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Boric acid catalysted novel synthesis of 2,3,5,6-tetraryl-3,3*a*,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*]thiazole in aqueous medium

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ABSTRACT

Three component, simple and direct cyclocondensation method has been developed for the synthesis of 2,3,5,6-tetraryl-3,3*a*,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*]thiazole by combining aniline (1 mmole) **1**, benzaldehyde (2 mmole) **2**, mercaptoacetic acid (1 mmole) in presence of boric acid (20 mol%) as catalyst and surfactant CTAB (15 mol%) in aqueous medium with excellent yield, followed by cyclocondensation with arylhydrazene. Simple reaction conditions, short reaction time, ease of product isolation, use of cheap and readily available catalyst makes this manipulation very interesting from an economic and environmental perspective. The catalyst was easily recovered and reused without any considerable loss of activity.

1. Introduction

The challenge in chemistry to develop practical process, reaction media, conditions and/or utility of materials based on the idea of integrated chemical process is one of the important issues in the scientific society[1]. By consolidating multi-steps in one-pot, toxic intermediates generated *in-situ* in reaction sequences are consumed without exposure to environment[2]. Pollution free synthesis of organic compounds in presence of non toxic solvents is an important challenge[3]. This requires a new approach which will reduce the material and energy consumption, and eliminate or minimize the dispersion of harmful chemicals in the environment.

In the mainstream of current interest, a new concept for consolidation of multi-step reaction in one-pot, so-called 'integrated chemical process' has introduced. In this approach reaction conditions which could be tolerated by each steps is optimized with-in the frame work of these conditions and have gained considerable interest due to economic and ecological point of view. Rational approaches involes the consolidation of multi-step procedures into a one-pot, single-step process has environmental advantage because it decreases or eliminates the generation of hazardous substances. In-situ generation followed by consumption of toxic intermediates, which may be formed in the process, enables their complete isolation from the environment.

The present day industrialization has led to immense environmental worsening. One of the biggest sources of environmental pollution and threat to human health is the toxic and hazardous organic solvents released from the chemical industry. The solvent vapors contaminate the atmosphere/ environment. The increasing awareness throughout the world has brought in a pressing need to develop an alternative synthetic approach for biologically and synthetically important compounds. Since water is non-flammable, nonhazardous, non toxic, uniquely redox stable, inexpensive, green solvent therefore, using water as a reaction medium has been considerable interest[4] because reactions in this medium have several advantages including the fact that the solvent and substrates can be used directly without drying. Also, it is believed that reactions in water contribute to green chemistry.

Similarly number of reactions[5] in which water soluble catalyst, boric acid have been used to accelerate organic reactions synergistically as well as reduce the generation of by-products. Prevent/minimize the decomposition of product and are effective in various organic transformations such as esterification of hydroxycarboxylic acids[6], aza Michael[7], thia Michael addition[8], bromination[9], synthesis of imidazole[10], 1,1-diacetate[11], synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines[12] etc. Boric acid is selected as catalyst because of its most fundamental properties; it produces a Brønsted acid when it reacts with water:

$$B(OH)_3 + H_2O \longrightarrow H^+ + B(OH)_4^-$$

Thus, boric acid in water is expected to be ideal catalyst for this manuscript.

The key element in the current approach is the novel utilization of thiazolidin-4-one[13] and pyrazole ring as a building block. Thiazolidin-4-one and its derivatives are known to exhibit interesting pharmacological activities such as anti-diabetic[14],

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antidiarrheal[15], anti-convulsant[16], anti-platelet activating factor[17], anti-histaminic[18], Ca^{2+}-channel blocker[19], cyclooxygenase (COX) inhibitory[20], platelet activating factor (PAF) antagonist[21], cardioprotective[22], anti-ischemic[23], anti-cancer[24], tumor necrosis factor-α antagonist[25] and nematicidal[26]. Furthermore, some aryl pyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory[27], COX-2 inhibitory[28]. Similarly pyrazole and its derivatives shows antimicrobial[29], antiarthritic[30], antidepressant[31], inhibitors of protein kinase[32], and cerebroprotector activity[33].

Prompted by the above report and in continuation of our research work on development of novel environmentally benign synthesis[34] herein we report a simple, efficient and green protocol for the synthesis of 2,3,5,6-tetraryl-3,3*a*,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*]thiazole, catalyzed by boric acid in aqueous medium, but the basic problem in performing of reaction in water is lower solubility of organic compounds in water. To overcome this problem we introduced surfactant (CTAB) in water to form micelles[35].

2. Experimental

5-Benzylidene-2,3-diarylthiazolidin-4-one (5): Aniline (1 mmole) **1**, benzaldehyde (2 mmole) **2**, mercaptoacetic acid (1 mmole), boric acid (20 mol%) and CTAB (15 mol%) were dissolved 5 ml water and the whole was stirred at room temperature. The progress of the reaction was monitored by TLC (silica gel). After completion of the reaction, the mixture was extracted with ethyl acetate (3×10mL). The combined organic extracts (dried over Na_2SO_4) were concentrated under reduced pressure and the resulting product was purified by flash chromatography with hexane and ethyl acetate (8:2 v/v) to afford the pure adduct **5**. The aqueous layer containing boric acid was reused for the next run.

5a. m.p.213°C. MS, m/z: 343 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 7.26-7.75 (m, 15H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{17}NOS$: C, 76.90; H, 4.90; N, 4.00; Found: C, 76.94; H, 4.99; N, 4.08%.

5b. m.p.233°C. MS, m/z: 371 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.34 (s, 6H, 2×-CH_3), 5.92 (s, 1H, S-CH-N), 7.11-7.75 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{24}H_{21}NOS$: C, 77.59; H, 5.70; N, 3.77; Found: C, 77.50; H, 5.60; N, 3.71%.

5c. m.p. 250°C. MS, m/z: 403 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.83 (s, 6H, 2× -OCH_3), 5.92 (s, 1H, S-CH-N), 6.87-7.77 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47; Found: C, 71.41; H, 5.22; N, 3.40%.

5d. m.p. 255°C. MS, m/z: 411 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 6.87-7.77 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{15}Cl_2NOS$: C, 64.08; H, 3.67; N, 3.40; Found: C, 64.00; H, 3.52; N, 3.39%.

5e. m.p. 240°C. MS, m/z: 433 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 6.87-8.14 (m, 13H, ArH), 8.2 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{15}N_3O_5S$: C, 60.96; H, 3.49; N, 9.69; Found: C, 60.90; H, 3.44; N, 9.62%.

5f. m.p. 248°C. MS, m/z: 403 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.83 (s, 6H, 2× -OCH_3), 5.92 (s, 1H, S-CH-N), 6.87-7.77 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47; Found: C, 71.43; H, 5.21; N, 3.40%.

5g. m.p. 253°C. MS, m/z: 357 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.34 (s, 3H, -CH_3), 5.92 (s, 1H, S-CH-N), 7.21-7.60 (m, 14H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{23}H_{19}NOS$: C, 77.28; H, 5.36; N, 3.92; Found: C, 77.24; H, 5.32; N, 3.90%.

5h. m.p. 230°C. MS, m/z: 373 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.83 (s, 3H, -OCH_3), 5.92 (s, 1H, S-CH-N), 6.97-7.92 (m, 14H, ArH), 8.0 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{23}H_{19}NO_2S$: C, 73.97; H, 5.13; N, 3.75; Found: C, 73.90; H, 5.10; N, 3.71%.

5i. m.p. 220°C. MS, m/z: 377 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 7.26-7.70 (m, 14H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{16}ClNOS$: C, 69.92; H, 4.27; N, 3.71; Found: C, 69.90; H, 4.22; N, 3.70%.

5j. m.p. 210°C. MS, m/z: 388 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 7.26-8.24 (m, 14H, ArH); Anal. Calc. for $C_{22}H_{16}N_2O_3S$: C, 68.02; H, 4.15; N, 7.21; Found: C, 68.00; H, 4.11; N, 7.17%.

2,3,5,6-tetraryl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (7): Mixture of 5-benzylidene-2,3-diarylthiazolidin-4-one 5 (0.25 mmol), substituted phenylhydrazene (0.5 mmol) and sodium acetate (0.25 mmol) in gl. acetic acid (20 ml) was refluxed for 2 hr, concentrated, cooled and poured ice-cold water. The solid thus separated, was filtered, washed well with cold water and crystallized with gl. acetic acid to obtained analytical pure 7.

7a. m.p. 213°C. MS, m/z: 343 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 7.26-7.75 (m, 15H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{17}NOS$: C, 76.90; H, 4.90; N, 4.00; Found: C, 76.94; H, 4.99; N, 4.08%.

7b. m.p. 233°C. MS, m/z: 371 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.34 (s, 6H, 2×-CH_3), 5.92 (s, 1H, S-CH-N), 7.11-7.75 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{24}H_{21}NOS$: C, 77.59; H, 5.70; N, 3.77; Found: C, 77.50; H, 5.60; N, 3.71%.

7c. m.p. 242°C. MS, m/z: 403 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.83 (s, 6H, 2× -OCH_3), 5.92 (s, 1H, S-CH-N), 6.87-7.77 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47; Found: C, 71.41; H, 5.22; N, 3.40%.

7d. m.p. 245°C. MS, m/z: 411 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 6.87-7.77 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{15}Cl_2NOS$: C, 64.08; H, 3.67; N, 3.40; Found: C, 64.00; H, 3.52; N, 3.39%.

7e. m.p. 243°C. MS, m/z: 433 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 6.87-8.14 (m, 13H, ArH), 8.2 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{15}N_3O_5S$: C, 60.96; H, 3.49; N, 9.69; Found: C, 60.90; H, 3.44; N, 9.62%.

7f. m.p. 235°C. MS, m/z: 403 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.83 (s, 6H, 2× -OCH_3), 5.92 (s, 1H, S-CH-N), 6.87-7.77 (m, 13H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47; Found: C, 71.43; H, 5.21; N, 3.40%.

7g. m.p. 240°C. MS, m/z: 357 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.34 (s, 3H, -CH_3), 5.92 (s, 1H, S-CH-N), 7.21-7.60 (m, 14H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{23}H_{19}NOS$: C, 77.28; H, 5.36; N, 3.92; Found: C, 77.24; H, 5.32; N, 3.90%.

7h. m.p. 225°C. MS, m/z: 373 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 3.83 (s, 3H, -OCH_3), 5.92 (s, 1H, S-CH-N), 6.97-7.92 (m, 14H, ArH), 8.02 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{23}H_{19}NO_2S$: C, 73.97; H, 5.13; N, 3.75; Found: C, 73.90; H, 5.10; N, 3.71%.

7i. m.p. 240°C. MS, m/z: 377 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 7.26-7.70 (m, 14H, ArH), 7.79 (s, 1H, Ar-CH=C); Anal. Calc. for $C_{22}H_{16}ClNOS$: C, 69.92; H, 4.27; N, 3.71; Found: C, 69.90; H, 4.22; N, 3.70%.

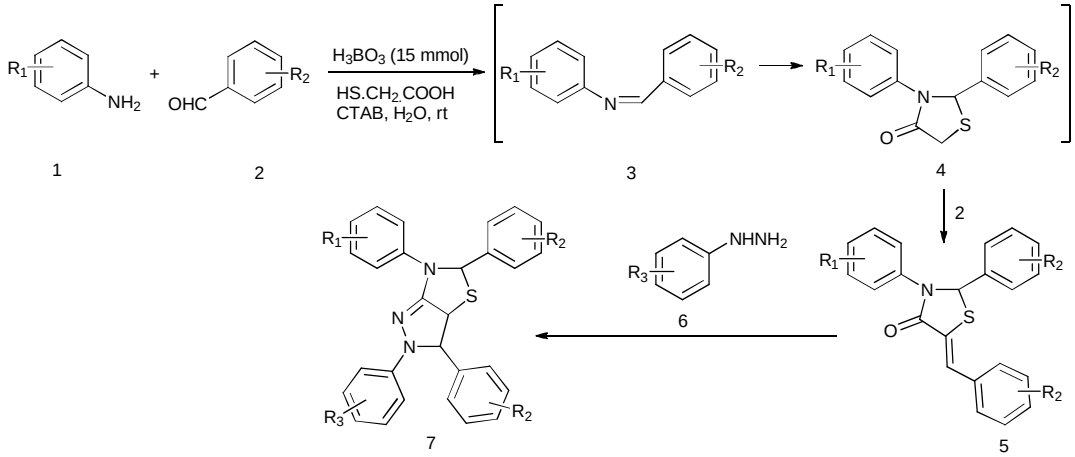
7j. m.p. 238°C. MS, m/z: 388 (M+); ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 5.92 (s, 1H, S-CH-N), 7.26-8.24 (m, 14H, ArH); Anal. Calc. for $C_{22}H_{16}N_2O_3S$: C, 68.02; H, 4.15; N, 7.21; Found: C, 68.00; H, 4.11; N, 7.17%.

3. Results and discussion

In our initial study, reaction of aniline (1 mmole) **1**, benzaldehyde (2 mmole) **2**, mercaptoacetic acid (1 mmole), boric acid (20 mol%) and CTAB (15 mol%) in 5 ml water was considered as a standard model reaction (**Scheme 1**). During this

investigation efforts were mainly focused on a variety of surfactants as well as catalysts molar concentration.

Since water was our choice for selecting the reaction medium to perform the proposed condensation reaction but problem in conducting the reaction in water is insolubility or partial solubility of substrates, which may cause them to react slowly leads to get sticky products and relatively longer reaction time for completion. Since Surfactant reduces the interfacial tension between organic and aqueous layer and increases the solubility of organic substrates in water as well as concentration of substrates due to formation of micelle particles in water[36], hence we have decided to employ surfactant to conduct the reaction.



Cpd.	R^1	R^2	R^3
5a	H-	H-	---
5b	H-	*p*-CH_3-	---
5c	H-	*p*-CH_3O-	---
5d	H-	*p*-Cl-	---
5e	H-	*p*-NO_2-	---
5f	H-	*o*-CH_3-	---
5g	*p*-CH_3-	H-	---
5h	*p*-CH_3O-	H-	---
5i	*p*-Cl-	H-	---
5j	*p*-NO_2-	H-	---
6a	H-	H-	*p*-CH_3-
7b	H-	*p*-CH_3-	*p*-CH_3O-
7c	H-	*p*-CH_3O-	*p*-Cl-
7d	H-	*p*-Cl-	*p*-NO_2-
7e	H-	*p*-NO_2-	*o*-CH_3-
7f	H-	*o*-CH_3-	*p*-CH_3-
7g	*p*-CH_3-	H-	*p*-CH_3O-
7h	*p*-CH_3O-	H-	*p*-Cl-
7i	*p*-Cl-	H-	*p*-NO_2-
7j	*p*-NO_2-	H-	*o*-CH_3-

Scheme 1

Encouraged by these results we further investigated effect of catalyst on the reaction we found that, there is significant decrease in time along with excellent enhancement of yield using boric acid as a catalyst in aqueous micelle system. However in the absence of surfactant, the reaction takes longer time for completion and leads to a sticky product due to insolubility or partial solubility of substrates in water, which may cause them to react slowly, hence we have decided to employ different cationic surfactants such as cetyl trimethyl ammonium bromide (CTAB), methyl triphenylphosphonium bromide (MTPPB), cetyl pyridinium chloride (CPC) as well as an anionic surfactant, sodium dodecyl sulphate (SDS) at ambient temperature. Surfactant reduces the interfacial tension between organic and aqueous layer and increases the concentration of substrates due to formation of micelle particles in water[36]. It was assured that the anionic surfactant, SDS and cationic surfactants, CPC and MTPPB gave the desired product in low yields (50, 29, 51%) respectively, in contrast, the cationic surfactant, CTAB accelerated the model reaction to afford the desired product in excellent yield 91% (**Table-1**).

Efforts were mainly focused on the optimization of the catalyst concentration as well as surfactants. We investigated effect of different catalyst concentration on the reaction. We found that, reduction of time decrease significantly along with excellent increase in yield using boric acid as a catalyst in aqueous micellar system. The amount of catalyst was varied from 0 to 25 mol%.

Table 1 - Optimization of catalyst concenteration

Entry	Catalyst (mol%)	Time(min)	Yield[a] (%)
1	0	180	40
2	5	45	55
3	10	40	76
4	15	35	84
5[b]	20	30	91, 90, 88
6	25	30	91

[a]Isolated yields

[b]catalyst was used three times without any considerable loss of activity.

As shown in the **Table-1**, elevated amount of catalyst improved the reaction percentage yield and shortened the

reaction time. When catalyst concentration was 0 mol%, the yield was found to be 40% in even after 3 hours but when 5 mol% the catalyst was added, there reaction time decreases with increased yield of 55%. On further increasing the concentration of catalyst 10, 15, 20 (mol%) there is enhancement of yield from 76%, 84% up to 91% respectively **(Table 1)**. But on further increase in catalyst concentration (25 mol%) no significant rise in yield occurs. Therefore, the proposed one-pot multi-component condensation was carried out taking 20 mol% as catalyst concentration.

Further effect of various surfactants on the model reaction was also examined for e.g. Cationic surfactants such as cetyl trimethyl ammonium bromide (CTAB), methyl triphenylphosphonium bromide (MTPPB), cetyl pyridinium chloride (CPC) as well as anionic surfactant, sodium dodecyl sulphate (SDS) at ambient temperature. It was found that the anionic surfactant, SDS and cationic surfactants, CPC and MTPPB gave the desired product in low yields (50, 29, 51%) respectively, in contrast, the cationic surfactant, CTAB accelerated the model reaction to afford the desired product in excellent yield (91%) at room temperature (45°C) (**Table-2**).

Table 2 - Screening of surfactants[a]

Entry	Surfactant	Temperature (^oC)	Time (hour)	Yield[b] (%)
1	SDS	rt	4.30	50
2	CPC	rt	4.0	29
3	MTPPB	rt	4.0	51
4	TEAB	rt	4.0	40
5	CTAB	rt[c]	30 min	91

[a]Reaction condition: aniline (1 mmole) **1**, benzaldehyde (2 mmole) **2**, mercaptoacetic acid (1 mmole), boric acid (20 mol%) and CTAB (15 mol%) in 5 ml water
[b]Isolated yields
[c]Room temperature 45°C.

Finally, upon completion of the reaction, activity of the recycled $B(OH)_3$ was also investigated with the optimized reaction conditions. The desired product was isolated after the completion of reaction by simple filtration (as monitored by TLC). The filtrate was extracted with ethylacetate. The aqueous layer of extract contain CTAB and $B(OH)_3$ was reused for the next run. It is found that the product was obtained 91, 90, 88% yield after 1-3.

4. Conclusion

In conclusion, we have developed an efficient and environmentally benign, clean protocol for the synthesis of 2,3,5,6-tetraryl-3,3*a*,5,6-tetrahydro-2*H*-pyrazolo[3,4-d]thiazole by the one-pot three-component cyclo-condensation of aniline (1 mmole) **1**, arylaldehyde (2 mmole) **2**, mercaptoacetic acid (1 mmole) catalyzed by boric acid (20 mol%) surfactant CTAB (15 mol%) in aqueous medium with excellent yield, followed by cyclocondensation with arylhydrazene. The advantages of this method over the other existing methods is short reaction time, higher yields, simple reaction conditions, easier purification and economic viability and use of cheap and readily available catalyst made this protocol very interesting from the environmental and economic perspective. The catalyst was easily recovered and reused without any considerable loss of activity. We feel that this economically viable procedure will find practical utility for the synthesis 2,3,5,6-tetraryl-3,3*a*,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole.

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