J. Chem. Sci. Vol. 125, No. 4, July 2013, pp. 745–749.

Phenylboronic acid catalysed synthesis of 1,5-benzodiazepines via cyclocondensation of *o*-phenylenediamine and ketones

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MS received 28 November 2012; revised 27 January 2013; accepted 1 March 2013

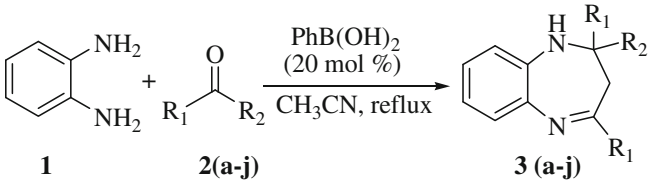
Abstract. Phenylboronic acid has been found to be an efficient catalyst for the synthesis of 1,5-benzodiazepine derivatives via cyclocondensation of *o*-phenylenediamine and various ketones in good to excellent yields (82–91%) using acetonitrile as solvent at reflux condition. The remarkable advantages offered by this method are easy mild reaction condition, experimental work up and good to excellent yields of products.

Keywords. Phenylboronic acid; o-phenylenediamine; ketones; 1,5-benzodiazepines.

1. Introduction

Benzodiazepine is significant class of biologically active compounds and gaining great consideration in the field of medicinal and pharmaceutical chemistry due to their application as anticonvulsant, antiinflammatory, analgesic, sedative agents and hypnotic activity.[1–5] The 1,5-benzodiazepine derivatives are also employed as dyes for acrylic fibers in photography.[6] Moreover benzodiazepines are effective precursors for the synthesis of other fused ring compounds such as triazolo, oxadiazolo, oxazino or furano-benzodiazepines.[7–10] In general, cyclocondensation of *o*-phenylenediamines with carbonyl compounds is one of the conventional synthetic methods for the synthesis of 1,5-benzodiazepine derivatives.[11]

A variety of catalysts, such as $CeCl_3$-NaI/SiO_2,[12] SmI_2,[13] $YbCl_3$,[14] MgO/$POCl_3$,[15] zeolites,[16] $Ga(OTf)_3$,[17] Amberlyst-21-$Yb(OPf)_3$,[18] $Ag_3PW_{12}O_{40}$,[19] boric acid,[20] fluorous aqueous emulsion[21] FeAlP–550,[22] iodine,[23] Ytterbium perfluorooctanesulphonate [$Yb(OPf)_3$],[24] 2,4,6-Trichloro-1,3,5-triazine[25] and multicite solid catalyst[26] have been utilized for this synthesis. However, these protocols are related with some disadvantages like hazardous reaction condition, extended reaction time and also use of harmful catalyst and organic solvent. Since, 1,5-benzodiazepines having great significance in pharmaceutical and medicinal fields. Thus, there is still necessity to develop an efficient protocol for the synthesis of 1,5-benzodiazepines. Recently boronic acids have been employed as an efficient Lewis acid catalyst in synthetic organic chemistry.[27–34] Herein we describe the use of phenylboronic acid as Lewis acid catalyst for the synthesis of 1,5-benzodiazepine derivatives. This transformation was performed by condensation reaction of *o*−phenylenediamine and ketones in the presence of catalytic amount of phenylboronic acid in acetonitrile solvent under reflux condition (scheme 1).



Scheme 1. Synthesis of 1,5-benzodiazepines via condensation of *o*-phenylenediamine with ketone.

2. Experimental

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 × 20 cm, Silica gel 60 $F_{254,}$ Merck grade was used for thin-layer chromatography (TLC) to determine progress of reaction. Column chromatography was carried out over silica gel (80–120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker–300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. ^{13}C NMR

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spectra were recorded on a Bruker–300 MHz spectrometer using $CDCl_3$ as solvent. Mass spectra were taken on Polaris-Q Thermo–scientific GC–MS.

2.1 *General procedure for the synthesis of derivatives (**3a–j**)*

A mixture of *o*-phenylenediamine (1 mmol), ketones (2.5 mmol) and phenylboronic acid (20 mol%) in acetonitrile solvent (15 mL) was refluxed for the appropriate (see table 2). After completion of reaction indicated by TLC (pet ether: ethyl acetate 8:2), the reaction mixture was diluted with 10 mL water and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained product was purified by column chromatography using silica gel mesh 80–120 to afford the pure product.

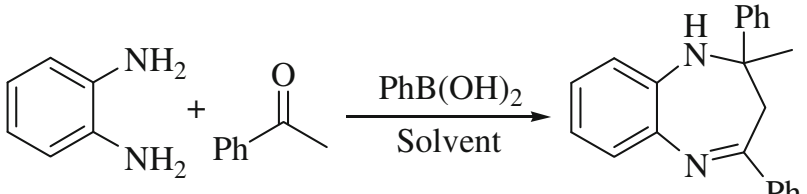
2.2 *Characterization*

2.2a *2,3-Dihydro-2,2,4-trimethyl-1H-benzo-[1,4]diazepine (**3a**)*: Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 6H), 2.46 (s, 2H), 2.68 (s, 3H), 3.10 (br s, 1H, NH), 6.72-7.10 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 30.8, 33.5, 43.6, 66.4, 118.4, 122.6, 127.2, 128.8, 135.7, 142.1, 170.3; GC-MS, *m/z*: 188 (M+).; Elemental Analysis: Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88; Found C, 76.52; H, 8.59; N, 14.84.

2.2b *2,3-dihydro-2-methyl-2,4-diphenyl-1H-benzo-[1,4]diazepine (**3c**)*: Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3H), 3.14 (s, 2H), 3.60 (br s, 1H, NH), 6.72-7.14 (m, 2H), 7.30–7.49 (m, 10H), 7.64–7.74 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 32.3, 44.2, 72.5, 122.5, 123.8, 125.9, 127.8, 128.2, 128.9, 130.0, 130.6, 131.2, 132.5, 137.5, 139.8, 142.1, 147.2, 168.3; GC-MS, *m/z*: 312 (M+); Elemental Analysis: Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found C, 84.55; H, 6.47; N, 8.94.

2.2c *10-Spirocyclohexan-2,3,4,10,11,11a-hexahydro-1H-dibenzo[1,4]diazepine (**3j**)*: Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02–2.49 (m, 17H), 3.15(m, 2H), 3.54 (br s, 1H, NH), 6.89–7.42 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 22.3, 22.8, 23.9, 24.3, 24.9, 26.8, 34.5, 35.4, 39.9, 42.4, 55.2, 65.6, 122.4,

Table 1. Effect of solvent and catalytic loading on synthesis of 1,5-benzodiazepines under different condition.[a]



1 **2c** **3 c**

Entry	Solvent	Ph-B(OH)$_2$ (mol %)	RT/reflux	Time (h)	Yield (%)[b]
1	Ethanol	10	RT	16	68
2	Ethanol	10	Reflux	17	64
3	Water	10	Reflux	24	52
4	Acetonitrile	10	RT	14	72
5	Acetonitrile	10	Reflux	14	78
6	Chloroform	10	RT	24	42
7	Dichloromethane	10	Reflux	28	38
8	MeOH	10	Reflux	16	65
9	Acetonitrile	5	Reflux	18	68
10	Acetonitrile	15	Reflux	12	80
11	Acetonitrile	20	Reflux	10	89
12	Acetonitrile	30	Reflux	10	85
13	Acetonitrile	50	Reflux	10	88
14	Acetonitrile	0	Reflux	30	Trace

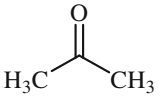
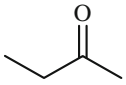
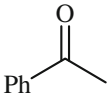
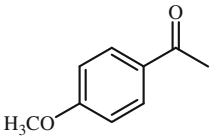
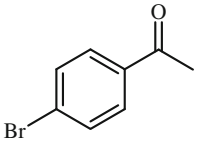
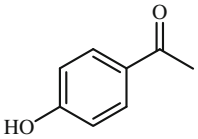
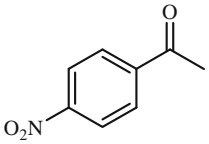
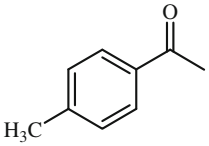
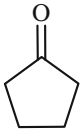
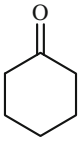
[a]Conditions: *o*-phenylenediamine (1 mmol), acetophenone (2.5 mmol), solvent (15 ml). Reaction was monitored by TLC
[b]Isolated yield
RT: Room temperature

127.5, 130.5, 139.7, 144.3, 176.4; GC-MS, *m/z*: 268 (M+); Elemental Analysis: Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44; Found C, 80.53; H, 9.04; N, 10.48.

3. Results and discussion

In continuation of our interest in synthesis of heterocycles using boronic acids,[35–37] herein we explain the

Table 2. Synthesis of 1,5-benzodiazepines catalysed by phenylboronic acid.[a]

S No.	Ketones	Product	Time (h)	Mp. (Lit. Mp.)	Yield (%)[b]
1	 2a	**3a**	10	142 (139-141)	89
2	 2b	**3b**	10	136-138(138-139)	87
3	 2c	**3c**	12	150 (150-151)	89
4	 2d	**3d**	11	119 (117)	91
5	 2e	**3e**	12	148 (146)	82
6	 2f	**3f**	10	218-220 (217)	88
7	 2g	**3g**	13	155-157(157)	84
8	 2h	**3h**	10	98-100 (99)	90
9	 2i	**3i**	12	137 (137-139)	82
10	 2j	**3j**	13	136(137-138)	85

[a]Conditions: *o*-phenylenediamine (1 mmol), ketone (2.5 mmol), phenylboronic acid (20 mol%) acetonitrile (15 mL). Reaction was monitored by TLC

[b]Isolated yield

synthesis of 1,5-benzodiazepine derivatives. The synthesis of this heterocycles was accomplished by condensation reaction of *o*-phenylenediamine and ketones in the presence of catalytic amount of phenylboronic acid in acetonitrile solvent under reflux condition.

Initially we studied the effect of solvent and catalytic loading on the synthesis of 1,5-benzodiazepine derivatives under different condition using model reaction of *o*−phenylenediamine and acetophenone. In the initial stage, for the optimization of suitable condition a model reaction screened using different solvent at room temperature and reflux condition to check the effectiveness of phenylboronic acid (10 mol%). The results are summarized in table 1 (entry 1–12). In the solvent ethanol, reaction was completed within 16 h at room temperature and 17 h at reflux condition but the product yield was not meeting our expectations (table 1, entry 1 and 2, respectively). In the solvent water, 52% yield was observed at reflux condition after 24 h. Satisfactorily yield (78%) was observed when reaction was carried out in acetonitrile solvent at reflux condition (table 1, entry 5). Moreover the reaction in solvents chloroform, dichloromethane needed more reaction time and gave low yield 42 and 38%, respectively (table 1, entry 6 and 7, respectively) and in the solvent methanol 65% yield of desired product was obtained after 16 h. So we continued our investigation in the solvent acetonitrile at reflux condition.

Further, we examined the effect of catalytic loading on the model reaction to get the excellent yield of desired product **3c**. At the catalytic loading 5 mol% and 15 mol%, reaction afforded 68% and 80% yield, respectively (table 1, entry 9 and 10, respectively). The excellent result for the reaction was offered at the catalytic loading 20 mol% of the catalyst phenylboronic acid. The reaction was completed within 10 h and offered the desired product **3a** in excellent yield 89% (table 1, entry 11). Further, increasing the catalytic loading up to 50 mol% did not show any enhancement in the progress of reaction time and yield of desired product (table 1, entry 12 and 13).

To test the significance of phenylboronic acid as catalyst, reaction was carried out in the absence of catalyst. We noticed that, trace amount of yield was observed after 30 h (table 1, entry 14).

Under the optimized reaction conditions, different ketones were allowed to react with *o*-phenylenediamine. All the reactions proceeded efficiently with wide range of ketones affording good to excellent yield of the corresponding products (table 2). Cyclic ketones such as cyclopentanone and cyclohexanone also reacted effectively to produce the corresponding fused ring benzodiazepines (table 2, entry 9 and 10, respectively). The results are listed in (table 2).

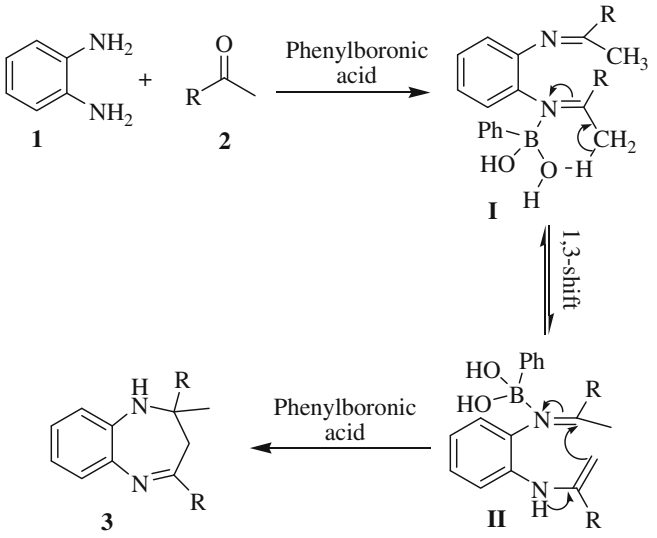


Figure 1. Plausible mechanism for synthesis of 1,5-benzodiazepines.

A plausible mechanism for the formation of 1,5-benzodiazepine is shown in figure 1. Amino groups of *o*-phenylenediamine attack carbonyl group of ketone in the presence of phenylboronic acid, giving the intermediate diimine **I**. Then, 1,3-shift of the hydrogen attached methyl group occurs to afford an intermediate enamine **II,** which cyclizes to produce desired product 1,5-benzodiazepine **3**.

4. Conclusion

In conclusion, we have presented simple and facile method for the synthesis of 1,5-benzodiazepine derivatives by cyclocondensation of *o*-phenylenediamine and ketones using phenylboronic acid as catalyst in acetonitrile solvent under reflux condition. This transformation was successfully studied for different range of ketones. The mild reaction condition, easy experimental operation and good to excellent yield with a wide range of ketones are some of the striking features of this protocol.

Acknowledgements

We thank Dr. P L More and Dr. W N Jadhav, Dnyanopasak College, Parbhani for providing necessary facilities and financial support for this work by DST-SERC, New Delhi (SR/FT/CS-023/2008) is highly appreciated.

References

1. de Baun J R, Pallos, F M and Baker D R 1977 *Chem. Abstracts* **86** 5498

2. Schultz H 1982 *Benzodiazepines* (Heidelberg: Springer)
3. Smiley R K 1979 *Comprehensive organic chemistry* (Oxford: Pergamon)
4. Landquist J K 1984 *Comprehensive heterocyclic chemistry*, vol. 1 (Oxford: Pergamon)
5. Randall L O, Kappel B Garattini S and Mussini E 1973 *Pharmacological activity of some benzodiazepines and their metabolites*, in *Benzodiazepines*, (eds) (New York: Raven)
6. Haris R C and Straley J M 1968 *US Patent* 1, 537, 757
7. El-Sayed A M, Abdel-Ghany H and El-Saghier A M M 1999 *Synth. Commun.* **29** 3561
8. Xu J X, Wu H T and Jin S 1999 *Chin. J. Chem.* **17** 84
9. Zhang X Y, Xu J X and Jin S 1999 *Chin. J. Chem.* **17** 404
10. Kim K, Volkman S K and Ellman J A 1998 *J. Braz. Chem. Soc.* **9** 375
11. Ried W and Torinus E 1959 *Chem. Ber.* **92** 2902
12. Sabitha G, Reddy G S, Reddy K B, Reddy N M and Yadav J S 2004 *Adv. Synth. Catal.* **346** 921
13. Luo Y Q, Xu F, Han X Y and Shen Q 2005 *Chin. J. Chem.* **23** 1417
14. Wu J T, Xu F, Zhou Z Q and Shen Q 2006 *Synth. Commun.* **36** 457
15. Balakrishna M S and Kaboundin B 2001 *Tetrahedron Lett.* **42** 1127
16. Tajbakhsh M, Heravi M M, Mohajerani B and Ahmadia A N 2006 *J. Mol. Catal. A: Chem.* **247** 213
17. Pan X Q, Zou J P, Huang Z H and Zhang W 2008 *Tetrahedron Lett.* **49** 5302
18. Tao F and Yi W B 2008 *Lett. Org. Chem.* **5** 655
19. Yadav J S, Reddy B V S, Praveenkumar S, Nagaiah K, Lingaiah N and Saiprasad P S 2004 *Synthesis* **6** 901
20. Zhou X, Zhang M Y, Gao S T, Ma J J, Wang C and Liu C 2009 *Chin. Chem. Lett.* **20** 905
21. Yi W B and Cai C 2009 *J. Fluorine Chem.* **130** 1054
22. Vijayasankar A V, Deepa S, Venugopal B R and Nagaraju N 2010 *Chin. J. Catal.* **31** 1321
23. Bandgar B P, Bettigeri S V and Joshi N S 2004 *Synth. Commun.* **34** 1447
24. Yi W and Cai C 2007 *Synth. Commun.* **37** 3827
25. Kuo C W, Wang C C, Kavala V and Yao C F 2008 *Molecules* **13** 2313
26. Climent M J, Corma A, Iborra S and Santos L L 2009 *Chem. A Eur. J.* **15** 8834
27. Zheng H and Hall D G 2010 *Tetrahedron Lett.* **51** 3561
28. Frutos R P, Tampone T, Mulder J A, Xu Y, Reeves D, Wang X-J, Zhang L, Krishnamurthy D and Senanayake C H 2011 *Tetrahedron Lett.* **52** 2465
29. Tale R H and Adude R N 2006 *Tetrahedron Lett.* **47** 7263
30. McCubbin J A, Hosseini H and Krokhin O V 2010 *J. Org. Chem.* **75** 959
31. Sridhar R and Perumal P T 2005 *Tetrahedron* **61** 2465
32. Debache A, Boumoud B, Amimour M, Belfaitah A, Rhouatia S and Carbonib B 2006 *Tetrahedron Lett.* **47** 5697
33. Lopez-Ruiz H, Briseno-Ortega H, Rojas-Lima S, Santillan R and Farfan N 2011 *Tetrahedron Lett.* **52** 4308
34. Tibhe G D, Bedolla-Medrano M, Cativiela C and Ordonez M 2012 *Synlett* **23** 1931
35. Goswami S V, Thorat P B and Bhusare S R 2012 *Tetrahedron Lett.* **53** 6771
36. Goswami S V, Thorat P B and Bhusare S R 2012 *Heterocycl. Commun.* **18** 245
37. Adude R N, Tigote R M, Goswami S V and Bhusare S R 2012 *Int. J. Ind. Chem.* **3** 6