2-Methoxyethanol as an alternative reaction solvent for the synthesis of 1,5-benzodiazepines under microwave irradiation

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ABSTRACT: An improved condensation reaction between substituted 2'-hydroxychalcones and o-phenylenediamine using piperidine in 2-methoxyethanol as an efficient and alternative reaction medium. The clean reaction conditions, easy work up, time saving and higher yields are notable advantages of present method.

Keywords: 2'-hydroxychalcones; 2-methoxyethanol; green chemistry; microwave irradiation

Introduction

Benzodiazepines have attracted attention as an important class of heterocyclic chemistry [1]. They are finding numerous new applications and widely used as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative and antidepressive agents [2]. Moreover, 1,5-benzodiazepines are also useful precursor for the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino- or furano benzodiazepines [3].

A classical synthesis of these compounds involves condensation reaction between o-phenylenediamine with α,β-unsaturated carbonyl compounds, β-diketones. Recently some well known modified method have reported for synthesis of 1,5-benzodiazepines such as BF3-etherate [4], NaBH4 [5], SiO2 [6], Amberlyst [7], Yb(Otf)3 [8], MgO/POCl3 [9], Al2O3/P2O5 [10], TiCl4/THF [11], ionic liquid [12], silica gel [13], CeCl3/silica gel [14].

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However, many of these reported procedures have one or more disadvantages such as use of expensive catalyst, low selectivity, harsh reaction time, low yield, relatively long reaction time and environmental concern. In recent years replacement of hazardous-solvent with environmentally benign solvents is one of the major focus areas of green chemistry. The utility of alternative reaction solvents such as water [15], Ionic liquid [16], flourous [17], supercritical media [18] and polyethylene glycol [19] (PEG) is rapidly growing.

Microwave-induced Organic Reaction Enhancement [MORE] chemistry has gained popularity as a non-conventional technique for rapid organic synthesis [20]. Many researchers have described accelerated organic reactions toward proving the synthetic utility of MORE chemistry in routine organic synthesis [21]. It can be termed as ‘e-chemistry’ because it is easy, effective, economical and eco-friendly and believed to be a step towards green chemistry. Due to the wide range of pharmacological activity and application of microwave technique in organic synthesis, promoted us towards the synthesis of 1,5-benzodiazepines using piperidine in 2-methoxyethanol as an alternative reaction solvent.

**Material and Methods**

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. \(^1\)H NMR spectra were recorded in CDCl\(_3\) on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

**Typical procedure for synthesis of 1,5-benzodiazepines 3(a-h)**

A mixture of substituted 2'-hydroxychalcones 1 (0.01mol), O-phenylenediamine (0.012mol) and piperidine (3-4 drops) in 2-methoxyethanol (15mL) was irradiated in microwave for 4-7 minutes, with short interval of time for 10 sec. to avoid evaporation of excessive solvent. Then reaction mixture was cooled to room temperature. Solid separated was isolated by simple Buchner filtration; final purification was achieved by crystallization from ethanol.

**Spectral and analytical data of some novel 1,5-benzodiazepines**

2-(3,4,5-trimethoxyphenyl)-2,3-dihydro-4-(2'-hydroxy-7'-iodo-1'-naphthyl)-1,5-benzodiazepines (3a): IR \(v\) max cm\(^{-1}\): 3335 (N-H), 1589 (C=N), 1504, 1458 (C=C). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.37 (s, 3H, OCH\(_3\)), \(\delta\) 3.80 (s, 6H, OCH\(_3\)), \(\delta\) 3.02 (dd, 1H, H\(_A\)), \(\delta\) 3.58 (dd, 1H, H\(_B\)), \(\delta\) 5.80 (dd, 1H, H\(_X\)), \(\delta\) 6.92 (s, 1H, N-H), \(\delta\) 7.52-8.32 (m, 11H, Ar-H), 12.01 (s, 1H, OH). MS (m/z): 580 (M\(^+\)), 551, 523, 441, 424, 317, 290, 277, 91, 77. Anal. Calcd. for C\(_{28}\)H\(_{25}\)O\(_4\)N\(_2\)I: C, 58.03; H, 4.14; X (I), 21.93. Found: C, 58.12; H, 4.16;
X (I), 21.98.

2-(4-chloro-phenyl)-2,3-dihydro-4-(2’-hydroxy-1’-naphthyl)-1,5-benzodiazepines (3b): IR v max cm⁻¹: 3345 (N-H), 1591 (C=N), 1515, 1466 (C=C). ¹H NMR (CDCl₃): δ 3.09 (dd, 1H, Hₐ), δ 3.52 (dd, 1H, Hₐ), δ 5.76 (dd, 1H, Hₓ), δ 6.88 (s, 1H, N-H), δ 7.32-8.21 (m, 14H, Ar-H), 12.10 (s, 1H, OH). MS (m/z): 399 (M⁺), 368, 317, 289, 261, 241, 235, 185, 121, 91, 79. Anal. Calcd. for C₂₅H₁₉N₂OCl: C, 75.18; H, 4.76; Cl, 31.82. Found: C, 75.10; H, 4.80; Cl, 31.78.

2-(4-fluoro-phenyl)-2,3-dihydro-4-(2’-hydroxy-1’-naphthyl)-1,5-benzodiazepines (3d): IR v max cm⁻¹: 3339 (N-H), 1585 (C=N), 1505, 1478 (C=C). ¹H NMR (CDCl₃): δ 3.05 (dd, 1H, Hₐ), δ 3.57 (dd, 1H, Hₐ), δ 5.74 (dd, 1H, Hₓ), δ 6.88 (s, 1H, N-H), δ 7.32-8.45 (m, 14H, Ar-H), 12.08 (s, 1H, OH). MS (m/z): 382 (M⁺), 363, 283, 255, 178, 91, 77. Anal. Calcd. for C₂₅H₁₉N₂OF: C, 78.53; H, 4.97; F, 4.97. Found: C, 78.62; H, 5.01; F, 5.10.

2-(4-chloro-phenyl)-2,3-dihydro-4(2’-hydroxy-7’-bromo-1’-naphthyl)-1,5-benzodiazepines (3f): IR v max cm⁻¹: 3328 (N-H), 1591 (C=N), 1510, 1472 (C=C). ¹H NMR (CDCl₃): δ 3.10 (dd, 1H, Hₐ), δ 3.54 (dd, 1H, Hₐ), δ 5.74 (dd, 1H, Hₓ), δ 6.88 (s, 1H, N-H), δ 7.32-8.40 (m, 13H, Ar-H), 12.12 (s, 1H, OH). MS (m/z): 477 (M⁺). Anal. Calcd. for C₂₅H₁₈N₂OCIBr: C, 62.89; H, 3.77; Cl + Br, 24.10. Found: C, 62.95; H, 3.81; Cl + Br, 24.18.

Results and Discussion

In continuation of earlier research work [22], herein we wish to report first time a typical condensation reaction of α,β-unsaturated carbonyl compounds 1a-h with o-phenylenediamine (2) using piperidine in 2-methoxyethanol as a green reaction solvent (Scheme 1).

Scheme 1. Synthesis of some novel 1,5-benzodiazepines.

The chalcones were prepared by well-known Claisen-Schmidt condensation under solvent-free condition [23]. Synthesis of 1,5-benzodiazepines using 2-methoxyethanol under microwave irradiation was completed in 4-7 minutes giving 82 to 95% yield of desired product (Table 1). Microwave irradiation has been used to accelerate organic reactions because of high heating efficiency, providing remarkable rate enhancement, dramatic reduction in reaction times with improvement in yield and quality of products.
Reactions that require hours or even days by conventional heating can often be accomplished in second or minutes by microwave heating.

**Table 1.** Synthesis of some 1,5-benzodiazepines using 2-methoxyethanol under microwave irradiation

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<th>Time (min)</th>
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Initially, we attempted the condensation of 1-(1-Hydroxy-4-iodo-naphthalen-2-yl)-3-(3,4,5-trimethoxy-phenyl)-propenone with o-phenylenediamine using piperidine in 2-methoxyethanol as reaction solvent. The reaction went to completion within 4 min and corresponding product 3a was obtained in 95% yield. In order to optimize the reaction conditions, we carried out the above reaction in different reaction medium such as ethanol, acetic acid, dioxane, DMF and 2-methoxyethanol (Table 2). We found that 2-
methoxyethanol as an efficient reaction medium in terms of clean reaction conditions, not expensive, yields and environmentally eco-friendly. In view of these results, we turned our attention towards variety of substituted 2'-hydroxychalcones. In all cases, reaction proceeded efficiently in high yields using 2-methoxyethanol.

**Table 2.** Effect of solvent on the condensation reaction of 1-(1-Hydroxy-4-iodonaphthalen-2-yl)-3-(3,4,5-trimethoxy-phenyl)-propenone with o-phenylenediamine under microwave irradiation

<table>
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<th>Entry</th>
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<td>2-methoxyethanol</td>
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</table>

**Conclusion**

In summary, we have carried out a simple condensation reaction between substituted 2'-hydroxychalcones with o-phenylenediamine using piperidine in 2-methoxyethanol as an efficient and green reaction solvent is described. The advantages of present protocol are simplicity of operation, time saving, high yields of products and avoidance of expensive catalyst and usage of volatile organic solvent.

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**References and Notes**


