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HETEROCYCLIC SYNTHESIS USING NITRILIMINES: PART 8†. SYNTHESIS OF AROMATIC 1,2,4-TRIAZOLES

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Abstract: A series of new 1,2,4-triazole derivatives (**6a-p**) have been synthesized by the reaction of amidines **3** with certain nitrilimines **2**. The structures of newly synthesized compounds are confirmed by their analytical and spectral data including IR and NMR.
Key words: 1,2,4-triazoles, amidines, nitrilimines, cycloaddition.

استخدام ايمينات النيترايل في التخليق الحلقي غير المتجانس: جزء 8 . تخليق 4,2,1- ترايزولات الاروماتية

ملخص: سلسلة جديدة من مشتقات 4,2,1-ترايزول (**6a-p**) نتجت من تفاعل الاميـــدينات **3** و ايمينات النيترايل **2** ، وقد تم تحديد بنى المركبات المحضرة بناء على التحليل العنصري ودراســـة أطيافها المختلفة مثل طيف الأشعة تحت الحمراء وأطياف الرنين النووي المغناطيسي.

Introduction

The reactive 1,3-dipoles, Nitrilimines **2**, are well known to undergo two main cyclization reactions: 1,3-dipolar cycloaddition with multiple bonds leading to five membered ring heterocycles, such as 1,2,4-triazole derivatives [1-4], and Cyclocondensation reactions with nucleophiles incorporating suitably located electrophilic centers leading to five or six membered heterocycles [4,5].

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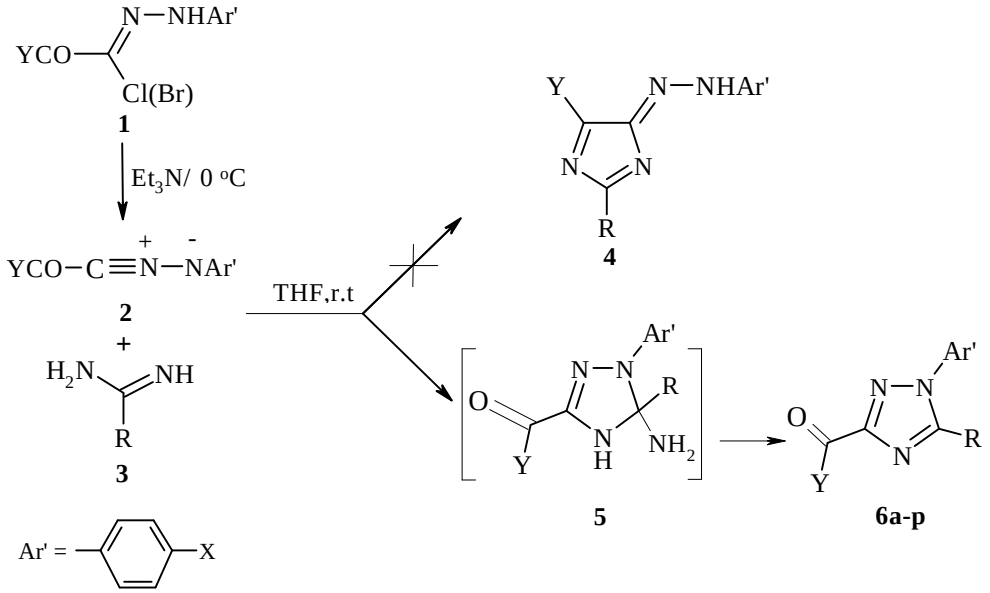
A large number of 1,2,4-triazole derivatives are reported to show a broad spectrum of biological properties, such as anti-inflammatory[6,7], antimicrobial[8,9,10],antifungal[10,11],antiviral[12],hypoglycemic[13],antihypertensive[14],antiparasitic[15],analgesic[16],diuretic[17],anticonvulsants[18] and antitumor activities [10,19,20]. In continuation of our work concerning the utility of nitrilimines in the synthesis of heterocyclic compounds, we investigated the reaction of C-substituted-N-arylnitrilimines **2** with various amidines **3** in an attempt to synthesize new derivatives of 1,2,4-triazoles (**6a-p**) in anticipation of expected interesting biological activities.

Results and Discussion

The synthesis of the 1,3,5-trisubstituted 1,2,4-triazoles (**6a-p**) was carried out by reacting acetamidine, benzamidine, and benzylthioformamidine hydrochloride **3** with hydrazonoyl halides **1** in the presence of triethylamine as a base in tetrahydrofuran (THF) or dioxane at room temperature (Scheme 1). Both analytical and spectroscopic data of all the synthesized compounds are in full agreement with the proposed structures. The purity of the synthesized compounds was checked by TLC in different solvents.

The formation of compounds (**6a-p**) is assumed to involve the formation of 5-amino-1,2,4-triazoles **5** (Scheme 1), through nucleophilic addition of the electron pair of the amino amidine then cyclization at the imine carbon, or by cycloaddition on to C=N of the amidine moiety or (group). The intermediate aminotriazole **5** can not be isolated nor observed by TLC, it ultimately undergos the elimination of NH_3 molecule yielding the aromatic 1,2,4-triazole derivatives (**6a-p**) (Scheme 2). The imidazole derivatives **4** were not observed.

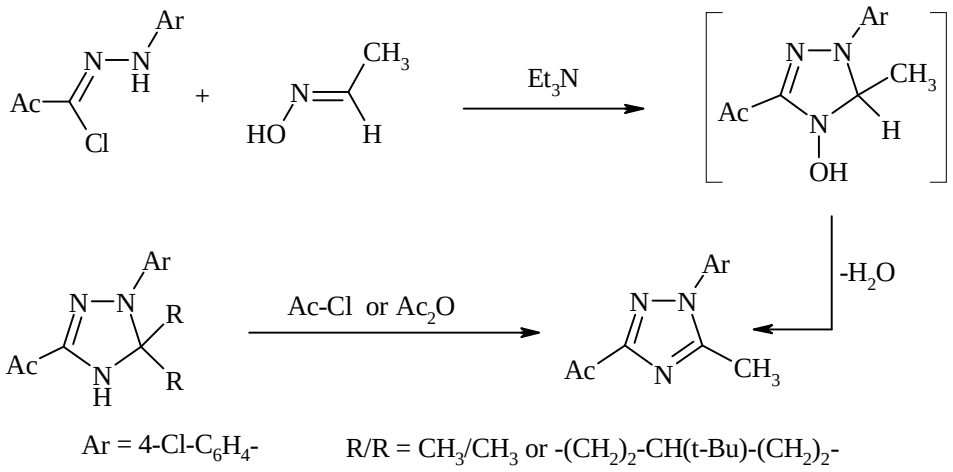


Entry	Y	R	X
a	Me	Me	Br
b	Me	Ph	H
c	Me	BzS-	Cl
d	Ph	Me	Cl
e	Ph	Ph	Cl
f	Ph	BzS-	Cl
g	PhNH-	Me	H
h	PhNH-	Ph	F

Entry	Y	R	X
i	PhNH-	BzS-	Me
j	2-Naphthyl	Me	H
k	2-Naphthyl	Ph	Cl
l	2-Naphthyl	BzS-	Me
m	2-Furyl	Me	Cl
n	2-Furyl	BzS-	Cl
o	2-Thienyl	Me	Cl
p	2-Thienyl	BzS-	Cl

Scheme 1: Synthetic pathway for 1,3,5-trisubtituted 1,2,4-triazoles (**6a-p**).

Some of these triazoles are known and can be prepared directly via interaction between the hydrazonoyl chlorides and acetaldoxime at ambient temperature for 48 hours [21] or via acetylation of 4,5-dihydro-1,2,4-triazoles as ring transformation products [22] (Scheme 2).



Scheme 2

Spectral data analysis: The characterization data of synthesized compounds (**6a-p**) are given in the experimental section. These compounds gave satisfactory microanalysis for the proposed structures which are also confirmed on the bases of their spectroscopic data . The IR spectra showed a strong absorption band of Ar-C=O in the region 1690-1640 cm^{-1}, in addition to, the characteristic band of C=N of the ring at about 1620-1590 cm^{-1}.

The ^{1}H NMR confirmed the formation of compounds **6** rather than **5**. The ^{1}H NMR spectra of compounds (**6a,d,g,j,m,o**) showed, in addition to aromatic protons signals, a characteristic signal due to the CH_3 proton at C-5 of the ring resonating at 2.4-2.5 ppm, in agreement with values reported in the literature [21-23].

The structures of compounds (**6a-p**) were further confirmed by ^{13}C NMR spectra, which account for the different carbons of these triazoles. The signals at about 157-150 ppm were attributed to the C-3 and C-5 carbons of the triazoles, and are in accordance with reported values of triazoles [21-23].

In conclusion, the reaction of nitrilimines **2** with acetamidine, benzamidine, and benzylthioformamidine hydrochloride **3** leads to formation of aromatic heterocyclic triazoles (**6a-p**).

Biological activity

Most of the newly synthesized compounds (**6a-p**) were tested for their antibacterial and antifungal activity *in vitro* against bacterial strains such as *Escherichia coli, Staphylococcus aureus, Klebsiella spp, Proteus spp* and *Pseudomonas* employing the nutrient agar disc diffusion method [24] at (1-10 mg/ml) in dimethyl formamide (DMF) by measuring the inhibition zone in mm. It is worthy to note that these aromatic triazoles (**6a-p**) showed weak

degree of activity against tested bacteria in comparison to DMF which was used as control. That may be due to lack of active substituted groups.

EXPERIMENTAL

Melting points were determined on a Stuart Electrothermal Apparatus and are uncorrected. The IR spectra were obtained by using Satellite 3000 Mid infrared spectrophotometer in potassium bromide pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (400.13 MHz) at room temperature in $CDCl_3$ if not noted otherwise stated, using tetramethylsilane (TMS) as an internal reference. All chemical shifts (δ) were reported in ppm from TMS. Elemental analysis are performed at Cairo University, Egypt and the results agreed with the calculated values within experimental errors. The hydrazonoyl halides **1a-c**[25], **1d-f**[25], **1g-h**[26], **1j-l**[27], **1m-p**[28] were prepared according to previously described procedures [25-28]. The amidines hydrochlorides **3** were purchased from Avocado research chemicals company, England and used without further purification.

Synthesis of the title compounds (6a-p).

To a stirred solution of the particular hydrazonoyl halides **1** (0.005 mol) and amidine hydrochlorides **3** (0.005 mol) in tetrahydrofuran or 1,4-dioxane (50-70 ml), triethylamine (4 ml, 0.03 mol) in tetrahydrofuran (10 ml) was dropwise added at room temperature. The resulting reaction mixture was stirred overnight at room temperature. The solvent was then evaporated under reduced pressure and the residue washed with water (100 ml) to get of the triethylamine salt. The crude product was triturated with ethanol or methanol (20 ml) and the insoluble solid was collected and recrystallized from appropriate solvents to afford the desired compounds.

The following compounds were prepared utilizing this procedure.

3-Acetyl-1-(4-bromophenyl)-5-methyl-1,2,4-triazole (6a).

Yield 72%; M.p. 213-215 ^{o}C (ethanol); IR: ν = 1680 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.50-7.25 (m, 4H, Ar-H), 2.65 (s, 3H, CH_3), 2.52 (s, 3H, CH_3CO) ppm; ^{13}C NMR: δ = 189.5 (C=O), 157.9, 154.2 (C=N), 141.3-115.6 (Ar-C), 26.6 (CH_3CO), 13.2 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 280.13): calcd. C 47.17, H 3.60, N 15.00. found: C 47.45, H 3.65, N 14.90.

3-Acetyl-1,5-diphenyl-1,2,4-triazole (6b).

Yield 67%; M.p. 202-204 ^{o}C (ethanol); IR: ν = 1680 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.60-7.7.20 (m, 10H, Ar-H), 2.50 (s, 3H, CH_3CO) ppm; ^{13}C NMR: δ = 189.5 (C=O), 157.7, 154.1 (C=N), 142.3-119.2 (Ar-C), 26.7 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 263.30): calcd. C 72.99, H 4.98, N 15.96. found: C 72.84, H 5.10, N 16.20.

3-Acetyl-5-benzylthio-1-(4-chlorophenyl)-1,2,4-triazole (6c).
Yield 82%; M.p. 183-185 ^{o}C (ethanol); IR: ν = 1680 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.67-7.7.22 (m, 9H, Ar-H), 3.20 (s, 2H, CH_2), 2.50 (s, 3H, CH_3CO) ppm; ^{13}C NMR: δ = 189.5 (C=O), 156.9, 152.5 (C=N), 142.3-116.8 (Ar-C), 32.1 (CH_2), 26.6 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 343.84): calcd. C 59.39, H 4.10, N 12.22. found: C 59.50, H 3.95, N 12.10.

3-Benzoyl-1-(4-chlorophenyl)-5-methyl-1,2,4-triazole (6d).
Yield 62%; M.p. 210-212 ^{o}C (ethanol); IR: ν = 1680 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.30-7.7.20 (m, 9H, Ar-H), 2.60 (s, 3H, CH_3) ppm; ^{13}C NMR: δ = 189.5 (C=O), 156.3, 153.6 (C=N), 142.1-116.5 (Ar-C), 13.6 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 297.75): calcd. C 64.54, H 4.06, N 14.11. found: C 64.20, H 3.90, N 14.29.

3-Benzoyl-1-(4-chlorophenyl)-5-phenyl-1,2,4-triazole (6e).
Yield 62%; M.p. 220-222 ^{o}C (ethanol); IR: ν = 1680 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.30-7.7.20 (m, 9H, Ar-H) ppm; ^{13}C NMR: δ = 189.5 (C=O), 156.6, 153.1 (C=N), 142.3-116.9 (Ar-C) ppm; $C_{21}H_{24}N_4O$ (MW 359.82): calcd. C 70.10, H 3.92, N 11.68. found: C 71.85, H 4.10, N 11.52.

3-Benzoyl-5-benzylthio-1-(4-chlorophenyl)-1,2,4-triazole (6f).
Yield 62%; M.p. 198-200 ^{o}C (ethanol); IR: ν = 1680 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.30-7.7.20 (m, 14H, Ar-H), 3.20 (s, 2H, CH_2) ppm; ^{13}C NMR: δ = 189.5 (C=O), 156.4, 152.7 (C=N), 142.0-116.2 (Ar-C), 32.1 (CH_2) ppm; $C_{21}H_{24}N_4O$ (MW 405.91): calcd. C 65.10, H 3.97, N 10.35. found: C 64.90, H 4.15, N 10.23.

5-Methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4-triazole (6g).
Yield 62%; M.p. 184-186 ^{o}C (ethanol); IR: ν = 3275 (N-H), 1650 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.30-7.7.20 (m, 10H, Ar-H), 8.85 (s, 1H, N-H), 2.68 (s, 3H, CH_3) ppm; ^{13}C NMR: δ = 162.5 (C=O), 156.7, 152.2 (C=N), 143.1-114.7 (Ar-C), 13.7 (CH_3), ppm; $C_{21}H_{24}N_4O$ (MW 278.32): calcd. C 69.05, H 5.07, N 20.13. found: C 68.85, H 4.90, N 20.21.

1-(4-Flourophenyl)-5-phenyl-3-phenylaminocarbonyl-1,2,4-triazole (6h). Yield 62%; M.p. 192-194 ^{o}C (ethanol); IR: ν = 3270 (N-H), 1645 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.30-7.7.20 (m, 14H, Ar-H), 8.75 (s, 1H, N-H) ppm; ^{13}C NMR: δ = 162.3 (C=O), 157.2, 152.7 (C=N), 142.6-115.7 (Ar-C) ppm; $C_{21}H_{24}N_4O$ (MW 358.38): calcd. C 70.38, H 4.22, N 15.63. found: C 70.12, H 4.35, N 15.50.

5-Benzylthio-1-(4-methylphenyl)-3-phenylaminocarbonyl-1,2,4-triazole (6i). Yield 62%; M.p. 208-210 ^{o}C (ethanol); IR: ν = 3275 (N-H), 1650 (C=O) cm^{-1}; ^{1}H NMR: δ = 7.30-7.7.20 (m, 14H, Ar-H), 8.55 (s, 1H, N-H), 3.20 (s, 2H, CH_2), 2.70 (s, 3H, CH_3) ppm; ^{13}C NMR: δ = 189.5 (C=O), 156.9, 152.4 (C=N), 143.0-116.2 (Ar-C), 33.1 (CH_2), 21.7 (CH_3) ppm;

$C_{21}H_{24}N_4O$ (MW 400.51): calcd. C 68.98, H 5.03, N 13.99. found: C 69.22, H 4.95, N 14.13.

5-Methyl-1-phenyl-3-(2-naphthoyl)-1,2,4-triazole (6j).

Yield 62%; M.p. 179-181 ^oC (ethanol); IR: ν = 1640 (C=O) cm^{-1}; ^1H NMR: δ = 7.30-7.7.20 (m, 12H, Ar-H), 2.61 (s, 3H, CH_3) ppm; ^{13}C NMR: δ = 182.3 (C=O), 157.6, 154.1 (C=N), 141.6-119.3 (Ar-C), 13.9 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 313.36): calcd. C 76.66, H 4.82, N 13.41. found: C 76.80, H 5.00, N 13.33.

1-(4-Chlorophenyl)-3-(2-naphthoyl)-5-phenyl-1,2,4-triazole (6k).

Yield 62%; M.p. 211-213 ^oC (ethanol); IR: ν = 1640 (C=O) cm^{-1}; ^1H NMR: δ = 7.30-7.7.20 (m, 16H, Ar-H) ppm; ^{13}C NMR: δ = 182.5 (C=O), 157.5, 154.0 (C=N), 142.1-115.5 (Ar-C) ppm; $C_{21}H_{24}N_4O$ (MW 409.88): calcd. C 73.26, H 3.93, N 10.25. found: C 73.50, H 4.13, N 10.11.

5-Benzylthio-1-(4-methylphenyl)-3-(2-naphthoyl)-1,2,4-triazole (6l).

Yield 62%; M.p. 223-225 ^oC (ethanol); IR: ν = 1640 (C=O) cm^{-1}; ^1H NMR: δ = 7.30-7.7.20 (m, 10H, Ar-H), 3.20 (s, 2H, CH_2), 2.60 (s, 3H, CH_3) ppm; ^{13}C NMR: δ = 189.5 (C=O), 157.4, 153.8 (C=N), 142.5-115.4 (Ar-C) 33.1 (CH_2), 21.7 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 435.55): calcd. C 74.46, H 4.86, N 9.65. found: C 74.35, H 5.05, N 9.53.

1-(4-Chlorophenyl)-3-(2-furoyl)-5-methyl-1,2,4-triazole (6m).

Yield 62%; M.p. 193-195 ^oC (ethanol); IR: ν = 1660 (C=O) cm^{-1}; ^1H NMR: δ = 7.30-7.7.20 (m, 7H, Ar-H), 2.64 (s, 3H, CH_3) ppm; ^{13}C NMR: δ = 174.5 (C=O), 156.7, 153.7 (C=N), 143.3-125.5 (Ar-C), 14.0 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 287.71): calcd. C 58.45, H 3.50, N 14.61. found: C 58.66, H 3.37, N 14.70.

5-Benzylthio-1-(4-chlorophenyl)-3-(2-furoyl)- 1,2,4-triazole (6n).

M.p. 209-211 ^oC (ethanol); Yield 62%; IR: ν = 1660 (C=O) cm^{-1}; ^1H NMR: δ = 7.30-7.7.20 (m, 12H, Ar-H), 3.20 (s, 2H, CH_2) ppm; ^{13}C NMR: δ = 174.3 (C=O), 156.3, 153.5 (C=N), 143.1-116.8 (Ar-C), 32.6 (CH_2) ppm; $C_{21}H_{24}N_4O$ (MW 395.87): calcd. C 60.68, H 3.56, N 10.61. found: C 60.45, H 3.70, N 10.53.

1-(4-Chlorophenyl)- 5-methyl-3-(2-thenoyl)-1,2,4-triazole (6o).

Yield 62%; M.p. 187-189 ^oC (ethanol); IR: ν = 1660 (C=O) cm^{-1}; ^1H NMR: δ = 7.30-7.7.20 (m, 7H, Ar-H), 2.65 (s, 3H, CH_3) ppm; ^{13}C NMR: δ = 173.2 (C=O), 155.9, 152.6 (C=N), 142.7-125.2 (Ar-C), 14.1 (CH_3) ppm; $C_{21}H_{24}N_4O$ (MW 303.77): calcd. C 55.36, H 3.32, N 13.83. found: C 55.55, H 3.43, N 16.05.

5-Benzylthio-1-(4-chlorophenyl)-3-(2-thenoyl)- 1,2,4-triazole (6p).

Yield 62%; M.p. 210-212 ^oC (ethanol); IR: ν = 1655 (C=O) cm^{-1}; ^1H NMR: δ = 7.30-7.7.20 (m, 12H, Ar-H), 3.20 (s, 2H, CH_2) ppm; ^{13}C NMR: δ = 173.3 (C=O), 156.1, 152.9 (C=N), 142.8-115.9 (Ar-C), 32.1 (CH_2) ppm;

$C_{21}H_{24}N_4O$ (MW 411.94): calcd. C 58.32, H 3.43, N 10.20. found: C 58.07, H 3.60, N 10.34.

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