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ORIGINAL ARTICLE

Microwave assisted synthesis of 2,6-diaryl-4-piperidones and 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones

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Abstract One pot, three-component synthesis of 2,6-diaryl-4-piperidones and 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones under microwave irradiation, was found to be efficient to afford good to excellent yields. This method has many advantages, which avoids the use of catalysts, accelerates the rate of reaction, high yields, methodological simplicity and eco-friendliness.

1. Introduction

In recent years, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. Among the family of heterocycles, nitrogen heterocycles especially piperidin-4-ones gain considerable importance owing to their varied biological properties such as antiviral (El-Subbagh et al., 2000), antitumour (Perumal et al., 2001), analgesic (Mobio et al., 1989), local anaesthetic (Katritzky and Fan, 1990; Ganellin and Spickett, 1965), antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, anti-histaminic, anti-inflammatory, anticancer, CNS stimulant and depressant activities (Ramalingam et al., 2006; Balasubramanian et al., 2006; Murugesan et al., 2006). The skeletal ring of piperidine nucleus can also be often found in the molecular framework of many synthetic and natural medicaments. The 3,7-diazabicyclo[3.31]nonan-9-ones (3,7-DABN) nucleus is also having the biological significance due to its presence in the molecular structure of various alkaloids (diterpene/norditerpene and lupin) and drugs (Hosken et al., 1995; Gallagher et al., 1995). Piperidin-4-ones and 3,7-DABN are generally synthesized by one pot cyclocondensation of aryl aldehydes, dicarbonyls/β-ketoesters and ammonium acetate/ammonia/primary amine in refluxing with alcohol leading to low yields with longer reaction times. Thus the development of a simple and efficient method for the synthesis of both piperidin-4-ones and 3,7-DABN is an active area of research and hence has the scope for further improvement with milder reaction conditions and higher product yields. In continuation of our earlier interest in piperidin-4-ones (SubhaNandhini et al., 2003; Vijayakumar et al., 2010; Rajesh et al., 2010a) and 3,7-DABN (Vijayakumar et al., 2000, 2001, 2005; Chinar et al., 2007; Natarajan et al., 2008; Fun et al., 2009; Loh et al., 2010; Rajesh et al., 2010b) as well as considering their significance herein we report an efficient and simple procedure for the synthesis of these

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compounds under microwave irradiation, which gives good yields in shorter reaction times.

2. Experimental

The melting points were recorded in open capillaries and corrected with benzoic acid. Thin-layer chromatography (TLC) was carried out to monitor the course of the reaction and the purity of the product. IR spectra recorded in an Avatar-330 FTIR spectrophotometer (Thermo Nicolet), and only noteworthy absorption levels (reciprocal centimetres) were listed. ^{1}H NMR spectra were recorded on Bruker AMX 400-MHz or 300-MHz spectrometer using $CDCl_3$ or DMSO-d6 as a solvent and TMS as an internal standard. The microwave assisted reactions were carried out in synthetic microwave: CATA R with a maximum power of 700 W. The mass spectra were recorded on LC–MS.

*2.1. General procedure for the synthesis of 2,6-diaryl-4-piperidones **1**(**a**–**g**)*

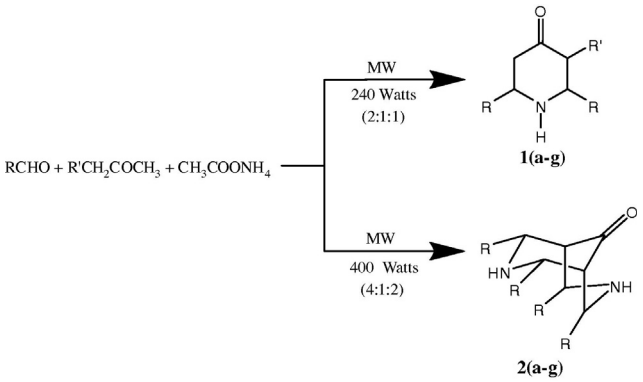
The 2,6-diaryl-4-piperidones were synthesized by irradiating the mixture of aryl aldehyde, ammonium acetate and ketone (2:1:1 ratio) in alcohol under M.W. till it changed to reddish orange colour (2–3 min), then the reaction mixture was kept aside at room temperature for 12 h. Then diethyl ether was added followed by concentrated hydrochloric acid and cooled in ice water. The precipitated hydrochloride was filtered, washed with ethanol–ether mixture and then suspended in acetone and made alkaline by using ammonia solution. On dilution with excess water the base was precipitated which was filtered and dried.

*2.2. General procedure for the synthesis of 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones **2**(**a**–**g**)*

The 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones were synthesized by irradiating the mixture of arylaldehyde, ammonium acetate and ketone (4:2:1 ratio) in alcohol under M.W. till it changed to reddish orange colour (2–3 min) then diethyl ether was added to the reaction mixture and kept aside at room temperature for 1–2 days. The obtained solid was washed with a mixture of diethyl ether and acetone (1:1).

3. Results and discussion

The 2,6-diaryl-4-piperidones have been synthesized by the conventional method, which will consume more time to complete the reaction and also gives lesser yields, so here we have used microwave irradiation, under which the reaction has been completed within 2–3 min at 240 W power level with a good yield (arylaldehyde, ammoniumacetate, ketones are taken in the mole ratio of 2:1:1) (Scheme 1). The same reactants arylaldehyde, ammoniumacetate, ketones with the mole ratio of 4:2:1 afforded bicyiclic-4-piperidones namely 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-one under the microwave irradiation with the power level of 400 W for 2–3 min (Scheme 1). Completion of the reaction was monitored by TLC, then the reaction mixture was filtered and dried. The obtained solid is washed with ether and acetone. (Yield, melting point of the compounds and required time are given in Table 1.)



Scheme 1 Synthesis of 2,6-diaryl-4-piperidones and 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones.

The purified compounds were characterized through IR, ^{1}H NMR and mass spectral data. The stretching frequencies observed at 3303, 1738, and 1707 cm^{-1} are due to –NH, C═O at C_4 and C═O in carboethoxy group at C_3 of **1a** respectively. The proton chemical shift assignment of **1a** is the doublet at 3.68 ppm which is due to one proton at the C2 position. The doublet at 4.39 ppm is due to one proton at the C3 position. The quartet at 4.08 ppm is due to methylene protons of carboethoxy group at C3. The triplet at 1.08 ppm is due to methyl protons of carboethoxy group at C3 with the coupling constant of 7.2 Hz. The doublet at 2.68 ppm is due to methylene protons at C5. The triplet at 4.17 ppm is due to one proton at the C6 position. The examination of H, H-COSY spectrum of **2a** reveals the singlet at 2.82 ppm integrated for two protons coupled with the singlet at 4.37 ppm and the doublet at 4.66 ppm due to the bridgehead protons at H-1,5. The singlet at 4.37 ppm integrating for two protons coupled with the singlet at 2.82 ppm may be due to protons at H-2,4. The doublet at 4.66 ppm with a coupling constant of 2.7 Hz may be due to protons at H-6,8. The chemical shift values of two NH groups which appeared at 1.60 and 2.12 ppm inferred that those two groups are not in the same environment. The signal at 2.12 ppm appeared as a sharp singlet may be due to NH in the boat form and the other signal at 1.60 ppm appeared as a broad singlet may be due to NH in the chair form. The singlet at 2.12 ppm is having the vicinal coupling with the singlet at 2.82 ppm and the singlet at 4.37 ppm also confirms the above statement. The singlet at 4.37 ppm having vicinal coupling with the doublet at 7.58 ppm intuits that the doublet may be due to *ortho* protons in the chair form. The doublet at 7.16 ppm with 8.7 Hz as coupling constant couples with the doublet at 7.58 ppm with a coupling constant of 8.7 Hz may be due to *ortho* protons and the doublet at 7.58 ppm due to *meta* protons. The doublet at 6.80 ppm with 8.7 Hz as the coupling constant, couples with the doublet at 6.72 ppm with a coupling constant of 8.7 Hz may be due to *ortho* protons and the doublet at 6.72 ppm due to *meta* protons.

3.1. Spectral data for respective compounds

*3.1.1. 3-Ethoxy carbonyl-2,6-phenylpiperidin-4-one (**1a**)*

IR (cm^{-1}): ν_{max} 3302, 1738, 1707, 3059, 2982, 2957, 2911, 2857. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (d, 2H, J = 8.4 Hz),

Table 1 Synthesis of various substituted 2,6-diaryl-4-piperidones **1(a–g)** and 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones **2(a–g)**.

Entry	R	R′	Time (s)	Yield (%)	M. Pt (°C)
1a	C_6H_5	$COOC_2H_5$	180	70	95–97
1b	4-F C_6H_4	$COOC_2H_5$	180	72	92–93
1c	C_6H_5	CH_3	120	70	93–96
1d	4-MeO C_6H_4	CH_3	120	68	95–97
1e	C_6H_4	H	120	65	90–92
1f	3-CH_3 C_6H_4	H	180	75	94–96
1g	3-MeO C_6H_4	H	180	62	88–90
2a	C_6H_5	CH_3	150	72	230–232
2b	C_6H_5	H	120	64	220–221
2c	4-F C_6H_4	H	120	62	224–225
2d	2-F C_6H_4	H	150	68	239–240
2e	3-MeO C_6H_4	H	150	65	218–220
2f	4- CH_3 C_6H_4	CH_3	180	71	211–213
2g	4-MeO C_6H_4	CH_3	120	63	202–203

Reaction conditions.
Reaction conditions For the synthesis of compounds **2a–g** aldehyde (4 mmol), ketone (1 mmol), ammonium acetate (2 mmol) have been used. For the synthesis of compounds **1a–g** aldehyde (2 mmol), ketone (1 mmol), ammonium acetate (1 mmol) have been used.

4.39 (d, 3H, J = 8.2 Hz), 4.08 (q, 2H, J = 8.4 Hz), 1.08 (t, 3H, J = 7.2 Hz), 2.68 (d, 2H, J = 8.4 Hz), 4.17 (t, 1H, J = 8.4 Hz), 2.11 (s, 1H).

*3.1.2. 3-Ethoxy carbonyl-2,6-difluorophenylpiperidin-4-one (**1b**)*

IR (cm^{-1}): ν_{max} 3318, 1732, 1704, 3058, 2980, 2931, 2822. ^1H NMR (400 MHz, $CDCl_3$): δ 3.60 (d, 2H, 8.4 Hz), 4.39 (d, 3H, J = 8.4 Hz), 4.07 (q, 2H, J = 8.4 Hz), 1.10 (t, 1H, J = 7.2 Hz), 2.62 (d, 2H, J = 8.6 Hz), 4.14 (t, 1H, J = 8.4 Hz), 2.05 (s, 1H).

*3.1.3. 2,6-Bis-(4-methoxyphenyl)-3-methylpiperidin-4-one (**1c**)*

IR (cm^{-1}): ν_{max} 3321, 1706. ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (d, 2H, J = 10.4 Hz), 2.57 (dd, 4H, J = 11.0 Hz), 2.62 (dd, 4H, J = 11.0 Hz), 2.69 (dd, 3H, J = 12 Hz), 4.01 (dd, 6H, J = 11.0 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 6.87–7.36 (aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): 209.84, 55.24, 67.81, 60.96, 113.84, 113.96, 127.58, 128.68, 134.22, 135.09, 159.12, 159.24.

*3.1.4. 3-Methyl-2,6-diphenyl-piperidin-4-one (**1d**)*

IR (cm^{-1}): ν_{max} 3298, 1702, 3085, 3061, 3027, 2989, 2930, 2811.

*3.1.5. 2,4,6,8-Tetrakis(4-fluorophenyl)-3,7-diazabicyclo[3.3.1] nonan-9-one (**2a**)*

IR (cm^{-1}): ν_{max} 1710, 3323, 3312. ^1H NMR (400 MHz, $CDCl_3$): δ 3.19 (s, 1H, 5H), 4.69 (s, 2H, 4H), 4.98 (s, 6H, 8H), 1.56 (s, 3H), 1.95(s, 7H), 6.77–8.07 (aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): 210.02, 57.10, 57.84, 54.29, 115.3, 124.24, 127.39, 128.89, 129.2, 129.49, 158.5, 160.9.

*3.1.6. 2,4,6,8-Tetrakis(2-fluorophenyl)-3,7-diazabicyclo[3.3.1] nonan-9-one (**2b**)*

IR (cm^{-1}): ν_{max} 1725, 3313. ^1H NMR (400 MHz, $CDCl_3$): δ 2.82 (s, 5H), 4.37 (s, 4H), 4.66 (s, 6H), 1.60 (s, 3H), 2.12 (s, 7H), 6.72–7.58 (aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): 210.48, 61.47, 62.38, 57.95, 115.96, 115.24, 115.46, 115.74, 127.69, 127.80, 127.93, 128.04, 159.52, 159.91, 140.69, 140.73, 160.15, 160.55, 163.37, 163.83.

*3.1.7. 2,4,6,8-Tetrakis(3-methoxyphenyl)-3,7-diazabicyclo [3.3.1]nonan-9-one (**2c**)*

IR (cm^{-1}): ν_{max} 1712, 3329, 3297. ^1H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 5H), 4.81 (s, 4H), 4.67 (s, 6H), 4.45 (s, 3H), 6.42–7.42 (aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): 210.91, 61.34, 63.06, 58.13, 110.69, 112.69, 112.66, 113.06, 118.17, 118.75, 128.99, 129.47, 141.93, 146.75.

*3.1.8. 1-Methyl-2,4,6,8-tetrakis(4-methylphenyl)-3,7-diazabi cyclo[3.3.1]nonan-9-one (**2d**)*

IR (cm^{-1}): ν_{max} 1716, 3312. ^1H NMR (400 MHz, $CDCl_3$): δ 2.92 (s, 5H), 3.79 (s, 2H), 4.30 (s, 4H), 4.71 (d, 6H, J = 8.24), 5.20 (s, 8H), 1.44 (s, 3H), 2.07 (s, 7H), 6.62–7.59 (aromatic), 0.62 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): 55.11, 58.43, 63.37, 70.36, 61.48, 62.78, 126.33, 127.87, 128.25, 128.78, 129.21, 136.26, 137.81, 137.17, 139.8, 143.08.

*3.1.9. 1-Methyl-2,4,6,8-tetrakis(4-fluorophenyl)-3,7-diazabi cyclo[3.3.1]nonan-9-one (**2e**)*

IR (cm^{-1}): ν_{max} 1712, 3318. ^1H NMR (400 MHz, $CDCl_3$): δ 2.93 (s, 5H), 3.85 (s, 2H), 4.35 (s, 4H), 4.69 (d, 6H, J = 8.4 Hz), 5.20 (s, 8H), 1.25 (s, 3H), 2.10 (s, 7H), 6.78–7.52 (aromatic protons), 0.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 54.58, 62.61, 61.14, 114.5, 115.31, 127.99, 130.14, 129.25, 135.2, 136.08, 137.63, 141.1, 137.61.

4. Conclusion

An efficient and environmentally friendly method has been developed for the synthesis of 2,6-diaryl-4-piperidones and 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones under microwave irradiation. The use of microwave in the three-component condensation gives different products by increasing the watts of microwave and mole ratios of the reactants and also

this kind of reaction brings up merits like milder conditions, low pollution, good yields and simple work-up.

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