

Microwave Assisted Synthesis of Anticancer Active Carbazoles

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Abstract: Microwave assisted organic synthesis (MAOS) is a new and quickly growing technique in synthetic organic chemistry. This synthetic technique is based on the empirical observation that some organic reactions proceeds much faster and with higher yield under microwave irradiation compared to conventional heating. Development of new methods for the synthesis of heterocyclo-fused carbazoles is currently attracting the organic chemist due to the discovery of many carbazole alkaloids with varied biological activities. It has been revealed from the literature that carbazole possess various biological activities including anticancer activity especially against breast cancer. The present study deals with the synthesis of some substituted carbazoles by greener method using dimedone and substituted aromatic amines. This greener method yields 85-90% but conventional method yields maximum of 70%. The products are identified and isolated. The compounds are characterized using IR, ¹H NMR, ¹³C NMR and Mass spectra. The compounds found to possess good anticancer activity.

Keywords: Hetero cyclic compound, aromatic amines, dimedone, carbazole derivatives, greener method

1. Introduction

During the past 50 years the focus on the synthesis of indole derivatives¹ is due to its undisputable importance in nature, where this particular heterocycle is embedded in countless number of nature products and medicinally relevant compounds². Among the indole alkaloids, the carbazole system is the most explored one. Ever since the first isolation of carbazole alkaloid, murraynine³, organic chemists have been interested in the synthesis of carbazole and its derivatives⁴ due to their promising biological activities. Knolker and Reddy have extensively reviewed⁵ the synthesis and biological activities of carbazolealkaloids.

Several annulations strategies based on the Michael addition followed by intramolecular cyclization have been reported⁶. Over the years, the synthesis of large number of carbazole derivatives has been achieved through Diel – Alder reaction⁷ of 2/3 vinylindoles. Similarly, the synthesis of different types of carbazole derivatives has also been realized through Pd – mediated reactions⁸. Jagtap and Mali have reported⁹ an annelation of ethyl – N – methyl – 2 – benzylindole – 3 – carboxylate.

Microwave assisted organic synthesis (MAOS) is a new and quickly growing technique in synthetic organic chemistry. This synthetic technique is based on the empirical observation that some organic reactions proceeds much faster and with higher yields under microwave irradiation compared to conventional heating. In many cases, reactions that normally require many hours at reflux temperature under classical conditions can be completed within several minutes or even seconds in a microwave oven, even at comparable reaction temperatures.

Development of new methods for the synthesis of heterocyclo – fused carbazole is currently attracting the organic chemists due to the discovery of many carbazole alkaloids with varied biological activities¹⁰. Ellipticine and other pyridocarbazoles are usually classified as indole alkaloids¹¹ and are important owing to their antitumor

activity which is in turn due to inhibition of DNA replication and RNA transcription both *in vivo* and *in vitro*¹². Many elegant approaches have been developed for the synthesis of benzo and heterocycle – fused carbazoles¹³⁻¹⁶ and other related natural products involving annulations of indoles. Ellipticine, in particular has found clinical applications in advanced breast cancer, myeloblastic leukemia and solid tumors¹⁷.

A survey of the pertinent literature reveals that carbazole have been found to possess a wide spectrum of biological activity such as antibacterial¹⁸, antiheumatoid arthritis¹⁹, antitubercular²⁰, antiviral²¹, antiepileptic²², antiinflammatory²³, and anticancer²⁴⁻²⁶ activities. Since we have made an attempt to synthesize carbazole derivatives incorporated with antibacterial pharmacophore like imidazole²⁷⁻³² by using both microwave assisted³³⁻³⁵ as well as conventional synthetic method and screened them as potential antibacterial and anticancer agents.

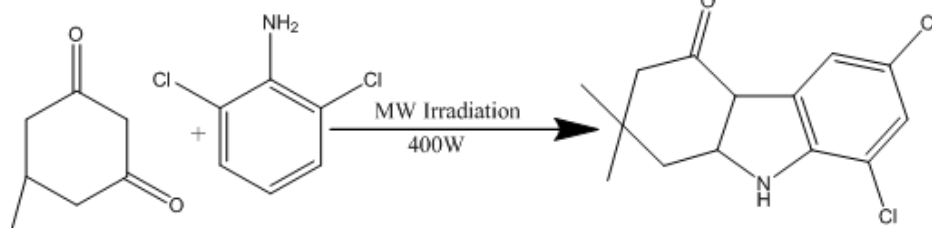
It has been revealed from the literature that carbazole fused with imidazole nucleus possess various biological activities including anticancer activity especially against breast cancer. Carbazole constitutes an important class of naturally occurring heterocycles with interesting biological activities including their special affinity towards DNA³⁶.

2. Material and Methods

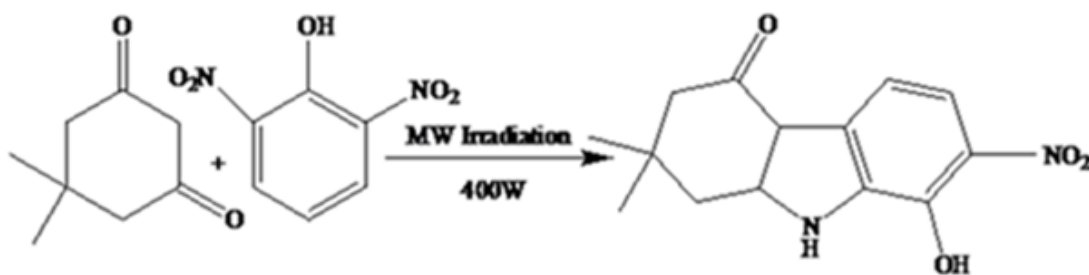
All chemicals and the reagents used in the study were of synthetic grade purity. Aromatic amines and dimedone are purchased from Qualigens Fine Chemicals Company. Solvent used were purified by distillation. All substance prepared for studies were purified by crystallization using appropriate solvents and established procedures. Melting points were measured on a Sigma melting point apparatus using capillary tubes. Analytical TLC was performed on precoated sheets of silica gel to monitor the progress of the reaction as well as to check the purity. The spot were visualized by using iodine vapour. NMR spectra were

recorded on Jeol – FXQ (90 MHz), Jeol GSX (400 MHz) and DPX 200 (200 MHz).

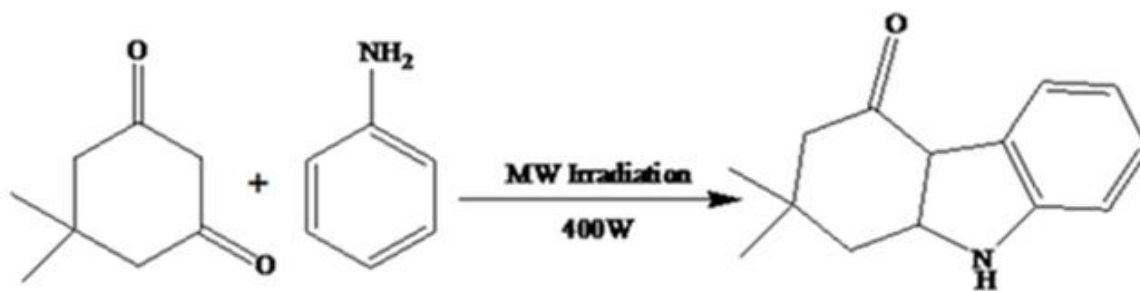
Scheme 1:
Synthesis of aromatic amine substituted carbazole derivatives



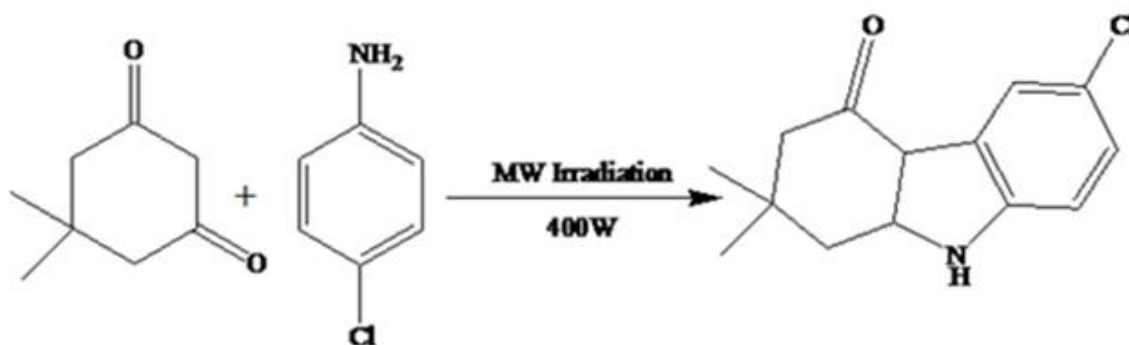
1 (a)



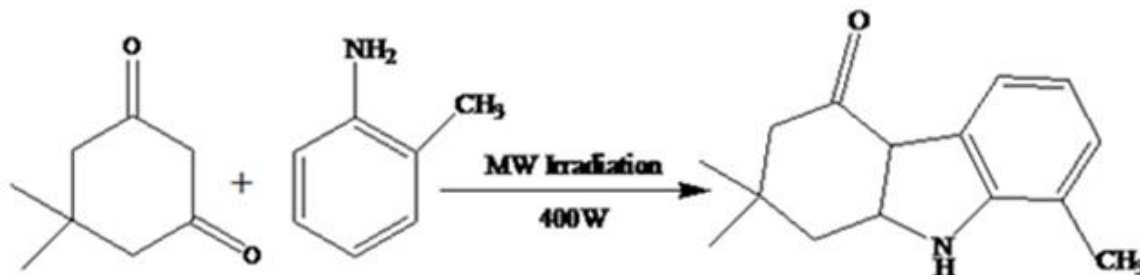
1 (b)



1 (c)



1 (d)



1 (e)

Microwave irradiation of dimedone and aromatic amines are treated in a solvent free condition for 3 minutes. The formation of orange solid mass, confirm carbazole

derivatives in an excellent yield (85 – 90%). Various substituted carbazoles were prepared and reported below.

Table 1: Comparison of thermal and Microwave method (Yield and reaction time of carbazole derivatives)

Compound	Thermal method (Hrs.)	Yield %	Microwave method (min)	Yield %	M. P. °C
1a	6-7	65	3	89	98-100
1b	5-6	60	2	88	108-110
1c	4-5	62	2	90	156-158
1d	3-4	60	1	93	168-170
1e	7-8	55	3	90	141-143

3. Result and discussion

Chemical and pharmaceutical industries are facing constraints regarding environmental aspects and saving energy. To overcome such problems in organic synthesis, the microwave (MW) irradiation as a source of energy is used. In this study we use as excellent synthetic method for new aromatic amine substituted carbazole derivatives (1a – e) by microwave technique.

Characterization:

6,8-dichloro-2,2-dimethyl-2,3,9,9a-tetrahydro-1H-carbazol-4(4aH)-one

¹H NMR: δ 1.0 – 1.10 (gem dimethyl), 2.25– 2.53 (d, C2 & C4), 3.33– 3.76 (m, 4H), 5.51 (br, 2H), 5.99 (s, 1H) 7.26– 7.33 (m, Ar – H), 8.11– 8.13 (br, 1H, N-H). ¹³C NMR: δ 28.16, 28.24, 28.35, 30.93, 31.78, 32.72, 34.07, 43.65, 46.21, 46.98, 50.99, 54.12, 57.28 (aliphatic carbons), 76.78, 77.03, 77.29 (aromatic carbons), 103.12, 115.98, 118.12, 119.66, 127.82, 128.53 (aryl carbons), 140.15 (olefinic carbons), 157.77 (amide carbonyl), 201.72, 203.71 (keto carbonyl).

8-Hydroxy- 2,2- dimethyl-7-nitro-2,3,9,9a-tetrahydro-1H-carbazol-4(4aH)-one

¹H NMR: δ 1.04–1.16 (gem dimethyl), 2.25–2.53 (d, C2 & C4), 3.33 – 3.69 (m, 4H), 5.48 (br, 2H), 6.01 (s, 1H), 7.26 – 7.30 (m, Ar – H), 8.10 (br, 1H, N-H). ¹³C NMR: δ 28.15, 28.24, 30.93, 31.76, 32.60, 34.05, 43.63, 44.72, 46.15, 50.92, 51.03, 54.13, 57.27 (aliphatic carbons), 76.77, 77.02, 77.28 (aromatic carbons), 116.01, 128.51 (aryl carbon), 157.37 (amide carbonyl), 201.32, 203.70 (keto carbonyl).

2,2-dimethyl-2,3,9,9a-tetrahydro-1H-carbazol-4(4aH)-one

¹H NMR: δ 1.00 & 1.16 (2s, gem dimethyl); 2.20 (s, CH₃), 2.25 & 2.57 (s, 4H, C₁ & C₃), 3.37 (s, C₉, 1H), 7.11–7.27 (m, Ar-H). ¹³C NMR: δ 26.8, 47.4, 51.0, 58.6, 61.12 (Aliphatic Carbons), 115.32, 119.5, 121.0, 127.0, 136.8, 151.0 (Aromatic Carbons), 210 (C=O).

6-chloro-2,2-dimethyl-2,3,9,9a-tetrahydro-1H-carbazol-4(4aH)-one

¹H NMR: δ 1.02 & 1.14 (2s, gem dimethyl); 2.24 & 2.54 (s, 4H, C₁ & C₃), 3.77 (s, C₉, 1H), 4.34 (s, NH), 7.25–7.33 (m, Ar-H). ¹³C NMR: δ 26.8, 47.4, 51.0, 58.6, 61.12 (Aliphatic Carbons), 115.32, 119.5, 121.0, 127.0, 136.8, 151.0 (Aromatic Carbons), 210 (C=O).

2,2,8-trimethyl-2,3,9,9a-tetrahydro-1H-carbazol-4(4aH)-one

¹H NMR: δ 1.09 & 1.11 (2s, gem dimethyl); 2.25 & 2.41 (s, 4H, C₁ & C₃), 4.35 (s, C₉, 1H), 4.90 (s, NH), 7.14–7.48 (m, Ar-H). ¹³C NMR: δ 26.8, 47.4, 51.0, 58.6, 61.12 (Aliphatic Carbons), 115.32, 119.5, 121.0, 127.0, 136.8, 151.0 (Aromatic Carbons), 210 (C=O).

4. Conclusion

Synthesized carbazoles were confirmed by spectral studies and they possess anticancer activity. The biological studies may be focused for their future research.

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