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A comparative study on the synthesis of N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives using microwave irradiation and conventional thermal methods

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ABSTRACT: A convenient synthesis of , n-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives under microwave irradiation as well as conventional thermal method using by a one-pot condensation reaction of the aromatic dial, 2,7naphthalenediol, carboxylic acids and aqueous ammonia (25 %) is reported. Microwave irradiation has resulted in the reduction of time from 10-20 min to a 1-2 minutes.

Keywords: *2-Azaphenalene, Microwave irradiation, One-pot, Thermal.*

INTRODUCTION

There has been a growing interest in the use of microwave irradiation in organic synthesis during the past decade, since the first contribution by Gedye *et al.*, [1] and Giguere *et al.*, [2] in 1986. The number of publications and reviews that have advocated the advantages and the use of microwave irradiation over conventional technology have increased significantly [3, 4]. Remarkable decreases in reaction time and, in some cases, cleaner reaction and better yields have made this technique widely applicable in organic synthesis. At the beginning of the 20th century, Mario Betti discovered the three-component reaction of 2-naphthol, aryl aldehydes and ammonia or amines for the synthesis of aminobenzylnaphthols [5]. Now, this process has been known as the Betti reaction and the aminonaphthol product known as a Betti base [6]. The phenolic hydroxyl and amino groups in Betti bases can be used in synthetic building blocks. Aminonaphthols have several interesting biological applications, such as antibacterial, hypotensive, and bradycardiac activities [7-9]. Optically active Betti bases can be used as ligands to chelate with organometallic reagents in different reactions to provide highly efficient asymmetric reaction [10, 11]. The classical synthesis of Betti bases generally involves a modified Mannich pathway by the condensation of 2-naphthol, aldehydes, and amines. However, various modifications have been made to prepare Betti base derivatives by using other naphthols, quilinols, and alkylamines [12-15]. In recent years, several more convenient and green procedures for Betti reactions

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have also been successfully developed [16-23]. In continuation of our ongoing effort to develop new environmentally benign multicomponent reactions [24-26]. Azaphenalenyl, a heteroatomic modification of the phenalenyl system, is an important building block in the synthesis of organic multifunctional [27-29]. Azaphenalene derivatives extremely promising antioxidants in biological systems [30]. Several alkaloid-based compounds with a tricyclic azaphenalene core have been isolated from a variety of ladybird species are precoccinelline and hippodamine [31]. Because of their high biological activity, scarce natural supply, and difficult, only small-scale, isolation from natural sources, synthesis of this heterocyclic nucleus is currently of major importance. We thought it is worth attempting the synthesis of N benzoiel-1,3-diaryl-2 -(para formyl) azaphenalene derivatives to high yield by exploiting microwave and the catalyst-free five-component condensation reaction under solvent-free classical heating conditions. However, there are few examples of the preparation of the title compounds from azaphenalene in the literature [7]. Here, we describe our results on the synthesis of azaphenalene derivatives using microwave irradiation.

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka and used without further purification. Melting points were determined in capillary tubes on an electro thermal digital apparatus and are uncorrected. Infrared spectra were recorded as KBr pellets on a Unicom Galaxy Series FT-IR 5000 spectrophotometer in the region 4,000–400 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz respectively, using DMSO-d6 solvent with TMS as the internal standard. Microwave reactions were carried out in microwave oven MW939.

General procedure for preparation of N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives (5a–5d) under conventional heating method

A mixture of 2,7-naphthalenediol (1 mmol), aldehyde (2 mmol), the carboxylic acid (1.2 mmol), and aqueous ammonia (0.5 mmol, 25 %) was stirred under solvent-free conditions at 135 °C for an appropriate time (indicated in Table1). The progress of the reaction was monitored by TLC. After completion of the reactions, saturated aqueous NaCl (20 mL) was added, the suspension was stirred for 40 min, and the precipitate was isolated by filtration, washed with water, and air-dried. The crude products were washed with ethyl acetate–n-hexane, (20 mL, 1: 4) and dried at 100 °C under vacuum for 6hr to afford the pure products.

General procedure for preparation of N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives (5a–5d) under microwave irradiation method

A mixture of 2,7-naphthalenediol (1.2 mmol), aldehyde (2 mmol), the carboxylic acid (1.2 mmol), and aqueous ammonia (1.2 mL, 25 %) was subjected to microwave irradiation at 800W for different times and temperatures (table 2). Progress of the reaction was monitored by TLC. After the completion of the reaction, saturated aqueous NaCl (20 mL) was added, the suspension was stirred for 15 min, and the precipitate was isolated by filtration, washed with water, and dried. The crude products were washed with ethyl acetate–n-hexane, (20 mL, 1: 4), dried at 100 °C under vacuum for 24hr and recrystallized with ethanol to afford the pure products.

4,4'-(2-benzoyl-4,9-dihydroxy-2,3-dihydro-1H-benzo[de]isoquinoline1,3diyl)

dibenzaldehyde (Compound 5a): IR (KBr, cm^{-1}): ν_{max} = 3268, 3030, 2818,1698, 1625, 1585, 1514, 1431, 1325, 1273, 1133, 1024, 881, 736, 701, 671 ; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 5.18 (s, 2H, 2-CH), 6.86 (d, J = 8.7 Hz, 2H, Ar-H), 7.09 (d, J = 7.0 Hz, 4H, Ar-H), 7.15-7.24 (m, 6H, ArH), 7.46-7.63 (m, 5H, Ar-H), 7.95 (d, J = 7.6 Hz, 2H, Ar-H), 9.19 (br, 2H, disappeared on D_2O exchange) ,9.78 (s, 2H, disappeared on D_2O exchange) ; ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 54.0, 115.3, 115.9, 122.7, 126.8, 127.9, 128.2, 128.4, 128.9, 129.7, 132.0, 132.1, 133.0, 144.5, 150.7, 168.0, 191ppm.

4,4'-(4,9-dihydroxy-2-(3-nitrobenzoyl)-2,3-dihydro-1H-benzo[de]isoquinoline-1,3-diyl)

dibenzaldehyde (Compound 5b) IR (KBr): mmax = 3371, 3076, 2864,1730, 1626, 1526, 1512, 1424,

1346, 1321, 1275,1156, 1024, 832, 699 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): d = 5.30 (s, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.67–7.48(m, 8H), 7.94 (s, 4H), 8.08 (d, J = 7.6 Hz, 2H),9.45 (s, 2H, disappeared on D_2O exchange), 9.83 (s, 2H, disappeared on D_2O exchange); ^{13}C NMR(75 MHz, DMSO-d_6):d = 53.5, 114.9,115.4,122.0,122.8, 123.0, 128.5, 129.0, 129.7, 131.3, 131.7,133.2, 135.4, 147.2, 148.1, 150.9, 167.9, 189.

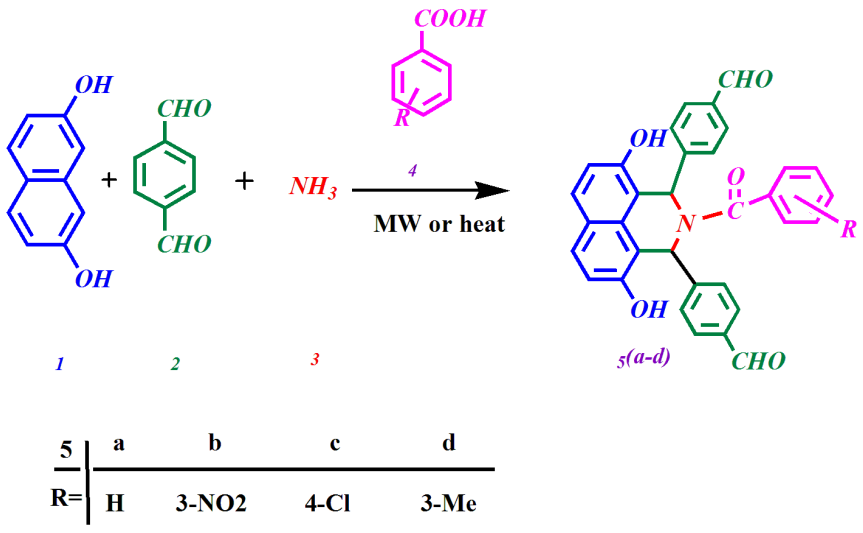
4,4'-(2-(4-chlorobenzoyl)-4,9-dihydroxy-2,3-dihydro-1H-benzo[de]isoquinoline-1,3-diyl) **dibenzaldehyde (Compound 5c)**: IR (KBr): mmax = 3464–2885, 2681, 1732,1631, 1589, 1512, 1454, 1388, 1313, 1089,1012, 829, 775, 694 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): d=5.50 (s, 2H),6.68–6.75 (m, 10H), 7.00 (d, J=8.7Hz, 2H), 7.53(d,J=8.1Hz, 2H), 7.69 (d,J=8.7Hz, 2H),7.93(d, J=8.1Hz,2H), 9.43 (br, 2H, disappeared on D_2O exchange); 9.82 (s, 2H, disappeared on D_2O exchange); ^{13}C NMR (75 MHz, DMSO- d_6): d=52.8, 113.7, 114.8, 122.7, 125.7, 126.9, 128.3, 128.8, 128.9, 131.0, 131.5, 131.9, 137.4, 141.9, 151.3,167.5, 179.

4,4'-(4,9-dihydroxy-2-(3-methylbenzoyl)-2,3-dihydro-1H-benzo[de]isoquinoline-1,3-diyl) **dibenzaldehyde (Coumpound 5d)**: IR (KBr): mmax = 3460–2818, 2671, 2521,1731, 1620, 1591, 1539, 1516, 1433, 1388,1319, 1273, 835, 761, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): d = 2.36 (s,3H), 5.19 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 7.2 Hz,4H),7.14–724 (m,6H), 7.34–7.43 (m, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 9.20(br, 2H, disappeared on D_2O exchange); 9.82 (s,2H,disappeared on D_2O exchange); ^{13}C NMR (75 MHz, DMSO- d_6): d = 21.4,54.1, 115.3, 122.7, 127.0, 128.1, 128.3, 128.7, 128.8, 129.7, 130.3, 132.1,132.9, 133.4, 138.1, 143.9, 151.0, 168.4, 186.

RESULTS AND DISCUSSION

2,7-naphthalenediol, aromatic aldehydes, carboxylic acids, and aqueous ammonia (25%) under solvent-free conditions was subjected to condensation reaction (Scheme 1). After 10 min at room temperature, the content of the flask was subjected to microwave irradiation at 800W for different times and temperatures (Table 2). The creamy yellow precipitate obtained was found to be N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives 5 after usual work-up. The same compounds were also synthesized by conventional heating method for comparison. In conventional heating method, the reaction mixture was heated on an oil bath at 135 °C for 10-20 min. The reaction yielded the same azaphenalene derivatives 5 with slight variation in the yield. The results are summarized in Table 1.

To optimize the reaction conditions, the reaction of dial 2a (2 mmol), 2,7-naphthalenediol 1, benzoic acid



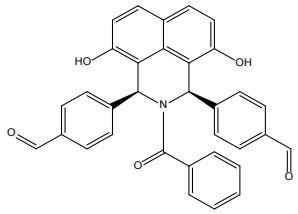
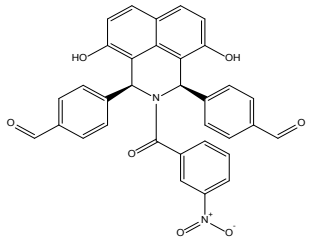
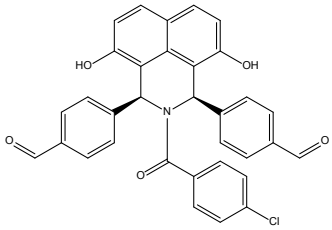
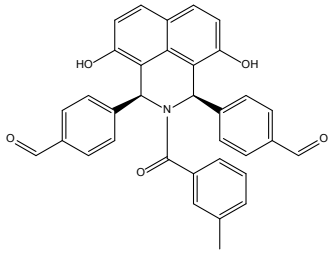
Scheme 1. Synthesis of N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives.

Table 1. Reaction of the conditions for synthesis of N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives (5a-d) under microwave irradiation at 800W and thermal method.

Product	Substituents	Time		Yield (%)		m.p (°C)
		[a] MW (min)	[b] Δ (min)	MW	Δ	
5a	H	2.5	10	91	89	316-317
5b	3-NO_2	2.5	20	90	80	296-298
5c	4-Cl	2.5	15	96	87	303-305
5d	3-Me	2.5	10	94	74	321-322

[a] The reaction was carried at 90 °C; [b] The reaction was carried at 135 °C

Table 2. Reaction of the conditions for synthesis of N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives (5a-d) under microwave irradiation at 800W

Entry	Compound	Reaction Time (min)	Temperature (°C)	Yeild (%)
5a		1	75	60
		1.5	80	78
		2	85	89
		2.5	90	91
		3	95	decomposed
5b		1	75	58
		1.5	80	72
		2	85	84
		2.5	90	90
		3	95	decomposed
5c		1	75	62
		1.5	80	76
		2	85	81
		2.5	90	96
		3	95	Decomposed
5d		1	75	59
		1.5	80	73
		2	85	86
		2.5	90	94
		3	95	Decomposed

4a, and aqueous ammonia (25 %) was used as a model, and was conducted under different reaction conditions for example, time and temperature (Table 2). The use of microwave irradiation has drastically reduced the reaction time from with good yields. When the same reaction was conducted at 75 °C, yields were low. Increasing the reaction temperature to 90 °C did increase the yield of the product but with increasing temperature to 95 °C the product decomposed. The results are summarized in Table 2. All reactions proceeded efficiently at 90 °C obtained in good yields (90-96 %) in relatively short reaction times, without the formation of any side products.

CONCLUSIONS

In conclusion, we have disclosed a one-pot efficient microwave assisted synthesis of N-benzoiel-1,3-diaryl-2-(para formyl) azaphenalene derivatives in good yields via condensation reaction. In this method, the reaction time has been brought down from 10-15 minutes to a few minutes compared to conventional heating method. Its broad scope as well as the easy access to the starting materials and short reaction time under microwave irradiation should make this methodology widely applicable in organic synthesis without heating.

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