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Research Article

Energy Efficient Synthesis of Various Pharmaceutically Important Benzodiazepin-2-ones Using Microwave Synthesizer

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Abstract

Benzodiazepine-2-one moiety consists of a seven-member heterocyclic ring, a derivative of benzodiazepine group, which is a class of medications that works in the central nervous system and used for a variety of medical conditions, such as anxiety, seizures, and alcohol withdrawal. Microwave-assisted synthesis of certain medically important benzodiazepin-2-ones was carried out using hexamine and ammonium chloride starting from 2-aminobenzophenones. Feasibility and optimization of the reaction conditions under closed vessel CEM microwave synthesizer provide the desired product with excellent yields (~90%), within minutes of focused microwave irradiation, without the use of catalyst, thereby, revealing the benefit of saving energy and time.

Keywords: Microwave Synthesizer; Cyclization, Benzodiazepin-2-one; Hexamine; Focused Microwave Irradiation; Pharmacological

Abbreviations

m.p.: Melting Point; Ar: Aromatic; br: Broad; ppm: Parts Per Million; IPA: Isopropyl Alcohol; mmol: Milli Mol

Introduction

Finding effective and gentle ways for the manufacture of heterocycles is becoming increasingly crucial for scientists working on the development of organic molecules with higher complexity and chemical variety [1].

Because of their crucial biological effects, compounds containing diazepine groups are of great interest in medical and pharmaceutical research. For recent decades, seven-membered-ring 1,4-benzodiazepine heterocycles have captivated the attention of medicinal and organic chemists. Diazepines, in addition to being the basic unit of commercial pharmaceuticals such as diazepam and oxazepam, exhibit a wide range of biological activity. It has been demonstrated that benzodiazepines combined with other heterocyclic systems have tranquilizing, antispasmodic, and prenascrotic effects. They are well-known depressants of the Central Nervous System (CNS) having anticancer and antibacterial properties [2-5].

The pharmaceutical compound's huge commercial success as well as their social benefits in the present management of mental illness have catapulted the chemistry of these compounds to the top of the list in heterocyclic chemistry.

Moreover, considering the pharmacological application and commercial success of 1,4-benzodiazepin-2-one, we performed an extensive search of literature [6-17] to identify the route of synthesis of these moieties. Several benzodiazepine syntheses processes, according to a review of the literature, include disadvantages such as severe reaction conditions, costly reagents, extensive reaction durations, and the formation of side products. The fundamental problem with current approaches is that catalysts are lost throughout the workup process and cannot be retrieved or reused. Therefore, the hunt for simpler, more reusable, ecologically

friendly, and economically effective benzodiazepine synthesis techniques continues.

According to the literature study, the most generally used procedure of reacting o-Aminobenzophenone with chloroacetyl chloride/bromoacetyl bromide to yield the amidic group, followed by amination and finally cyclization was one of the most effective methods of synthesizing the moiety of benzodiazepine-2-ones. However, these reactions took a long time for the amination and cyclization when carried out conventionally [16,17].

The current study highlights the use of a microwave synthesizer in place of a traditional energy source, which provides concentrated microwave radiation on the reaction vessel with fine control over power, temperature, and pressure generated in a reaction mixture in a sealed tube. In addition, relatively inexpensive chemicals such as Hexamine and ammonium chloride are utilized to achieve the necessary cyclization yielding benzodiazepine-2-ones, reducing the reaction time from several hours, as reported in the literature, to a few minutes. Furthermore, shorter reaction times allow optimization studies since we can quickly analyze the influence of various factors in the reaction condition on the yield of the desired product produced, saving valuable time and energy.

Materials and Methods

Keeping in mind their intrinsic worth, we envisaged developing a protocol that could address all these problems and allow the process to be synthetically more viable.

We, therefore decided to carry out further development of the procedure in view of increasing the simplicity, greenness and economic viability.

Microwave radiation has been used effectively in the past for the enhancement of reactivity and in certain cases has resulted in the formation of a product that under normal conditions would not be possible. Rapid advancements taking place in the field of microwave technology have made it convenient for chemists to safely attain higher values of temperature and pressure in a short period of time. understanding its benefits and potential scope in near future, we decided to use microwaves as our principal source of energy employing CEM Microwave synthesizer discover module for focused synthesis (Figure 1).

Figure 1: CEM Microwave synthesizer discover module.

Chemicals and solvents

All chemicals were purchased from Alfa Aesar, Spectrochem and Aldrich chemicals Co. and were used without further purification.

Microwave

CEM microwave synthesizer Discover module, mono-mode microwave reactor was used as the source of microwave energy.

Thin layer chromatography

The adsorbent used for TLC was silica gel GF-254 procured from Merck (India Ltd.). Visualisation of the spot was carried out in UV chamber.

Column chromatography

Column chromatography was performed using 230-400 mesh size using n-Hexane : Ethyl acetate system.

1H NMR and 13C NMR

NMR data (1H, 13C) were recorded on Varian 300 MHz spectrometers in the solvents indicated; chemical shifts are given in ppm.

IR spectroscopy

IR was performed on an FTIR spectrometer from Shimadzu-prestige 21.

All conversions and yields are rounded up to the nearest significant value. The isolated compounds are in their purest form as determined by 1H NMR (300 MHz).

Results and discussion must illustrate and interpret the reliable results of the study.

General procedure

Preparation of 2-Chloroacetamido-5-chlorobenzophenone

A dropwise addition of chloroacetyl chloride (0.85 mL, 1.2 g, 0.011 mol, 1.06 equiv) in toluene (2 mL) at 5–10 °C was done to a solution of 2-amino-5-chlorobenzophenone (2.31g, 0.01 mol) in toluene (20 mL). The reaction mixture was stirred for 3-4 hours at room temperature. The conversion was monitored by TLC. The resultant reaction mixture was dried out by evaporation. Ethanol (10 mL) was added to the crude product and stirred at room temperature for 20 hours to purify it. Filtration was used to separate the crystals, which were then washed with Ethanol (3 x 2 mL) and dried in a hot oven overnight at 50°C to give crystals of 2-chloroacetamido-5-chlorobenzophenone, 3 g (97.3%). mp 119°C - 121°C.

Using a similar procedure chloroacetamido of different benzophenones was obtained.

Characteristics of 2-Chloroacetamido-5-chlorobenzophenone (2a):

Yield: 97%. m.p. 119-121°C. IR (KBr): 3275.5 cm^{-1} (w, N-H stretch), 1638.48 cm^{-1} (s, C=O stretch), 1639.20 cm^{-1} (s, C=O stretch), 1519.66 cm^{-1} and 1577.49 cm^{-1} (s, Ar C-C vibration/N-H deformation, 771.38 cm^{-1} and 847.56 cm^{-1} (m. Ar out of plane deformation/C-Cl stretch.

^{1}HNMR (300 MHz, $CDCl_3$, **δ**ppm): 4.2 (s, 2H, $–CH_2$), 7.5-7.75 (m, 7H, Ar-H), 8.584-8.617(m, 1H, Ar-H), 11.478 (br s, 1H, -NH).

Characteristics of 2-Chloroacetamido-2',5-chlorobenzophenone (2b)

Yield: 95%. m.p. 160°C-162°C. IR (KBr): 3196.43 cm^{-1} (s, N-H stretch), 3006.48 cm^{-1} (w, Ar C-H stretch), 1689.34 cm^{-1} (m, C=O stretch), 1509.99 cm^{-1} and 1577.49 cm^{-1} (s&m, Ar C-C skeletal vibration), 1288.22 cm^{-1} and 1396.21 cm^{-1} (m, C-N stretch), 759.816 cm^{-1} (m, Ar C-H out of plane deformation).

^{1}HNMR (300 MHz, $CDCl_3$, **δ**ppm): 4.25 (s, 2H, $–CH_2$), 7.352-7.595 (m, 6H, Ar-H), 8.769-8.798 (d, 1H, Ar-H), 12.189 (br s, 1H, –NH).

Characteristics of 2-Chloro-N-[4-chloro-2-(2'-fluorobenzoyl) phenyl]acetamido (2c)

Yield: 94%, m.p. 203°C-206°C. IP (KBr), 3213.79 cm^{-1} (m, N-H stretch), 3010.34 cm^{-1} (m, Ar C-H stretch), 1649.8 and 1691.27 cm^{-1} (s, C=O stretch), 1518.67 cm^{-1} and 1579.41 cm^{-1} (s, Ar C-C vibration), 1216.86 cm^{-1}, 1289.18 cm^{-1} and 1397.17 cm^{-1} (s, C-N stretch), 760.78 cm^{-1} (s, Ar C-H out of plane deformation).

^{1}HNMR (300 MHz, $CDCl_3$, **δ**ppm): 4.23 (s, 2H, $–CH_2$), 7.179-7.338 (m, 2H, Ar-H), 7.491-7.632 (m, 4H, Ar-H), 8.700-8.730 (d, 1H, Ar-H), 11.956 (br s, 1H, -NH).

Preparation of 7-Chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one

General cyclization procedure

Take 2-chloroacetamido-5-chlorobenzophenone (0.24g, 0.8 mmol) in a 10 mL seal tube. Add hexamethylenetetramine (0.25g, 1.8 mol, 2.2 equiv), ammonium chloride (0.192g, 3.6 mol, 4.5 equiv) and methanol: water (4 mL) then irradiate it microwave in CEM Microwave synthesizer in a closed vessel mode using the following settings.

- Temperature: 80°C
- Pressure: 20PSI
- Power: 30W
- Time: 2 mins. x 3
- Stirring: High

The progress of the reaction is monitored by TLC. After the completion of the reaction, 2-3 mL of water is added to the reaction mixture and the product formed is isolated under cold conditions to yield a crude product which was dried at 75°C for 5 h and then purified using column chromatography with a 5-20% Ethyl acetate: n-Hexane system. Alternatively, the crude product was purified with ethanol (3 mL) at 70°C for 0.5 h. The obtained suspension was cooled to +10 °C and filtered, and the crystals were washed with cold ethanol (3 x 2 mL) and then dried at 75°C for 5 h to give0.19g (90%) of 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one.

Using a similar procedure different diazepin-2-ones were obtained.

7-Chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one (3a)

Yield: 90%, m.p. 210°C-213°C. IR (KBr): 3179.08 cm^{-1} (w, N-H stretch), 3042.16 cm^{-1} (w, Ar C-H stretch), 2956.34 (w, C-H stretch of CH_2), 1618.62 cm^{-1} (s, C=O stretch), 1606.41 cm^{-1} (m, Ar C-C skeletal vibration/C=N stretch), 1479.13 cm^{-1} (m, Ar C-C skeletal vibration), 1360.53 cm^{-1} (m, C-N stretch), 700.034 cm^{-1}, 738.603 cm^{-1}, 790.671 cm^{-1} and 820.563 cm^{-1} (Ar C-H out of plane deformation).

^{1}HNMR (300 MHz, $CDCl_3$, **δ**ppm): 4.332 (br s, 2H, CH_2), 7.144-7.542 (m, 8H, Ar-H), 9.831 (s, 1H,-NH).

7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepinone (3b)

Yield: 85%, m.p. 198°C-200°C. IR (KBr): 3344.93 cm^{-1} (w,N-H stretch), 2957.3 cm^{-1} (w, Ar C-H stretch), 1684.52 cm^{-1}(s, C=O stretch), 1607.38 cm^{-1} (w, C=N stretch), 1485.88 (m, Ar C-C skeletal vibration), 1360.53 (m, C-N stretch), 748.245 cm^{-1} (w, Ar C-H out of plane deformation).

^{1}HNMR (300Hz, $CDCl_3$, **δ**ppm): 4.401 (s, 2H,-CH_2), 7.043 (d, 1H, Ar-H), 7.149 (d, 1H, Ar-H), 7.388 (m, 4H, Ar-H), 7.512 (m, 1H, Ar-H), 10.205 (br s, 1H,-NH)

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benmzodiazepin-2-one (3c):

Yield: 88%, m.p. 202°C-205°C. ^{1}HNMR (300 Hz, $CDCl_3$ ppm): 4.379 (s, 2H, CH_2), 7.156 (m, 4H, Ar-H), 7.515 (br s, 1H, N-H).

^{13}CNMR (75MHz, $CDCl_3$, δppm): 56.858, 116.303 and 116.594, 122.956, 124.550 and 124.596, 127.309 and 127.478, 129.332, 129.501, 131.586 and 131.616, 132.107, 132.367 and 132.475, 136.537, 158.902, 162.243, 166.811, 171.762.

Results and Discussion

Giving importance to incorporating a greener solvent into the synthetic procedures for sustainable development we first screened a variety of solvents that were moderate to high absorbers of microwave radiation. Initial studies involved optimization of the reaction conditions for the synthesis of 1,4-benzodiazepin-2-ones without employing any specialty chemicals. A reaction between 2-Choroacetamido-5-chloro benzophenone and hexamethylenetetramine (hexamine) was chosen as a representative reaction (Figure 2).

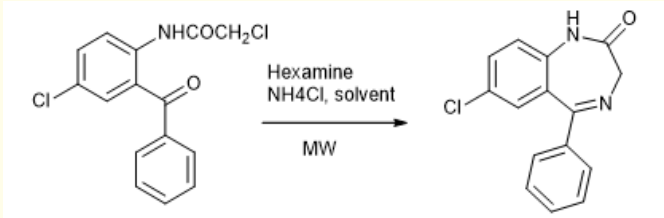

Figure 2: Representative reaction scheme undertaken for optimization.

Organic protic polar solvents such as methanol, ethanol, IPA, which are high absorbers of microwave radiation gave good yields. Lower yields were obtained with low absorbing solvents such as ethyl acetate and chloroform. Aprotic polar solvents such as DMF and DMSO showed similar trends as ethyl acetate suggesting the importance of hydrogen bonding interactions (induced by polar protic solvents) having a facilitating effect on the synthesis of 1,4-benzodiazepin-2-ones. In order to make the protocol environmentally benign and synthetically viable, water and a combination of organic solvents with water were employed which gave good yields of the desired product. It was decided to continue further studies with methanol and water as the solvent of choice. The effect of solvents on the optimization studies is reported in table 1.

Entry	Solvent	Time (mins)	Yield (%)
1	Methanol	10	64
2	Ethanol	10	74
3	Ethyl acetate	10	42
4	DMF	10	45
5	DMSO	10	40
6	Chloroform	10	20
7	IPA	10	65
8	Ethanol: Water	10	72
9	Methanol: Water	10	80
10	IPA: Water	10	70
11	Water	10	25
1 mmol of 2-Choroacetamido-5-chloro benzophenone, 2 mmol of Hexamine, 5 mmol of NH_4Cl, 70°C, MW @50W, reactions monitored by TLC, all yields are isolated yields.			

Table 1: Optimization studies involving the effect of solvent.

Further optimization of temperature was carried out. Thus, several reactions were conducted at different temperatures under pressurized closed vessel conditions of the microwave synthesizer. The disappearance of the starting material was monitored and it was observed as a reference point for the completion of the reaction by thin layer chromatography.

It was observed that the combination of methanol and water gave the desired yield. The ratio of Methanol: to water at 4:1 was sufficient to get the desired yields. The best results were obtained at 80°C. The optimization studies involving the effect of temperature and time is reported in table 2.

Entry	Temperature (°C)	Time (min)	Yield %
1	40	15	64
2	60	10	72
3	70	8	75
4	80	8	85
5	100	6	68
1 mmol of 2-Choroacetamido-5-chloro benzophenone, 2 mmol of Hexamine, 5 mmol of NH_4Cl, 4 mL MeOH:H_2O (4:1), MW @50W, reactions monitored by TLC, all yields are isolated yields.			

Table 2: Optimization studies involving the effect of temperature.

Also, during the optimization studies carried out for temperature, it was observed that the minimum energy required to attain the given temperature was 30W and therefore for further studies, it was decided to use 30W of power to attain the desired temperature. The effect of power (in wattage) on the rate of reaction is reported in table 3.

Entry	Power (W)	Time (min)	~Yield %
1	10	8	54
2	20	8	68
3	30	8	75
4	40	8	80
5	30	4+4	82
6	30	2+2+2	88
1 mmol of 2-Choroacetamido-5-chloro benzophenone, 2 mmol of Hexamine, 5 mmol of NH_4Cl, 4mL MeOH:H_2O (4:1), @80°C, reactions monitored by TLC, all yields are isolated yields.			

Table 3: Optimization studies involving the effect of power.

Further, optimization of the molar ratio of Hexamine and NH_4Cl was carried out using the optimized parameter. The study of the change in the molar ratio of the reagents Hexamine and Ammonium chloride is given in table 4.

Entry	Hexamine ('x' mmol)	NH_4Cl('y'mmol)	Time (min)	Yield%
1	4	10	6(2+2+2)	75
2	2	5	6(2+2+2)	88
3	3	5	6(2+2+2)	85
4	2.2	4	6(2+2+2)	90
1 mmol of 2-Choroacetamido-5-chloro benzophenone, x mmol of Hexamine, y mmol of NH_4Cl, 4 mL MeOH:H_2O (4:1), @80°C and Power 30W, reactions monitored by TLC, all yields are isolated yields.				

Table 4: Optimization studies involving mole ratios of reagents Hexamine and ammonium chloride.

Based on the optimization of the reaction condition with respect to solvent combination, temperature, power, the molar ratio of reagents and time cycle, further reactions were carried out with these optimized conditions to prepare a mini library of benzidiazepin-2-ones based on the type of benzophenone used as the starting material. Shown below (Figure 3) is the schematic diagram and table of the molecules synthesized using the above-discussed optimized condition.

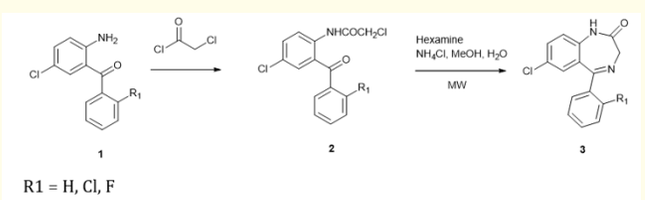

Figure 3: Pathway followed for the conversion of different amino benzophenones to benzodiazepin-2-ones.

Using the optimized conditions several 1,4-benzodiazepine-2-ones were synthesized by reacting 2-chloroacetamido benzophenone with hexamine and ammonium chloride using the microwave as an energy source and a combination of methanol-water as a reaction medium.

Conclusion

Using the CEM microwave synthesizer, an energy-efficient technique for the synthesis of benzodiazepin-2-one from their corresponding 2-aminobenzophenones was devised in a closed

vessel by optimization of parameters like time, temperature, power and molar ratio of the reagents to obtain great yields (90 percent) in a very quick reaction time (6 minutes) without the need of a catalyst. Therefore considerably reduced time of reaction, excellent yields and avoiding the need for costly chemicals/catalysts are the advantage of this approach over conventional processes. The formation of the products was confirmed by m.p. IR, and NMR methods. This straightforward approach may be used to synthesize a variety of pharmaceutically important benzodiazepines. Furthermore, this improved reaction condition will be quite useful for the manufacture of benzodiazpin-2-ones when applied to a commercial model of a Microwave synthesizer.

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Conflict of Interest

The authors declare no conflict of interest.

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