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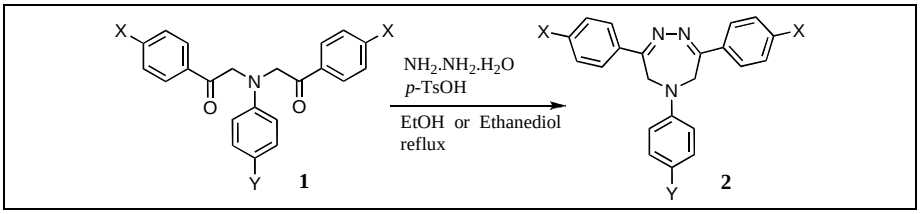
Received April 6, 2006



Several hitherto unknown 3,5,7-triaryl-5,6-dihydro-4*H*-1,2,5-triazepines have been synthesised by cyclocondensation of *N,N*-bis(phenacyl)anilines with hydrazine hydrate in ethanol or ethyleneglycol under reflux condition. Increased yields were obtained in the presence of *p*-toluenesulfonic acid compared to the uncatalysed reaction.

J. Heterocyclic Chem., **44**, 133 (2007).

INTRODUCTION

The 1,2,5-triazepine system has received considerable attention in recent times [1-3], though it is less significant compared to the corresponding benzofused analogues [4,5]. Besides being used as immunomodulating agents [6], 1,2,5-triazepine derivatives are found to exhibit antifungal [7], anti-inflammatory, analgesic [8] and sedative activities [9]. This prompted us to synthesize several novel 3,5,7-triaryl-5,6-dihydro-4*H*-1,2,5-triazepines by a new route. Related 5-benzyl and 5-tosyl-3,7-diaryl-4*H*-1,2,5-triazepines have been synthesized by a different route from substituted α-bromoacetophenone azine and respective amines [10].

RESULTS AND DISCUSSION

There are only a few reports [11,12] on the synthesis and other studies of *N,N*-bis(phenacyl)anilines **1**, the precursors planned for the synthesis of the title compounds. In the present method, compounds **1** were obtained under solvent-free condition in good yields by mixing anilines (1.25 mmol) with phenacyl bromides (2.50 mmol) in the presence of potassium carbonate (1.25 mmol).

The reaction of **1** with hydrazine hydrate has been carried out (Scheme 1) under reflux in ethanol or ethyleneglycol. The products obtained were identified as 3,5,7-triaryl-5,6-dihydro-4*H*-1,2,5-triazepines **2**. The reaction has also been carried out in the presence of a catalyst, *viz*., *p*-toluenesulfonic acid. Vastly improved yields of **2** in most cases and significant reduction in reaction time were observed by refluxing **1** with 1.5 equivalent of hydrazine hydrate in the presence of a catalytic amount of *p*-toluenesulfonic acid compared to the uncatalysed reaction (Table 1). Obviously, the catalyst facilitates the cyclocondensation by increasing the electrophilicity of the carbonyl groups. Reaction conditions employed and the yields of **2** are summarized in Table 1.

Table 1:

Yield of the compound **2** in the presence and in the absence of catalyst

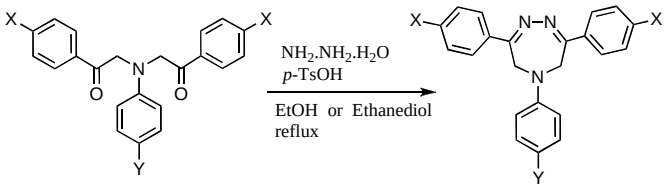
Compound	In the absence of catalyst		In the presence of *p*-TsOH		M. Pt (°C)
	Time (min)	Yield (%)	Time (min)	Yield (%)	
2a	300	35	15	40	>200
2b	240	42	60	85	172
2c	360	43	80	83	104[a]
2d	240	38	75	89	154[a]
2e	300	40	20	42	>200
2f	300	40	60	82	168
2g	360	38	90	80	146[a]
2h	300	42	90	83	152[a]
2i	240	45	60	79	142[a]

[a] decomposition occurs

All the new compounds **2** were characterized by their NMR spectral data. The ^{1}H NMR spectrum of a representative compound, 3,7-bis(4-chlorophenyl)-5-phenyl-5,6-dihydro-4*H*-1,2,5-triazepine (**2b**), showed a broad signal at 4.18 ppm accounting for the four methylene hydrogen atoms. This broad singlet indicates that the methylene hydrogen atoms of the ring are not equivalent and at room temperature there is a flipping around these positions. Such a flipping around the 5 position has already been envisaged [13]. In the aromatic region, multiplets were obtained in the following regions (in ppm): 6.92-6.99 (m, 3H), 7.33-7.39 (m, 6H), 7.65-7.68 (m, 4H). The ^{13}C NMR spectrum of **2b** showed signals at 47.5, 115.6, 120.5, 128.4, 129.1, 129.7, 134.2, 136.6, 152.5, 160.0 ppm.

The semi-empirical PM3 computations were performed with Hyperchem (version 7.5) at the RHF level. It was found that the total energy of **2a** was E = –4948.6442 kcal/mol with Gradient 0.044. The theoretically optimized geometry of **2a** is shown in Figure 1.

Scheme 1



1 **2**

1&2	X	Y
a	H	H
b	Cl	H
c	Me	H
d	OMe	H
e	H	Me
f	Cl	Me
g	Me	Me
h	OMe	Me
i	Me	OMe

EXPERIMENTAL

All chemicals were of reagent grade quality and used without further purification. All melting points reported in this work were measured in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 300 MHz (Ultrashield) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. The reactions were routinely monitored by thin layer chromatography (TLC) on silica gel plates.

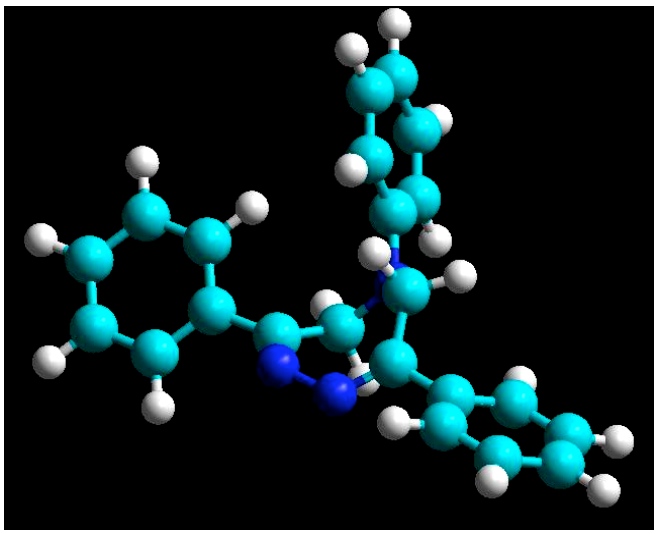


Figure: 1

General Procedure for the Preparation of Differently Substituted *N,N*-Bis(phenacyl)anilines (1). *N,N*-Bis(phenacyl)-anilines (**1**) were prepared by grinding a solventless mixture of substituted phenacyl bromide, substituted aniline and potassium carbonate in 2:1:1 molar ratio and leaving the reaction mixture at room temperature for one hour. The reaction mixture was then treated with chloroform and the chloroform extract was dried over anhydrous sodium sulphate and evaporated. The crude product was purified over silica column to give pure **1**. The conversion is in the range of 60-70 % for different **1**.

***N,N*-Bis(phenacyl)aniline (1a).** This compound was obtained as colorless crystals (dichloromethane), yield 62 %, mp 198 °C (236-240 °C)[14]; ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.95 (s, 4H), 6.50-6.76 (m, 3H), 7.12-7.20 (m, 2H), 7.50-7.59 (m, 4H), 7.61-7.68 (m, 2H), 8.01-8.04 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 58.0, 112.6, 118.0, 127.8, 128.9, 129.2, 133.7, 140.7, 148.4, 196.5.

***N,N*-Bis(4-chlorophenacyl)aniline (1b).** This compound was obtained as yellow crystals (ethanol), yield 70 %, mp 110 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.90 (s, 4H), 6.51- 6.79 (m, 3H), 7.12-7.20 (m, 2H), 7.46-7.49 (m, 4H), 7.93-7.96 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 57.9, 112.7, 118.3, 129.2, 129.3, 130.3, 133.3, 140.3, 148.2, 195.4. *Anal.* Calcd. for $C_{22}H_{17}Cl_2NO_2$: C, 66.34; H, 4.30; N, 3.52 %. Found: C, 66.32; H, 4.29, N, 3.51 %.

***N,N*-Bis(4-methylphenacyl)aniline (1c).** This compound was obtained as yellow crystals (ethanol), yield 64%, mp, 103 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.40 (s, 6H), 4.90 (s, 4H), 6.45-6.72 (m, 3H), 7.11-7.16 (m, 2H), 7.27-7.30 (m, 4H), 7.90-7.93 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 21.7, 57.9, 112.5, 117.8, 129.0, 129.1, 129.5, 132.6, 144.6, 148.5, 196.1.

Anal. Calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92 %. Found: C, 80.62; H, 6.47, N, 3.91 %.

***N,N*-Bis(4-methoxyphenacyl)aniline (1d).** This compound was obtained as yellow crystals (ethanol), yield 62 % mp, 152 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 3.9 (s, 6H), 4.84 (s, 4H), 6.50-6.76 (m, 3H), 6.90-6.98 (m, 2H), 7.10-7.21 (m, 3H), 7.92-8.05 (m, 3H), 8.20-8.22 (m, 2H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 57.0, 58.1, 111.7, 112.7, 113.1, 118.5, 129.4, 129.5, 129.6, 133.8, 148.7, 160.4, 194.5. *Anal.* Calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60 %. Found: C, 74.06; H, 5.92, N, 3.58 %.

***N,N*-Bis(phenacyl)-*p*-toluidine (1e).** This compound was obtained as colorless crystals (dichloromethane), yield 63 %, mp, 158 °C (255 °C)[15]; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 4.90 (s, 4H), 6.52-6.58 (m, 3H), 6.96-7.03 (m, 3H), 7.36-7.45 (m, 4H), 7.87-7.92 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 21.0, 58.0, 118.6, 128.2, 128.7, 129.5, 134.2, 141.2, 149.0, 197.2.

***N,N*-Bis(4-chlorophenacyl)-*p*-toluidine (1f).** This compound was obtained as yellow crystals (ethanol), yield 68 % mp, 140 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 4.86 (s, 4H), 6.45-6.48 (m, 2H), 6.95-6.98 (m, 2H), 7.45-7.49 (m, 4H), 7.92-7.95 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 20.3, 56.2, 113.0, 130.0, 130.4, 131.0, 134.0, 141.2, 149.0, 196.2. *Anal.* Calcd. for $C_{23}H_{19}Cl_2NO_2$: C, 67.00; H, 4.64; N, 3.40 %. Found: C, 67.05; H, 4.62, N, 3.39 %.

***N,N*-Bis(4-methylphenacyl)-*p*-toluidine (1g).** This compound was obtained as yellow crystals (ethanol), yield 70% mp,128 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.20 (s, 6H), 4.91 (s, 4H), 6.49-6.50 (m, 2H), 6.90-7.00 (m, 2H), 7.28-7.35 (m, 4H), 7.90-7.95 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 20.6, 22.1, 58.5, 113.2, 127.4, 129.8, 130.1, 130.6, 133.1, 144.9, 146.7,

196.8. *Anal.* Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77 %. Found: C, 80.85; H, 6.77, N, 3.74 %.

***N,N*-Bis(4-methoxyphenacyl)-*p*-toluidine (1h).** This compound was obtained as yellow crystals (ethanol), yield 68 % mp,170 ºC; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.90 (s, 6H), 4.80 (s, 4H), 6.40-6.47 (m, 2H), 6.93-6.98 (m, 4H), 7.95-7.99 (m, 4H), 8.20-8.28 (m, 2H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 19.0, 54.5, 56.0, 109.2, 110.2, 111.0, 125.4, 127.0, 127.7, 131.3, 144.2, 158.0, 192.2. *Anal.* Calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47 %. Found: C, 74.44; H, 6.24, N, 3.45 %.

***N,N*-Bis(4-methylphenacyl)- *p*-anisidine (1i).** This compound was obtained as pale yellow crystals (ethanol), yield 65 %, mp, 128 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.42 (s, 6H), 3.70 (s, 3H), 4.92 (s, 4H), 6.51-6.54 (m, 2H), 6.72-6.75 (m, 2H), 7.26-7.29 (m, 4H), 7.89-7.92 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 22.1, 56.1, 58.8, 114.9, 115.1, 128.4, 129.8, 133.1, 143.5, 144.9, 152.7, 197.0. *Anal.* Calcd. for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61 %. Found: C, 77.47; H, 6.48, N, 3.60 %.

General Procedure for the Preparation of 5,7-Triaryl-5,6-dihydro-4*H*-1,2,5-triazepines (2). A mixture of 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanone **1** (3 mmol) and hydrazine hydrate (4.5 mmol) in ethanol or ethyleneglycol (8-10 ml) was heated under reflux until the starting ethanone had disappeared. The mixture was cooled to room temperature and the resulting precipitate filtered and crystallized from an appropriate solvent.

The reaction was also carried out in the presence of *p*-toluenesulfonic acid (5 mg) with other conditions being similar.

3,5,7-Triphenyl-5,6-dihydro-*4H*-1,2,5-triazepines (2a). This compound was obtained as pale yellow crystals (Petroleum ether), mp > 200 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.24 (bs, 4H), 6.93-6.97 (m, 3H), 7.34-7.40 (m, 8H), 7.73-7.75 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 47.5, 115.4, 121.3, 127.1, 128.7, 129.6, 130.2, 136.0, 153.4, 159.6. *Anal.* Calcd. for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91 %. Found: C, 81.24; H, 5.86; N, 12.90 %.

3,7-Bis(4-chlorophenyl)-5-phenyl-5,6-dihydro-4*H*-1,2,5-triazepine (2b). This compound was obtained as yellow crystals (ethanol), ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.18 (bs, 4H), 6.92-6.99 (m, 3H), 7.33-7.39 (m, 6H), 7.65-7.68 (m,4H); ^{13}C nmr (75 MHz, CDCl3): δ 47.5, 115.6, 120.5, 128.4, 129.1, 129.7, 134.2, 136.6, 152.5, 160.4. *Anal.* Calcd. for $C_{22}H_{17}C_{12}N_3$: C,67.01; H, 4.35; N, 10.66 %. Found: C, 67.04; H, 4.33; N, 10.65 %.

3,7-Bis(4-methylphenyl)-5-phenyl-5,6-dihydro-4*H*-1,2,5-triazepine (2c). This compound was obtained as yellow crystals (ethanol), ^{1}H nmr (300 MHz, $CDCl_3$) δ 2.36 (s, 6H), 4.25 (bs, 4H), 6.89-6.95 (m, 3H), 7.15-7.23 (m, 4H), 7.30-7.37 (m, 2H), 7.59-7.65 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 21.3, 47.3, 115.4, 119.7, 127.0, 129.4, 129.5, 133.1, 140.4, 148.4, 153.3, 161.0. *Anal.* Calcd. For $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89 %. Found: C, 81.58; H, 6.85; N, 11.97 %.

3,7-Bis(4-methoxyphenyl)-5-phenyl-5,6-dihydro-4*H*-1,2,5-triazepine (2d). This compound was obtained as yellow crystals (ethanol), ^{1}H nmr (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 4.19 (bs, 4H), 6.87-6.98 (m, 8H), 7.32-7.37 (m, 2H), 7.69-7.72 (m, 3H); ^{13}C nmr (75 Hz, $CDCl_3$): δ 47.6, 55.7, 114.5, 115.7, 120.2, 128.9, 129.0, 129.9, 148.8, 153.4, 161.6. *Anal.*Calcd.for $C_{24}H_{23}N_3O_2$: C, 74.78; H,6.01; N, 10.90 %. Found: C, 74.81; H, 6.00; N, 10.88 %.

5-(4-Methylphenyl)-3,7-diphenyl-5,6-dihydro-4*H*-1,2,5-triazepine(2e). This compound was obtained as Pale yellow crystals (Petrolium ether), ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 4.20 (bs, 4H), 6.85-6.88 (m, 3H), 7.14-7.20 (m, 4H), 7.32-7.40 (m,4H), 7.72-7.75 (m,3H); ^{13}C nmr 75 MHz, $CDCl_3$): δ 20.5, 47.8, 115.6, 127.1, 128.7, 129.5, 133.5, 135.6, 153.2, 159.6. *Anal.* Calcd. for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38 %. Found: C, 81.33; H, 6.26, N, 12.41 %.

3,7-Bis(4-chlorophenyl)-5-(4-methylphenyl)-5,6-dihydro-4*H*-1,2,5-triazepine (2f). This compound was obtained as yellow crystals (ethanol), ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 4.13 (bs, 4H), 6.83-6.86 (m, 2H), 7.14-7.17 (m, 2H), 7.33-7.35 (m, 4H), 7.64-7.67 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 21.0, 48.2, 116.2, 128.8, 129.4, 130.5, 134.6, 136.8, 154.4, 160.8. *Anal.* Calcd.for $C_{23}H_{19}Cl_2N_3$: C, 67.65; H, 4.67; N, 10.29 %. Found: C, 67.61; H, 4.70; N, 10.32 %.

3,5,7-Tris(4-methylphenyl)-5,6-dihydro-4*H*-1,2,5-triazepine (2g). This compound was obtained as yellow crystals (ethanol), ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.35 (s, 6H), 4.17 (bs, 4H), 6.83-6.86 (m, 2H), 7.13-7.19 (m, 6H), 7.62-7.65 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 20.8, 21.3, 47.7, 115.6, 127.0, 129.4, 129.9, 133.2, 140.4, 153.3, 161.3. *Anal.* Calcd. for $C_{25}H_{25}N_3$: C, 81.71; H, 6.86; N, 11.43 %. Found: C, 81.75; H, 6.85; N, 11.40 %.

3,7-Bis(4-methoxyphenyl)-5-(4-methylphenyl)-5,6-dihydro-4H-1,2,5-triazepine (2h). This compound was obtained as yellow crystals (ethanol), ^{1}H nmr (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.82 (s, 6H), 4.14 (bs, 4H), 6.70-6.95 (m, 6H), 7.15-7.20 (m, 2H), 7.68-7.84 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 20.9, 48.0, 55.8, 114.3, 114.5, 116.0, 129.0, 130.4, 130.6, 153.5, 161.6. *Anal.* Calcd. for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found: C, 75.20; H, 6.28; N, 10.51

3,7-Bis(4-methylphenyl)-5-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2,5-triazepine (2i). This compound was obtained as yellow crystals (ethanol), ^{1}H nmr (300 MHz, $CDCl_3$) δ: 2.35 (s, 6H), 3.81 (s, 3H), 4.10 (bs, 4H), 6.88-6.92 (m, 4H), 7.15-7.25 (m, 4H), 7.60-7.62 (m, 4H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 21.7, 48.8, 56.0, 115.1, 117.9, 127.4, 129.8, 133.6, 140.7, 143.3, 153.7, 154.1. *Anal.* Calcd. for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96 %. Found: C, 78.35; H, 6.60; N, 10.94 %.

Acknowledgment. The authors thank DST-IRHPA NMR facility at School of Chemistry, Madurai Kamaraj University, for recording NMR spectra.

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