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Synthesis and Characterization of Some New 3-(4-*tert*-Butylphenyl)-5-phenyl-4*H*-1,2,4-triazole Derivatives

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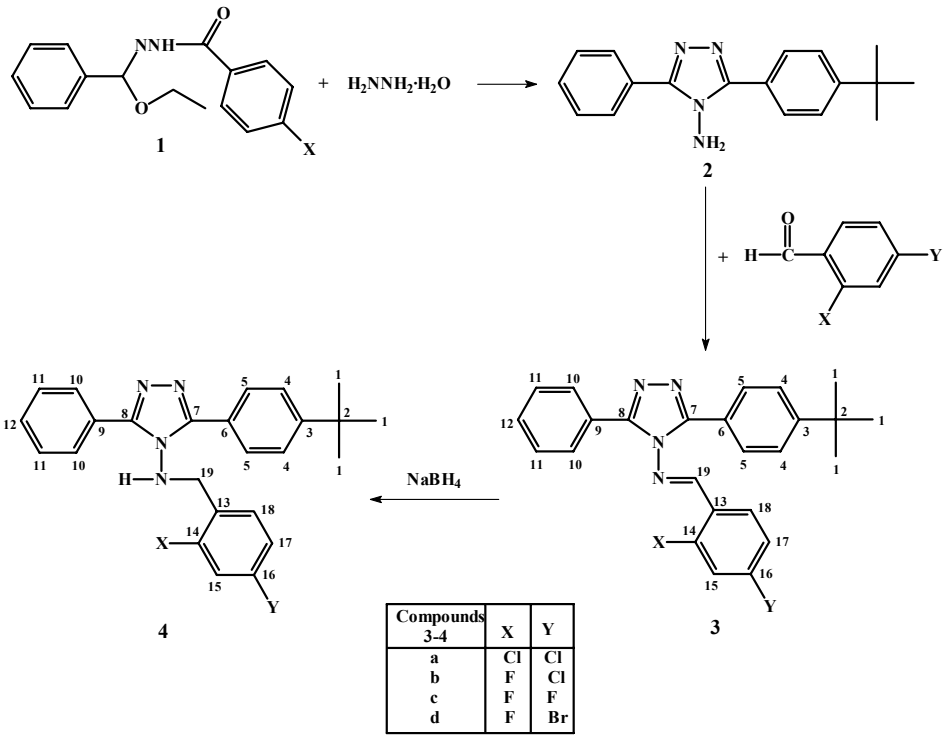
A series of new 3-(4-*t*-butylphenyl)-5-phenyl-4-(arylmethyleneamino)-4*H*-1,2,4-triazole derivatives **3** were prepared in good yields by treatment of 4-amino-3-(*t*-butyl-phenyl)-5-phenyl-4*H*-1,2,4-triazole **2** with selected aldehydes. Compounds **3** were reduced with $NaBH_4$ to afford the corresponding 3-(4-*t*-butylphenyl)-5-phenyl-4-(arylmethylamino)-4*H*-1,2,4-triazole derivatives **4**. Ten new compounds were synthesized and characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, IR and mass spectral data.

Key Words: 4*H*-1,2,4-Triazoles, 4-Arylmethyleneamino-4*H*-1,2,4-triazoles, 4-Arylmethylamino-4*H*-1,2,4-triazoles, Spectral studies.

INTRODUCTION

Many substituted 1,2,4-triazoles widely applied in medicine and agriculture; for example, they are used as anticonvulsant, antimicrobial, antihypertensive, analgesic, antiviral, antiinflammatory, antitumor, anti-HIV, pesticidal, insecticidal, herbicidal and fungicidal agents[1-15]. In addition to this, certain schiff bases are also known to have biological activities such as antimicrobial, antifungal, antitumor, anticonvulsant, antiviral activity[16-20]. Prompted by these observations, it is aimed to obtain new 1,2,4-triazole derivatives as possible biological active compounds.

In this study, *p-tert*-butylbenzoate benzoylhydrazone **1** was synthesized from the reaction of ethyl imido-phenylbenzoate hydrochloride with 4-*t*-butylbenzohydrazide. 4-Amino-3-(4-*t*-butylphenyl)-5-phenyl-4*H*-1,2,4-triazole **2** was obtained from the reaction of compound **1** with hydrazine hydrate. Compound **2** was treated with some aromatic aldehyde, such as 2,4-dichlorobenzaldehyde, 4-chloro-2-fluorobenzaldehyde, 2,4-difluorobenzaldehyde, 4-bromo-2-fluorobenzaldehyde, in acetic acid and obtained 3-(4-*t*-butylphenyl)-5-phenyl-4-(arylmethyleneamino)-4*H*-1,2,4-triazoles (**3**). Subsequently, compounds **3** were converted to compounds 3-(4-*t*-butylphenyl)-5-phenyl-4-(arylmethylamino)-4*H*-1,2,4-triazoles (**4**) by treating $NaBH_4$ in methanol (**Scheme-I**).



Compounds 3-4	X	Y
a	Cl	Cl
b	F	Cl
c	F	F
d	F	Br

Scheme-I: Synthetic pathway for the preparation of target compounds **1-4**

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. The mass spectra were recorded on a Micro-Mass Quattro LC-MS/MS spectrometer. Elemental analyses were performed on a ECS 4010 Elemental Combustion System. The required chemicals were purchased from Merck and Fluka companies.

Synthesis of hydrazone (1): A solution of 4-*t*-butylbenzohydrazide (0.01 mol) in 25 mL of absolute ethanol was added to a solution of ethyl imidophenylbenzoate hydrochloride (0.01 mol) in 25 mL of absolute ethanol. The mixture was stirred for 6 h at 0-5 ºC and subsequently for 2 h at room temperature. The reaction mixture was poured into a beaker containing 40 mL of cold water and 10 g of ice. The precipitate formed was washed with 50 mL of ice-water and then dried. The product was recrystallized from benzene-petroleum ether (40-60 ºC) to afford pure compound **1**. Yield 72 %, m.p. 130 ºC, IR (KBr, ν_{max}, cm^{-1}): 3245 (NH), 2963 (*t*-Bu), 1670 (C=O), 1611 (C=N), ^{1}H NMR (DMSO-d_6) δ: 1.10 (t, 3H, CH_3), 1.29 (s, 9H, $3CH_3$),

4.05 (q, 2H, CH_2), 7.50-7.57 (m, 4H, Ar-H), 7.60-7.64 (m, 2H, Ar-H), 8.01-8.13 (m, 3H, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 163.94 (C=O), 163.70 (C=N), Ar-C: [154.90, 131.90, 130.63, 129.33 (2C), 128.95, 127.50 (2C), 126.78(2C), 125.79 (2C)], 66.61 (OCH_2), 34.73 [C-(CH_3)$_3$], 30.78 [C-(CH_3)$_3$], 15.02 (CH_3).

Synthesis of amino compound (2): Compounds **1** (0.01 mol) was added to a solution of hydrazine hydrate (0.01 mol) in 50 mL of 1-propanol and the mixture was refluxed for 24 h. On cooling, a precipitate was formed. This product was filtered and after drying, was washed with 20 mL of benzene. The insoluble part in benzene was recrystallized from ethanol to afford pure compound **2**. Yield 87 %, m.p. 245 ºC, IR (KBr, ν_{max}, cm^{-1}): 3339, 3185 (NH_2), 2959 (*t*-Bu), 1633, 1527 (C=N), ^{1}H NMR (DMSO-d_6) δ: 1.33 (s, 9H, 3CH_3), 6.29 (s, 2H, NH_2), 7.52-7.98 (m, 5H, Ar-H), 8.02-8.04 (m, 4H, Ar-H), ^{13}C NMR (DMSO-d_6) δ: 154.18 (triazole C_3), 153.96 (triazole C_5), Ar-C: [152.06, 129.40, 128.82 (2C), 128.16 (2C), 127.98 (2C), 127.18 (2C), 125.19 (2C), 124.32], 34.45 [C-(CH_3)$_3$], 30.88 [C-(CH_3)$_3$].

Synthesis of Schiff bases (3a-e): The corresponding aldehyde (0.01 mol) was added to a solution of compound **2** (0.01 mol) in 20 mL of glacial acetic acid and the mixture was refluxed for 4 h. After cooling, the mixture was poured into a beaker containing 100 mL of ice-water. The precipitate formed was filtered. After drying *in vacuo*, the product was recrystallized from an appropriate solvent to give the desired compound. Experimental data for compounds **3a-e** are given in Table-1.

Synthesis of reduced compounds (4a-e): The corresponding compound (**3a-e**) (0.01 mol) was dissolved in 50 mL of dried methanol and $NaBH_4$ (0.01 mol) was added in small portions to this solution. The mixture was refluxed for 0.5 h and then allowed to cool. After evaporation at 30-35 ºC under reduced pressure, the solid residue was washed with cold water. After drying *in vacuo*, the solid product was recrystallized from an appropriate solvent to afford the desired compound. Experimental data for compounds **4a-e** are given in Table-1.

RESULTS AND DISCUSSION

Because of imine character, the reduction of compounds **3** can be possible and taken into consideration[16,17, 21-24]. But the reduction of the 3-(4-*t*-butylphenyl)-5-phenyl-4*H*-1,2,4-triazole ring may also occur[25]. Hence, the attempts of the reduction of compounds **3** may result in the formation of various products. However in the study, the reduction of only the imino group of compounds **3** was achieved using $NaBH_4$ in methanol as a selective reducing agent. So, a general and convenient method was established for the synthesis of type **4** compounds. Thus, four new 3-(4-*t*-butylphenyl)-5-phenyl-4-(arylmethyleneamino)-4*H*-1,2,4-triazole derivatives (**3**) and four new 3-(4-*t*-butylphenyl)-5-phenyl-4-(arylmethylamino)-4*H*-1,2,4-triazoles derivatives (**4**) were synthesized in good yields. Synthesized compounds are expected to exhibit some biologically active properties[16-18]. Elemental analysis and physical data for **3** and **4** compounds are given in Table-1.

TABLE-1
PHYSICAL CHARACTERIZATION AND ANALYTICAL DATA OF COMPOUNDS **3** AND **4**

Compd.	Yield (%)	m.p. (ºC) (Recrys. Solvent)	m.f. (m.w.)	Elemental analysis %: Calcd. (Found)		
				C	H	N
3a	85	158 (Ethyl acetate)	$C_{25}H_{22}N_4Cl_2$ (449.38)	66.82 (66.72)	4.93 (5.27)	12.47 (12.65)
3b	88	183 (Ethanol-water)	$C_{25}H_{22}N_4ClF$ (432.93)	69.36 (69.13)	5.12 (5.51)	12.94 (12.87)
3c	87	161 (Ethanol-water)	$C_{25}H_{22}N_4F_2$ (416.47)	72.10 (72.10)	5.32 (5.45)	13.45 (13.57)
3d	85	195 (Ethanol-water)	$C_{25}H_{22}N_4BrF$ (477.38)	62.90 (62.92)	4.65 (4.67)	11.74 (11.93)
4a	97	225 (Ethyl acetate)	$C_{25}H_{24}N_4Cl_2$ (451.40)	66.52 (66.55)	5.36 (5.27)	12.41 (12.84)
4b	98	238 (Ethyl acetate)	$C_{25}H_{24}N_4ClF$ (434.94)	69.04 (69.04)	5.56 (5.69)	12.88 (12.82)
4c	98	251 (Ethanol-water)	$C_{25}H_{24}N_4F_2$ (418.49)	71.75 (71.60)	5.78 (6.17)	13.39 (13.36)
4d	97	242 (Ethanol-water)	$C_{25}H_{24}N_4BrF$ (479.39)	62.64 (62.76)	5.05 (5.22)	11.69 (11.81)

Infrared spectra of compound **1** showed absorption bands in the 3245, 2963, 1670 and 1611 cm^{-1} regions resulting from the NH, *tert*-butyl, C=O and C=N functions, respectively. Compound **2** showed two peaks in the regions 3339-3185 cm^{-1} due to asymmetric and symmetric vibration of the primary amino group. Compounds **3** showed characteristic C=N stretching bands between 1615 and 1570 cm^{-1}. Characteristic NH stretching bands of **4** were observed around 3320 cm^{-1}. The characteristic infrared bands of **3** and **4** compounds are presented in Table-2.

TABLE-2
IR DATA (KBr, cm^{-1}) OF COMPOUNDS **3** AND **4**

Compd.	ν(NH)	ν(*t*-Bu)	ν(C=N)	$\nu_{arm.\ ring}$ (monosubst.)	$\nu_{arm.\ ring}$ (disubst.)	$\nu_{arm.\ ring}$ (trisubst.)	ν(C-F)	ν(C-Cl)	ν(C-Br)
3a	-	2963	1615, 1584	746, 696	824	860, 763	-	1050, 1096	-
3b	-	2966	1607, 1561	744, 695	825	869, 773	1267	1075	-
3c	-	2967	1613, 1570	744, 696	825	862, 775	1279, 1142	-	-
3d	-	2965	1602, 1557	744, 695	821	870, 773	1220	-	1065
4a	3320	2965	1642, 1591	752, 695	834	865, 769	-	1058, 1105	-
4b	3325	2960	1610, 1582	753, 692	833	893, 770	1269	1075	-
4c	3322	2963	1619, 1604	753, 692	846	846, 770	1268, 1136	-	
4d	3323	2960	1605, 1578	752, 692	833	874, 770	1208	-	1068

In the ^{1}H NMR spectra of compound **1** characteristic OCH_2CH_3 signals appeared at δ 4.05 ppm (q, 2H, CH_2) and δ 1.10 ppm (t, 3H, CH_3). Characteristic amino proton (NH_2) of compound **2** was detected at δ 6.29 ppm. The ^{1}H NMR characteristic signals of Schiff bases (**3**) were observed around 8.60 ppm (s, 1H, N=CH). Characteristic -NH-CH_2- signals of reduced compounds (**4**) were detected around δ 7.28 (NH) and δ 3.75 (-CH_2). The ^{1}H NMR data of the compounds **3** and **4** are presented in Table-3.

TABLE-3
^{1}H NMR (δ ppm in DMSO-d_6) DATA OF COMPOUNDS **3** AND **4**

Compd.	$C(CH_3)_3$	CH_2	N=CH	NH	Ar-H
3a	1.28 (s, 9H)	-	8.64 (s, 1H)	-	7.51-7.61 (m, 5H), 7.71 (d, 2H, J = 8.80 Hz), 7.80-7.75 (m, 3H), 8.06 (d, 2H, J = 8.8 Hz)
3b	1.28 (s, 9H)	-	8.62 (s, 1H)	-	7.46-7.55 (m, 6H), 7.58-7.64 (m, 2H), 7.74-7.79 (m, 3H), 8.01 (t, 1H, J = 8.00)
3c	1.28 (s, 9H)	-	8.62 (s, 1H)	-	7.25-7.38 (m, 1H), 7.48-7.55 (m, 6H), 7.75-7.79 (m, 4H), 8.02-8.13 (m, 1H)
3d	1.28 (s, 9H)	-	8.61 (s, 1H)	-	7.47-7.58 (m, 6H), 7.74-7.78 (m, 5H), 7.92 (t, 1H, J = 8.00 Hz)
4a	1.31 (s, 9H)	3.78 (bs, 2H)	-	7.30 (bs, 2H)	6.72 (d, 1H, J = 8.40 Hz), 6.99 (d, 1H, J = 8.40 Hz), 7.35-7.62 (m, 5H), 7.74 (d, 2H, J = 8.40 Hz), 7.73-7.88 (m, 3H)
4b	1.33 (s, 9H)	3.74 (d, 2H, J = 3.50 Hz)	-	7.28 (d, 2H, J = 3.50 Hz)	6.709 (t, 1H, J = 8.00 Hz), 6.86-6.98 (m, 2H), 7.47-7.51 (m, 5H), 7.78 (d, 2H, J = 8.40 Hz), 7.83-7.89 (m, 2H)
4c	1.32 (s, 9H)	3.74 (d, 2H, J = 3.50 Hz)	-	7.26 (d, 2H, J = 3.50 Hz)	6.70-6.80 (m, 3H), 7.50-7.53 (m, 5H), 7.83 (d, 2H, J = 8.40 Hz), 7.85-7.88 (m, 2H)
4d	1.33 (s, 9H)	3.73 (bs, 2H)	-	7.26 (bs, 2H)	6.50 (t, 1H, J = 8.00 Hz), 7.00 (d, 2H, J = 8.40 Hz), 7.48-7.52 (m, 5H), 7.77 (d, 2H, J = 8.40 Hz), 7.86-7.88 (m, 2H)

In the ^{13}C NMR spectra of compound **1** characteristic C=O signal appeared at δ 163.94 ppm. The triazole C-3 and C-5 signals of compound **2** were recorded at δ 154.18 ppm and δ 153.96 ppm, respectively. Characteristic N=CH carbon signal of compound **3** were recorded at around δ 163 ppm. The ^{13}C NMR data of the compound **3** are presented in Table-4. Characteristic NH-CH_2 carbon signal of compound **4** were recorded around δ 47 ppm. The ^{13}C NMR data of the compound **4** is presented in Table-5. The ^{13}C NMR spectral data belonging to compounds **3** and **4** are numbered in **Scheme-I**.

The mass spectral decomposition modes of various 1,2,4-triazoles derivatives have been investigated[26-28]. The mass spectral of compounds **3** and **4** showed an intense molecular ion peak at m/z 449, 432, 416, 477, 451, 435, 419 and 479 corresponding to the compounds **3a**, **3b**, **3c**, **3d**, **4a**, **4b**, **4c** and **4d**, respectively. The molecular ion $(M)^+$ peaks were found to be the base peaks in the all compounds. The main fragments and relative intensity in the mass spectra of the compounds **3** and **4** are given in Table-6.

TABLE-4
^{13}C NMR (δ ppm in DMSO-d_6) DATA OF COMPOUNDS **3**

	Compounds			
	3a	**3b**	**3c**	**3d**
C1	30.79	31.56	30.76	30.67
C2	34.47	35.28	34.46	34.35
C3	152.53	153.34	152.48	152.43
C4	125.70	126.41	125.57	125.46
C5	128.20	127.93	127.91	127.86
C6	126.34	126.79	126.27	126.52
C7	150.70	150.77	149.95	149.85
C8	149.92	150.65	149.83	149.76
C9	129.30	130.22	130.14	129.44
C10	128.51	128.75	128.32	128.23
C11	128.82	129.11	128.78	128.68
C12	127.80	129.15	129.74	127.65
C13	129.77	117.77	116.02	118.27
C14	135.71	164.62	164.76	163.54
C15	129.77	118.86	105.09	120.12
C16	138.23	139.78	167.98	126.19
C17	123.54	124.26	113.52	123.39
C18	129.85	130.60	130.30	129.65
C19	163.45	163.38	162.70	162.50

TABLE-5
^{13}C NMR (δ ppm in DMSO-d_6) DATA OF COMPOUNDS **4**

	Compounds			
	4a	**4b**	**4c**	**4d**
C1	30.78	30.87	31.69	30.85
C2	34.40	34.43	35.27	34.38
C3	152.12	152.19	153.06	152.15
C4	124.18	125.04	125.95	124.97
C5	127.54	127.44	128.29	127.42
C6	126.65	123.04	127.67	123.89
C7	153.80	153.65	154.68	153.63
C8	153.57	153.55	154.44	153.50
C9	129.60	129.59	130.40	129.15
C10	127.79	127.73	128.57	127.69
C11	128.33	128.32	129.13	128.28
C12	126.78	126.80	130.40	128.85
C13	134.30	132.27	119.46	118.29
C14	133.04	162.80	162.12	162.77
C15	132.13	115.60	104.60	121.35
C16	132.44	133.34	163.51	121.76
C17	123.87	121.73	111.83	122.06
C18	128.23	132.38	138.28	132.63
C19	50.90	47.07	47.80	47.12

TABLE-6
MASS SPECTRAL DATA OF COMPOUNDS **3** AND **4**

Compd.	m/e With Relative Intensity in Parenthese
3a	449(100) $[M]^+$, 331(10), 315(15), 293(22), 278(15), 262(8), 262(7), 229(8), 218(14), 149(10), 132(7).
3b	433(100) $[M]^+$, 419(8), 293(10), 278(38), 262(8), 232(12), 222(15), 156(7), 149(9), 121(7).
3c	417(100) $[M]^+$, 278(10), 262(5), 232(10), 222(13), 193(5), 149(12), 139(10), 121(18).
3d	477(100) $[M]^+$, 451(15), 293(17), 278(40), 262(14), 232(10), 222(5), 121(5).
4a	451(100) $[M]^+$, 411(10), 379(8), 325(12), 278(15), 246(12), 169(25), 147(15), 121(5).
4b	435(100) $[M]^+$, 278(37), 222(5), 158(7).
4c	419(100) $[M]^+$, 278(23), 222(4), 142(8), 127(5).
4d	479(100) $[M]^+$, 401(8), 318(7), 278(37), 252(7), 193(7), 178(5), 149(12), 121(10).

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