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SYNTHESIS AND X-RAY CRYSTAL STRUCTURE ANALYSIS OF SUBSTITUTED-2,3-DIHYDRO-1,3,4-OXADIAZOLES VIA REACTION OF ACETONE- AND CYCLOALKANONE BENZOYLHYDRAZONES WITH PHENYLISOCYANATE

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ملخص: تتفاعل بنزويل هيدرازولنات الأسيتون والسيكلوألكانونات (**1a-f**) بسهولة مع فينيل أيسوسيانات (**2**) عند درجة حرارة الغرفة لتعطي مركبات اوكساديازول المستبدلة (**3**). وقد تم تحديد بنى المركبات الناتجة بناء على على دراسة أطيافها المختلفة. وتم تأكيد ذلك من خلال عمل أشعة إكس لمركب (**3d**). عند معالجة مركبات (**3**) بأنهيدريد حمض ثلاثي فلورو أسيتك يتكون مركب 5،2-ثنائي أكسو-5،1-ثنائي فينيل-4،3،1-ثلاثي أزا بنتان (**5**) عن طريق حذف الألكين المقابل.

Abstract: Acetone and cycloalkanones benzoylhydrazones (**1a-f**) react readily with phenyl isocyanate **2** at room temperature to give the corresponding dimethyl- and spiro-substituted 2,3-dihydro-1,3,4-oxadiazoles (**3a-f**), respectively. Structure elucidation of these compounds was based on spectral data and confirmed by X-ray crystal structure analysis for compound **3d**. Treatment of **3** with trifluoroacetic anhydride resulted in the formation of the acyclic adduct 2,5-dioxo-1,5-diphenyl-1,3,4-triazapentane **5** *via* elimination of the respective alkene in moderate yields.

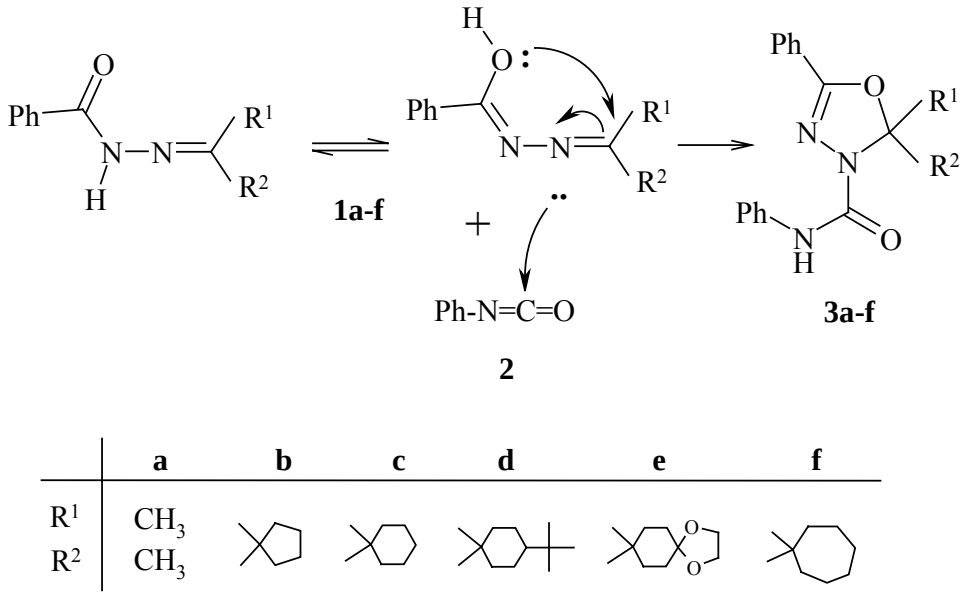
Key Words: Oxadiazoles, Benzoylhydrazones, Phenylisocyanate, Spiro Compounds.

INTRODUCTION

1,3,4-Oxadiazoles represent an important class of heterocyclic compounds that have many applications in the daily life. Some of these compounds are employed as herbicides [1,2], nervous system depressings [3], analgesics, [4,5], and as muscle relaxants [6]. Aromatic oxadiazoles are usually prepared from cyclization of dihydrazides [7]. However, the less common 1,3,4-oxadiazolidines are known with fewer methods of preparation. In the present work, our main objective is to synthesize a selected set of substituted 1,3,4-oxadiazoles, which might have biological activities.

Results Aan Discussion

The reaction of acetone and cycloalkylbenzoylhydrazones **1a-f** with phenyl isocyanate **2** was carried out in chloroform under dry conditions at room temperature (Scheme 1).



	a	b	c	d	e	f
R^1	CH_3					
R^2	CH_3					

Scheme 1

The small quantity of the formed precipitate of diphenyl urea was removed by suction filtration and the solvent was evaporated. Trituration of the residual solid with ethanol gave white products **3a-f** in 60-80% yields. The physical data are depicted in Table 1.

Table 1 Physical Data for Compounds 3a-f, 5

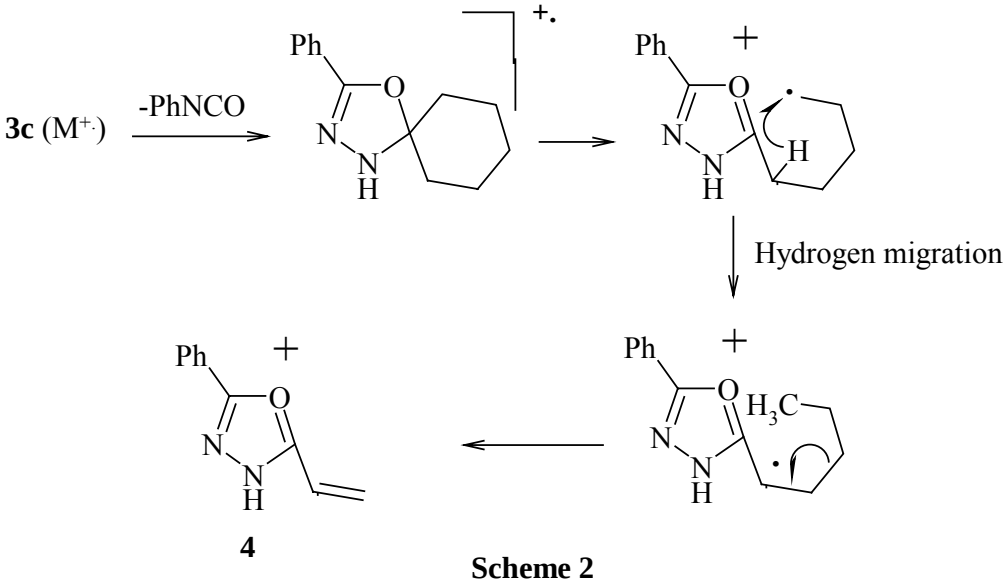
Compd.	m.p (^oC)	Yield (%)	M. F.	$M^{+\cdot}$
3a	155	60	$C_{17}H_{17}N_3O_2$	295
3b	150	70	$C_{19}H_{19}N_3O_2$	321
3c	136	60	$C_{20}H_{21}N_3O_2$	335
3d	157	76	$C_{24}H_{29}N_3O_2$	391
3e	165	80	$C_{22}H_{23}N_3O_4$	393
3f	101	75	$C_{21}H_{23}N_3O_2$	349
5	210	60	$C_{16}H_{13}N_3O_2$	255

The structures of **3a-f** were assigned and confirmed on the basis of their spectral data (IR, ^1H NMR, ^{13}C NMR, and MS).

The IR spectra of the products exhibit characteristic bands near 3300 and 1660 cm^{-1} assignable to the N-H and C=O groups, respectively in addition to the aliphatic and aromatic C-H bands at about 3000 $cm.^{-1}$

In their EI mass spectra they display peaks that correspond to the molecular ions suggested by the molecular formulae (Table1) as well as fragment ions

resulted from the loss of PhNCO ($M^{+\cdot}$ -119). Compound **3a** undergoes an additional loss of CH_3 to give a base peak at 161 ($M^{+\cdot}$ - 119 - 15 = 161). In the case of spiro compounds **3b-f,** the resulting molecular ion ($M^{+\cdot}$ - 119) undergoes further α-cleavage followed by H-migration and subsequent C-C homolysis to give the vinyl oxadiazoline cation **4** which appears as a base peak for these compounds at 173. Scheme 2 shows the fragmentation pattern for compound **3c**. This pattern is well known in the literature for cycloalkanone fragmentations [8].



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Scheme 2

The NMR spectra were performed in DMSO-d_6. The ^{13}C NMR signal at about 100 ppm is very significant. It refers to the spiro carbon of these compounds. This value is similar to reported values of spiro carbons flanked by oxygen and nitrogen atoms in five-membered oxadiazoline rings [2]. The ^{13}C NMR signals at about 152 and at about 150 ppm are assigned to the (C=O) and (C=N) of these compounds. These values are in accordance with reported values for the same groups in other molecules [9]. The detailed NMR data are presented in the experimental section.

The position of the N-H group around 9 ppm is that of an N-H near a phenyl group, while the N-H at an oxadiazolidine ring appears usually near 5 ppm [10]. HMBC analysis of **3e** (Figure 1) indicated that the N-H (8.8) is near the aromatic carbon (120.0).

X-Ray crystal structure analysis of these compounds is consistent with structure **3**. Figure 2 shows the X-Ray structure of compound **3d** as an example. Bond lengths and bond angles are shown in tables 2 and 3.

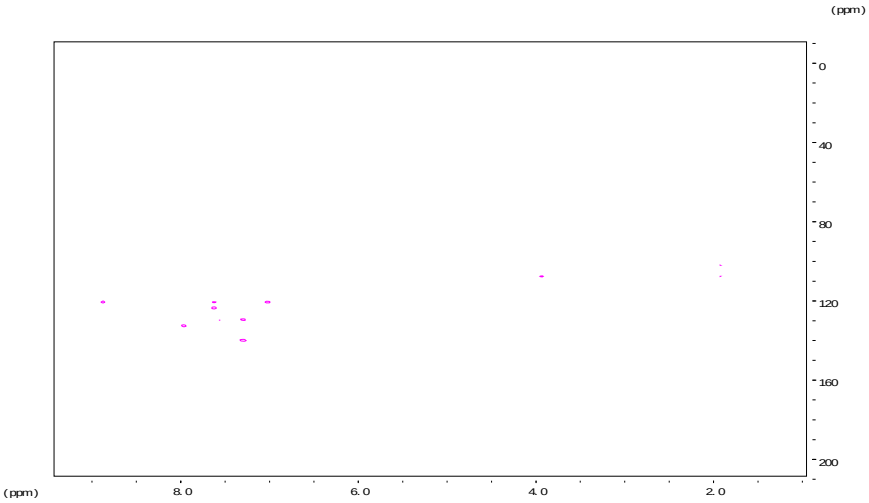

Figure 1: HMBC spectrum of **3e**

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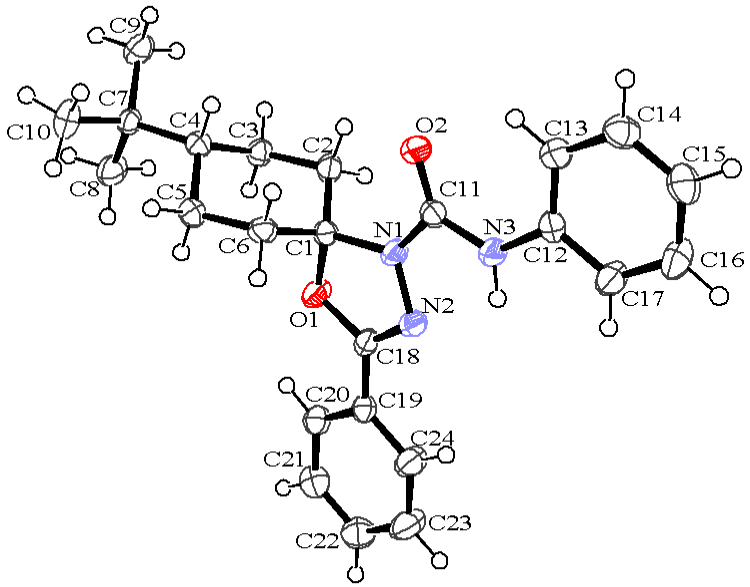


Figure 2: X- ray structure of **3d**

Table 2. Crystal data and structure refinement for **3d**.

Empirical formula		C24 H29 N3 O2
Formula weight		391.50
Temperature		150(2) K
Wavelength		0.71073 Å
Crystal system		Orthorhombic
Space group		P n a 21
Unit cell dimensions	a = 35.8841(8) Å	α= 90°.
	b = 5.95660(10) Å	β= 90°.
	c = 9.9087(2) Å	γ = 90°.
Volume		2117.96(7) $Å^3$
Z		4
Density (calculated)		1.228 Mg/m^3
Absorption coefficient		0.079 mm^{-1}
F(000)		840
Crystal size		0.25 x 0.20 x 0.10 mm^3
Theta range for data collection		3.06 to 25.99°.
Index ranges		-44<=h<=0, 0<=k<=6,
0<=l<=12		
Reflections collected		2087
Independent reflections		2087 [R(int) = 0.0710]
Completeness to theta = 25.99°		94.2 %
Absorption correction		None
Max. and min. transmission		0.9922 and 0.9805
Refinement method		Full-matrix least-squares on F^2
Data / restraints / parameters		2087 / 1 / 270
Goodness-of-fit on F^2		1.093
Final R indices [I>2sigma(I)]		R1 = 0.0387, wR2 = 0.0700
R indices (all data)		R1 = 0.0610, wR2 = 0.0789
Absolute structure parameter		0.5(16)
Extinction coefficient		0.0153(14)
Largest diff. peak and hole		0.174 and -0.165 $e.Å^{3-}$

Table 3. Selected Bond lengths [Å] for **3d**.

1.463(3)	C(1)-O(1)	1.365(3)	C(11)-N(3)
1.475(3)	C(1)-N(1)	1.369(3)	C(11)-N(1)
1.504(4)	C(1)-C(2)	1.381(4)	C(12)-C(13)
1.516(4)	C(1)-C(6)	1.390(4)	C(12)-C(17)
1.533(3)	C(2)-C(3)	1.411(4)	C(12)-N(3)
0.9900	C(2)-H(2A)	1.390(4)	C(13)-C(14)
0.9900	C(2)-H(2B)	0.9500	C(13)-H(13)
1.529(3)	C(3)-C(4)	1.378(4)	C(14)-C(15)
0.9900	C(3)-H(3A)	0.9500	C(14)-H(14)
0.9900	C(3)-H(3B)	1.380(4)	C(15)-C(16)
1.531(4)	C(4)-C(5)	0.9500	C(15)-H(15)
1.558(4)	C(4)-C(7)	1.380(4)	C(16)-C(17)
1.0000	C(4)-H(4)	0.9500	C(16)-H(16)
1.526(4)	C(5)-C(6)	0.9500	C(17)-H(17)
0.9900	C(5)-H(5A)	1.280(3)	C(18)-N(2)
0.9900	C(5)-H(5B)	1.368(3)	C(18)-O(1)
0.9900	C(6)-H(6A)	1.451(4)	C(18)-C(19)
0.9900	C(6)-H(6B)	1.381(4)	C(19)-C(20)
1.522(4)	C(7)-C(8)	1.394(4)	C(19)-C(24)
1.530(4)	C(7)-C(10)	1.377(4)	C(20)-C(21)
1.530(4)	C(7)-C(9)	0.9500	C(20)-H(20)
0.9800	C(8)-H(8A)	1.371(4)	C(21)-C(22)
0.9800	C(8)-H(8B)	0.9500	C(21)-H(21)
0.9800	C(8)-H(8C)	1.379(4)	C(22)-C(23)
0.9800	C(9)-H(9A)	0.9500	C(22)-H(22)
0.9800	C(9)-H(9B)	1.385(4)	C(23)-C(24)
0.9800	C(9)-H(9C)	0.9500	C(23)-H(23)
0.9800	C(10)-H(10A)	0.9500	C(24)-H(24)
0.9800	C(10)-H(10B)	1.399(3)	N(1)-N(2)
0.9800	C(10)-H(10C)	0.90(3)	N(3)-H(3)
1.227(3)	C(11)-O(2)		

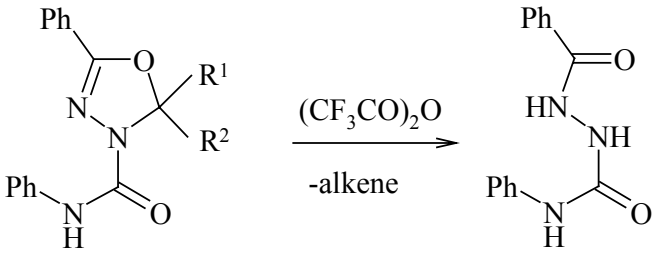
Table 3. Selected Bond angles [°] for 3d

99.50(18)	O(1)-C(1)-N(1)	109.2	C(1)-C(6)-H(6A)
108.7(2)	O(1)-C(1)-C(2)	109.2	C(5)-C(6)-H(6A)
114.0(2)	N(1)-C(1)-C(2)	109.2	C(1)-C(6)-H(6B)
109.24(19)	O(1)-C(1)-C(6)	109.2	C(5)-C(6)-H(6B)
112.5(2)	N(1)-C(1)-C(6)	107.9	H(6A)-C(6)-H(6B)
112.0(2)	C(2)-C(1)-C(6)	108.8(2)	C(8)-C(7)-C(10)
112.0(2)	C(1)-C(2)-C(3)	108.5(2)	C(8)-C(7)-C(9)
109.2	C(1)-C(2)-H(2A)	108.3(2)	C(10)-C(7)-C(9)
109.2	C(3)-C(2)-H(2A)	112.0(2)	C(8)-C(7)-C(4)
109.2	C(1)-C(2)-H(2B)	109.5(2)	C(10)-C(7)-C(4)
109.2	C(3)-C(2)-H(2B)	109.6(2)	C(9)-C(7)-C(4)
107.9	H(2A)-C(2)-H(2B)	109.5	C(7)-C(8)-H(8A)
112.2(2)	C(4)-C(3)-C(2)	109.5	C(7)-C(8)-H(8B)
109.2	C(4)-C(3)-H(3A)	109.5	H(8A)-C(8)-H(8B)
109.2	C(2)-C(3)-H(3A)	109.5	C(7)-C(8)-H(8C)
109.2	C(4)-C(3)-H(3B)	109.5	H(8A)-C(8)-H(8C)
109.2	C(2)-C(3)-H(3B)	109.5	H(8B)-C(8)-H(8C)
107.9	H(3A)-C(3)-H(3B)	109.5	C(7)-C(9)-H(9A)
108.4(2)	C(3)-C(4)-C(5)	109.5	C(7)-C(9)-H(9B)
113.7(2)	C(3)-C(4)-C(7)	109.5	H(9A)-C(9)-H(9B)
114.5(2)	C(5)-C(4)-C(7)	109.5	C(7)-C(9)-H(9C)
106.6	C(3)-C(4)-H(4)	109.5	H(9A)-C(9)-H(9C)
106.6	C(5)-C(4)-H(4)	109.5	H(9B)-C(9)-H(9C)
106.6	C(7)-C(4)-H(4)	109.5	C(7)-C(10)-H(10A)
111.7(2)	C(6)-C(5)-C(4)	109.5	C(7)-C(10)-H(10B)
109.3	C(6)-C(5)-H(5A)	109.5	H(10A)-C(10)-H(10B)
109.3	C(4)-C(5)-H(5A)	109.5	C(7)-C(10)-H(10C)
109.3	C(6)-C(5)-H(5B)	109.5	H(10A)-C(10)-H(10C)
109.3	C(4)-C(5)-H(5B)	109.5	H(10B)-C(10)-H(10C)
107.9	H(5A)-C(5)-H(5B)	125.6(2)	O(2)-C(11)-N(3)
112.2(2)	C(1)-C(6)-C(5)	121.4(2)	O(2)-C(11)-N(1)

It is worthwhile mentioning that compounds such as **1** have never been observed to undergo self cyclization to 1,3,4-oxadiazolines. However, in the presence of the strong electophile phenylisocyanate **2**, these compounds readily underwent cyclization to the corresponding oxadiazoline rings carrying the phenylisocyanate moiety.

Reflux of **1** with phenylisothiocyanate in chloroform several hours showed no reaction and the starting materials of **1** were recovered unchanged. The unreactivity of phenylisothiocyanate towards **1** can be attributed to its low electrophilicity compared with phenylisocyanate

Treatment of compounds **3** with trifluoroacetic anhydride yielded 2,5-dioxo-1,5-diphenyl-1,3,4-triazapentane **5** *via* elimination of the respective alkene in moderate yields. This structure gives also a strong support of the assigned structure. The assignment of structure **5** was based on its melting point [10], spectral data including IR, mass spectra, ^{1}H- and ^{13}C-NMR.



3a-f **4**

Scheme 3

Experimental

Melting points were determined on an Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared specrometer (KBr discs). ^{1}H- and ^{13}C NMR spectra were recorded on a Brucker 300 MHz instrument for solutions in DMSO-d_6 at 21 ^{o}C, using TMS as an internal reference. Chemical shifts are expressed in δ (ppm) downfield from TMS. Electron impact mass spectra were run on Finnigan Mat 8200 and 8400 series double focusing sector field spectrometers at 70 eV. Benzoylhydrazones **1a-f** were prepared as described in the literature [11-13].

Synthesis of the title compounds 3a-f

To a stirred solution of the respective benzoylhydrazone (**1**, 0.005 mol) in chloroform (30 mL) was dropwise added phenyl isocyanate (**2**, 0.006 mol) in chloroform (10 mL) at room temperature. Stirring was continued for further 3 hours. A small quantity of precipitated diphenylurea was filtered and the solvent was evaporated. The residual solid was triturated with ethanol and collected by suction filtration. Further purification was achieved by crystallization from chloroform / petroleum ether (40-60 ºC). The yields were in the range of 60-80%. The following compounds were prepared utilizing this procedure.

4-Carbanilino-2,2-dimethyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole (3a)

^{1}H NMR: 8.8; (s, 1H, N-H), 6.7-8.1 (m, 10 H, aromatics), 1.8, (s, 6H, CH_3).

^{13}C NMR: 152.9 (C=O), 150.4 (C=N), 139.3, 131.5, 129.1, 128.8, 126.8, 124.9, 122.1, 120.0 (Aromatic carbons), 100.7 (Spiro carbon C2), 25.4, 25.1 (CH_3)

IR (cm^{-1}): 3288 (NH), 3050 (aromatic hydrogens), 2981 (aliphatic hydrogens), 1659 (C=O)

4-Carbanilino-2-phenyl-1,3,4-oxadiazaspiro[4.4]non-2-ene (3b)

^{1}H NMR: 8.9, (s, 1H, N-H), 6.7-8.1 (m, 10H, aromatics), 1.7-2.6 (m, 8H, cyclopentane hydrogens).

^{13}C NMR: 152.9 (C=O), 150.1 (C=N), 109.8 (Spiro carbon C5), 33.4, 24.7 (cyclopentane CH_2)

IR (cm^{-1}): 3286 (NH), 3054 (aromatic hydrogens), 2973 (aliphatic hydrogens), 1653 (C=O)

4-Carbanilino-2-phenyl-1,3,4-oxadiazaspiro[4.5]dec-2-ene (3c)

^{1}H NMR: 8.8, (s, 1H, N-H), 7.0-8.0 (m, 10H, aromatics), 1.2-2.6 (m, 10H, cyclohexane hydrogens).

^{13}C NMR: signal doubling; 152.1 (C=O), 150.3 (C=N), 139.4, 131.7, 129.1, 128.5, 126.8, 125.0, 122.8, 122.1 (aromatic carbons), 102.0 (Spiro carbon C5), 33.1, 24.5, 22.8 (cyclohexane carbons).

IR (cm^{-1}): 3358 (NH), 3057 (aromatic hydrogens), 2935 (aliphatic hydrogens), 1668 (C=O)

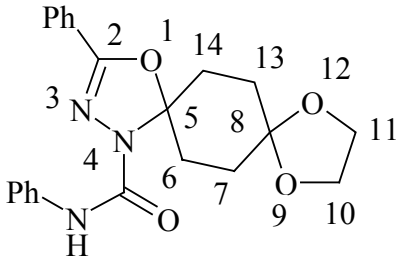
8-tert-Butyl-4-carbanilino-2-phenyl-1,3,4-oxadiazaspiro[4.5]dec-2-ene (3d)

^{1}H NMR: 8.8, (s, 1H, N-H), 6.5-7.9 (m, 10H, aromatics), 1.0-3.0 (m, 9H, cyclohexane hydrogens), 0.93 (s, 9H, $3CH_3$).

^{13}C NMR: 152.0 (C=O), 150.0 (C=N), 101.9 (Spiro carbon C5), 46.2, 33.1, 32.6, 27.7, 23.7 (tert-butyl cyclohexane carbons)

IR (cm^{-1}): 3391 (NH), 3057 (aromatic hydrogens), 2953 (aliphatic hydrogens), 1680 (C=O)

4-Carbanilino-2-phenyl-1,9,12-trioxa-3,4-diazaspiro[4.2.4.2]tetradec-2-ene (3e)



3e

^{1}H NMR: 8.8, (s, 1H, N-H), 6.9-8.0 (m, 10H, aromatics), 3.9 (s, 4H, $2OCH_2$), 1.7-2.8 (m, 8H, cyclohexane hydrogens).
^{13}C NMR: 152.1 (C=O), 150.2 (C=N), 139.3, 131.9, 129.2, 128.8, 127.0, 124.9, 122.9, 120.0 (aromatic carbons), 107.0 (spiro carbon C8), 101.2 (Spiro carbon C5), 64.2 (OCH_2), 31.2, 30.5 (cyclohexane carbons)
IR (cm^{-1}): 3358 (NH), 3057 (aromatic hydrogens), 2935 (aliphatic hydrogens), 1668 (C=O)

4-Carbanilino-2-phenyl-1,3,4-oxadiazaspiro[4.6]undec-2-ene (3f)

^{1}H NMR: 8.9, (s, 1H, N-H), 6.8-8.0 (m, 10H, aromatics), 1.4-2.6 (m, 12H, cyclohexane hydrogens).
^{13}C NMR: 151.8 (C=O), 150.3 (C=N), 105.5 (Spiro carbon C5), 43.6, 30.2, 22.0 (cycloheptane carbons)
IR (cm^{-1}): 3345 (NH), 3057 (aromatic hydrogens), 2930 (aliphatic hydrogens), 1678 (C=O)

Reaction of compounds 3a-f with trifluoroacetic anhydride (Formation of 2,5-dioxo-1,5-diphenyl-1,3,4-triazapentane (5)

Compounds **3** (0.003 mol) in chloroform (60 mL) were stirred with trifluoroacetic anhydride (1.5 mL) at room temperature for two hours. The solvent was then evaporated and the residual solid triturated with ethanol and filtered. The yields were in the range of 40 to 60 %. m. p = 210 ^{o}C.
^{1}H NMR: 6.8 – 8.1 (m, 10 H, aromatics), 8.8 (s, 1H, NH), 10.3 (s, 1H, NH)
^{13}C NMR: 166.8 (PhC=O), 156.0 (NHC=O), 140.0, 132.9, 132.1, 129.0, 128.7, 127.9, 122.2, 118.8 (Aromatic carbons)
IR (cm^{-1}): 3300, 3273, 3180, (3N-H), 1660.0 (PhC=O), 1649.0 (NHC=O).

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