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Der Pharma Chemica, 2012, 4(3):956-960
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Boric acid promoted an efficient and practical synthesis of fused pyrimidines in aqueous media

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ABSTRACT

A very efficient, convenient, mild and practical method is described for the synthesis of fused pyrimidines by three component reaction of β-keto ester, aldehyde and heterocyclic amine in the presence of boric acid in water. The reaction proceeds at rt and yields are high. The method is also amenable for the synthesis of new thiazodihydropyrimidine compounds.

Key Words: 2-Amino benzimidazole, 2-Amino benzthiazole, 2-Amino thiazole, β-ketoester, Aldehyde and Boric acid.

INTRODUCTION

Pyrimidine nucleus plays important role in biological systems. Particularly, benzthiazo and benzimidazo pyrimidine unit containing marine alkaloids are shown to possess wide range of medicinal properties such as antiviral, antibacterial, and anti-inflammatory[1]. Recently, there has been growing interest in the combinatorial synthesis for the design of new pyrimidines. Some of the fused pyrimidines like benzthiazo pyrimidine and benzimidazo pyrimidine are known to posses vasorelaxant activity[2]. Due to their pharmaceutical importance, there is a continuous research interest to develop a simple and convenient method for the preparation of fused pyrimidines. There are few methods for the synthesis of fused pyrimidines such as, a solvent free method[3] is reported using TMGT as ionic liquid at 100^0C. Another synthesis[4] accomplished in refluxing butanol for longer reaction time (50 hrs). In addition to this, fused pyrazopyrimidines[5] were prepared in two steps in DMF at higher temperature. However, most of the methods require heating and higher boiling solvent which makes procedure tedious for the isolation of product. Moreover, most of the procedure need longer reaction time for the completion of reaction and have limitations for fused benzimidazo and benzthiopyrimidines. In this context there is need to search for efficient, convenient and practical procedure which avoids the drawbacks of earlier methods.

Boric acid has been used as an alternate acidic catalyst for various organic transformations[6] because of easy handling, availability and environmentally safe. Water is considered as a universal solvent due to availability, non-toxicity and ampoteric nature. We envision explore the combination of boric acid and water to promote three component reactions. In continuation of our research for the development of green methodologies[7], herein we wish

to report the synthesis of fused dihydropyrimidine by the reaction of heterocyclic amines, β-keto ester and aromatic aldehyde in presence of boric acid in water.

MATERIALS AND METHODS

All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from *Fluka* and *S. D. Fine Chemicals*. TLC: pre coated silica gel plates (*60 F_{254}*, 0.2 mm layer; *E. Merk* ^{1}H-NMR Spectra: *Varian 200* or *Bruker 300* spectrometer; in $CDCl_3$; δ in ppm, *J* in Hz. Mass spectra: *VG Autospec*; in *m/z*. All the products were characterized by IR, Mass and NMR spectroscopy.

General procedure. A mixture of aldehyde (1.2 mmol), β-keto ester(1.2 mmol) and boric acid (20 mol%) in water (2 ml) was stirred for 5 minutes then hetero cyclic amine (1 mmol) was added and the reaction mixture was stirred for stipulated time at rt (see Table 2). The reaction was monitored by TLC, after completion of reaction; the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over sodium sulphate and solvent removed under reduced pressure. The residue was purified by column chromatography using hexane and ethyl acetate.

The characteristic data of new compounds are given below.

Compound (6a). yellow solid. mp 110-112 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1078, 1204, 1484, 1686, 3402. ^{1}HNMR (CDCl3, 300MHz): δ(ppm) 1.16 (t, 3H, J = 7.5 Hz), 2.39 (s, 3H), 3.89-4.70 (m, 2H), 6.13 (s, 1H), 6.23 (d, 1H, J = 4.5 Hz), 6.43 (d, 1H, J = 4.5 Hz), 7.28-7.31 (m, 3H), 7.35 (d, 2H, J = 7.5 Hz). ESI-MS: m/z 323(M+Na).

Compound (6b). yellow solid. mp 109-111 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1075, 1201, 1493, 1696, 2979, 3373. ^{1}HNMR ($CDCl_3$, 300MHz): δ(ppm) 1.90 (t, 3H, *J* = 7.1 Hz), 2.46 (s, 3H), 3.98 (q, 2H, *J* = 7.1 Hz), 6.21 (d, 1H, *J* = 4.7 Hz), 6.70 (s, 1H), 6.79 (d, 1H, *J* = 4.7 Hz), 7.17-7.35 (m, 3H), 7.50-7.54 (dd, 1H, *J* = 1.3, 1.5 Hz). ESI-MS: m/z 357(M^+Na).

Compound (6c). yellow solid. mp 108-110 ^{0}C; IR (KBr) ν_{max}(cm^{-1}): 1071, 1200, 1495, 1576, 1692, 2920, 3380. ^{1}HNMR ($CDCl_3$, 300MHz) δ(ppm): 1.19 (t, 3H, *J* = 7.5 Hz), 2.40 (s, 3H), 4.08 (m, 2H), 6.11 (s, 1H), 6.26 (d, 1H, *J* = 4.5 Hz), 6.50 (d, 1H, *J* = 4.5 Hz), 7.28 (m, 4H). ESI-MS: m/z 357(M^+Na).

Compound (6d). yellow solid. mp 114-116 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1190, 1245, 1469, 1736, 2925, 3118. ^{1}HNMR ($CDCl_3$, 300MHz) δ(ppm): 1.06 (t, 3H, *J* = 7.5 Hz), 1.50 (t, 3H, *J* = 7.5 Hz), 2.44 (s, 3H), 3.90-4.22 (m, 4H), 6.13 (d, 1H, *J* = 4.5 Hz), 6.42 (d, 1H, *J* = 4.5 Hz), 6.61 (s, 1H), 6.77-7.34 (m, 4H). ESI-MS: m/z 367(M^+Na).

Compound (6e). yellow solid. mp 106-108 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1003, 1073, 1172, 1475, 1561, 1692, 2923, 3370. ^{1}HNMR ($CDCl_3$, 300MHz): δ(ppm): 1.06 (t, 3H, *J* = 7.1 Hz), 2.41 (s, 3H), 4.01 (q, 2H, *J* = 7.1 Hz), 6.32 (d, 1H, *J* = 4.7 Hz), 6.80 (s, 1H), 6.94-7.70 (m, 5H). ESI-MS: m/z 368(M^+ Na).

Compound (6f). yellow solid. mp 104-106 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1000, 1070, 1280, 1480, 1688, 2925, 3367. ^{1}HNMR ($CDCl_3$, 300MHz): δ(ppm) 1.23 (t, 3H, *J* = 7.5 Hz), 2.40 (s, 3H), 4.00-4.16 (m, 2H), 6.29 (s, 1H), 6.34 (d, 1H, *J* = 4.5 Hz), 6.58 (d, 1H, *J* = 4.5 Hz), 7.49-8.18 (m, 4H). ESI-MS: m/z 368(M^+ Na).

Compound (6g). yellow solid. mp 112-114 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1198, 1285, 1364, 1561, 1696, 2928, 3162, 3368. ^{1}HNMR ($CDCl_3$, 300MHz): δ(ppm): 1.18 (t, 3H, *J* = 7.7 Hz), 2.38 (s, 3H), 3.76 (s, 3H), 3.99-4.11 (m, 2H), 6.07 (s, 1H), 6.20 (d, 1H, *J* = 4.7 Hz), 6.51 (d, 1H, *J* = 4.7 Hz), 6.79 (d, 2H, *J* = 8.4 Hz), 7.22 (d, 2H, *J* = 8.4 Hz). ESI-MS: m/z 353(M^+Na).

Compound (6h). yellow solid. mp 120-122 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1078, 1205, 1484, 1681, 2854, 2923, 3116, 3321. ^{1}HNMR ($CDCl_3$, 300MHz): δ(ppm) 1.29 (t, 3H, *J* = 7.1 Hz), 2.92 (s, 3H), 4.10-4.20 (m, 2H), 5.10 (d, 1H, *J* = 4.5 Hz), 5.20 (s, 1H), 6.40 (d, 1H, *J* = 4.5 Hz), 7.50-8.20 (m, 7H). ESI-MS: m/z 373(M^+Na).

Compound (6i). yellow solid. mp 131-133 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1088, 1188, 1282, 1500, 1699, 2924, 3447. ^{1}HNMR ($CDCl_3$, 300MHz): δ(ppm) 1.30 (t, 3H, *J* = 7.5 Hz), 4.70-4.90 (m, 2H), 4,59 (s, 1H), 5.10 (d, 1H, *J* = 4.5 Hz), 6.40 (d, 1H, *J* = 4.5Hz), 7.28-7.32 (m, 5H). ESI-MS: m/z 377(M^+Na).

Compound (6j). yellow solid. mp 130-132 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1090, 1192, 1493, 1670, 3448. ^{1}HNMR ($CDCl_3$, 300MHz): δ(ppm) 1.14 (t, 3H, *J* = 7.1 Hz), 4.04-4.12 (m, 2H), 6.37 (d, 1H, *J* = 4.7 Hz), 6.80 (d, 1H, *J* = 4.7 Hz), 6.82 (s, 1H), 7.25-7.40 (m, 4H). ESI-MS: m/z 411(M^+Na).

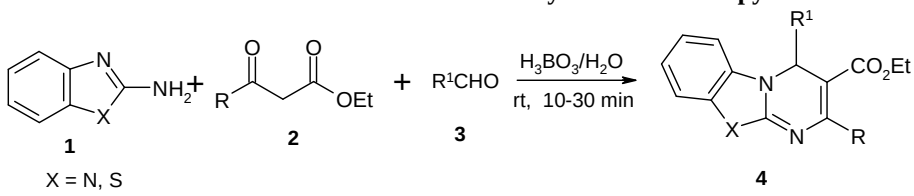
Compound (6k). yellow solid. mp 128-130 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1088, 1188, 1282, 1501, 1704, 3440. ^{1}HNMR ($CDCl_3$, 300MHz:) δ(ppm) 0.89 (t, 3H, *J* = 7.5 Hz), 4.03-4.15 (m, 2H), 6.22 (s, 1H), 6.40 (d, 1H, *J* = 4.5 Hz), 6.52-6.55 (d, 1H, *J* = 4.5 Hz), 6.83 (d, 1H, *J* = 9.0 Hz), 7.24-7.32 (m, 3H). ESI-MS: m/z 411(M^+Na).

Compound (6l). yellow solid. mp. 134-136 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 1038, 1088, 1190, 1282, 1469, 1738, 2925, 3110 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300MHz) δ(ppm) 1.13 (t, 3H, *J* = 7.5 Hz), 1.48 (t, 3H, *J* = 6.7 Hz), 3.98-4.20 (m, 4H), 6.25 (d, 1H, *J* = 4.5 Hz), 6.60 (s, 1H), 6.69 (d, 1H, *J* = 4.5 Hz), 6.86 (d, 2H, *J* = 8.3 Hz), 6.95 (t, 2H, *J* = 7.5 Hz). ESI-MS: m/z 421(M^+Na).

RESULTS AND DISCUSSION

Initially the reaction of 2-Amino benzimidazole (1 mmol), aldehyde (1.2 mmol) and β-keto ester (1.2 mmol) in water in presence of boric acid (20 mol %) at rt and gave comparatively less yield of product. Similarly, 2-aminobenzothiazole also reacted analogously to furnish expected oxindole in good yield. (Scheme 1) (Table 1)

Scheme 1: Boric acid mediated efficient and convenient synthesis of fused pyrimidine derivatives.



1 **2** **3** **4**

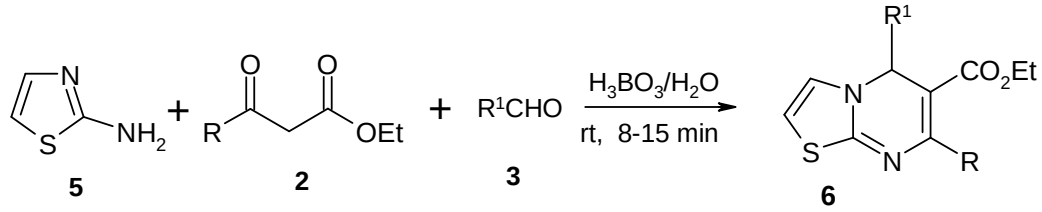
X = N, S

Table 1: Synthesis of fused pyrimidine derivatives.

S.No.	X	R	R^1	Product	Time(min)	Yield(%)
1	S	CH_3	C_6H_5	4a	25	77
2	S	CH_3	4-$OMeC_6H_4$	4b	23	79
3	S	CH_3	4-ClC_6H_4	4c	26	77
4	S	CH_3	4-$NO_2C_6H_4$	4d	27	78
5	S	CF_3	C_6H_5	4e	15	82
6	S	CF_3	4-ClC_6H_4	4f	17	81
7	S	CF_3	4-$MeOC_6H_4$	4g	10	85
8	S	CF_3	4-BrC_6H_4	4h	16	81
9	NH	CH_3	C_6H_5	4i	30	75
10	NH	CH_3	4-$OMeC_6H_4$	4j	27	78
11	NH	CH_3	4-$NO_2C_6H_4$	4k	30	75
12	NH	CH_3	2-$OEtC_6H_4$	4l	20	79
13	NH	CH_3	4-ClC_6H_4	4m	18	80

Thus the reaction of 2-aminothiazole, ethylacetoacetate and benzaldehyde were performed in the standard reaction condition proceeded smoothly and completed in 30 min. After work up, fused thiazolopyrimidine was the sole product isolated in high yield (95%). (Scheme 2)

Scheme 2: Boric acid mediated efficient and convenient synthesis of fused thiazolo pyrimidine derivatives.



The plausible mechanistic pathway was given in scheme 3. Initially, benzaldehyde reacts with active methylene of ketoester to form alkene. Subsequent aza-Michael type addition and cyclisation gave desired fused thiazolopyrimidines. (Scheme 3)

Scheme 3: Plausible mechanism for the fused thiazolo pyrimidine formation.

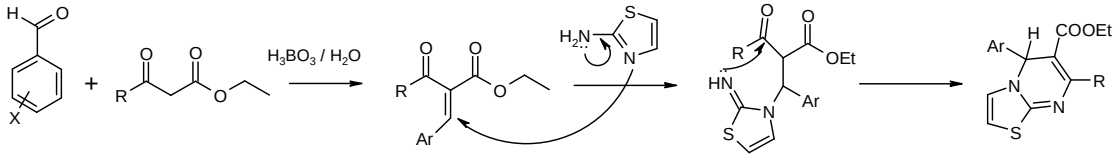


Table 2: Synthesis of fused thiazolopyrimidine derivatives

S.No.	R	R^1	Product	Time(min)	Yield(%)
1	CH_3	C_6H_5	6a	15	81
2	CH_3	2-ClC_6H_4	6b	13	85
3	CH_3	4-ClC_6H_4	6c	14	83
4	CH_3	2-$OEtC_6H_4$	6d	11	90
5	CH_3	2-$NO_2C_6H_4$	6e	15	82
6	CH_3	3-$NO_2C_6H_4$	6f	14	83
7	CH_3	4-$MeOC_6H_4$	6g	12	90
8	CH_3	$C_4H_4C_6H_3$ [a]	6h	15	80
9	CF_3	C_6H_5	6i	12	90
10	CF_3	2-ClC_6H_4	6j	9	93
11	CF_3	4-ClC_6H_4	6k	9	93
12	CF_3	2-$OEtC_6H_4$	6l	8	95

Further, we have studied various mol% of boric acid and 20 mol% ratio was found suitable for optimum conversion. Further to extend the scope of this reaction, various heterocyclic amines, β-ketoesters and aldehydes were examined in standard condition. Next to show the electronic influence on the rate of reaction, various substituted aldehydes were examined. During investigation it was observed that electron rich substituent facilitate the reaction. For example, 4-methoxy benzaldehyde (Table 1, entry- 2, 7, 4 and Table 2, entry- 7) and 2-ethoxy benzaldehyde (Table

1, entry- 12 and Table 2, entry- 4, 12) underwent smooth reaction in standard reaction condition to give high yield of corresponding product. The reaction of nitro benzaldehyde and other substituted benzaldehyde gave comparatively less yield of oxindole. As the trifluoro group is important in medicinal point of view, we have screened trifluoroester. Thus the reaction trifluoroacetoacetate was very rapid as compared to ethylacetoacetate and resulted in to high yield of product in the optimized condition. We believe that although the Beginelli reaction is reported in water[5], the use of boric acid has severely reduced the reaction time and yields are high. Moreover, the present method provides access for the synthesis of new molecules which are not synthesized earlier. The protocol was also proved to be efficient on a multigram scale which can be transforming into industrial process. In this context, we have performed the reaction of 2-aminothiozole, triflouro ethylacetoacetate and ortho ethoxy benzaldehyde in standard condition and the corresponding product was isolated in high yield. (Table 2)

CONCLUSION

In conclusion we have demonstrated very efficient and practical method for the synthesis of fused pyrimidines. The simple experimental procedure, inexpensive and readily available catalyst with high yield of product are great advantages of present protocol. Moreover the use of water as reaction media makes the procedure more ecofriendly.

Acknowledgments
A S K, G S K, A S, B C K R and P R thank CSIR-UGC for the award of a fellowship and to Dr. J. S. Yadav, Director IICT, for his support and encouragement.

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