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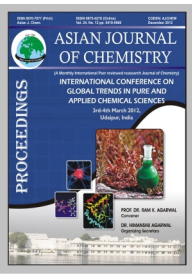

A Simple, Efficient and Eco-Friendly Synthesis of 2,3-Dihydro-1*H*-1,5-benzodiazepines Mediated by Tannic Acid under Solvent-Free Condition†

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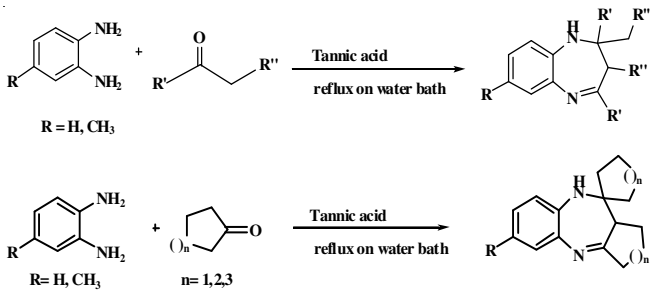
A rapid and efficient environment friendly multicomponent one-pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines catalyzed by tannic acid has been described under solvent free condition. Simple and effective method, use of non-hazardous and cheap catalyst, much faster reaction time (50-60 min) and good to excellent yields are the important features of this method.

Key Words: One-pot synthesis, 1,5-Benzodiazepines, Tannic acid.

INTRODUCTION

Multicomponent reactions are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product[1]. Multicomponent reactions are a promising and vital field of chemistry because the complicated molecules can be synthesized in a very fast, efficient and time saving manner without the isolation of any intermediate[2].

Benzodiazepines are widely used class of bioactive compounds due to their remarkable biological and pharmacological properties[3,4]. They are well documented for antianxiety, hypnotic, tranquilizing, antiinflammatory, anticonvulsant, antifeedant, antibacterial, analgesic, sedative and anti-depressive properties[3]. They are also commercially employed as dyes for acrylic fibers and as an antiinflammatory agent[3-5]. Recently, their use has been extended to various diseases such as cancer, viral infections (non-nucleoside inhibitors of HIV-1 reverse transcriptase) and cardiovascular diseases[6]. Additionally, they are valuable synthons for the synthesis of various fused ring benzodiazepine derivatives such as triazolo[7], oxadiazolo[8], oxazino[9] and furano-benzodiazepines[10]. Because of this unique position in synthetic as well as medicinal chemistry, there have been intensive searches for their efficient and facile synthesis. One established method for the production of these molecules seems to be condensation of 1,2-diamines with ketones in the presence of various catalysts such as silica sulfuric acid[11], sulfanilic acid[12], sulfamic acid[13], tetranitrile-silver complex[14], I_2[15], iron aluminophosphate[16], sodium tetrachloroaurate(III) dehydrate[17], polyethylene glycol[18], $AlCl_3$[19] *etc*. However, in spite of their utility, many of these methods suffer major or minor limitations like tedious work up procedure, the necessity of neutralization of strong acidic media, producing undesired washes, application of expensive and hazardous catalyst and reagents, long reaction times, unsatisfactory yields, separation of the catalyst from the product and formation of side products.



Scheme-I: Chemical reaction for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines using tannic acid

Tannic acid is a specific commercial form of tannin, a type of polyphenol. It is non-toxic pharmacognostic product which has never been used as reaction mediator in chemistry. Its weak acidity (pK_α around 6) is due to the numerous phenol groups in the structure. In chemistry, tannic acid is used in the conservation of ferrous (iron based) metal objects to passivate and inhibit corrosion. It also finds use as a natural clarifying agent, colour stabilizer and taste enhancer. People apply tannic

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acid directly to the affected area to treat cold sores and fever blisters, skin rashes and to stop bleeding. Tannic acid is also taken by mouth for chronic diarrhoea, dysentery, bloody urine, painful joints, persistent coughs and cancer.

EXPERIMENTAL

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (^{1}H) nuclear magnetic resonance spectra were obtained using Brucker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane as internal standard Infrared spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using potassium bromide pellets (cm^{-1}). Elemental analyses for C, H and N were performed on Perkin-Elmer 2400 CHN elemental analyzer. Reactions were monitored and the homogeneity of the products was checked by TLC, which were prepared with silica gel G and activated at 110 ºC for 0.5 h. The plates were developed by exposure to iodine vapours. Anhydrous sodium sulphate was used as drying agent.

General procedure for the preparation of 2,3-dihydro-1*H*-1,5-benzodiazepines: *ortho*-Phenylenediamine (1 mmol) and tannic acid (2 mol % or 0.02 mmol) were crushed in mortar and pestle to a fine powder and transferred to round bottom flask and various ketone (2.2 mmol) was added. Reaction mixture was refluxed on water bath for 50-60 min with occasional stirring. After completion of the reaction [monitored *via* TLC using $CHCl_3$ and MeOH (9.5:0.5 mL) as eluent], the reaction mass was poured into crushed ice and basified with ammonia solution, if required. The precipitated solid was separated, washed thoroughly with water and dried. The residue was recrystallized from ethanol or subjected to column chromatography to get the pure product/s.

2,3-Dihydro-2-methyl- 2,4-diphenyl-1*H*-1,5-benzodiazepine: (Entry 1): IR (KBr, ν_{max}, cm^{-1}): 3277 (sec N-H), 3061 (aromatic C-H), 2972 (aliphatic C-H), 1559 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 1.8 (s, 3H, $-CH_3$), δ 3.1 (d, 1H, -CH), δ 3.2 (d,1H, -CH), δ 6.8-7.7 (m, 14H, ArH); Anal. calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found: C, 84.60; H, 6.42; N, 8.94.

2,2,4- Trimethyl- 2,3-dihydro -1*H*-1,5-benzodiazepine: (Entry 2): IR (KBr, ν_{max}, cm^{-1}): 3292 (NH), 2955 (aromatic CH), 1632 (alkene C=C), 1474 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 6H, $-C(CH_3)_2$), δ 2.2 (s, 2H, $-CH_2$), δ 2.4 (s, 3H, $-CH_3$), δ 6.7-7.2 (m, 4H, ArH); Anal. calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88; Found: C, 76.51; H, 8.52; N, 14.92.

2,4- Dimethyl-2-ethyl-2,3-dihydro-1*H*-1,5-benzodiazepine: (Entry 3): IR (KBr, ν_{max}, cm^{-1}): 3339 (sec N-H), 3058 (aromatic C-H), 2968 (aliphatic C-H), 1639 (C=N), 1472 (aromatic C=C), 1253 (C-N); ^{1}H NMR ($CDCl_3$): δ 0.8 (t, 3H, $-CH_3$), δ 1.3 (t, 3H, $-CH_3$), δ 1.3 (s, 3H, $-CH_3$), δ 1.7 (q, 2H, $-CH_2$), δ 2.2 (m, 2H, $-CH_2$), δ 2.6 (q, 2H, $-CH_2$), δ 3.3 (brs, 1H, NH), δ 6.5-7.3 (m, 4H, ArH); Anal. calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.88; N, 13.85; Found: C, 77.25; H, 8.88; N, 14.01.

11-Spirocyclocyclohexane-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[b,e][1,4] diazepine: (Entry 4): IR (KBr, ν_{max}, cm^{-1}): 3279 (sec. NH), 3059 (aromatic CH), 2859 (alkane CH), 1635 (imine C=N), 1481 (aromatic C=C), 751 (*ortho*-substitutedoop); ^{1}H NMR ($CDCl_3$): δ 1.2-1.9 (m, 16H, $-CH_2$), δ 2.3-2.6 (m, 3H, -CH), δ 4.5 (1H, br, NH), δ 6.8-7.9 (m, 4H, ArH); Anal. calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44; Found: C, 80.62; H, 9.05; N, 10.54.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[b]cyclohepta[e][1,4]diazepine: (Entry 5): IR (KBr, ν_{max}, cm^{-1}): 3328 (*sec*. NH), 3060 (aromatic CH), 2923 (alkene CH), 2852 (alkane CH), 1617 (imine C=N), 1493 (aromatic C=C). ^{1}H NMR ($CDCl_3$): δ 1.5-2.4 (m, 21H, $-CH_2$, -NH), δ 2.6 (m, 2H, $-CH_2$), δ 2.8 (m, 1H, -CH), δ 6.6-7.4 (m, 4H, ArH); Anal. calcd. for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45; Found: C, 81.15; H, 9.56; N, 9.54.

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine:(Entry 6): IR (KBr, ν_{max}, cm^{-1}): 3454 (sec. NH), 2924 (aromatic CH), 2854 (alkane CH), 1437 (aromatic C=C), 1237 (C-N), 946 (1,2,4-substituted oop); ^{1}H NMR ($CDCl_3$): δ 1.2 (s, 6H, $-CH_3$), δ 1.35 (s, 3H, $-CH_3$), δ 2.3 (m, 5H, $-CH_3$, -CH, -CH), δ 6.5 (s, 1H, ArH), δ 6.79 (d, 1H, *J* = 7.4, ArH), δ 7.0 (d, 1H, *J* = 8.7, ArH); Anal. calcd. for $C_{18}H_{13}N_2$: C, 77.17; H, 8.97; N, 13.85; Found: C, 77.22; H, 8.91; N, 13.93.

2,3-Dihydro-2,8- dimethyl- 2,4- diphenyl-1*H*-1,5-benzodiazepine: (Entry 7): IR (KBr, ν_{max}, cm^{-1}): 3335 (sec. NH), 3058 (aromatic CH), 2970 (alkene CH), 2858 (alkane CH), 1613 (imine C=N), 1493 (aromatic C=C), 1328 (C-N), 759 (*Ortho* substituted oop); ^{1}H NMR($CDCl_3$): δ 1.75 (s, 3H, $-CH_3$), δ 2.6 (br, 4H,$-CH_3$, -NH), δ 2.9 (d, 1H, -CH), δ 3.1 (d, 1H, -CH), δ 7.2-7.9 (m, 14H, ArH); Anal. calcd. for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58; Found: C, 84.68; H, 6.84; N, 8.45.

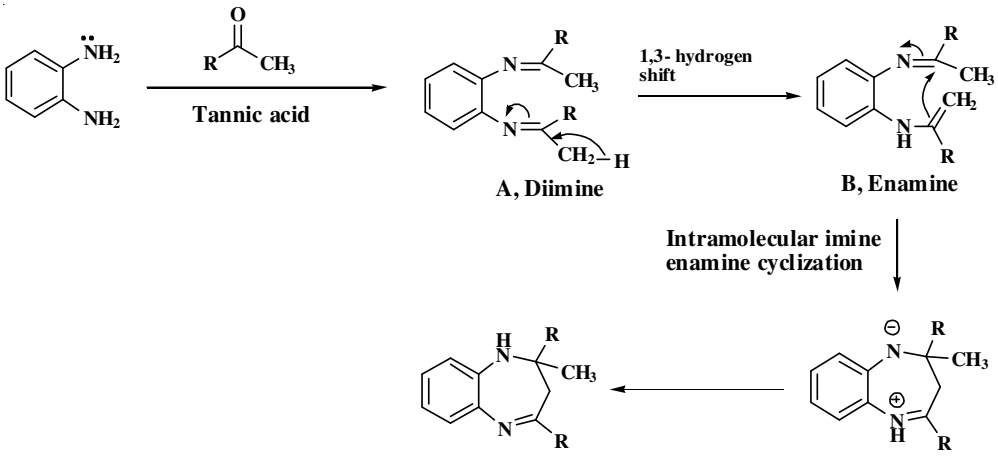
11-Spirocyclocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1*H*-dibenzo[b,e][1,4]diazepine: (Entry 8): IR (KBr, ν_{max}, cm^{-1}): 3351 (Sec. NH), 2931 (alkene CH), 2857 (alkane CH), 1633 (imine C=N), 1484 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 1.7-2.5 (m, 18H, $-CH_2$), δ 3.0 (s, 3H, $-CH_3$), δ 3 (t, 1H,-CH), δ 7.3-7.9 (m, 3H, ArH); Anal. calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92; Found: C, 80.86; H, 9.34; N, 9.98.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydro-8-methylbenzo[b]cyclohepta[e][1,4]diazepine: (Entry 9): IR (KBr, ν_{max}, cm^{-1}): 3266 (NH), 2916 (aromatic CH), 1633 (imine C=N), 1484 (aromatic C=C). ^{1}H NMR ($CDCl_3$), δ/ppm: δ 1.6 (m, 22H, $-CH_2$), δ 2.2 (s, 3H, $-CH_3$), δ 3.1 (br, 2H, -NH, -CH), δ 6.5 (s, 1H, -CH), δ 6.76 (d, 1H, *J* = 7.8, -CH), δ 7.1 (d, 1H, *J* = 7.9, -CH); Anal. calcd. for $C_{21}H_{30}N_2$: C, 81.24; H, 9.74; N, 9.02; Found: C, 81.29; H, 9.79; N, 9.15.

RESULTS AND DISCUSSION

Initially we studied the influence of tannic acid for the synthesis of 1,5-benzodiazepine using *o*-phenylenediammine and acetophenone as a model and varying the amount of tannic acid by simple optimization study (Table-1). The catalyst quantity was optimized to 2 mol % of tannic acid and excellent results (92 % yields) were achieved. Similarly, other 1,5-benzodiazepine derivatives have been synthesized from *o*-phenylenediamines and ketones in 85-92 % yields (Table-2).

The proposed mechanism of the reaction (**Scheme-II**) involves an intramolecular imine enamine cyclization promoted by tannic acid. Amine of *o*-phenylenediamine attacks carbonyl group of ketone giving the intermediate diimine A. 1,3-Hydrogen shift of the attached methyl group



Scheme-II: Proposed mechanism and possible intermediates

TABLE-2
CONDENSATION OF *o*-PHENYLENEDIAMINE WITH VARIOUS KETONES CATALYZED BY TANNIC ACID

Entry	R	R1	R2	R3	R4	Yield (%)	Time (h)	m.p. (ºC)	m.p.[lit] (ºC)
1	H	CH_3	C_6H_5	H	C_6H_5	92	60	149-150	151-152[10]
2	H	CH_3	CH_3	H	CH_3	88	50	138-139	137-138[10]
3	H	CH_3	C_6H_5	H	CH_3	85	50	137-139	137-139[10]
4	H	-	$(CH_2)_5$-	-	$(CH_2)_5$-	87	40	137-138	138-139[11]
5	H	-	$(CH_2)_6$-	-	$(CH_2)_6$-	90	40	133-134	136-137[11]
6	CH_3	CH_3	CH_3	H	CH_3	89	50	126-128	127-128[12]
7	CH_3	C_6H_5	CH_3	H	C_6H_5	87	60	91-92	92-96[12]
8	CH_3	-	$(CH_2)_5$-	-	$(CH_2)_5$-	92	60	140-142	142-143[12]
9	CH_3	-	$(CH_2)_6$-	-	$(CH_2)_6$-	85	60	121-122	124-125[12]

then occurs to form an isomeric enamine B, which cyclize to afford seven membered ring.

TABLE-1
OPTIMIZATION OF CONCENTRATION OF TANNIC ACID FOR THE SYNTHESIS OF 2,3-DIHYDRO-1*H*-1, 5-BENZODIAZEPINES UNDER SOLVENT-FREE CONDITION

Amount of catalyst mol (%)	Time (min)	Yield (%)
3.0	60	92
2.5	60	92
2.0	60	92
1.5	60	88
1.0	60	85

Conclusion

An efficient, inexpensive, non-hazardous ecofriendly new catalyst tannic acid for the multicomponent one pot synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines is reported. The advantages of presented green protocol are shorter reaction time, clean reaction profile, simple work up, reliable, environmentally benign, safe, non-toxic and moreover, under solvent-free conditions.

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REFERENCES

1. I. Ugi, *Pure Appl. Chem.*, **73**, 187 (2011).
2. D.J. Ramon and M.Yus, *Angew. Chem. Int. Ed.*, **44**, 1602 (2005).
3. L.O. Randall and B Kappel, Raven Press: New York, 27 (1973).
4. H. Schutz, Benzodiazepines. Springer: Heidelberg (1982).
5. L.K. Landquist, Comprehensive Heterocyclic Chemistry, Pergamon: Oxford, **1**, 166 (1984).
6. R. Varala, R. Enugala and R. Srinivas and R. Adapa, *J. Braz. Chem. Soc.*, **18**, 291 (2007).
7. A.M. El-Sayed, A. Khodairy, H. Salah and H. Abdel-Ghany, *Phosphorous Sulphur Silicon Rel. Elem.*, **182**, 711 (2007).
8. G.K. Nagaraja, V.P. Vaidya, K.S. Rai and K.M. Mahadevan, *Phosphorous Sulphur Silicon Relat. Elem.*, **181**, 2797 (2006).
9. K. Nabih, A. Baouid, A. Hasnaoui and A. Kenz, *Synth. Commun.*, **36**, 1825 (2006).
10. K.V.V. Reddy, P.S. Rao and D. Ashok, *Synth. Commun.*, **30**, 1825 (2000).
11. S. Ahmad and M. Ali, *Iran. J. Chem. Eng.*, **26**, 93 (2007).
12. D.B. Shinde, J.N. Sangshetti and N.D. Kokare, *Chinese Chem. Lett.*, **18**, 1305 (2007).
13. Z. Li, Y. Sun, X. Ren, W. Li, Y. Shi and P. Ouyang, *Synth. Commun.*, **37**, 1609 (2007).
14. G.R. Krishnan, S. Radhakrishnan and S. Krishnapillai, *Lett. Org. Chem.*, **6**, 17 (2009).
15. A.P. Parveen, A. Vishal, M.A. Baseer and S. Ahmed, *Int. J. Ind. Chem.*, **2**, 144 (2010).
16. A.V. Vijayashankar, S. Deepa, B.R. Venugopal and N. Nagaraju, *Chin. J. Catal.*, **31**, 1321 (2010).
17. R.X. Shi, Y.K. Liu and Z.Y. Xu, *J. Zhejiang Univ.*, **11**, 102 (2010).
18. S.G. Konda, B.M. Shaikh, S.A. Chavan and B.S. Dawane, *Chin. Chem. Lett.*, **22**, 65 (2011).
19. U.B. More, R.S. Kharat and P.P. Mahulikar, *Asian J. Chem.*, **23**, 4311 (2011).