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Phenylboronic acid as an efficient and convenient catalyst for a three-component synthesis of tetrahydrobenzo[*b*]pyrans

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ABSTRACT

Phenylboronic acid, a non-toxic compound, is used as catalyst for an efficient, rapid, and one-pot three-component synthesis of tetrahydrobenzo[*b*]pyrans in good to excellent yields. This new procedure has the advantages of operational simplicity, shorter reaction time, higher yields and minimum pollution of the environment.

Mots clés :
Réaction multicomposants
Synthèse en une seule étape
Tetrahydrobenzo[*b*]pyrans
Acide phénylboronique

RÉSUMÉ

L'acide phénylboronique, composé non-toxique, est utilisé comme catalyseur dans une synthèse à composants multiples efficace, rapide et en une seule étape de tétrahydrobenzo[*b*]pyranes avec des rendements bons à excellents. Cette nouvelle approche a les avantages de la simplicité de mise en œuvre, des temps de réaction courts, des rendements élevés et une pollution minimum de l'environnement.

1. Introduction

Benzo[*b*]pyrans and their derivatives constitute an important class of organic compounds due to their attractive pharmacological and biological properties [1,2]. They are widely used as anticoagulant, anticancer, diuretic, spasmolitic and antianaphylactin agents [3,4] and can be used as cognitive enhancers for the treatment of neurodegenerative disease, including Alzheimer's disease, Huntington's disease, Parkinson's disease and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [5,6]. 4*H*-pyrans occur in a series of natural products [7,8] and some of 2-amino-4*H*-pyrans have photochemical activities [9]. Consequently, many methods for the synthesis of these compounds have been reported, including the use of microwave [10], ultrasonic irradiations [11] and a variety of reagents like sodium bromide [10], hexadecyldimethyl benzyl ammonium bromide [12], tetramethyl ammonium hydroxide [13], diammonium hydrogen phosphate [14], fluoride ion [15], magnesium oxide [16], sodium selenate [17], iodine [18], $H_6P_2W_{12}O_{62}.H_2O$ [19], tetrabutylammonium bromide [20], cerium(III) chloride [21], lithium bromide [22], Amberlite IRA-40 (OH^-) [23], acidic ion liquids [24], L-proline [25], ZnO-beta Zeolite [26], trisodium citrate [27], and basic ionic liquids [28].

Arylboronic acids have been used as catalysts in several reactions such as formation of ethers [29], 1,3-transposition of allylic alcohols [30], Diels Alder cycloadditions

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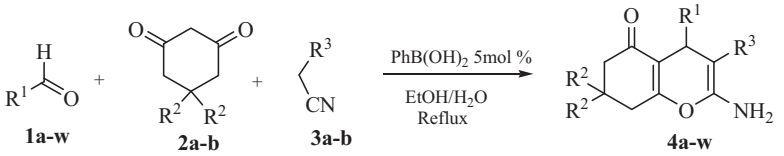


Scheme 1.

[31], [3+2] dipolar cycloaddition [32] and amidation of carboxylic acids [33–35].

Phenylboronic acid, a commercially available material, has been exploited previously by us in Biginelli and Hantzsch three-component reactions [36,37] as a nontoxic, inexpensive, easy handling and mild catalyst. Now we wish to report here the catalytic activity of $PhB(OH)_2$ in the one-pot synthesis of tetrahydrobenzo[*b*]pyrans **4** between aromatic aldehydes **1**, dimedone or 1,3-cyclohexanedione **2** and malonitrile (or ethyl cyanoacetate) **3** in refluxing H_2O/EtOH (Scheme 1).

2. Results and discussion

In order to optimize the conditions, we studied the reaction of benzaldehyde **1a** with dimedone **2a**, malonitrile **3**, and 20 mol % of phenylboronic acid as a simple model substrate in various conditions. First, we tested the effect of various solvents at different temperatures. When using aprotic polar solvent such as CH_3CN, the reaction afforded the corresponding 4*H*-benzopyran **4a** with a modest yield of after 6 h at reflux (Table 1, entry 1). However, the reactions in refluxing protic solvents such as H_2O or EtOH gave better yields (entries 2 and 3); nevertheless, it was not completed even after 3 days at ambient temperature (entry 4). Similarly, the reaction without any solvent at 80 °C was not very successful (entry 5). The 50% aqueous ethanol is proven to be the most suitable solvent for this condensation in terms of yield and reaction time (entry 6).

We also evaluated the amount of phenylboronic acid required for the reaction. It was found that when decreasing the amount of the catalyst from 20 to 10 mol %, the yield increased from 85 to 88% (entry 7). The use of 5 mol% of $PhB(OH)_2$ maintaining the yield at 88%, so this amount is sufficient to promote the reaction. In the presence of more than this amount of the catalyst, neither the yield nor the reaction time were improved (entries 9 and 10). Thus, the best result was obtained with 5 mol % of catalyst in 50% aqueous ethanol at reflux (entry 8).

In comparison with $PhB(OH)_2$, the use of Ph-CH=CH-$B(OH)_2$ as catalyst in the model reaction under refluxing condition showed good catalytic effects and afforded comparable yield of the desired product (entry 11).

In contrast, other Lewis acid catalysts such as $CeCl_3.7H_2O$ gave lower yield (entry 12).

All reactions delivered good to excellent products yields and accommodated a wide range of aromatic aldehydes containing electron-donating and electron-withdrawing groups (entries 1–12) without any significant substituent effect. This three-component condensation reaction also proceeded with heteroaromatic aldehyde, such as 2-furaldehyde and give the corresponding product in high yield (entry 13). The scope of this one-pot reaction was further extended by replacing dimedone **2a** with cyclohexane-1,3-dione **2b** and various highly functionalized 4*H*-benzo[*b*]pyrans were produced in good yields (entries 14–16). However, aliphatic aldehydes such as acetaldehyde, propionaldehyde and isobutyraldehyde needed longer reaction times to provide moderate yields of the corresponding products (entries 17–19).

To assess the generality and versatility of the catalyst, the same reaction conditions as described above were applied for the synthesis of ethyl 2-amino-4*H*-benzo[*b*]-pyrans-3-carboxylate by replacing malonitrile **3a** with ethyl cyanoacetate **3b**. The expected compounds were then obtained in good yields (entries 20–21).

In all cases, the final products were isolated by simple filtration, washed with cold water and purified by recrystallization from ethanol[1].

We propose the following mechanism to account for the reaction. We checked that, at reflux for 30 min in EtOH/H_2O (1/1) without phenylboronic acid, malonitrile reacts quite quantitatively with aromatic aldehyde **1** in a Knoevenagel transformation, while only small amounts of **4** was produced in such conditions. 1,3-Dicarbonyl compound would be therefore first activated by phenylboronic acid to give a boron enolate **2'**. Addition to

[1] *General procedure to synthesis of tetrahydrobenzo[b]pyran derivatives* **4** *using* $PhB(OH)_2$ *as catalyst*: a mixture of aldehyde (1 mmol), cyclohexane-1,3-dione or dimedone (1 mmol), malonitrile or ethyl cyanoacetate (1 mmol) and phenylboronic acid (5 mol%) in 6 ml of EtOH/H_2O (v:v:1:1) was refluxed for 30 min (the reaction was monitored by TLC). After completion of the reaction, the mixture was cooled to room temperature and cold water was added and stirring was continued for 10 min. The crude products were filtered, washed with water and recrystallized from ethanol (95%) to afford pure products which were identified by IR, ^{1}H NMR, ^{13}C NMR and melting points. Spectral data for:

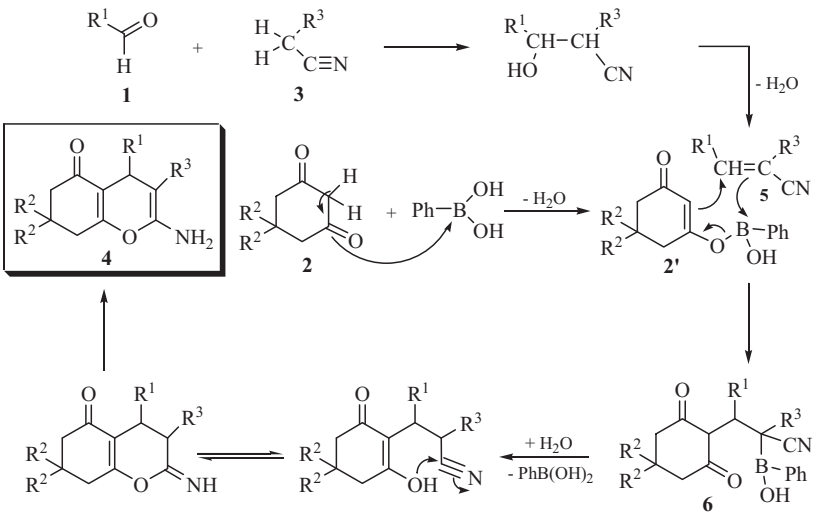
2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-benzopyran-3-carbonitrile (4a). IR (KBr, cm^{-1}) ν: 3402, 2966, 2195, 1651, 1369; ^{1}H NMR (250 MHz, DMSO-d_6) δ: 7.37–7.24 (m, 2H), 7.21–7.13 (m, 3H), 7.03 (s, 2H, NH_2), 4.18 (s, 1H), 3.37 (s, 2H), 2.23 (d, J = 16.1HZ, 1H), 2.13 (d, J = 16.1 Hz, 1H), 1.05 (s,3H), 0.96 (s, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 195.6, 162.5, 158.5, 144.7, 128.3, 127.1, 126.5, 119.7, 112.7, 58.2, 50.0, 38.7, 35.6, 31.4, 28.4, 26.8. **2-Amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran-3-carbonitrile (4o)**. IR (KBr, cm^{-1}) ν: 3384, 2982, 2195, 1690, 1516, 1346; ^{1}H NMR (250 MHz, DMSO-d_6) δ: 8.10 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 6.63 (s, 2H, NH_2), 4.37 (s, 1H), 3.28 (s, 2H), 2.60–2.51 (m, 2H), 2.27–2.24 (m, 2H), 2.05–1.85 (m, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 196.0, 164.8, 158.9, 152.0, 146. 6, 128.7, 123.6, 119.54, 113.6, 57.8, 39.6, 36.6, 35.9, 27.1, 20.1.

2-Amino-7,7-dimethyl-4-ethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran-3-carbonitrile (4s). IR (KBr, cm^{-1}) ν: 3417, 2191, 1654, 1380; ^{1}H NMR (250 MHz, DMSO-d_6) δ: 6.16 (s, 2H), 3.20 (t, J = 4.4 Hz, 1H), 2.31 (s, 2H), 2.17 (s, 2H), 1.53–1.38 (m, 2H), 1.03 (s, 3H), 1.01 (s, 3H), 0.69 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 201.30, 168.06, 164.90, 125.05, 117.63, 61.31, 55.50, 36.70, 35.08, 33.87, 32.71, 32.09, 31.77.

Table 1
Optimization of the reaction using different conditions.[a]

Entry	Solvent	Catalyst (mol %)	Time (h)	Temperature (°C)	Yield[b] (%)
1	CH_3CN	$PhB(OH)_2$ 20	6	Reflux	38
2	H_2O	$PhB(OH)_2$ 20	1	Reflux	75
3	EtOH	$PhB(OH)_2$ 20	3	Reflux	61
4	EtOH	$PhB(OH)_2$ 20	72	Ambient	10
5	None	$PhB(OH)_2$ 20	6	80	54
6	$EtOH/H_2O$	$PhB(OH)_2$ 20	0.5	Reflux	85
7	$EtOH/H_2O$	$PhB(OH)_2$ 10	0.5	Reflux	88
8	$EtOH/H_2O$	$PhB(OH)_2$ 5	0.5	Reflux	88
9	$EtOH/H_2O$	$PhB(OH)_2$ 50	0.5	Reflux	83
10	$EtOH/H_2O$	$PhB(OH)_2$ 100	0.5	Reflux	83
11	$EtOH/H_2O$	Ph-CH=CH-$B(OH)_2$ 5	0.5	Reflux	85
12	$EtOH/H_2O$	$CeCl_3.7H_2O$ 5	0.5	Reflux	57

[a] The reactions were conducted by condensation of benzaldehyde **1a** (1 equiv.), dimedone **2a** (1 equiv.), and malonitrile **3** (1 equiv.).
[b] Isolated yields.



Scheme 2.

Table 2
Synthesis of tetrahydrobenzo[*b*]pyrans **4a–w** by condensation of aldehydes, malonitrile or ethyl cyanoacetate and dimedone or 1,3-cyclohexanedione using $PhB(OH)_2$ as catalyst in refluxing H_2O:EtOH (1:1).

Entry	R^1	R^2	R^3	Time (h)	Product	Yield (%)[a]	Mp (°C) Measured	Mp (°C) Reported
1	C_6H_5	Me	CN	0.5	**4a**	88	236–238	234–235 [15]
2	4-Me-C_6H_4	Me	CN	0.5	**4b**	65	215–218	210–212 [13]
3	4-MeO-C_6H_4	Me	CN	0.5	**4c**	87	204–205	200–201 [26]
4	2-MeO-C_6H_4	Me	CN	0.5	**4d**	81	194–196	195–197 [38]
5	4-(NO_2)-C_6H_4	Me	CN	0.5	**4e**	88	180–182	177–178 [26]
6	3-(NO_2)-C_6H_4	Me	CN	0.5	**4f**	85	210–212	213–215 [16]
7	4-(OH)-C_6H_4	Me	CN	0.5	**4g**	84	216–218	213–214 [26]
8	4-(Br)-C_6H_4	Me	CN	0.5	**4h**	86	199–200	207–208 [26]
9	4-(Cl)-C_6H_4	Me	CN	0.5	**4i**	84	207–209	209–210 [26]
10	3-(Cl)-C_6H_4	Me	CN	0.5	**4j**	70	228–229	230–232 [13]
11	4-Me_2N-C_6H_4	Me	CN	0.5	**4k**	86	218–220	217–218 [15]
12	C_6H_5-CH=CH-	Me	CN	0.5	**4l**	74	208–210	205–207 [39]
13	2-Furyl	Me	CN	0.5	**4m**	85	222–224	226–228 [15]
14	4-MeO-C_6H_4	H	CN	0.5	**4n**	72	198–200	190–192 [16]
15	4-(NO_2)-C_6H_4	H	CN	0.5	**4o**	76	240–241	235–237 [16]
16	4-(Cl)-C_6H_4	H	CN	0.5	**4p**	61	229–230	225–227 [16]
17	CH_3	Me	CN	2	**4q**	43	177–179	171–173 [40]
18	CH_3CH_2	Me	CN	2	**4r**	41	193–194	190–194 [17]
19	$(CH_3)_2CH$	Me	CN	2.5	**4s**	38	154–156	156–157 [40]
20	3-(NO_2)-C_6H_4	Me	CO_2Et	1	**4t**	80	170–172	179–181 [13]
21	4-(Cl)-C_6H_4	Me	CO_2Et	1	**4u**	65	155–157	157–159 [13]

[a] The reaction was conducted in a non-toxic conditions.

arylidenemalonitrile **5** would lead to the formation of **6**. After a spontaneous deborylation that usually occurs when a boronated group is in an α-position to a cyano or keto group, tautomerism and intramolecular cyclization afforded the final product **4** (Scheme 2).

With the above results, we can realize that the phenylboronic acid catalyses only the second step of the reaction (Table 2).

3. Conclusion

In conclusion, we have reported an easy, convenient, inexpensive and friendly environmental synthetic approach for the preparation of tetrahydrobenzo[*b*]pyrans catalyzed by $PhB(OH)_2$ using a three-component condensation in aqueous ethanol. This procedure offers advantages like high yields, operational simplicity, non-toxic catalyst and solvents, short reaction time and minimum pollution of the environment, which makes it a useful and attractive process for the preparation of these compounds.

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