Article

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Water Mediated Domino Knoevenagel-Michael-cyclocondensation Reaction of Malononitrile, Various Aldehydes and Barbituric Acid Derivatives Using Boric Acid Aqueous Solution System Compared with Nano-titania Sulfuric Acid

Ardeshir Khazaei,[a]* Heidar Ali Alavi Nik[a] and Ahmad Reza Moosavi-Zare[b]*
[a]*Faculty of Chemistry, Bu-Ali Sina University, Hamedan, 6517838683, Iran*
[b]*Department of Chemistry, University of Sayyed Jamaleddin Asadabadi, Asadabad, 6541835583, Iran*

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Nano-titania sulfuric acid (TSA) and boric acid [$B(OH)_3$] were efficiently utilized for domino Knoevenagel-Michael-cyclocondensation reaction of malononitrile, various aldehydes and barbituric acid derivatives to synthesis of pyrano[2,3-d]pyrimidine diones. It is interesting that in boric acid aqueous solution system, H^+ which abstracted from water by the interaction with $B(OH)_3$, efficiently catalyzed the reaction.

Keywords: Pyrano[2,3-d]pyrimidine dione; Nano-titania sulfuric acid; Boric acid; Barbituric acid; Malononitrile; Aldehyde.

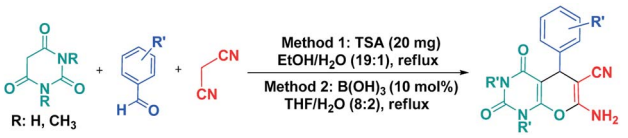
INTRODUCTION

Multi-component reactions (MCRs) achieve significant task in combinatorial chemistry due to the ability to prepare target compounds with more efficiency and atomic economy by the reaction of three or more compounds together in a single step. Moreover, MCRs increase simplicity and synthetic efficiency on the conventional organic transformations.[1–5]

The synthesis of pyrano[2,3-d]pyrimidine dione derivatives is important because of their significant antitumor,[6] antibacterial,[7] antihypertensive,[8] hepatoprotective,[8] cardiotonic,[8] vasodilator,[9] bronchiodilators[9] and antiallergic properties.[10] Moreover, some of them can be widely applied as antimalarial,[11] antifungal,[12] analgesics[13] and herbicidal[14] materials. Several methods have been used for the preparation of pyrano[2,3-d]pyrimidine dione derivatives.[15-27] However, some of them suffer from the drawbacks such as the use of toxic metals, the use of volatile organic solvents, high cost and low yields.

Having the above facts in mind, we have recently successfully synthesized pyrano[2,3-d]pyrimidine dione derivatives via the domino Knoevenagel-Michael-cyclocondensation reaction of malononitrile, various aldehydes and barbituric acid derivatives using nano-titania sulfuric acid and boric acid (Scheme 1).

Scheme 1 The condensation of barbituric acid derivatives, various aldehydes and malonitrile using TSA or $B(OH)_3$.



RESULTS AND DISCUSSION

At first, to optimize the reaction conditions, as model reaction, the condensation of barbituric acid, benzaldehyde and malonitrile was selected as model reaction. Then this reaction was studied under two different conditions. In the first condition, the model reaction was examined in the presence of different amounts of nano-titania sulfuric acid (Nano-TSA) at range of 25 °C to reflux temperature of ethanol and in another condition, the model reaction was tested using different amounts of boric acid [$B(OH_3)$] at range of 25 °C to reflux condition in tetrahydrofuran. The best results were obtained using 20 mg of TSA under reflux condition of aqueous ethanol and 10 mol% of $B(OH)_3$ under reflux condition of aqueous tetrahydrofuran. Increasing the reaction time did not improve the results (Table 1).

In the next step, the model reaction was examined using 20 mg of TSA and 10 mol% of $B(OH)_3$ with various solvents. The results are summarized in Table 2. As can be seen in Table 2, $EtOH/H_2O$ (19:1) and THF/H_2O (8:2) in the presence of TSA and $B(OH)_3$ were the best solvents in this reaction.

To study the generality and scope of the catalysts, we

* Corresponding author. Email: moosavizare@yahoo.com

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Table 1. Effect of different amounts of catalyst and temperature on the reaction between barbituric acid (2 mmol), benzaldehyde (2 mmol), malonitrile (2.2 mmol)

Catalyst	Amount of catalyst	Temp. (°C)	Time (min)	Yield[a] (%)
TSA	10 mg	reflux	90	67
TSA	15 mg	reflux	90	72
TSA	20 mg	reflux	90	88
TSA	30 mg	reflux	90	88
TSA	20 mg	25	90	45
TSA	20 mg	45	90	56
TSA	20 mg	reflux	90	88
$B(OH)_3$	7 mol % (8.5 mg)	reflux	40	60
$B(OH)_3$	10 mol % (12 mg)	reflux	40	79
$B(OH)_3$	12 mol % (14.5 mg)	reflux	40	87
$B(OH)_3$	15 mol % (18 mg)	reflux	40	87
$B(OH)_3$	10 mol % (14.5 mg)	25	40	53
$B(OH)_3$	10 mol % (14.5 mg)	45	40	74
$B(OH)_3$	10 mol % (14.5 mg)	reflux	40	87

[a] Isolated yield.

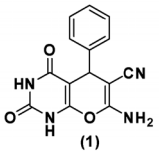
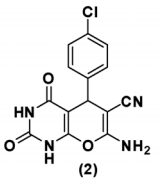
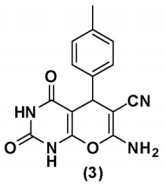
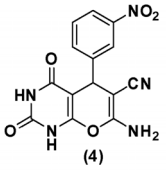
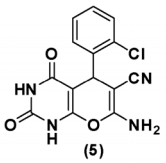
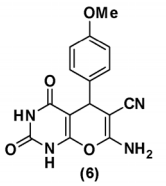
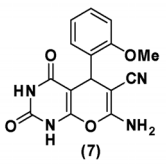
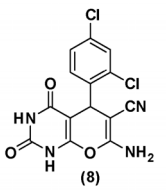
Table 2. Reaction of barbituric acid (2 mmol), benzaldehyde (2 mmol), malonitrile (2.2 mmol) using TSA (20 mg) or $B(OH)_3$ (10 mol%) in different solvents under reflux condition

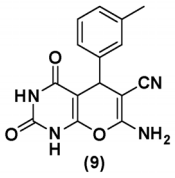
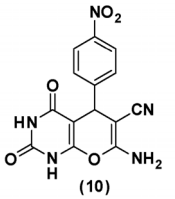
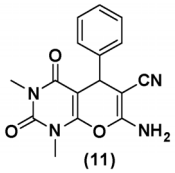
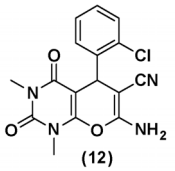
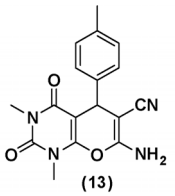
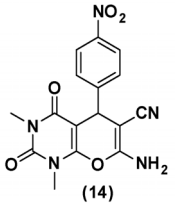
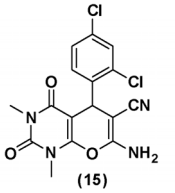
Entry	Catalyst	Solvent	Time (min)	Yield[a] (%)
1	TSA	H_2O	126	34
2	TSA	EtOH/H_2O (19:1)	90	88
3	TSA	EtOH/H_2O (7:3)	98	76
4	TSA	EtOH/H_2O (5:5)	113	58
5	TSA	EtOH/H_2O (2:8)	125	49
6	TSA	CH_3CN	85	82
7	$B(OH)_3$	H_2O	190	25
8	$B(OH)_3$	EtOH/H_2O (19:1)	125	81
9	$B(OH)_3$	EtOH/H_2O (7:3)	156	71
10	$B(OH)_3$	EtOH/H_2O (5:5)	160	52
11	$B(OH)_3$	EtOH/H_2O (2:8)	160	28
12	$B(OH)_3$	CH_3CN	112	48
13	$B(OH)_3$	THF/H_2O (2:8)	40	32
14	$B(OH)_3$	THF/H_2O (5:5)	40	55
15	$B(OH)_3$	THF/H_2O (8:2)	40	87

[a] Isolated yield.

extended our study using [Nano-TSA] (20 mg) and 10 mol% of $B(OH)_3$ in EtOH/H_2O (19:1) and THF/H_2O (8:2) with various aromatic aldehydes to give a series of pyrano[2,3-d]pyrimidine dione derivatives under reflux conditions (Table 3). Various aromatic aldehydes containing electron-with drawing substituents, electron-releasing substituents and halogens on their aromatic rings were utilized successfully in the reaction, and gave the corresponded products in high yields and in short reaction times.

Table 3. The condensation of barbituric acid derivatives (2 mmol), various aldehydes (2 mmol) and malonitrile (2.2 mmol) using TSA (20 mg) or $B(OH)_3$ (10 mol%) under reflux conditions

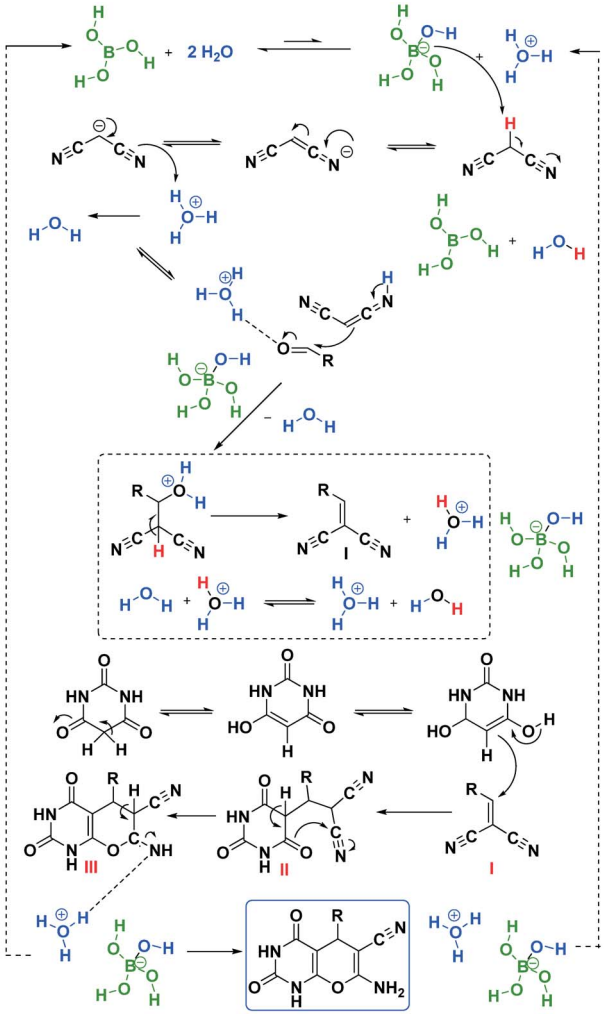
Product	TSA		$B(OH)_3$		Mp °C (Lit.)
	Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)	
 (1)	90	88	125	81	209-211 (208-210) [22]
 (2)	60	89	110	85	235-237 (234-235) [23]
 (3)	150	82	100	89	226 (226-227) [23]
 (4)	60	90	140	65	257-258 (226-255) [23]
 (5)	90	90	73	90	211-214 (213-215) [22]
 (6)	78	82	89	77	280-281 (280-281) [22]
 (7)	59	71	61	67	221-222
 (8)	57	91	57	77	240-242 (242-243) [23]

 (9)	140	53	142	66	226-227 (224-225) [23]
 (10)	100	89	100	89	225-227 (227-228) [23]
 (11)	40	88	41	88	237-238 (260-262) [24]
 (12)	34	82	36	87	242-244 (238-239) [25]
 (13)	47	79	65	82	205-207 (203-204) [26]
 (14)	21	88	25	87	214-216 (212) [27]
 (15)	33	84	55	85	211-212

[a] Isolated yield.

The acidity of aqueous boric acid solution is exclusively due to the interaction of $B(OH)_3$ with water and the attraction of OH^- by boric acid to give $B(OH)^{4-}$ and release of H^+ in the aqueous solution.[28] Therefore in a proposed mechanism that is shown in Scheme 2, at first, malononitrile is reacted to carbonyl group of aldehyde which is activated by produced H^+ and affords to intermediate **I** after removing one molecule of H_2O. Barbituric acid converts to enole form after tautomerisation and attacks to cyanoolefin compound (**I**) as Michael acceptor to give **II**. Finally, cyclocondensation of **II** gives III which is converted to desired product. It is interesting that produced H^+ from water could be successfully catalyzed the reaction. For this purpose, we tested the model reaction in the presence of $B(OH)_3$ and in the absence of solvent. In this condition the yield of product was very low. This observation clearly showed that $B(OH)_3$ could not be catalyzed the reaction lonely. Also, by increasing the water in the reaction media, the yield of the reaction was reduced due to the dissolution of starting materials in water (Table 2). In another method, nano-TSA as a Brønsted acid, by releasing H^+, was efficiently utilized for the synthesis of pyrano[2,3-d]pyrimidine diones with a similar mechanism.

Scheme 2 The proposed mechanism for the synthesis of Pyrano[2,3-d]pyrimidine diones catalyzed by $B(OH)_3$.



EXPERIMENTAL

General: All chemicals were purchased from Merck or Fluka Chemical Companies. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. Nano-titania sulfuric acid (TSA) was prepared according to previous literature.[29] Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were run on a Bruker Avance DPX FT-NMR spectrometer (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the synthesis of pyrano[2,3-d]pyrimidine diones using nano-titania sulfuric acid (TSA) and boric acid solution: A mixture of barbituric acid derivatives (2 mmol), aldehyde (2 mmol), malononitrile (2.2 mmol), nano-titania sulfuric acid (20 mg) and 7 mL EtOH/H_2O (19:1) or boric acid (10 mol%) and 7 mL THF/H_2O (8:2) was added to a 25 mL round-bottomed flask connected to a reflux condenser and stirred in an oil-bath under reflux condition. After completion of the reaction, as monitored by TLC, the reaction mixture was extracted with warm ethanol (10 mL) to separate the catalyst (TSA). Then, the crude product was purified by recrystalization in a mixture of ethanol and water to give the desired product.

CONCLUSIONS

In summary, we have introduced nano-titania sulfuric acid (TSA) and boric acid solution as efficient catalytic systems for the synthesis of pyrano[2,3-d]pyrimidine diones by the domino Knoevenagel-Michael-cyclocondensation reaction of malononitrile, various aldehydes and barbituric acid derivatives. Easy purification, high yields, short reaction times and compliance with green chemistry protocols are some important advantages in this work.

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