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MICROWAVE-ASSISTED SYNTHESIS OF SOME NOVEL AMINO ACIDS INCORPORATED DIAZABICYCLO COMPOUNDS AND A COMPARISON WITH CONVENTIONAL METHODS OF THEIR SYNTHESIS

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ABSTRACT

A novel and simple method have been developed for the synthesis of some amino acids incorporated 3, 4-diphenyl-2, 5-diaza-bicyclo [4.3.1] deca-1(9), 2, 4, 6(10), 7-pentaene-8-carbonyl chloride derivatives under microwave irradiation. In addition, these compounds were obtained with conventional heating procedures to compare them with those obtained with microwave irradiation. All the compounds synthesized were characterized by running TLC, Elemental analysis, IR, NMR and LCMS spectra. Consequently, the microwave irradiation method provided nearly the same or higher product yields in a very short period of time. These results suggest that the microwave irradiation method was more useful than the conventional method due to shorter reaction time and energy savings.

Keywords: Synthesis; microwave irradiation; conventional heating and amino acids.

INTRODUCTION

The analogues of bicyclic systems, 8, 10-diza-bicyclo [4.3.1]decane and 3,10-diza-bicyclo[4.3.1]decane bicyclo compounds, have been found to possess potent analgesic and anti-inflammatory activity and are considered as opioid receptor ligands. More specifically, such compounds are can be useful as μ opioid receptor ligands[1-2]. The bicyclo compounds are considered as interesting moiety due to its wide ranging biological activities, which include muscarinic receptor antagonist, antibacterial, antiviral, antiprotozoal, antispasmolytic and antitumor activities[3-10].

In the last decade increased interest has been focused on the application of microwave irradiation in organic synthesis. Numerous reactions can be performed under microwave-assisted conditions; significant rate enhancements, improved yield and selectivity, and a reduction in thermal by-products have been described. It is probable that the increased yields and drastically reduced reaction times are caused by an elevation in the boiling point of the solvent due to a non-nucleated boiling process[11-12].

This synthetic work demonstrates that it is possible to obtain amino acids incorporated diazabicyclo compounds with microwave irradiation, which is a new method for these derivatives. Additionally, these compounds have also been obtained by conventional heating procedures in order to compare them to each other. We preferred to use the same parameters and conditions for both procedures, including solvents and amount of catalyst. We compared the results and product yields of 2 different procedures.

EXPERIMENTAL

The microwave experiments were performed in a domestic microwave oven (Whirlpool, VIP 275/WP, 1000 W). Melting points were determined in open glass capillary tubes and are uncorrected. Infrared (IR)

spectra were recorded on an FT-IR Bruker Tensor 27 spectrometer and are expressed in cm^{-1}. The ^{1}HNMR spectra of the compounds were recorded on Bruker DRX-300 spectrometer. The chemical shifts were reported as parts per million (δ ppm) using tetramethylsilane (TMS) as an internal standard. The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer. The progress of the reaction was monitored on precoated silica gel 60 F254 plates (Merck) using different solvent systems. Spectral data (Elemental analysis, IR, NMR and LC mass spectra) confirmed the structures of the synthesized compounds.

Synthesis of 3, 5-dinitrobenzoyl chloride (1)

A mixture of 3, 5-dinitrobenzoic acid (1 mole) and phosphorous pentachloride (1.12 mole) was refluxed at 120 – 130 ^{0}C for 75 minutes. The reaction mixture was allowed to cool and phosphorous oxychloride so formed was removed by distillation under reduced pressure. The residual 3, 5-dinitrobenzoyl chloride solidified on cooling to a brown mass which was then recrystallized with carbon tetrachloride. The completion of reaction was monitored by running TLC and purified by column chromatography on silica gel (60-120 mesh) eluting with chloroform: methanol (9:1). Mol. Formula: $C_7H_3ClN_2O_5$, Yield 72%, m.p. 69˚C; IR (cm^{-1}): 1573(-NO_2), 1713(C=O), 2934(CH-Ar).

General procedure

Synthesis of 2-(3, 5-dinitrobenzamido) acetic acid (2a):

A solution of 3, 5-dinitrobenzoyl chloride (1 mole) in 1, 4-dioxan was added to glycine (1.2mole) in 0.1 N sodium hydroxide (10 ml) and refluxed for 6 hrs. The reaction mixture was allowed to cool and poured into 1N hydrochloric acid and crushed ice. The crude product was filtered, dried, recrystallized with methanol and column chromatographed on silica gel (60-120 mesh) eluting with methanol: ethyl acetate (8:2). Mol. Formula: $C_9H_7N_3O_7$, Yield 67%, m.p. 182˚C; IR (cm^{-1}): 1570(-NO_2), 3703(-OH), 3402(-NH_2), 2867(-CH_2), 1714, 1634(C=O), 2968(CH-Ar).

All the other compounds **2b-2e** were prepared by the same procedure using the corresponding amino acid.

2-(3, 5-Dinitrobenzamido) pentanedioic acid (2b): Mol. Formula: $C_{12}H_{11}N_3O_9$, Yield 62%, m.p. 178˚C; IR (cm^{-1}): 1571(-NO_2), 3714(-OH), 3378(-NH_2), 2863(-CH_2), 1713, 1630(C=O), 2969(CH-Ar).

1-(3, 5-Dinitrobenzoyl)-pyrrolidine-2-carboxylic acid (2c): Mol. Formula: $C_{12}H_{11}N_3O_7$, Yield 69%, m.p. 181˚C; IR (cm^{-1}): 1570(-NO_2), 3609(-OH), 2885(-CH_2), 1705, 1622(C=O), 3102(CH-Ar), 1346(tert.N).

2-(3, 5-Dinitrobenzamido)-3-mercapto propanoic acid (2d): Mol. Formula: $C_{10}H_9N_3O_7S$, Yield 61%, m.p. 202˚C; IR (cm^{-1}): 1593(-NO_2), 3752(-OH), 3605(-NH_2), 2873(-CH_2), 1698, 1645(C=O), 2978(CH-Ar), 2560(-SH).

2-Amino-6-(3, 5-dinitro-benzoyl amino)-hexanoic acid (2e): Mol. Formula: $C_{13}H_{16}N_4O_7$, Yield 54%, m.p. 196˚C; IR (cm^{-1}): 1552(-NO_2), 3409(-OH,-NH_2 merged), 2862, 2842(-CH_2), 1702, 1651(C=O), 2982(CH-Ar).

General procedure

Synthesis of 2-(3,5-diamino-benzamido)acetic acid (3a): A suspension of 2-(3,5-dinitrobenzamido)acetic acid (1 mole) and zinc dust (2.5 mole) in methanol was stirred with 5 ml of 90% formic acid at room temperature for 5hrs. After completion of the reaction (monitored by TLC), the reaction mixture was filtered off. The organic layer was evaporated and the residue was dissolved in ether and washed with saturated sodium chloride solution (5 times) to remove of ammonium formate. Then the etheral layer was evaporated to dryness[13]. The crude product was recrystallized with ethanol and purified by column chromatography on silica gel (60-120 mesh) eluting with chloroform: ethyl acetate (9:1). Mol. Formula: $C_9H_{11}N_3O_3$, Yield 65%, m.p. 173˚C; IR (cm^{-1}): 3727(-OH), 3634(-NH_2), 2858(-CH_2), 1680, 1619(C=O), 2938(CH-Ar). All the other compounds **3b-3e** were prepared similarly.

2-(3, 5-Diamino-benzamido)-pentanedioic acid (3b): Mol. Formula: $C_{12}H_{15}N_3O_5$, Yield 71%, m.p. 184˚C; IR (cm^{-1}): 3733(-OH), 3633(-NH_2), 2865(-CH_2), 1700(C=O), 2987(CH-Ar).
1-(3, 5-Diamino-benzoyl)–pyrrolidine-2-carboxylic acid (3c): Mol. Formula: $C_{12}H_{15}N_3O_3$, Yield 73%, m.p. 108˚C; IR (cm^{-1}): 3628(-OH), 3700, 3726(-NH_2), 2873(-CH_2), 1697, 1613(C=O), 2977(CH-Ar), 1342(tert.N).
2-(3, 5-Diamino-benzamido)-3-mercapto propionic acid (3d): Mol. Formula: $C_{10}H_{13}N_3O_3S$, Yield 68%, m.p. 115˚C; IR (cm^{-1}): 3732(-OH), 3618(-NH_2), 2853(-CH_2), 1618, 1702(C=O), 2934(CH-Ar), 2531(-SH).
2-Amino-6-(3, 5-diamino-benzamido) hexanoic acid (3e): Mol. Formula: $C_{13}H_{20}N_4O_3$, Yield 62%, m.p. 126˚C; IR (cm^{-1}): 3734(-OH), 3622(-NH_2), 2865(-CH_2), 1622, 1701(C=O), 2924(CH-Ar).

General procedure
Synthesis of 2-[(3, 4-diphenyl-2, 5-diaza-bicyclo [4.3.1] deca-1(9), 2, 4, 6(10), 7-pentaene-8-carbonyl) -amino]-pentanedioic acid (4a):

Conventional Method
2-(3, 5-diamino-benzamido) acetic acid (1 mole) was dissolved in 0.1N sodium hydroxide solution. To this, a mixture of benzil (1.1mole) and sodium ethoxide (2.3mole) in ethanol was dissolved with continuous stirring and refluxed for 55hrs. The reaction mixture was then allowed to cool and poured into 1N hydrochloric acid and crushed ice. The content was kept over night at room temperature, filtered, dried and recrystallized with methanol. The completion of the reaction was monitored by TLC and purified by column chromatography on silica gel (60-120 mesh) eluting with methanol: ethyl acetate (8:2).

Microwave method
2-(3, 5-diamino-benzamido) acetic acid (1 mole) was dissolved in 0.1N sodium hydroxide solution. To this, a mixture of benzil (1.1mole) and sodium ethoxide (2.3mole) in ethanol was dissolved with continuous stirring and finally whole the reaction mixture was placed in a conical flask, covered with a glass funnel and irradiated at 200 Wt. A beaker containing ice-cold water was also kept in oven to serve as a 'heat sink'. To monitor the progress of the reaction, a TLC was run after every one minute of microwave irradiation. After the completion of the reaction, the work-up was done in a manner similar to the conventional procedure.

Mol. Formula: $C_{23}H_{17}N_3O_3$; IR (cm^{-1}) : 3712(-OH), 3670(-NH_2), 2858(-CH_2), 1681(C=O), 2968(CH-Ar),1530(C=N); ^{1}H NMR(DMSO) : δ 2.5 (d, 2H, CH_2), 9.03 (t, 1H, NH), 8.86 (s, 1H, COOH), 7.60-7.93 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$384.4, $[M+2]^+$ 385.4.

2-[(3, 4-Diphenyl-2, 5-diaza-bicyclo[4.3.1]deca-1(9), 2, 4, 6(10), 7-pentaene-8-carbonyl)-amino]-pentanedioic acid (4b) : Mol. Formula: $C_{26}H_{21}N_3O_5$; IR (cm^{-1}): 3737(-OH), 3528(-NH_2), 2888(-CH_2), 1675, 1699(C=O), 3083(CH-Ar), 1588(C=N); ^{1}H NMR(DMSO) : δ 1.21 (s, 1H, CH), 8.66 (s, 1H, COOH), 2.5 (m, 4H, $(CH_2)_2$), 8.88 (t, 1H, NH), 9.10 (s, 1H, COOH), 7.53-7.93 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$ 456.

1-(3, 4-Diphenyl-2, 5-diaza-bicyclo[4.3.1]deca-1(9), 2, 4, 6(10), 7-pentaene-8-carbonyl)-pyrrolidine-2-carboxylic acid (4c) : Mol. Formula: $C_{26}H_{21}N_3O_3$; IR (cm^{-1}) : 3602(-OH), 2798(-CH_2), 1707, 1546(C=O), 3098(CH-Ar), 1493(C=N), 1336(tert.N) ; ^{1}H NMR(DMSO) : δ 1.20 (t, 1H, CH), 3.75 (m, 4H, $(CH_2)_2$ pyrrolidine ring), 2.5 (m, 2H, CH_2), 9.0 (s, 1H, COOH), 7.23-8.02 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$424.4.

2-[(3, 4-Diphenyl-2, 5-diaza-bicyclo[4.3.1]deca-1(9), 2, 4, 6(10), 7-pentaene-8-carbonyl)-amino]-3-mercapto propionic acid (4d) : Mol. Formula: $C_{24}H_{19}N_3O_3S$; IR (cm^{-1}) : 3506(-OH), 3399(-NH_2), 2877(-CH_2), 1711, 1626(C=O), 3084(CH-Ar), 1532(C=N), 2637(-SH) ; ^{1}H NMR(DMSO) : δ 1.20 (s, 1H, CH), 8.65 (s, 1H, COOH), 2.5 (d, 2H, CH_2), 9.09 (t, 1H, NH), 8.87 (s, 1H, SH), 7.27-7.93 (m, 13H, ArH) ; LCMS : m/z $[M-1]^+$428.3.

3, 4-Diphenyl-2, 5-diaza-bicyclo[4.3.1]deca-1(9), 2, 4, 6(10), 7-pentaene-8-carboxylic acid (5-amino-6-hydroxy-6-oxo-hexyl)-amide (4e) : Mol. Formula: $C_{27}H_{26}N_4O_3$; IR (cm^{-1}) : 3726(-OH), 3647(-NH_2), 2864(-CH_2), 1678(C=O), 2924(CH-Ar), 1569(C=N) ; ^{1}H NMR(DMSO) : δ 1.21 (t, 1H, CH), 8.66 (s, 1H, COOH), 2.5 (m, 2H, CH_2), 9.09 (t, 1H, NH), 8.88 (d, 2H, NH_2), 3.58 (m, 6H, CH_2) 7.60-7.93 (m, 13H, ArH) ; LCMS : m/z $[M+1]^+$455.4, $[M-1]^+$452.8.

RESULTS AND DISCUSSION

In the present study, we first performed the synthesis of diazabicyclo compounds by conventional heating as depicted in **Scheme 1** but to reduce the reaction time, it was decided to synthesize the compounds with microwave irradiation, which can be more effective, faster, and energy efficient in addition; we compared those with others that were obtained via conventional heating methods. For a realistic comparison we repeatedly scrutinized the same parameters and conditions, including the solvents and base-catalyst.

Comparing the conventional and microwave irradiation methods, we observed very similar results (**Table 1 & 2**). All the reaction conditions were successfully repeated a few times and then, optimum results were taken into consideration. By the microwave irradiation for heating, all the five compounds were prepared in yields that were appreciably higher than the conventional methods. The quality of the products formed was found to be better showing less number of impurities on TLC when compared to the conventional products. The yield of compound 4b via microwave irradiation was higher i.e. 69% than that of the other microwave irradiation products**.**

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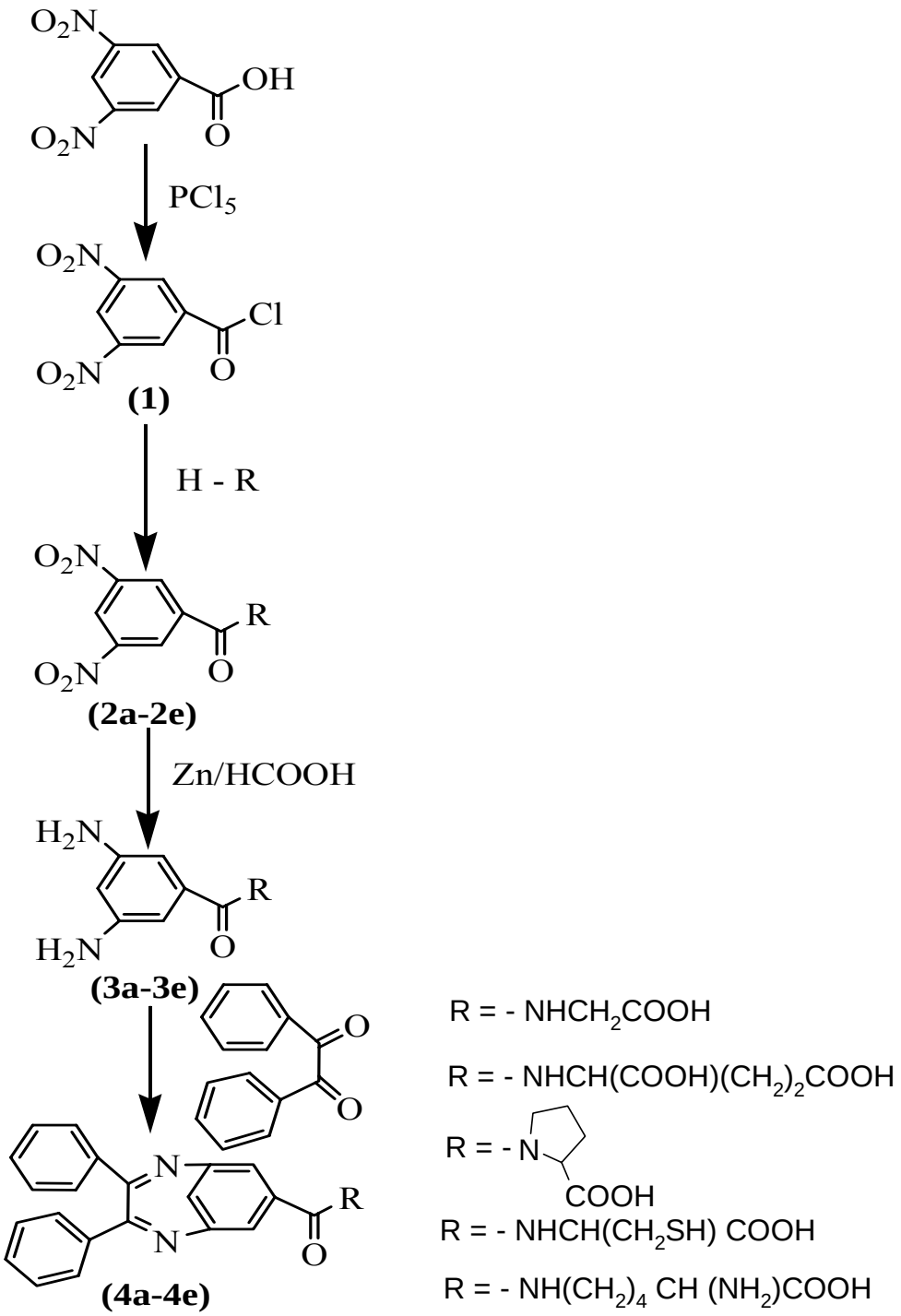
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H - R
O2N
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Zn/HCOOH
H2N
R
H2N
O
(3a-3e)
O
O
N
N
R
O
(4a-4e)
R = - NHCH2COOH
R = - NHCH(COOH)(CH2)2COOH
R = - N
COOH
R = - NHCH(CH2SH) COOH
R = - NH(CH2)4 CH (NH2)COOH

Scheme-1

Table-1: Comparative reaction time and percentage yield of amino acids incorporated diazabicyclo compounds by conventional and microwave methods

Compound No.	Reaction Time		Yield (%)	
	Conventional(hr)	*MW(min)*	*Conventional*	*MW*
4a	55	11	48	65
4b	152	26	43	69
4c	120	19	47	48
4d	134	22	50	67
4e	165	37	42	44

Table-2: Comparative characterization of amino acids incorporated diazabicyclo compounds by conventional and microwave methods

Com. No.	R_f Value		M.P. (˚C)		CHN calculated	CHN found	
	Conv.	*MW*	*Conv.*	*MW*		*Conv.*	*MW*
4a	0.64	0.63	83	82	**C** : 72.05 **H** : 04.47 **N** : 10.96	**C** : 72.16 **H** : 04.57 **N** : 10.89	**C** : 72.20 **H** : 04.52 **N** : 10.91
4b	0.65	0.67	68	67	**C** : 68.56 **H** : 04.65 **N** : 09.23	**C** : 69.18 **H** : 04.62 **N** : 09.31	**C** : 68.92 **H** : 04.58 **N** : 09.18
4c	0.69	0.68	55	56	**C** : 73.74 **H** : 05.00 **N** : 09.92	**C** : 74.46 **H** : 04.92 **N** : 09.76	**C** : 72.89 **H** : 05.06 **N** : 09.83
4d	0.66	0.65	73	74	**C** : 67.12 **H** : 04.46 **N** : 09.78	**C** : 66.88 **H** : 04.54 **N** : 09.65	**C** : 67.11 **H** : 04.39 **N** : 09.82
4e	0.57	0.59	77	76	**C** : 71.35 **H** : 05.77 **N** : 12.33	**C** : 70.90 **H** : 05.81 **N** : 12.42	**C** : 71.16 **H** : 05.69 **N** : 12.28

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Nobody climbs mountains for scientific reasons. Science is used to raise money for the expeditions, but you really climb for the hell of it.

-Edmund Hillary