An expeditious and efficient microwave assisted synthesis of 1,5-benzodiazepine derivatives

Preeti S. Salve* and Deepak S. Mali

Department of Pharmaceutical Chemistry, KLE University’s College of Pharmacy, Belgaum, Karnataka, India

ABSTRACT

The present work reports eco friendly synthesis of a new series of 2,4-disubstituted-1,5-benzodiazepine derivatives which is achieved by the condensation of o-phenylenediamine and various substituted chalcones under microwave irradiation. The structures of the synthesized compounds were confirmed through IR and $^1$H NMR spectroscopy. This method is based on the principles of ‘Green Chemistry’, rendering the method to be facile, efficient and environmentally benign. It afforded all the synthesized compounds in good to excellent yields and the reaction time was considerably short. The clean reaction conditions, easy work-up, time saving and higher yields are notable advantages of the present method.

Keywords: 1,5-benzodiazepines, o-phenylenediamine, chalcones, microwave.

INTRODUCTION

Benzodiazepines and their derivatives constitute an eminent class of drugs with a very wide range of biological activities. These are nitrogen containing heterocyclic compounds which exhibit applications in the fields of synthetic as well as medicinal chemistry and also various industries. Although immense work has been carried out on 1,5-benzodiazepines, due to their versatile nature, further work on them has always been promoted.

Benzodiazepines have demonstrated a diverse range of biological activities such as anticonvulsant, anti-anxiety, analgesic, sedative, hypnotic and antidepressant [1]. They have also shown to possess antimicrobial, anti-inflammatory and antipyretic activities [2] and have been used in the treatment of viral diseases [3] and cardiovascular disorders [4]. Besides, they also act as cholecystokinin (CCK) receptor antagonists [5].

Apart from their biological importance, benzodiazepine derivatives have also been commercially used as dyes for acrylic fibres [6]. Furthermore, 1,5-benzodiazepines are used as starting materials for the preparation of fused ring compounds such as triazolo-, oxadiazolo-, oxazino- or furano- benzodiazepines [7].

Synthesis of benzodiazepines occurs via condensation of o-phenylenediamines with α,β-unsaturated carbonyl compounds, β-haloketones or ketones in the presence of acid. A diverse range of reagents have been utilized such as BF$_3$-etherate [8a], NaBH$_4$ [8b], MgO and POCl$_3$ [8c], Yb(OTf)$_3$ [8d], polyphosphoric acid [8e], silica sulfuric acid [9a], sulfated zirconia [9b], GaCl$_3$ [9c], CdCl$_2$ [9d], LaCl$_3$, 7H$_2$O [9e], Al$_2$O$_3$, P$_2$O$_5$ or CH$_3$COOH under microwave conditions [10], 1,3-di-n-butylimidazolium bromide (ionic liquid) [11].

However most of these reactions experience various drawbacks like employing drastic reaction conditions, expensive reagents, longer reaction rates, the cropping up of a number of side reactions, low yields and tedious work-up procedures. This is where the emergence of microwaves has ushered in an era of ‘Green Chemistry’ which is now widely adopted to meet the scientific challenges of protecting the human health and environment while
simultaneously achieving commercial viability. The applications of microwave irradiation have gained popularity as a powerful tool to improve classical organic reactions, shorten reaction times, improve yields, as well as to promote new reactions.

**EXPERIMENTAL SECTION**

All melting points were determined in open capillary and are uncorrected. The IR spectra was recorded using a Shimadzu spectrometer. $^1$H-NMR spectra were recorded on a Bruker (400 MHz) spectrometer using DMSO as a solvent. Microwave irradiation was carried out using Onida Power Grill 25 at 100-200W. Thin layer chromatography (TLC) was performed in silica gel G (Rankem) for TLC and spots were visualized by iodine vapours or by irradiation with ultraviolet light (254nm).

**General procedure for synthesis of chalcones:**

A solution of substituted acetophenones (0.01 mol) and aromatic aldehydes (0.01 mol) in ethanolic KOH (0.02 mol, 10%), was stirred overnight at room temperature. The mixture was poured into crushed ice and neutralized with dilute hydrochloric acid. The solid obtained was washed with water, dried and recrystallised from alcohol.

**General procedure for synthesis of 2,4-disubstituted-1,5-benzodiazepines:**

A mixture of chalcone (0.01 mole) and substituted o-phenylenediamine (0.016 mole) was taken in a conical flask. To it added glacial acetic acid (5ml) in N,N-dimethyl formamide (DMF) (15ml). Placed the flask in a microwave oven and irradiated for 10-20mins with intermittent cooling at every 1 min interval. The cooling was essential in order to avoid loss of product by evaporation. The reaction mixture was allowed to attain room temperature and treated with cold water. The solid separated was filtered, washed with water and recrystallised from methanol.

**Characterization data for 1,5-benzodiazepines:**

2-(4-methylphenyl)-4-phenyl-1H-1,5-benzodiazepine (5a) :

IR(KBr,cm$^{-1}$): 3296 (NH), 1631 (C=N), 1593 (C=C);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.70-7.18 (m, 9H, Ar-H), 7.14-6.86 (m, 4H, Ar-H), 4.81 (s, 1H, CH), 4.13 (s, 1H, NH), 2.32 (s, 3H, CH$_3$)

4-(4-chlorophenyl)-2-(4-methylphenyl)-1H-1,5-benzodiazepine (5b) :

IR(KBr,cm$^{-1}$): 3305 (NH), 1658 (C=N), 1597 (C=C), 740 (C-Cl);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 8.19-7.52 (m, 8H, Ar-H), 7.37-7.08 (m, 4H, Ar-H), 4.42 (s, 1H, CH), 3.62 (s, 1H, NH), 2.38 (s, 3H, CH$_3$)

4-(4-methoxyphenyl)-2-(4-methylphenyl)-1H-1,5-benzodiazepine (5c) :

IR(KBr,cm$^{-1}$): 3363 (NH), 1631 (C=N), 1597 (C=C), 1228 (OCH$_3$);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.82-7.10 (m, 8H, Ar-H), 6.93-6.77 (m, 4H, Ar-H), 4.71 (s, 1H, CH), 4.20 (s, 1H, NH), 3.82 (s, 3H, OCH$_3$), 2.36 (s, 3H, CH$_3$)

4-(4-bromophenyl)-2-(4-methylphenyl)-1H-1,5-benzodiazepine (5d) :

IR(KBr,cm$^{-1}$): 3348 (NH), 1645 (C=N), 1578 (C=C), 585 (C-Br);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 8.24-7.53 (m, 8H, Ar-H), 7.38-7.17 (m, 4H, Ar-H), 4.69 (s, 1H, CH), 3.84 (s, 1H, NH), 2.36 (s, 3H, CH$_3$)

2-(4-methylphenyl)-4-(4-nitrophenyl)-1H-1,5-benzodiazepine (5e) :

IR(KBr,cm$^{-1}$): 3335 (NH), 1643 (C=N), 1589 (C=C), 1423 (NO$_2$);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.98-7.49 (m, 8H, Ar-H), 7.35-7.11 (m, 4H, Ar-H), 4.77 (s, 1H, CH), 3.92 (s, 1H, NH), 2.40 (s, 3H, CH$_3$)

4-(4-fluorophenyl)-2-(4-methylphenyl)-1H-1,5-benzodiazepine (5f) :

IR(KBr,cm$^{-1}$): 3310 (NH), 1650 (C=N), 1595 (C=C), 1230 (C-F);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 8.21-7.57 (m, 8H, Ar-H), 7.41-7.29 (m, 4H, Ar-H), 4.92 (s, 1H, CH), 3.78 (s, 1H, NH), 2.38 (s, 3H, CH$_3$)

2-(3,4-dimethoxyphenyl)-4-phenyl-1H-1,5-benzodiazepine (5g) :

IR(KBr,cm$^{-1}$): 3338 (NH), 1643 (C=N), 1589 (C=C), 1423 (NO$_2$);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.78-7.49 (m, 8H, Ar-H), 7.35-7.11 (m, 4H, Ar-H), 4.77 (s, 1H, CH), 3.92 (s, 1H, NH), 2.40 (s, 3H, CH$_3$)

4-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-1H-1,5-benzodiazepine (5h) :

IR(KBr,cm$^{-1}$): 3005 (NH), 1658 (C=N), 1589 (C=C), 1160 (OCH$_3$), 771 (C-Cl);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.78-7.02 (m, 9H, Ar-H), 6.87-6.63 (m, 3H, Ar-H), 4.92 (s, 1H, CH), 4.18 (s, 1H, NH), 3.60 (s, 6H, OCH$_3$)

2-(3,4-dimethoxyphenyl)-4-phenyl-1H-1,5-benzodiazepine (5i) :

IR(KBr,cm$^{-1}$): 3338 (NH), 1650 (C=N), 1585 (C=C), 1160 (OCH$_3$);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.78-7.02 (m, 9H, Ar-H), 6.87-6.63 (m, 3H, Ar-H), 4.92 (s, 1H, CH), 4.18 (s, 1H, NH), 3.60 (s, 6H, OCH$_3$)

4-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-1H-1,5-benzodiazepine (5j) :

IR(KBr,cm$^{-1}$): 3005 (NH), 1658 (C=N), 1589 (C=C), 1159 (OCH$_3$), 771 (C-Cl);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.71-6.88 (m, 8H, Ar-H), 6.70-6.42 (m, 3H, Ar-H), 4.81 (s, 1H, CH), 4.32 (s, 1H, NH), 3.63 (s, 6H, OCH$_3$)

2-(3,4-dimethoxyphenyl)-4-phenyl-1H-1,5-benzodiazepine (5k) :

IR(KBr,cm$^{-1}$): 3668 (NH), 1658 (C=N), 1585 (C=C), 1163 (OCH$_3$), 597 (C-Br);

$^1$H NMR (DMSO, 400 MHz) $\delta$ 7.80-6.75 (m, 8H, Ar-H), 6.69-6.48 (m, 3H, Ar-H), 4.88 (s, 1H, CH), 3.97 (s, 1H, NH), 3.90 (s, 6H, OCH$_3$)
2-(3,4-dimethoxyphenyl)-4-(4-nitrophenyl)-1H-1,5-benzodiazepine (5j) :
IR(KBr, cm⁻¹): 3363 (NH), 1660 (C=N), 1165 (OCH₃); ¹H NMR (DMSO, 400 MHz) δ 7.96-6.92 (m, 8H, Ar-H), 6.80-6.68 (m, 3H, Ar-H), 4.84 (s, 1H, CH), 3.88 (s, 1H, NH), 3.85 (s, 6H, OCH₃)

We present here the synthesis of a new series of 2,4-disubstituted-1,5-benzodiazepine derivatives through the condensation of o-phenylenediamine and various substituted α,β-unsaturated ketones (chalcones) in the presence of DMF and glacial acetic acid by employing microwave irradiation for this purpose. The principal aim of the present study was very precisely achieved which was to synthesize new 1,5-benzodiazepine derivatives by using 'Green Chemistry' principles so as to minimize environmental pollution, to obtain better yields and to save time.

In conclusion, we have proficiently synthesized a series of new 1,5-benzodiazepine derivatives in easy and environmentally friendly conditions, with short reaction time and in good to excellent yields.

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