An efficient synthesis of 1,5-benzodiazepines catalyzed by bismuth nitrate

Asish K Bhattacharya\textsuperscript{a,b}, Santoshkumar S Dange\textsuperscript{a}, Innaiah K Polanki\textsuperscript{a,b} & Hemender R Chand\textsuperscript{a}

\textsuperscript{a}Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India
\textsuperscript{b}Academy of Scientific and Innovative Research (AcSIR), CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

E-mail: ak.bhattacharya@ncl.res.in

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An efficient method has been developed for the synthesis of biologically active 1,5-benzodiazepines in one-pot by reacting \textit{o}-phenylenediamine and ketones catalyzed by bismuth nitrate pentahydrate at room temperature or under microwave irradiation.

Keywords: \textit{o}-Phenylenediamine, 1,5-benzodiazepines, bismuth nitrate pentahydrate, synthetic methods

Synthesis of small molecules utilizing one-pot methodologies have gained tremendous importance in recent years for the generation of compound libraries of novel chemical entities having diversified scaffolds to spearhead drug discovery programme aimed at discovering new pharmaceutical targets. 1,5-Benzodiazepines is one such class of molecules which has attracted the attention of organic chemists as well as medicinal chemists due to their immense biological activities. Some of the biological activities\textsuperscript{1} exhibited by them are anti-inflammatory, anti-anxiety, anti-convulsant, hypnotic, analgesic, anti-depressive, anti-histaminic, anti-allergic, antipyretic and anti-ulcerative. Additionally, 1,5-benzodiazepine derivatives have found profound uses as valuable synthetic intermediates for the synthesis of other heterocyclic compounds \textit{viz}. triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines\textsuperscript{2,3} and commercial uses in materials also\textsuperscript{4}. In general, 1,5-benzodiazepines are synthesized by the condensation of \textit{o}-phenylenediamines with ketones, \textit{\alpha,\beta}-unsaturated carbonyl compounds\textsuperscript{5}, or \textit{\beta}-haloketones\textsuperscript{6} in the presence of conventional or Lewis acid catalysts\textsuperscript{7}. However, a number of these reported methods do have some limitations, such as long reaction times, tedious work-up procedures and tedious isolation of the product from reaction mixture due to generation of by-products. One-pot multi-component reaction for the synthesis of benzodiazepinyl phosphonates (BDPs) as novel chemical entities has been recently reported\textsuperscript{8} and their remarkable cysteine protease inhibition activity demonstrated against clostripain, a disease model for gas gangrene. As part of our interest\textsuperscript{9} in the synthesis of bioactive molecules and development of novel ecofriendly and solvent-free synthetic methodologies, herein is reported an efficient and convenient method for the synthesis of 1,5-benzodiazepines catalyzed by Bi(NO\textsubscript{3})\textsubscript{3} \cdot 5H\textsubscript{2}O in one-pot (Scheme I).

Bismuth nitrate\textsuperscript{10} has widely been reported in the literature to be an efficient Lewis acid, which is inexpensive, has relatively low toxicity and remarkable ability to tolerate trace amounts of water. In the recent past, Bi(NO\textsubscript{3})\textsubscript{3} \cdot 5H\textsubscript{2}O has also been utilized as an efficient Lewis acid catalyst for carrying out one-pot synthesis of \textit{\alpha}-aminophosphonates\textsuperscript{11}. Keeping in mind above mentioned advantages, Bi(NO\textsubscript{3})\textsubscript{3} \cdot 5H\textsubscript{2}O was considered to be an ideal catalyst for the synthesis of 1,5-benzodiazepines\textsuperscript{12} and efforts were made to address some of the limitations posed by earlier reported methods.

Results and Discussion

First of all, \textit{o}-phenylenediamine (1.0 mmol, \textit{1a}) was reacted with acetone (2.1 mmol, \textit{2a}) in 1,2-dichloroethane (2 mL) for 5 hr at RT in the presence of Bi(NO\textsubscript{3})\textsubscript{3} \cdot 5H\textsubscript{2}O (10 mol %) resulting in the formation of benzodiazepine \textit{3a} in only 42\% yield. Then, a similar set of reactions was carried out in different organic solvents (Table I). However, not much tangible difference in reaction time and product yield was observed.

Thereafter, the same reaction was tried under solvent-free conditions. The reaction of \textit{o}-phenylenediamine \textit{1a} with acetone \textit{2a} and Bi(NO\textsubscript{3})\textsubscript{3} \cdot 5H\textsubscript{2}O...
(10 mol%) in neat condition at RT was complete within 10 min and the corresponding benzodiazepine 3a was obtained in 95% yield (Table I, entry 5). The structure of the synthesized compound 3a was elucidated based on its spectral data. The EI-mass spectrum furnished a molecular ion peak at \( m/z \) 188 indicating the formation of the desired product \( (C_{12}H_{16}N_2) \). The IR spectrum of compound 3a exhibited absorption bands at 1224, 1634, 2964 and 3290 cm\(^{-1}\) corresponding to C-N stretching, N-H bending, aromatic C-H stretching and N-H stretching, respectively. The \( ^1H \) NMR spectrum of 3a showed singlet at \( \delta \) 1.35, 2.23 and 2.37 indicating the presence of gem-dimethyls, methylene protons and a methyl on double bond, respectively in addition to other peaks. The \( ^{13}C \) NMR spectrum exhibited characteristic signals at \( \delta \) 29.9, 30.5, 45.1 and 172.4 corresponding to methyl on double bond, gem-dimethyls, methylene and imine carbon, respectively in addition to other peaks. In the HMBC spectrum (Figure 1), the protons of methyl on double bond (\( \delta \) 2.37) showed a correlation with carbons at \( \delta \) 45.1, 140.8 and 172.4 whereas protons of gem-dimethyls (\( \delta \) 1.35) showed correlation with carbons at \( \delta \) 45.1, 66.4 and 137.9 suggesting the formation of the desired product.

To generalize the present protocol further, reaction of structurally diverse diamines with various ketones (Table II) was studied under the optimal conditions (see Experimental Section). The reaction under the catalytic influence of Bi(NO\(_3\))\(_3\)-5H\(_2\)O (10 mol%) in neat condition at RT or microwave irradiation proceeded smoothly in all cases to furnish the corresponding 1,5-benzodiazepines 3a-s in high yields. It is pertinent to mention here that the use of microwave irradiation not only enhanced the yield of the product but also significantly reduced the reaction time. Also, tolerance of the present method towards various functionalities present in the substrate viz. methyl, halides, cyano, carbonyl and nitro groups thus generalizes scope of the present method.

**Experimental Section**

Melting points were determined in open capillaries using a Büchi B-5400 melting point apparatus and are uncorrected. Reagents and starting materials were obtained from commercial suppliers and were used as received. Thin layer chromatography (TLC) was performed using pre-coated silica gel F254 aluminium sheets, obtained from Merck, Germany. Chromatography refers to purification by column chromatography using silica gel (100-200 mesh size; Spectrochem, India). FT-IR spectra were recorded on a Shimadzu FT-IR-8300 spectrometer. NMR spectra were recorded on Bruker ACF 200 and AV200 instruments (200 MHz for \(^1H \) NMR and 50 MHz for \(^{13}C \) NMR), using CDCl\(_3\) as solvent. Tetramethylsilane (\( \delta \) 0.00 ppm) served as an internal standard for \(^1H \) NMR and CDCl\(_3\) (\( \delta \) 77.0 ppm) for \(^{13}C \) NMR, respectively. Chemical shifts are expressed in parts per million (ppm). Coupling constants (\( J \)) are given in Hz. In case of NMR data of mixture of regioisomers, the peaks corresponding to the major isomer is given. High-resolution mass spectra (HRMS) were recorded on Thermo Scientific ‘Q’ Exactive “Orbitrap” high-resolution mass spectrometer. All other chemicals were of analytical grade. The compounds 3a, 3j, 3k, 3l, 3n, 3r-s are known in the literature\(^7\). The spectral data of all the new compounds (3b-i, 3m, 3o-q) synthesized have been provided.

**Typical procedure: Method A:** To a mixture of o-phenylenediamine (1.0 mmol) and ketone (2.1 mmol),
Table II — Synthesis of 1,5-benzodiazepines 3a-s catalyzed by Bi(NO$_3$)$_3$·5H$_2$O

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**Table II — Synthesis of 1,5-benzodiazepines 3a-s catalyzed by Bi(NO$_3$)$_3$·5H$_2$O — Contd**

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</table>

$^a$Method A: reaction mixtures stirred at RT.

$^b$Method B: reactions carried out under microwave irradiation.

$^c$Yields refer to those of pure isolated products fully characterized by spectral data.

$^d$Product was formed as inseparable regioisomeric mixture.

Bi(NO$_3$)$_3$·5H$_2$O (10 mol%) was added and stirred at RT for the appropriate time (Table I) till the completion (TLC) of reaction. The reaction mixture was diluted with H$_2$O and extracted with EtOAc (3 × 25 mL). The combined EtOAc extract was washed with brine, dried (anhydrous Na$_2$SO$_4$), and evaporated to furnish crude product, which was purified by column chromatography (pet. ether-EtOAc, 7:3) over silica gel to provide pure 1,5-benzodiazepines. All the products were characterized by their spectral data.

Method B: To a mixture of o-phenylenediamine (1.0 mmol), ketone (2.1 mmol), and Bi(NO$_3$)$_3$·5H$_2$O (10 mol%) was added and the reaction mixture was irradiated with microwave (Samsung Model No. C103FL; 2450 MHz, 900 W) for the specified period of time in an open vessel. Work-up of the reaction was carried out as described above to afford pure 1,5-benzodiazepines.

**Spectral data of some selected compounds**

2, 2, 4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine, 3a. This compound was obtained as reddish yellow solid; m.p. 99-100°C; IR (CHCl$_3$): NH 3290, 2964, 1457 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$): δ$_H$ 1.35 (s, 6H), 2.23 (s, 2H), 2.37 (s, 3H), 2.78 (br s, 1H), 6.71-7.16 (m, 4H); $^{13}$C NMR (50 MHz, CDCl$_3$): δ$_C$ 29.9, 29.9.
7-Chloro-2,2,4-trimethyl-2, 3-dihydro-1H-1,5-benzodiazepine, 3b. This compound was obtained as reddish yellow solid; m.p. 158°C; IR (CHCl₃): NH (CHCl₃): δH 1.34 (s, 6H), 2.22 (s, 2H), 2.36 (s, 3H), 3.10 (br s, 1H), 6.63-7.12 (m, 3H); 13C NMR (50 MHz, CDCl₃): δC 29.9, 30.6, 45.1, 67.9, 122.6, 126.5, 128.3, 130.2, 136.5, 139.1, 172.7; EI-MS: m/z 222 [M⁺]; HRMS (ESI): m/z for C₁₂H₁₂ClN₂ [M + H⁺] Calcd 223.0997. Found: 223.0998.

2,2,4,9-Tetramethyl-2, 3-dihydro-1H-1,5-benzodiazepine, 3c. This compound was obtained as reddish yellow solid; m.p. 49-51°C; IR (CHCl₃): NH (CHCl₃): δH 1.34 (s, 6H), 2.23 (s, 2H), 2.35 (s, 3H), 2.38 (s, 3H), 6.52-6.90 (m, 3H); 13C NMR (50 MHz, CDCl₃): δC 18.3, 29.7, 30.3, 44.9, 69.1, 120.0, 124.3, 124.8, 134.0, 137.2, 172.1; EI-MS: m/z 202 [M⁺]; HRMS (ESI): m/z for C₁₂H₁₂N₂ [M + H⁺] Calcd 203.1543. Found: 203.1543.

7,8-Dichloro-2,2,4-trimethyl-2, 3-dihydro-1H-1,5-benzodiazepine, 3d. This compound was obtained as reddish yellow solid; m.p. 149-150°C; IR (CHCl₃): NH (CHCl₃): δH 1.34 (s, 6H), 2.25 (s, 2H), 2.34 (s, 3H), 3.21 (br s, 1H), 6.81 (s, 1H), 7.20 (s, 1H); 13C NMR (50 MHz, CDCl₃): δC 30.0, 30.6, 45.3, 67.8, 122.2, 124.5, 128.0, 128.4, 137.7, 139.8, 174.0; EI-MS: m/z 266 [M⁺]; HRMS (ESI): m/z for C₁₂H₁₄Cl₂N₂ [M + H⁺] Calcd 257.0607. Found: 257.0608.

7-Fluoro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine, 3e. This compound was obtained as reddish yellow solid; m.p. 151-152°C; IR (CHCl₃): NH (CHCl₃): δH 1.34 (s, 6H), 2.18 (s, 2H), 2.34 (s, 3H), 3.04 (br s, 1H), 6.40-7.11 (m, 3H); 13C NMR (50 MHz, CDCl₃): δC 29.9, 30.1, 45.1, 67.3, 107.3, 108.5, 111.6, 112.9, 122.8, 128.6, 171.6; EI-MS: m/z 206 [M⁺]; HRMS (ESI): m/z for C₁₂H₁₄F₂N₂ [M + H⁺] Calcd 207.1292. Found: 207.1291.

2,2,4-Tetramethyl-7-nitro-2,3-dihydro-1H-1,5-benzodiazepine, 3f. This compound was obtained as reddish yellow solid; m.p. 158-60°C; IR (CHCl₃): NH (CHCl₃): δH 1.39 (s, 6H), 2.35 (s, 2H), 2.47 (s, 3H), 4.10 (br s, 1H), 6.60 (d, J = 10 Hz, 1H), 7.85 (dd, J = 2, 10 Hz, 1H), 8.10 (d, J = 4 Hz, 1H); 13C NMR (50 MHz, CDCl₃): δC 30.5, 31.2, 46.6, 63.5, 119.2, 122.0, 126.2, 172.7; EI-MS: m/z 233 [M⁺]; HRMS (ESI): m/z for C₁₃H₁₄N₃O₂ [M + H⁺] Calcd 234.1237. Found: 234.1238.

2,2,4,6, 8-Pentamethyl-2,3-dihydro-1H-1,5-benzodiazepine, 3g. This compound was obtained as reddish yellow solid; m.p. 291-292°C; IR (CHCl₃): NH (CHCl₃): δH 1.37 (s, 6H), 2.28 (s, 2H), 2.40 (s, 3H), 4.01 (br s, 1H), 6.62 (d, J = 10 Hz, 1H), 7.75 (dd, J = 3, 20 Hz, 1H), 8.10 (d, J = 4 Hz, 1H); 13C NMR (50 MHz, CDCl₃): δC 30.5, 31.5, 46.6, 63.5, 119.2, 122.0, 126.2, 172.7; EI-MS: m/z 233 [M⁺]; HRMS (ESI): m/z for C₁₃H₁₄N₃O₂ [M + H⁺] Calcd 234.1237. Found: 234.1238.

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Conclusion

In summary, Bi(NO₃)₃·5H₂O has been found to be an efficient catalyst in the synthesis of 1,5-benzo-
diazepines by the condensation of various diamines and ketones. The main advantages of this method are
environmentally benign reagent and solvent-free reaction conditions. It is presumed that the developed
method will find synthetic utility in the preparation of a wide variety of biologically potent 1,5-benzo-
diazepines.

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