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Energy Efficient Synthesis of various Benzodiazepin-2-ones using Microwave Synthesizer

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ABSTRACT

Benzodiazepine-2-one moiety consists of a seven-membered heterocyclic ring, a derivative of benzodiazepine group, 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, Hexamine, Ammonium chloride, Benzodiazepin-2-one, Microwave irradiation.

INTRODUCTION

Finding effective and gentle ways for the preparation of heterocycles is becoming increasingly crucial for scientists working on the development of organic molecules with higher complexity and chemical variety [1]. Due to their crucial biological effects, compounds containing diazepine groups are of great interest in medical and pharmaceutical research [2]. In 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 tranquillizing, antispasmodic and prenascrotic effects. They are well-known depressants of the central nervous system (CNS) having anticancer and antibacterial properties [3-5].

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 applications 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 synthesis

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processes include several disadvantages such as tedious 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.

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 benzodiazepin-2-one moiety. However, these reactions took long time for the amination and cyclization when carried out conventionally [16,17].

Thus, in present work, keeping in mind their intrinsic worth, we envisaged developing a green protocol in terms of simplicity and economic viability using microwave radiation. Therefore, a simple, catalyst free, ecologically friendly and economically effective benzodiazepine synthesis is proposed.

EXPERIMENTAL

All chemicals were purchased from Spectrochem, Alfa Aesar & Aldrich Chemicals Co. and were used without further purification. The CEM microwave synthesizer Discover module, mono-mode microwave reactor was used as the source of microwave energy. The adsorbent used for TLC was silica gel GF_{254} procured from Merck (India Ltd.). Visualization of the spot was carried out in UV chamber. Column chromatography was performed using 230-400 mesh size using *n*-hexane:ethyl acetate system. The NMR data (^1H, ^{13}C) were recorded on the Varian 300 MHz spectrometers using DMSO as solvent. The IR analysis was conducted on the FTIR spectrometer from Shimadzu-prestige 21.

Synthesis 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 ºC was mixed with 2-amino-5-chlorobenzophenone (2.31 g, 0.01 mol) in 20 mL toluene. The reaction mixture was stirred for 3-4 h at room temperature. The conversion was monitored by TLC. The resultant reaction mixture was dried out by evaporation and washed with ethanol. Filtration was used to separate the crystals, which were then recrystallized with hot ethanol (3 × 2 mL) and dried in a hot oven overnight at 50 ºC to give crystals of 2-chloroacetamido-5-chlorobenzophenone. Yield: 3 g (97.3%); m.p.: 119-121 ºC. Using a similar procedure chloroacetamido of different benzophenones were obtained.

Spectral data

2-chloroacetamido-5-chlorobenzophenone (2a): Yield: 97%. m.p.: 119-121 ºC. IR (KBr, ν_{max}, cm^{-1}): 3275.5 (w, N-H *str.*), 1638.48 (s, C=O *str.*), 1639.20 (s, C=O *str.*), 1519.66 & 1577.49 (s, Ar C-C/N-H def., 771.38 and 847.56 (m. Ar out of plane def./C-Cl *str.*). ^1H NMR (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)

2-Chloroacetamido-2′,5-chlorobenzophenone (2b): Yield: 95%. m.p.: 160-162 ºC. IR (KBr, ν_{max}, cm^{-1}): 3196.43 (s, N-H *str.*), 3006.48 (w, Ar C-H *str.*), 1689.34 (m, C=O *str.*), 1509.99 and 1577.49 (s,m, Ar C-C skeletal vibration), 1288.22 and 1396.21 (m, C-N *str.*), 759.816 (m, Ar C-H out of plane def.). ^1H NMR (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)

2-Chloro-*N*-[4-chloro-2-(2′-fluorobenzoyl)phenyl]-acetamido (2c): Yield: 94%, m.p.: 203-206 ºC. IP (KBr, ν_{max}, cm^{-1}), 3213.79 (m, N-H *str.*), 3010.34 (m, Ar C-H *str.*), 1649.8 and 1691.27 (s, C=O *str.*), 1518.67 and 1579.41 (s, Ar C-C vibration), 1216.86, 1289.18 & 1397.17 (s, C-N *str.*), 760.78 (s, Ar C-H out of plane def.). ^1H NMR (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).

Synthesis of 7-chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one (3): 2-Chloroacetamido-5-chlorobenzophenone (0.24 g, 0.8 mmol) was added to a mixture of hexamethylenetetramine (0.25 g, 1.8 mol, 2.2 equiv), ammonium chloride (0.192 g, 3.6 mol, 4.5 equiv) and methanol:water (4 mL) then irradiated in a CEM Microwave synthesizer in a closed vessel mode. The progress of the reaction is monitored by TLC. After the completion of reaction, 2-3 mL of water was added to the reaction mixture and the product formed wass isolated under cold conditions to yield a crude product which was dried at 75 ºC 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 ºC for 0.5 h. The obtained suspension was cooled to 10 ºC and filtered and the crystals were washed with cold ethanol (3 × 2 mL) and then dried at 75 ºC for 5 h to give 0.19 g (90%) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3a**). Using a similar procedure different diazepin-2-ones were obtained (**Scheme-I**).

7-Chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one (3a): Yield: 90%, m.p.: 210-213 ºC. IR (KBr, ν_{max}, cm^{-1}): 3179.08 (w, N-H stretch), 3042.16 (w, Ar C-H stretch), 2956.34 (w, C-H stretch of CH_2), 1618.62 (s, C=O stretch), 1606.41 (m, Ar C-C skeletal vibration/C=N stretch), 1479.13 (m, Ar C-C skeletal vibration), 1360.53 (m, C-N stretch), 700.034, 738.603, 790.671 & 820.563 (Ar C-H out of plane defor-

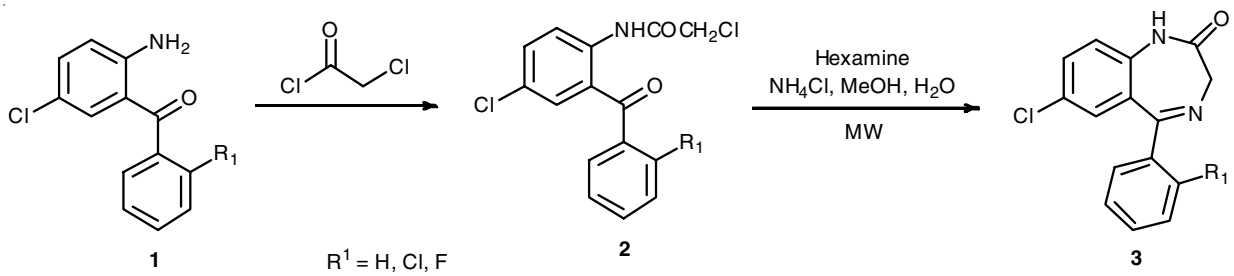


Fig. 1. Pathway followed for the conversion of different amino benzophenones to benzodiazepin-2-ones

mation). ^{1}H NMR (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-2*H*-1,4-benzodiazepinone (3b): Yield: 85%, m.p.: 198°C-200°C. IR (KBr, ν_{max}, cm^{-1}): 3344.93 (w,N-H *str.*), 2957.3 (w, Ar C-H *str.*), 1684.52 (s, C=O *str.*), 1607.38 (w, C=N *str.*), 1485.88 (m, Ar C-C skeletal vibration), 1360.53 (m, C-N *str.*), 748.245 (w, Ar C-H out of plane def.). ^{1}H NMR (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-2*H*-1,4-benzodiazepin-2-one (3c): Yield: 88%, m.p.: 202-205 ºC. ^{1}H NMR (300 Hz, $CDCl_3$ δ ppm): 4.379 (s, 2H, CH_2), 7.156 (m, 4H, Ar-H), 7.515 (br s, 1H, N-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 56.86, 116.30, 122.97, 124.55, 127.309, 127.48, 129.33, 129.50, 131.57, 132.11, 132.37, 136.537, 158.90, 162.24, 166.81, 171.76.

RESULTS AND DISCUSSION

Giving importance to incorporating a greener solvents 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 speciality chemicals. A reaction between 2-choroacetamido-5-chloro benzophenone and hexamethylenetetramine (hexamine) was chosen as a representative reaction.

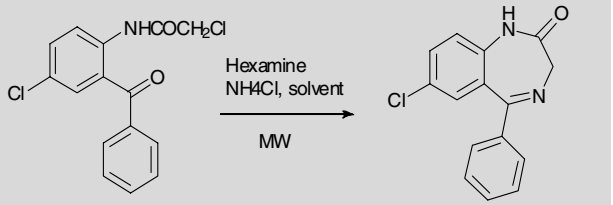
Optimized parameters

Choice of solvent: 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 facili-tating 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 and 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.

Temperature: 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 of the completion of the reaction by TLC. It was observed that the combination of methanol and water gave the desired yield. The ratio of methanol:water as 4:1 was sufficient to get the desired yields. The best results were obtained at 80 ºC. The optimization studies involving effect of time and temperature are reported in Table-2.

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

TABLE-1
OPTIMIZATION STUDIES INVOLVING EFFECT OF SOLVENT



Entry	Solvent	Time (min)	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 @50 W, reactions monitored by TLC, all yields are isolated yields.

TABLE-2
OPTIMIZATION STUDIES INVOLVING EFFECT OF TEMPERATURE

Entry	Temp. (°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 @50 W, reactions monitored by TLC, all yields are isolated yields.

TABLE-3
OPTIMIZATION STUDIES INVOLVING EFFECT OF POWER

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.

Reactant ratio: Further, optimization of the molar ratio of hexamine and NH_4Cl was carried out using the optimized parameters. The study of different molar ratio of hexamine and ammonium chloride is given in Table-4.

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

TABLE-4
OPTIMIZATION STUDIES INVOLVING MOLE RATIOS OF REAGENTS HEXAMINE AND AMMONIUM CHLORIDE

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	4.5	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 30 W, reactions monitored by TLC, all yields are isolated yields.

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%) in a very quick reaction time (6 min) without the need of a catalyst,which is the advantage of this approach over conventional process.

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