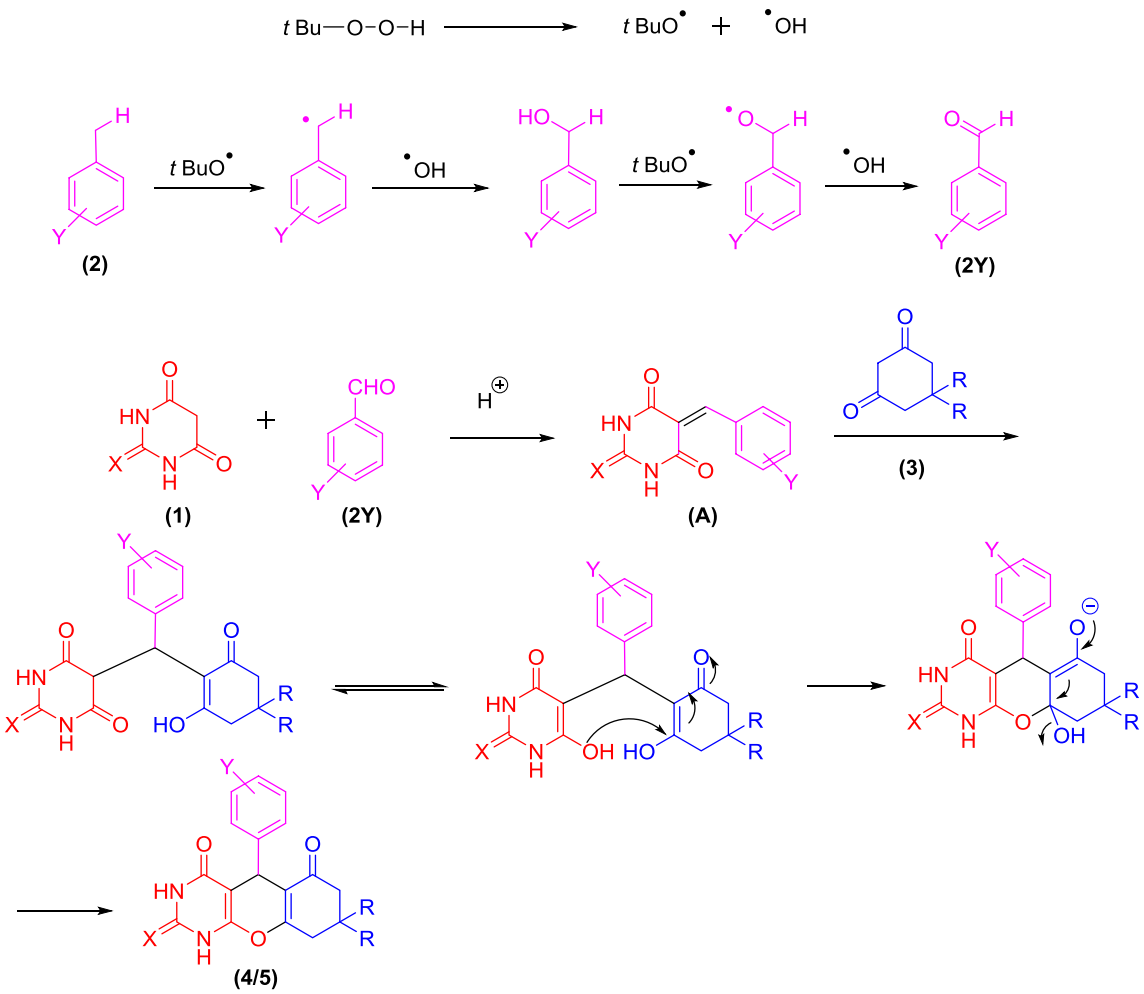
Scheme 2 Control experiments using radical scavengers

Experimental

Thiobarbituric acid/barbituric acid, methylarenes, 1,3-diketones and TBHP (70% in H_2O) were purchased from E. Merck, Germany and Sigma–Aldrich Chemicals, USA and were used as received. All the reactions were monitored by thin-layer chromatography (TLC) and visualized using UV light. Infrared (IR) spectra were recorded on a Perkin-Elmer FT–IR spectrometer. Melting points were determined by using Stuart Melting point apparatus SPM10. Elemental analyses (C, H and N) were carried out using Perkin-Elmer microanalyzer. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 500 MHz spectrometer in DMSO-d_6, and chemical shifts were expressed in δ ppm, using TMS as an internal reference.

General procedure for extraction of lemon juice (preparation of catalyst) [53]

Fresh fruits of *Citrus limon* (lemon) was bought from the local shop and washed with water thoroughly. The juice



Scheme 3 Plausible reaction mechanism

was extracted by fruit juicer and then filtered with cotton to remove the solid substance and to obtain a clear portion of juice. Now, clear juice was used as an acid catalyst after measuring its pH (between 2 and 3).

General procedure for the synthesis of chromenopyrimidine derivatives (4/5)

Methylarene (2.0 mmol) and TBHP (70% in H_2O, 3.0 equiv.) were stirred at room temperature for 10 min; then, thiobarbituric acid/barbituric acid (1.0 mmol), cyclic 1, 3-diketone (1.0 mmol) and extracted lemon juice (0.3 ml) were added to it. The reaction mixture was heated at 80 °C for 3 h. After the completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and mixed with water. The mixture was extracted with ethyl acetate, dried with sodium sulfate, and organic solvent was evaporated under reduced pressure to obtain the product. Pure compounds were obtained by column chromatography.

Conclusion

In conclusion, a practical and efficient protocol for the metal-free C–C bond formation via C–H activation of inexpensive methylarenes has been developed. Juice of lemon has been exploited as a natural and biodegradable catalyst for the green and environmentally benign synthesis of Chromenopyrimidine derivatives by multicomponent reaction of barbituric/thiobarbituric acid, 1, 3-diketones and methylarenes.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

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