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ORIGINAL ARTICLE

Biomimetic hydrogenation of electron deficient olefins using in situ generated 2-arylbenzimidazoline: synthesis of novel 3-benzylbenzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones

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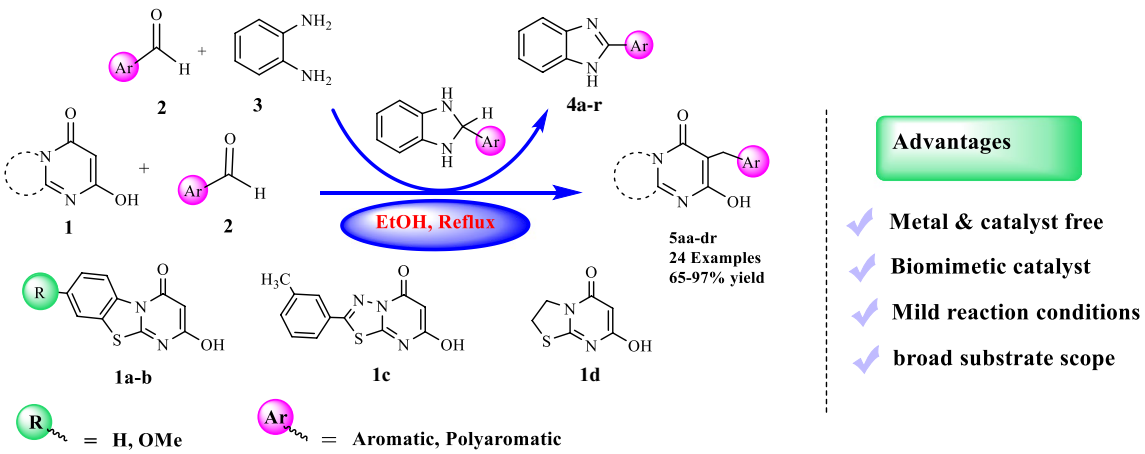
Abstract

In the present study, 2-Arylbenzimidazoline generated in situ from reaction of aromatic aldehydes and *o*-phenylenediamine used as biomimetic reductive agents for reductive alkylation of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one for synthesis of novel 3-benzyl-2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones is described. The main benefits of this protocol include simplicity, reaction mildness, high yield, easy work up, and simple purification. The molecular structures were characterized by IR spectrophotometry, mass spectrometry, NMR spectroscopy, and elemental analysis.

Graphic abstract



Keywords Biomimetic hydrogenation · 3-benzyl-2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one · *o*-phenylenediamine · benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one · 2-arylbenzimidazoline

Introduction

Heterocycles containing sulfur and nitrogen are highly important organic molecules, which are frequently found as classes of natural and synthetic organic molecules. Specifically, thiazolopyrimidines as fused hybrid heterocycles of pyrimidine and thiazole represent a valuable class of interesting biologically active compounds which abundantly exists in nature [1]. These fused ring systems exhibit a wide range of bioactivities, that include anti-bacterial, [2] antiviral, [3] anti-inflammatory, [4, 5] anti-nociceptive [5] anti-tubercular [6], and anti-malarial, [7] activity.

For instance, thiazolopyrimidine containing compounds have been reported with activities such as anti-Parkinson, [9] and antihistamine, [10] anti-bacterial [11](Figs. 1, 1–3). In

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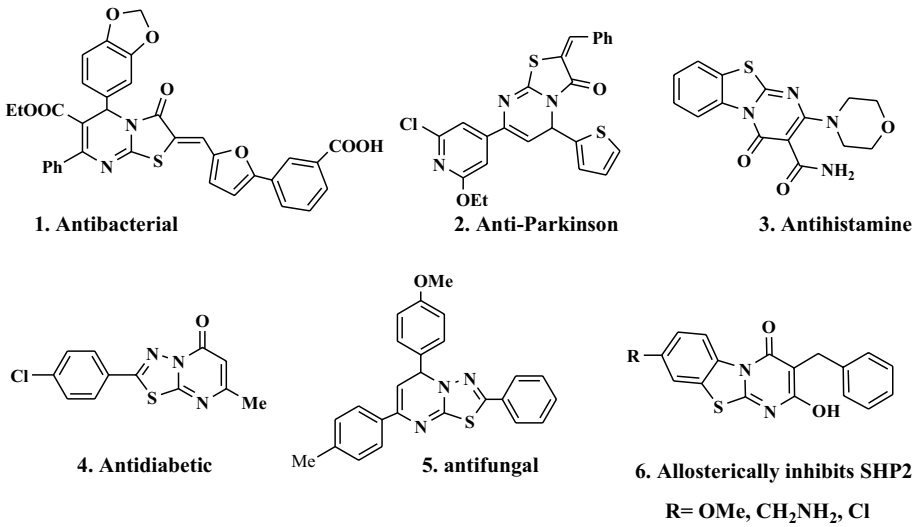


Fig. 1 Some biologically active thiazolopyrimidine and thiadiazolopyrimidine containing compounds

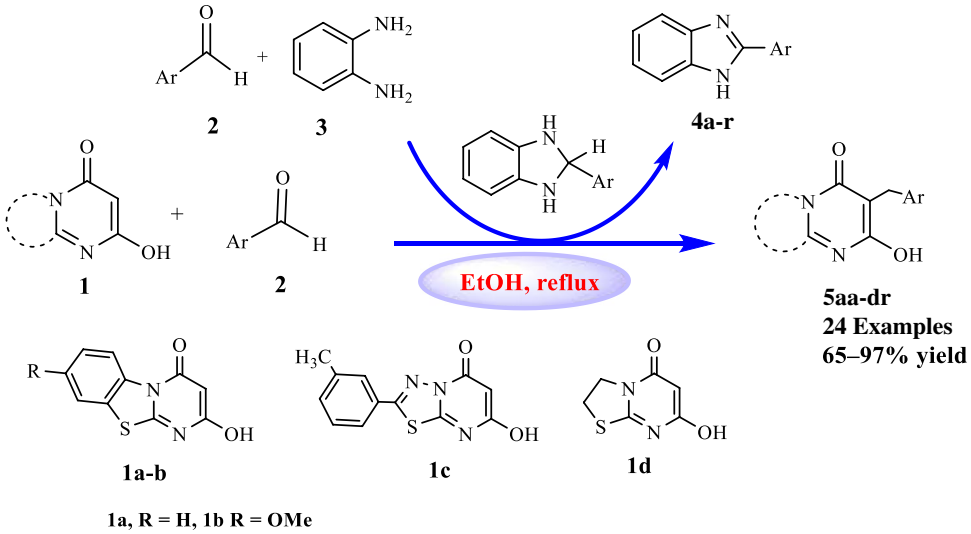
addition, thiadiazolopyrimidine as another pyrimidine-fused motif is potent anti-bacterial [12], antimicrobial [13] and anti-inflammatory [14] with significant inhibitory effects on cancer cells. [15] Selected examples of pharmacologically active compounds based on fused-thiadiazolopyrimidine and related scaffolds possessing antimicrobial [16] and antidiabetic activities [17]are depicted (Fig. 1, 4 and 5).

Selective reductive alkylation of organic compounds is an important reaction in synthetic organic chemistry. Today, metal-free biomimetic hydrogenation of olefins is considered as a major area of research, especially in green chemistry. Heterocyclic compounds with hydrogenation potential such as 1,4-dihydropyridine known as the NAD(P)H model and dihydrobenzazole derivatives are commonly used as biomimetic reductive agents for the selective reduction of organic compounds [18–20]. Many of these compounds contribute significantly to bio-antioxidation and biological processes and naturally exist in different forms such as flavin adenine dinucleotide, [21] nicotinamide adenine dinucleotide, [22] ascorbic acid (vitamin C) [23]and tetrahydrofolate. [24] A large body of literature has been dedicated to different types of synthetic hydride donors such as five membered heterocycles, including 2,3-dihydrobenzo[*d*]thiazoles, 2,3-dihydrobenzo[*d*]oxazoles, and 2,3-dihydrobenzo[*d*]imidazoles [25–31] and six membered heterocycles, including 10-methyl-9,10-dihydroacridine, 1-Benzyl-1,4-dihydronicotinamide and Hantzsch 1,4-dihydropyridine [32–44]. The main disadvantage in these useful reactions is removal of pyridine as by-product from the reaction mixture. Recently, 2-phenylbenzimidazoline (PBI) and other related organic hydride reagents have been extensively used to transfer hydride to a variety of electron deficient substrates, in the presence of catalysts under mild conditions [45]. According to this technique, hydrogen atoms are transferred during the reduction from the C-2 position of PBI as a hydride [46]. Ramachary et al. [47] in 2006 reported the direct organocatalytic chemo selective cascade of Knoevenagel–hydrogenation using 2-phenylbenzimidazoline.

Interestingly, LaRochelle et al. [48] have developed benzothiazolopyrimidone platform (Fig. 1, 6), for allosterically inhibits SHP2 in vitro and Erk phosphorylation and viability of cultured AML cells. Recently, Harutyunyan et al. synthesized 3-benzyl-2-hydroxy-8-methoxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one as a novel benzothiazolopyrimidone derivative via condensation reaction of 2-aminobenzothiazoles with Diethyl benzylmalonate. [49] This synthetic method suffers from poorer product yields, and high reaction temperature.

Inspired by these reports, and in continuation of our research in the reaction of heterocyclic 1,3-diones to synthesize useful novel benzothiazolopyrimidone heterocyclic compounds, [50–52] herein, we have focused our efforts on the design and metal-free and catalyst-free procedure for the one-pot synthesis of 3-benzyl-2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one **5aa-dr**, via reaction of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one, *o*-phenylenediamine and aromatic aldehydes using in situ generated 2-arylbenzimidazoline from *o*-phenylenediamine and arylaldehyde as a highly active biomimetic reducing agent (Scheme 1). To our delight, synthesized 3-benzyl-2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones can be evaluated for allosterically inhibits SHP2. Synthesized product **5**, in particular, could be exploited as allosterically inhibits SHP2 in vitro and Erk phosphorylation and viability of cultured AML cells (Table 2).

Cascade heterocyclic by-products 2-Aryl-benzimidazoles **4a-r** constitutes effective intermediate products in synthesizing muscarinic, anti-fungal and anti-bacterial agonists, estrogen antagonists/agonists, and inhibitors of HIV-1 reverse transcriptase, treating physiological disorders and



Scheme 1 Synthesis of alkylated benzothiazolopyrimidone and benzothiadiazolopyrimidone derivatives

preventing sleep apnea [53, 54]. A comprehensive review of literature showed no detailed studies on utilizing 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones as substrates for synthesizing 3-benzyl-2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones **5** (Scheme 1, Table 2).

Results and discussions

Initially, a model one-pot reaction was investigated with 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one (**1a**), 4-Chlorobenzaldehyde (**2b**) and *o*-phenylenediamine (**3**) in (1:2:1) equivalent was stirred in ethanol at reflux for 2 h, which resulted in the formation of desired product (**5ab**) and by-product (**4b**) in 95% and 94% yields, respectively (Table 1, entries 1). This result shows that the reagents have the self and auto-catalytic nature in cascade reactions. [55–56] The *o*-phenylenediamine enable the in situ construction of Knoevenagel condensation product from one equivalent of each aldehyde and heterocyclic-1,3-dione followed by the cascade leading to the desired products **5ab** and **4b**. [47] To evaluate the role of *o*-phenylenediamine, a reaction medium mixture of heterocyclic 1,3-dione **2b** with 4-Chlorobenzaldehyde **1a** in a molar ratio (**1**:**1**) was refluxed in ethanol for 4 h in the absence of *o*-phenylenediamine. It was observed that the reaction was not provided any product and mostly the starting material was remained.

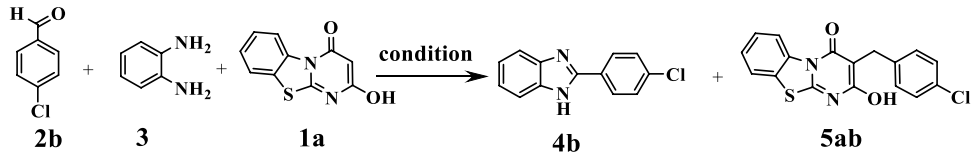
In order to increase the yield and develop the reaction conditions, the model reaction was carried out in polar solvents such as MeOH, H_2O, EtOH/H_2O (1:1), acetonitrile, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), $CHCl_3$ or under solvent-free conditions (Table 1, entries 10–14). It was found that higher product yields were obtained in ethanol. Furthermore, we considered the effect of temperature on the model reaction in ethanol at ambient or higher temperature such as 50 °C and 65 °C. As it can be clearly seen from Table 1, the best result was perceived only at reflux conditions (Table 1, entries 10–11).

A variety of either aromatic aldehydes were evaluated employing the best condition (Table 1, entry 1). A series of aromatic aldehydes having both electron-withdrawing and electron-donating groups such as Cl, Br, CH_3, OCH_3, OH, $(CH_3)_2N$ and CN in various positions of the benzene ring of benzaldehydes were successfully converted to the corresponding products with high yields in short reaction times (Table 2, **5aa–5ab, 5ad–5am**) except product **5ac** in moderate yield (Table 2, entry 3). In addition, polycyclic aromatic aldehyde like 2-naphthaldehyde and 1-naphthaldehyde also provided the desired products in very high yield (Table 2, 5an). Heteroaromatic aldehydes like 2-thiophenecarboxaldehyde, 4-Pyridinecarboxaldehyde and 3-Pyridinecarboxaldehyde also reacted effectively to give their corresponding products **5ao**, **5ap** and **5aq** in 95%, 90 and 95% yields, respectively. Also, aliphatic aldehydes such as acetaldehyde and butyraldehyde were also examined, but unfortunately a tarry complex mixture of products was obtained and no desired product was formed at all.

Subsequently, synthetic application of this protocol was investigated using three heterocyclic 1,3-dions such as 2-hydroxy-8-methoxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one (**1b**), 7-hydroxy-2-(*m*-tolyl)-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (**1c**) and 7-hydroxy-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**1d**) instead of 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one (**1a**). As it is clear, these reactions were also carried out with high yield (Table 2, **5ba–5dr**).

In the final step, we also examined the substituent effect on the reductive alkylation by arylbenzimidazoline using three various *o*-phenylenediamine and five various benzaldehyde under model reaction conditions. As shown in Table 3,

Table 1 Optimization of biomimetic reductions alkylation



Entry	Solvent[b]	T (°C)	Time (h)	Yield of 5ab (%)[c]
1	EtOH	Reflux	2	95
2	MetOH	Reflux	24	80
3	H_2O	Reflux	24	60
4	EtOH: H_2O (1:1)	Reflux	24	70
5	CH_3CN	Reflux	24	75
6	DMSO	100	24	60
7	DMF	100	24	70
8	$CHCl_3$	Reflux	24	10
9	neat	120	24	50
10	EtOH	RT	24	45
11	EtOH	50	24	75
12	EtOH	65	24	85

Reaction conditions: All reactants [1, 2(2 equivalents), 3] and were mixed and stirred at reflux. temperature. 50–94% of **4b** was isolated. [b] solvent [5 ml]. [c]Yield refers to the filtration followed by recrystalyzation in ethanol

using aldehyde and o-phenylenediamine substituted by electron-donating groups decreases the reaction time while increasing the yield. (Table 3, entries 1, 4, 7, 10 and 13). In contrast, using o-phenylenediamine and aromatic aldehyde bearing electron-withdrawing group decreased both the rate and the yield of the reaction (Table 3, entries 12 and 15). As a result, the substituents significantly influence the hydride transfer from **C-2** position of benzimidazoline to the electron deficient olefin.

The elucidation of the products **5aa–dr** were assumed from their IR, ^{1}H NMR, ^{13}C NMR spectra, elemental analyses and spectrometry (see ESI). The molecular ion peaks of these compounds showed molecular ion peaks at the suitable *m*/*z* values in their mass spectra. Spectroscopic data obtained for the products is exemplified by that for compound **5aa** where the FT-IR spectrum displayed characteristic absorption bands for carbonyl groups at 1636 cm^{-1}, and 1602 cm^{-1}. The ^{1}H NMR spectrum showed a singlet for methylene group protons at $\delta = 3.77$, the characteristic signals in the aromatic region of spectrum and a broad singlet for the enolic OH proton of pyrimidine ring. The ^{13}C NMR spectrum of **5aa** showed 15 distinct resonances in accordance with the proposed structure. The mass spectrum of **5aa** exhibited the molecular ion peak at m/z 307 which is consistent with the mass of the suggested product (see ESI).

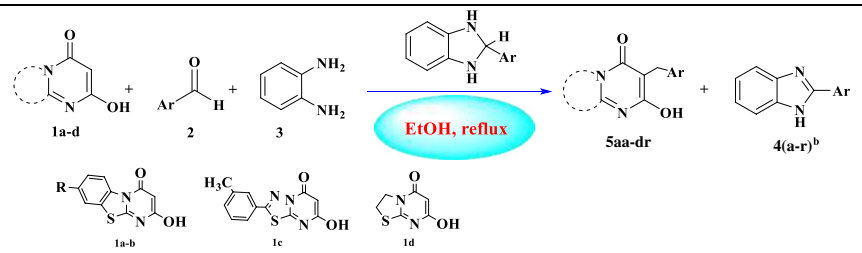
A plausible mechanism for synthesis of products based on of reported literature is proposed in Scheme 2. [58] Firstly, the reaction continues by formation of intermediate (**6**) by Knoevenagel condensation between heterocyclic CH acid (**1**) and aromatic aldehyde and at the same time, aldehyde (**2**) and *o*-phenylenediamine (**3**) undertake condensation to produce the reducing agent 2-phenylbenzimidazoline through the Schiff-based intermediate (**7**) which endures intramolecular cyclization and proton transfer. Finally, the biomimetic hydrogenation of active olefin **6** is done by 2-Arylbenzimidazoline (**8**) as reducing agent, furnishes the desired product **5.**

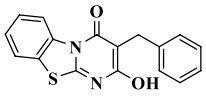
In summary, we have demonstrated a novel and efficient protocol for reductive alkylation of heterocyclic 1,3-diones using 2-Arylbenzimidazoline as a biomimetic agent produced in situ in the reaction medium in an environment-friendly and catalyst-free synthetic method to achieve the desired products which has many applications in the synthesis of natural products, drugs, and strategic materials. Easy preparation of reducing agent (in situ), simple purification process, no usage of hydrogen gas, the high to excellent yields, broad substrate profile, and being catalyst-free are among advantages of this protocol.

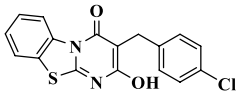
Experimental general

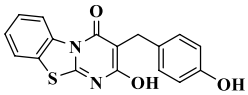
Melting points were confirmed on an Electro thermal type 9100 melting point device and are uncorrected. The IR spectra were achieved on an Avatar 370 FT-IR

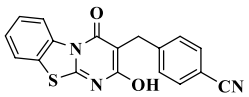
Table 2 Cascade in situ Reduction alkylation of **1** with *o*-Phenylenediamine and a variety of aldehyde

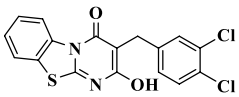


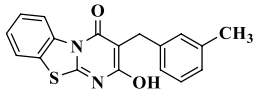

5aa[c] (95%), 2h

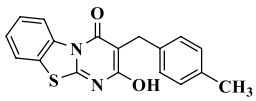

5ab (95%), 2h

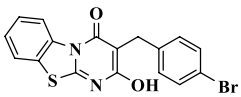

5ac (65%), 4h

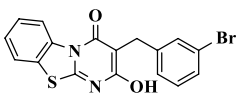

5ad (93%), 3h

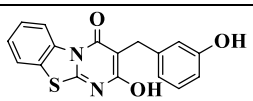

5ae (94%), 2h


5af (90%), 3h


5ag (95%), 4h


5ah (92%), 3h


5ai (95%), 2h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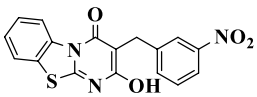
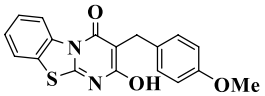
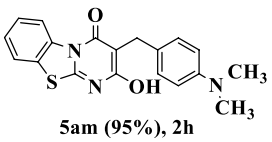
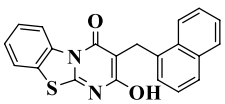
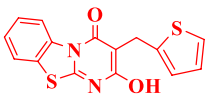
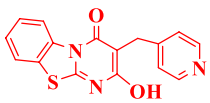

5ak (87%), 1h

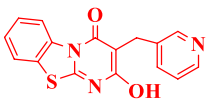

5al (94%), 1h

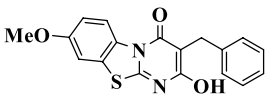

5am (95%), 2h

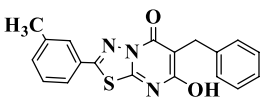

5an (95%), 3h

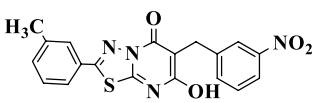

5ao (95%), 0.75h

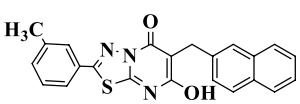

5ap (90%), 3h

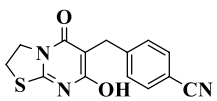

5aq (95%), 2h

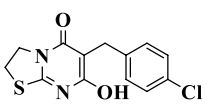

5ba[d] (96%), 3h


5ca (92%), 3h


5ck (92%), 3h


5cr (94%), 2h


5dd (90%), 2h


5db (90%), 2h

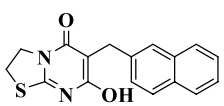

5dr (97%), 3h

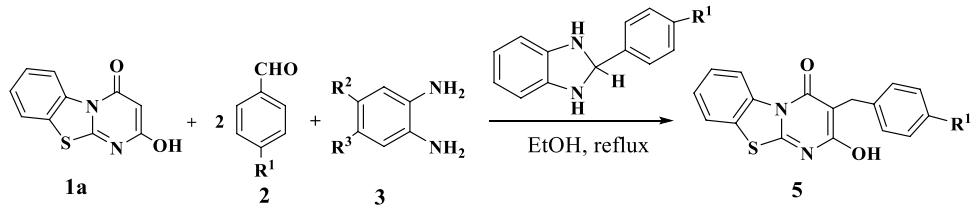
Table 2 (continued)

[a]Reaction condition:1,3-dione (**1** mmol), aldehyde (**2** mmol), *o*-phenylendiamine (**1** mmol) at reflux temperature (**5** ml)

[b]75–95% of 4a–o was isolated

[c]M.p (°C) [Lit.] [Ref.] = 248–250 [255] [57], [d]M.p (°C) [Lit.] [Ref.] = 276–278 [292–294] [49]

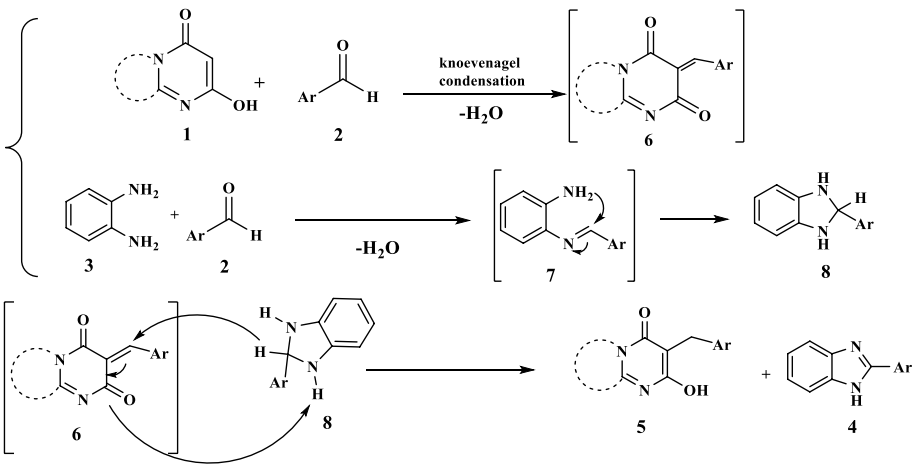
Table 3 Substituent effects on rates of reductive alkylation of electro deficient olefin



Entry	R^1	R^2	R^3	Time (h)	Yield 5 (%)
1	MeO-	CH_3	CH_3	0.5	5al (95)
2	MeO-	H	H	1	5al (94)
3	MeO-	Cl	H	3	5al (75)
4	$(CH_3)_2$ N-	CH_3	CH_3	1	5am (95)
5	$(CH_3)_2$ N-	H	H	2	5am (95)
6	$(CH_3)_2$ N-	Cl	H	4	5am (65)
7	H	CH_3	CH_3	1	5aa (95)
8	H	H	H	2	5aa (95)
9	H	Cl	H	3	5aa (54)
10	Cl	CH_3	CH_3	1	5ab (95)
11	Cl	H	H	2	5ab (95)
12	Cl	Cl	H	4	5ab (55)
13	CN	CH_3	CH_3	2	5ad (92)
14	CN	H	H	3	5ad (93)
15	CN	Cl	H	4	5ad (45)

[a]Reaction conditions:1,3-dione (**1** mmol), aldehyde (**2** mmol), *o*-phenylendiamine (**1** mmol) in ethanol (**5** ml) at reflux

Scheme 2 Plausible mechanism for the formation of product 5



Thermo-Nicolet spectrometer. ^{1}H and ^{13}C NMR spectra were run on BRUKER DRX-300 AVANCE spectrometer at 300 for ^{1}H NMR and 75 MHz for ^{13}C NMR. DMSO-d_6 was used as solvent. The mass spectra were scanned on a Varian

Mat CH-7 at 70 eV. 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one derivatives prepared in accordance with the procedures previously reported in literature [59].

General procedure for the synthesis of 4 and 5

A mixture of heterocyclic1,3-Dione **1** (1 mmol), aromatic aldehyde **2** (2 mmol) and *o*-Phenylenediamine **3** (1 mmol) in 5 mL of ethanol was mixed and stirred at reflux. The reaction was monitored by thin-layer chromatography (Hexane/Ethyl acetate, 10/7). After TCL indicated the completion of the reaction, the reaction mixture was cooled down to room temperature, the insoluble product (**5**) filtered out the isolated solid from the reaction mixture, washed with cold ethanol to give the desired products **5aa–dr** in good yield (65–97% yield). Then filtrate was concentrated in reduced pressure, and the solid residue was purified by plate chromatography eluted with n-hexane/ ethyl acetate (10/7) to afford pure products **4**. High purity products were obtained by recrystallization from ethanol to yield (**5**).

3-benzyl-2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-one (5aa)

white powder; (0.29 g, 95% yield); mp = 248–250 °C; IR(KBr) (υ_{max}/cm^{-1}): υ = 1636 (C=O), 1602 (C=N); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 3.77 (2H, s, CH_2), 7.14–7.33 (5H, m, ArH), 7.50–7.57 (2H, m, ArH), 7.98–8.03 (1H, m, ArH), 8.94–8.99 (1H, m, ArH), 11.98 (1H, s, OH); ^{13}C NMR (76 MHz, DMSO) δ 28,74, 97.39, 118.87, 123.36, 124.08, 126.10, 126.92, 127.16, 127.50, 128.50, 128.76, 136.51, 141.34, 159.89, 162.54, 164.81; (m/z, %), 307 (M, 47), 305 (100), 275 (68), 248 (29), 201 (72), 176 (98), 130 (97), 102 (73), 102(72), 91 (95), 65(87), 51 (64), 39 (40), 29 (94); Anal. Calcd for $C_{17}H_{12}N_2O_2S$ (307.06): C, 66.22; H, 3.92; N, 9.08; S, 10.40%. Found: C, 66.21; H, 3.93; N, 8.98; S, 10.39.

For physical and spectroscopy data of other product see Supplementary Material.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11030-021-10246-y.

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Declarations

Conflict of interest There are no conflicts to declare.

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