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Condensation of 3-Aza-1, 5-Diketones with *N*-Nucleophiles

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Abstract: The reaction of substituted diphenacyl anilines with ammonium acetate under microwave irradiation afforded 1,3,5-triaryl-1,2-dihydropyrazines. In the present paper the use of microwave irradiation allows to improve the yields and expedite the reaction. Phenylhydrazine is used as nitrogen nucleophile. The reaction pathways of prepared compounds are discussed in detail in this paper.

Keywords: Diphenacyl anilines; nucleophiles; dihydropyrazines; ammonium acetate; phenylhydrazine.

1. Introduction

From the beginning of organic chemistry, heterocycles have constituted one of the largest areas of research. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Also heterocycles play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on aromatic heterocycles.[1-2] Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately half are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Among them, nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis.

The applications of microwave technology to rapid synthesis of biologically significant heterocyclic molecules under solvent-free conditions are very promising and numerous due to benefit of pollution and economy. During the last few years the pyrazine synthesis has been a field of increasing interest in synthetic organic chemistry because of their potent flavouring properties.[3-4] Fourrey and co workers have noted that relatively stable 1,4-dihydropyrazine could be synthesized by condensation of diphenacyl anilines with arylamines.[5] Currently 1,2-dihydro pyrazine has been synthesized by employing a new pathway using ammonium acetate. The present study is unique in the synthesis method in terms of yield and timely by combining *N*-Nucleophile using microwave irradiation.

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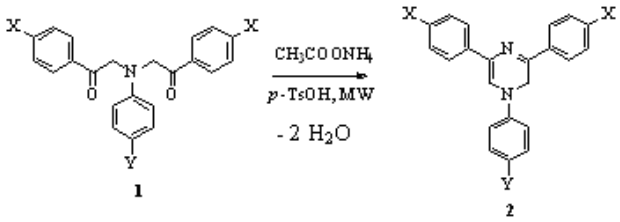
2. Results and Discussion

Starting materials have been recognized as versatile synthetic intermediates in various organic syntheses because of their applications as essential starting materials for the synthesis of many heterocyclic[6-8] and polyfunctional compounds.[9-12] While studying the chemistry of starting materials, we turned to their 3-aza analogs, among which the simplest and most accessible were diphenacyl aniline **1**.However, these compounds are not studied in detail, though they attract a certain interest, in particular as initial compounds for the synthesis of heterocycles with two heteroatoms. Recently we have successfully synthesized several nitrogen heterocyclic compounds using diphenacyl anilines.[13-14] In continuation of our work to investigate the reaction of diphenacyl aniline with different amines, ammonium acetate was used as the source of ammonia for the first time and this synthesis adopted microwave irradiation to achieve the product. By this technique the yield obtained is high which is indicated in Table 1.

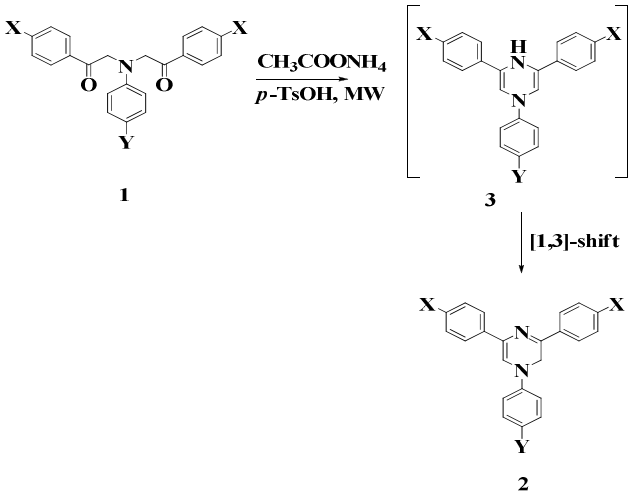


Scheme 1. Cyclocondensation of **1**

Table 1. Yield and melting points of 1,3,5-triaryl-1, 2-dihydropyrazines **2**

1,2	X	Y	Yields %	mp(^{o}C)
a	Cl	H	78	119
b	Cl	Me	82	128
c	Me	Me	70	132

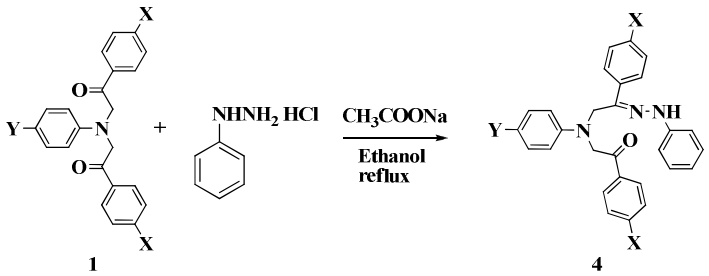
When a well ground mixture of **1** and ammonium acetate in 1:4 molar ratio with catalytic amount of *p*-toluenesulphonic acid without any solvent was kept under microwave irradiation a single product **2** is formed. The structure of **2** has been analysed by the NMR spectra of the compounds (*vide infra)* (Scheme 1). It must be stated that in the absence of microwave radiation, there is no significant conversion of the starting diphenacyl anilines even after prolonged heating. The yields and melting points of compounds **2** are summarized in Table 1. The possible mechanism of formation **2** is given below (Scheme 2).



Scheme 2. Possible mechanism for the formation of compounds **2**

The ^{1}H NMR spectrum of **2c** shows three equally intense singlets between 2.33 and 2.39 ppm, each accounting for three hydrogens. There is a singlet at 4.56 ppm accounting for two hydrogens and there is a one hydrogen singlet at 6.84 ppm. From the signals in the aromatic region, it is clear that there are three aryl rings corresponding to the three *p*-tolyl systems present in the starting material. The ^{13}C NMR spectrum of **2c** has a CH_2 carbon at 44.2 ppm apart from the three tolyl methyl carbons at 20.6, 21.1 and 21.4 ppm. There are 15 peaks in the aromatic / olefinic region of the ^{13}C NMR spectrum. The results clearly suggest that the product formed is 1,2-dihydropyrazine and not 1,4-dihydropyrazine. Thus the structure of **2** is unambiguously assigned as 1,3,5-triphenyl-1,2-dihydropyrazine. All the three compounds prepared using ammonium acetate are new and it is obvious that the initially formed 1,4-dihydropyrazine **3** (**Scheme II**) should have undergone 1,3-migration of hydrogen under the condition of the reaction.

The present paper is focused on another synthetic application of diphenacyl anilines. The reaction of diphenacyl anilines 1, phenylhydrazine hydrochloride, and sodium acetate in 1:1:1 molar ratio took place easily in ethanol at room temperature to afford the monohydrazones **4** in high yields. The yields could not be improved by using an excess of phenylhydrazine. Changes in the solvent, reaction time, and temperature did not result in changes of the composition of the reaction mixture. Thus, the reaction appeared to be product specific.



1, 4	X	Y
a	Cl	H
b	Me	H
c	OMe	H
d	Cl	Me
e	Me	Me
f	Me	OMe

Scheme 3. Condensation of **1** with phenylhydrazine

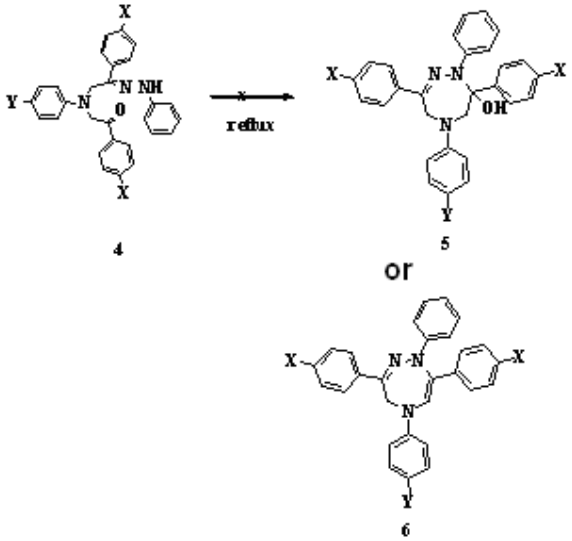
All the compounds prepared by this method **(4a-f)** have been fully characterized by NMR spectra. The yields and the melting points of compounds (**4a-f)** are summarized in **Table 2**.

Table 2. Yields and melting points of phenylhydrazones **4**

Compounds	X	Y	Yield (%)	m.p. (^{o}C)
4a	Cl	H	78	164
4b	Me	H	74	158
4c	OMe	H	68	162
4d	Cl	Me	76	168
4e	Me	Me	74	156
4f	Me	OMe	74	154

The structure of **4** has been analysed by NMR spectral analysis. Compound **4e** exhibits three singlets, each accounting for three hydrogens, at 2.23, 2.32, and 2.40 ppm in its ^{1}H NMR spectrum. Two singlets each accounting for two protons appear at 4.55 and 4.66 ppm. Signals, which appear as overlapping multiplets, between 6.84 and 7.82 ppm account for seventeen hydrogens. There is a one hydrogen singlet appearing at 10.02 ppm, which disappears on D_2O treatment. In the ^{13}C NMR spectrum of **4e** signals appear at 20.4, 21.2, 21.7, 50.0, 58.4, 113.1, 117.5, 119.7, 125.4, 128.0, 129.0, 129.1, 129.5, 129.8, 130.5, 132.6, 136.1, 137.4, 138.0, 144.7, 145.5 and 146.6 ppm, besides a carbonyl signal at 197.0 ppm. A closer analysis reveals the presence of four aryl rings, three of them being tolyl, one carbonyl group and two isolated CH_2 groups in **4e**. From the left out carbon and hydrogen signals, the presence of an azomethine carbon and a lone NH can also be inferred. It is thus clear that the phenylhydrazone formation has taken place at only one end of the diphenacyl system, leaving the other carbonyl intact.

It is interesting that the reaction has stopped with the monohydrazone formation. The fact that the other carbonyl group is not derivitasied, even under drastic condition with excess phenylhydrazine is surprising. While the simple hydrazine undergoes facile ring closure with diphenacyl aniline[15] to yield the 1,2,5-triazepine systems, no such cyclisation has been noticed here under different conditions employed during this investigation. Two reasons may be put forwarded to account for this observation. The nucleophilicity of the second nitrogen (NH) atom in phenylhydrazone is not as good as the first one as the former is attached to the aryl ring. Delocalisation of the electrons on NH to the ring may decrease the availability of the electrons for the nucleophilic attack. Steric hinderance may also play a role in preventing the attack of the second nitrogen on the carbonyl carbon leading to the possible formation of **5** or **6** (Scheme 4). Thus all the attempts to effect the cyclisation with excess phenylhydrazine or prolonged reaction time proved to be disappointing.



Scheme 4. Possible mechanism for formation of **5** and **6**

3. Conclusion

We showed that the reaction of substituted diphenacyl anilines with ammonium acetate under microwave irradiation afforded 1,3,5-triaryl-1,2-dihydropyrazines. The use of microwave irradiation improved the yields and shortened the reaction time.

4. Experimental

All chemicals were of reagent grade quality and used without further purification. Melting points were measured on a melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker 300 (75) MHz (Ultrashield) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. A domestic microwave oven (2450 MHz, 600 W) was used for the microwave-assisted reaction. The reactions were routinely monitored by thin layer chromatography (TLC) on silica gel plates.

General procedure for the preparation of Compound 2: An intimate mixture of **1** (1.5 mmol), ammonium acetate (1.5 g, 6.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid (50 mg) was irradiated in a microwave apparatus (600 W) for 7 min. The reaction mixture was partitioned between water (100 ml) and dichloromethane (50 ml). The organic layer was separated, dried over anhydrous calcium chloride, and then evaporated to dryness. The residue was recrystallized from ethanol to give pure **2**.

3,5-bis(4-chlorophenyl)-1-phenyl-1,2-dihydropyrazine (2a). Yield 78%, ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 4.60 (s, 2H), 6.91 (s, 1H), 7.10-7.13 (m, 3H), 7.32-7.43 (m, 6H), 7.73 (d, 2H, *J*= 8.4 Hz), 7.93 (d, 2H, *J* = 8.4 Hz)**.** ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 42.0, 115.0, 116.4, 121.0, 122.2, 125.4, 125.6, 126.4, 126.6, 127.4, 127.7, 129.2, 133.7, 135.8, 141.6, 142.0. Anal.Calcd.for. $C_{22}H_{16}Cl_2N_2$: C, 69.67 %; H, 4.25 %; N, 7.39 %. Found: C, 69.72 %; H, 4.29 %, N, 7.41%.

3,5-bis(4-chlorophenyl)-1-(4-methylphenyl)-1,2-dihydropyrazine (2b). Yield 82%, ^{1}H NMR(300 MHz, $CDCl_3$) (δ/ppm): 2.34 (s, 3H), 4.55 (s, 2H), 6.87 (s, 1H), 7.01 (d, 2H, *J* = 6.6 Hz), 7.18-7.41(m, 6H), 7.71 (d, 2H, *J* =7.2 Hz), 7.91 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 21.0, 44.7, 117.6, 119.3, 124.6, 128.2, 129.0, 129.1, 130.4, 131.6, 133.3, 135.7, 136.1, 136.7,140.2, 142.3, 143.3. Anal.Calcd.for. $C_{23}H_{18}Cl_2N_2$: C, 70.24 %; H, 4.61 %; N, 7.12 %. Found: C, 70.30 %; H, 6.59 %; N, 7.15 %.

1,3,5-tris(4-methylphenyl)-1,2-dihydropyrazine (2c). Yield 70%, ^{1}H NMR(300 MHz, $CDCl_3$) (δ/ppm): 2.33 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 4.56 (s, 2H), 6.84 (s, 1H), 7.00 (d, 2H, *J* =8.7 Hz), 7.16-7.22 (m, 6H), 7.72 (d, 2H, *J* = 8.1 Hz), 7.93 (d, 2H, *J* =8.1 Hz). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 20.6, 21.1, 21.4, 44.2, 116.8, 117.4, 123.1, 124.5, 126.5, 129.1, 129.2, 129.5, 130.0, 132.0, 134.4, 135.2, 139.8, 142.2, 144.6. Anal. Calcd. for. $C_{25}H_{24}N_2$: C, 85.19 %; H, 6.86 %; N, 7.95 %. Found: C, 85.23 %; H, 6.89 %; N, 7.91 %.

General procedure for the preparation of N-phenylhydrazones 4: A mixture of **1** (0.3 mmol), phenylhydrazine hydrochloride (58 mg. 0.4 mmol) and sodium acetate (28.4 mg, 0.4 mmol) in ethanol (10 mL) was heated under reflux for 2 hrs. After cooling, the precipitated solid was collected by filtration and recrystallized from ethanol to afford pure **4**.

1-(4-chlorophenyl)-2-[2-(4-chlorophenyl)-2-oxoethyl]anilino-1-ethanone N-phenylhydrazone (4a). Yield 78%, ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 4.50 (s, 2H), 4.72 (s, 2H), 6.85-6.87 (m, 4H), 7.21-7.30 (m, 8H), 7.42-7.46 (m, 2H), 7.61-7.65 (m, 2H), 7.83-7.87 (m, 2H). 10. 2 (s, NH). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 49.7, 58.6, 113.6, 117.8, 120.7, 121.8, 127.0, 129.0, 129.5, 129.6, 129.8, 130.2, 133.4, 133.8, 136.4, 137.5, 141.0, 145.4, 149.0, 196.5. Anal. Calcd. for $C_{28}H_{23}Cl_2N_3O$: C, 68.86 %; H, 4.75 %; N, 8.60 %. Found: C, 68.88 %; H, 4.71 %; N, 8.62 %.

1-(4-methylphenyl)-2-[2-(4-methylphenyl)-2-oxoethyl]anilino-1-ethanone N -phenylhydrazone (4b). Yield 74%, ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 2.37 (s, 3H), 2.42 (s, 3H), 4.60 (s, 2H), 4.64 (s, 2H), 6.50-6.53 (m, 6H), 7.11-7.24 (m, 6H), 7.56-7.60 (m, 3H), 7.82-7.86 (m, 3H). 10.01 (s, NH). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 21.2, 21.7, 49.5, 57.7, 113.2, 116.7, 119.8, 120.7, 125.3, 128.0, 129.0, 129.1, 129.3, 129.4, 129.5, 132.5, 136.0, 137.8, 144.8, 145.4, 148.8, 196.8. Anal. Calcd. for $C_{30}H_{29}N_3O$: C, 80.51 %; H, 6.53 %; N, 9.39 %. Found: C, 80.48 %; H, 6.55 %; N, 9.35 %.

1-(4-methoxyphenyl)-2-[2-(4-methoxyphenyl)-2-oxoethyl]anilino-1-ethanone N-phenylhydrazone (4c). Yield 68%, ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 3.81 (s, 3H), 3.85 (s, 3H), 4.61 (s, 2H), 4.68 (s, 2H). 6.81-6.94 (m, 10H), 7.21-7.25 (m, 4H), 7.65-7.70 (m, 2H), 7.86-7.89 (m, 2H). 9. 80 (s, NH). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 49.7, 55.7, 56.0, 57.0, 113.5, 114.2, 114.4, 117.0, 117.6, 120.1,

121.0, 127.2, 128.4, 129.4, 129.7, 130.5, 131.6, 138.3, 145.7, 159.8, 164.4, 196.1. Anal. Calcd. for $C_{30}H_{29}N_3O_3$: C, 75.13 %; H, 6.10 %; N, 8.76 %. Found: C, 75.15 %; H, 6.12 %; N, 8.73 %.

1-(4-chlorophenyl)-2-[2-(4-chlorophenyl)-2-oxoethyl]-4-methylanilino-1-ethanoneN-phenyl-hydrazone (4d). Yield 76%, ^{1}H NMR (300 MHz,$CDCl_3$) (δ/ppm): 2.25 (s, 3H), 4.50 (s, 2H), 4.57 (s, 2H), 6.84-6.87 (m, 3H), 7.03-7.05 (m,2H), 7.24-7.27 (m, 5H), 7.41-7.44 (m, 3H), 7.60-7.63 (m, 2H), 7.85-7.88 (m, 2H). 10.02 (s, NH). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 20.6, 50.2, 58.5, 113.5, 113.6, 118.6, 120.6, 127.0, 129.0, 129.6, 130.0, 130.2, 130.3, 133.8, 135.8, 137.0, 137.6, 140.6, 143.3, 146.5, 196.0. Anal. Calcd. for $C_{29}H_{25}Cl_2N_3O$: C, 69.32 % ; H, 5.02 % ; N, 8.36 %. Found: C, 69.28 %; H, 5.05 %; N, 8.35 %.

2-{4-methyl[2-(4-methylphenyl)-2-oxoethyl]anilino}-1-(4-methylphenyl)-1-ethanoneN-phenylhydra-zone (4e). Yield 74%, ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 2.23 (s, 3H), 2.32 (s, 3H), 2.40 (s, 3H), 4.55 (s, 2H), 4.66 (s, 2H), 6.84-6.87 (m, 3H), 7.01-7.04 (m, 3H), 7.07-7.10 (m, 3H), 7.22-7.26 (m, 4H), 7.62 (d, 2H, *J* = 8.1 Hz), 7.82 (d, 2H, *J* = 8.1 Hz), 10.02 (s, NH). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 20.4, 21.1, 21.7, 50.0, 58.4, 113.1, 117.5, 119.7, 125.4, 128.0, 129.0, 129.1, 129.5, 129.8, 130.5, 132.6, 136.1, 137.4, 138.0, 144.7, 145.5, 146.6, 197.0. Anal. Calcd. for $C_{31}H_{31}N_3O$: C, 80.66 ; % H, 6.77 %; N, 9.10 %. Found: C, 80.62 %; H, 6.75 %; N, 9.07 %.

2-{4-methoxy[2-(4-methyphenyl)-2-oxoethyl]anilino}-1-(4-methylphenyl)-1-ethanoneNphenylhydra-zone (4f). Yield 74%, ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 2.31 (s, 3H), 2.40 (s, 3H), 3.71 (s, 3H), 4.42 (s, 2H), 4.61 (s, 2H), 6.74-6.77 (m, 2H), 6.96-6.99 (m, 2H), 7.08-7.10 (m, 2H), 7.23-7.30 (m, 7H), 7.53 (d, 2H, *J* = 8.4 Hz), 7.84(d, 2H, *J* = 8.4 Hz), 10.60 (s, NH). ^{13}C NMR(75 MHz, $CDCl_3$) (δ/ppm): 21.1, 21.7, 51.5, 55.5, 60.2, 113.1, 114.5, 119.5, 121.0, 125.3, 128.0, 129.0, 129.5, 132.3, 134.6, 136.2, 137.2, 138.0, 140.2, 143.0, 144.7, 146.2, 197.0. Anal. Calcd. for $C_{31}H_{31}N_3O_2$: C, 77.96 %; H, 6.54 %; N, 8.80 %. Found: C, 77.98 %; H, 6.56 %; N, 8.76 %.

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