One-Pot Multicomponent Synthesis of 2-Azapyrrolizidine Alkaloid Derivatives under Microwave Irradiation

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Abstract

A series of Pyrrolizidine alkaloid derivatives were synthesized by multicomponent reaction of Malononitrile, substituted aryl aldehydes and 2-Thiohydantoin/Hydantoin in the presence of Triethylamine and ethanol as a solvent using microwave irradiation. Microwave irradiation facilitates better thermal management of chemical reactions. The Microwave heat transfer allowed the reaction to be carried out faster compared to conventional heating methods and also resulted in increased yield.

Keywords: Aromatic aldehydes, malononitrile, 2-Thiohydantoin/ Hydantoin, Pyrrolizidine alkaloid, Microwave irradiation.

Introduction

Five and six-membered nitrogen heterocycles belong to a largest class of heterocyclic compounds possessing a diverse biological activities[1-2].The biological activity of hydantoin and 2-thiohydantoin derivatives has been known for a long time. The hydantoin nucleus containing an active urea moiety is responsible for a variety of biological activities such as antiarrhythmic, antihypertensive, antiviral, antineoplastic, anticonvulsant, antimycobacterial, antiulcer, anti-inflammatory agents, as well as pesticides[3]. Additionally, 2-Thiohydantoin derivatives have been identified as molecules which may interact with a wide range of applications as therapeutics[4-6], as well as fungicides and herbicides[7].

Pyrrolizidine alkaloids consist of a number of natural products which have been used in many studies. They have various biological applications in the treatment of cancer, diabetes, and viral infections such as HIV.[8] The pyrrolizidine alkaloids (PAs) are regarded as typical secondary metabolites that illustrate the chemically mediated plant-herbivore interactions. They play a key role in the plant defense against the attack of the insects, nematodes, mammalians and other herbivores[9-10] and they also show anesthetic[11] and antiviral activities[12].

They are derived from amino acids ornithine and lysine with addition of acetate/malonate units. Putrescine, hygrine and cuscohygrine are some of the important examples of pyrrolidine alkaloids. A lot of research is being carried out on these compounds and they have shown to possess exceptional

antibacterial, antifungal and antitubercular properties[13-15]. They produced by the grass endophytic fungus increase resistance to insect feeders, drought and inhibit the germination of seeds of the others plants [16-17].

The occurrence of PAs in the plant world is scattered in several unrelated botanic families: Asteraceae, Boraginaceae, Fabaceae, Apiaceae, Convolvulaceae, Celestraceae, Proteaceae, Santalaceae, Sapotaceae, Ranunculaceae, Euphorbiaceae, Orchidaceae, Scrophulariaceae, and also Poaceae[18-22] and the most important herbal species originated from families: Asteraceaeand Boraginaceae[23]and have a wide variety of biological activities such as antitumor, antibacterial, antifungal, insecticide, antispasmodic, mydriatic, mutagenic, teratogenic and hepatotoxic activity[24].

Microwave (MW) provides a powerful way to do synthetic chemistry in the light of the current paradigm shift to "Green Chemistry". It provides many chemical reactions with attributes, such as enhanced reaction rates, higher yields of pure products, better selectivity, improved ease of manipulation, rapid optimization of reactions and several ecofriendly advantages.[25] Thus this technique is simple, clean, fast, efficient and economic for synthesis of organic molecules. Therefore this synthesis wereprepared by using microwave irradiation.

Due to biological activities of PAs they have been a target molecule for synthesis over the last few decades.

The conventional synthesis involves three component reaction between hydantoin, malononitrile and benzaldehyde in water to obtain (trans-7,7a)-5-amino-7-phenyl-1,3-dioxo-1H-pyrrolo[1,2-c]-imidazole-6-carbonitrile[26]in the presence of piperidine as a base catalyst.This method suffers from the disadvantage of long reaction time.

The current work involves synthesis of 2-Azapyrrolizidine Alkaloid derivatives using microwave irradiation.

Experimental Section

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. All reactions were monitored by thin layer chromatography using aluminium sheets precoated with silica gel 60 F254 (Merck) using either UV light or iodine vapours as visualizing agents. IR spectra was recorded on Bruker FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker FTNMR (500MHz) spectrophotometer with DMSO-d_6 as solvent and TMS as internal standard.

General Experimental procedure

A mixture of 2-Thiohydantoin **(1)**/ Hydantoin(**1a)** (3 mmol), substituted aldehyde **(2)** (3 mmol), and malononitrile **(3)** (3 mmol), in ethanol (10ml) and (20mol%) triethylamine were irradiated in microwave for 5-10min.The reaction was monitored by TLC. Upon completion, the reaction mass was cooled to room temperature. The solid thus obtained, was filtered, washed with hot water and recrystallized from alcohol to afford pure compound.

Spectral Data

(trans-7,7a)-5-amino-1,3-dioxo-7-phenyl-2,3,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole-6-carbonitrile (4a):

White solid, yield 96%; m.p. (°C): 266-270; IR (KBr, cm-1): 3320, 3372 (NH_2), 3270 (NH), 2195 (CN), 1784, 1712 (Ar-H), 1680,1610 (C=O), ^{1}H NMR (500 MHz, DMSO, δ ppm): 12.70 (s, 1H, NH), 7.92 (br,

s, 2H, NH_2), 7.60-7.42 (m, 5H, Ar-H), 4.67 (d, 1H), 4.72 (d, 1H) ppm, ^{13}C NMR (500 MHz, DMSO, δ ppm):189.9, 175.3, 170.1, 168.6, 135.8, 142.9, 148.5, 133.5, 79.4, 71.8, 58.9.

***(trans-7,7a)-5-amino-1,3-dioxo-7-(4-chlorophenyl)-2,3,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole-6-carbonitrile* (4b):**

Pale yellow solid, yield 90%; m.p. (°C): 275-280; IR (KBr, cm-1):3328, 3390 (NH_2), 3217 (NH), 2185 (CN), 1783, 1723(Ar-H), 1652, 1601(C=O), ^1H NMR (500 MHz, DMSO, δ ppm): 12.56 (s, 1H, NH), 7.86 (br, s, 2H, NH_2), 7.52-7.42 (m, 4H, Ar-H), 4.69 (d, 1H), 4.65 (d, 1H) ppm, ^{13}C NMR (500 MHz, DMSO, δ ppm): 186.9, 172.3, 171.1, 168.6, 145.8, 141.9, 135.5, 130.5, 77.4, 72.8, 56.9.

***(trans-7,7a)-5-amino-1-oxo-3-thioxo-7-phenyl-2,3,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole-6-carbonitrile* (4h):**

White solid, yield 90%; m.p. (°C): 272-274; IR (KBr, cm-1): 3220, 3310 (NH_2), 3240 (NH), 2165 (CN), 1760, 1719 (Ar-H), 1658,1613 (C=O), 1260(C=S), ^1H NMR (500 MHz, DMSO, δ ppm):12.80 (s, 1H, NH), 7.90 (br, s, 2H, NH_2), 7.82-7.70 (m, 5H, Ar-H), 4.80 (d, 1H), 4.86 (d, 1H) ppm, ^{13}C NMR (500 MHz, DMSO, δ ppm):195.9, 185.3, 160.1, 172.6, 145.8, 149.9, 152.5, 120.5, 82.4, 70.8, 55.9.

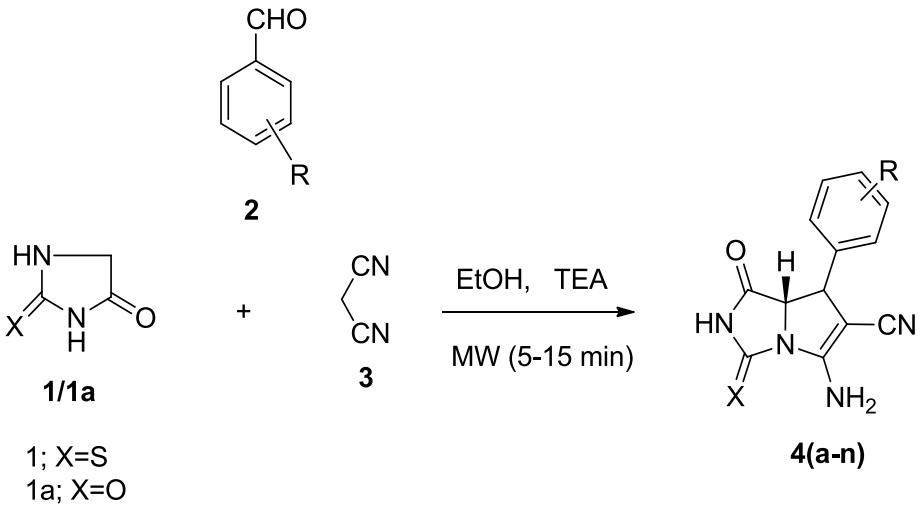
***(trans-7,7a)-5-amino-1-oxo-3-thioxo-7-(4-chlorophenyl)-2,3,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole-6-carbonitrile* (4i):**

Pale yellow solid, yield 85%; m.p. (°C): 280-282; IR (KBr, cm-1):3428, 3290 (NH_2), 3201(NH), 2120(CN), 1775, 1718(Ar-H), 1622, 1605(C=O), 1250(C=S), ^1H NMR (500 MHz, DMSO, δ ppm): 12.32(s, 1H, NH), 7.92 (br, s, 2H, NH_2), 7.65-7.35(m, 4H, Ar-H), 4.75(d, 1H), 4.72(d, 1H)ppm, ^{13}C NMR (500 MHz, DMSO, δ ppm):176.9, 169.3, 178.1, 142.6, 149.8, 133.9, 139.5, 136.5, 75.4, 70.8, 57.9.

Results and Discussion

In the present study, Pyrrolizidine alkaloid derivatives were synthesized by microwave techniques. As compared to conventional reported method, microwave synthesis requires lesser reaction time. The reported conventional method requires 3-8 hrs for completion of the reaction while in microwave synthesis the reaction time was reduced to 5-15 mins as shown in **Table no. 2.**

Scheme 1: Synthetic route of the titled compounds 4(a-n)



The effect of several protic and aprotic solvents on the yield of the reaction was studied (**Table no. 1**).Ethanol gave best yield of the product as compared to other solvents.

Table No. 1. Optimization of solvent for the reaction of Hydantoin (3mmol) benzaldehyde(3mmol), malononitrile (3mmol), Triethylamine (20 mol%), under Microwave Irradiation.

Sr. No.	Solvent (10ml)	Time(min)	Yield of product (%)
1	H_2O	15	88
2	**EtOH**	**11**	**95**
3	MeOH	14	86
4	DMF	17	69
5	DMSO	16	65
6	Toluene	18	18
7	DCM	16	25

Table No. 2: Synthesis of Pyrrolizidine alkaloid derivatives 4(a-n)

Compound code	R	X	Time (min)	Yield (%)	Melting Point (°C)	
					Found	Reported
4a	H	O	11	95	268-270	269[26]
4b	4-Cl	O	13	89	276-278	278[26]
4c	2-Cl	O	12	82	270-272	272[26]
4d	4-Br	O	10	90	275-277	278[26]
4e	3-OCH_3	O	14	91	255-257	256[26]
4f	4-OCH_3	O	15	88	258-260	258[26]
4g	3-NO_2	O	10	92	265-267	268[26]
4h	H	S	12	90	272-274	-
4i	4-Cl	S	14	85	280-282	-
4j	4-OH	S	15	82	256-258	-
4k	3-OH	S	14	80	257-259	-
4l	4-OH-3-OCH_3	S	10	89	262-265	-
4m	3-NO_2	S	12	91	269-271	-
4n	4-NO_2	S	11	93	270-272	-

(Microwave energy in watt for reaction purpose is 210)

Conclusions

- New series of Pyrrolizidine alkaloids derivatives was synthesized successfully by microwave irradiation. The reaction time is reduced from 3–8 h to 5–15min.

- Microwave synthesis minimize the formation of by product. The predominant use of protic solvents leads to quicker, greener, and therefore more environmentally friendly reaction.

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