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HETEROCYCLIC SYNTHESIS USING NITRILE IMINES. 6*. SYNTHESIS OF SOME NEW SUBSTITUTED 4,5-DIHYDRO-1H-1,2,4-TRIAZOLES

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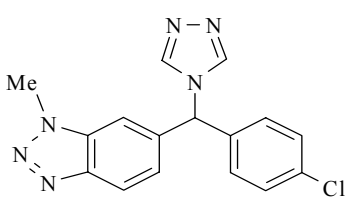
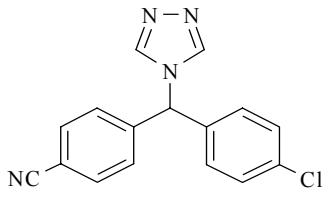
A new series of substituted 1,2,4-triazoles was synthesized from the cycloaddition reaction of alkanal and cycloalkanal hydrazones containing electron-withdrawing groups (MeCO, PhCO, and MeOCO) with appropriate hydrazonoyl halides.

Keywords: hydrazonoyl halides, hydrazones, 1,2,4-triazoles, cycloaddition.

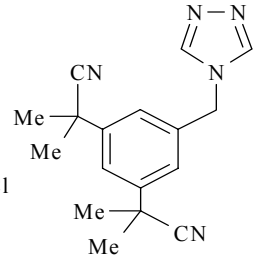
The synthesis of compounds incorporating 1,2,4-triazole rings has been attracting wide attention due to their diverse pharmacological properties such as antimicrobial, anti-inflammatory, analgesic, and antitumor activities [2-7]. It was reported that compounds having triazole moieties such as Vorozole, Letrozole, and Anastrozole (Chart) appear to be very effective aromatase inhibitors, very useful for preventing breast cancer [8-10]. Furthermore, some 1,2,4-triazol-5-one derivatives were found to possess antitumor activity [11-13]. Therefore, as a part of our continuing studies on triazole and their derivatives, we aimed to synthesize (Scheme) a new series of substituted 1,2,4-triazoles **4a–o** as possible biologically active compounds from the reaction of different hydrazones **3** with N-aryl-substituted C-benzoyl-, C-(2-furoyl)-, C-(2-naphthoyl)-, and C-(2-thenoyl)formonitrile imines **2**.



Vorozole



Letrozole



Anastrozole

Nitrile imines **2** were generated *in situ* from the reaction of hydrazonoyl halides **1** with triethylamine. The nitrile imines were not isolated but immediately reacted with the alkanal or cycloalkanal hydrazones **3** affording the corresponding 4,5-dihydro-1,2,4-triazoles **4a–o** in moderate yields. No elimination of acetamide,

* Part 5 [1].

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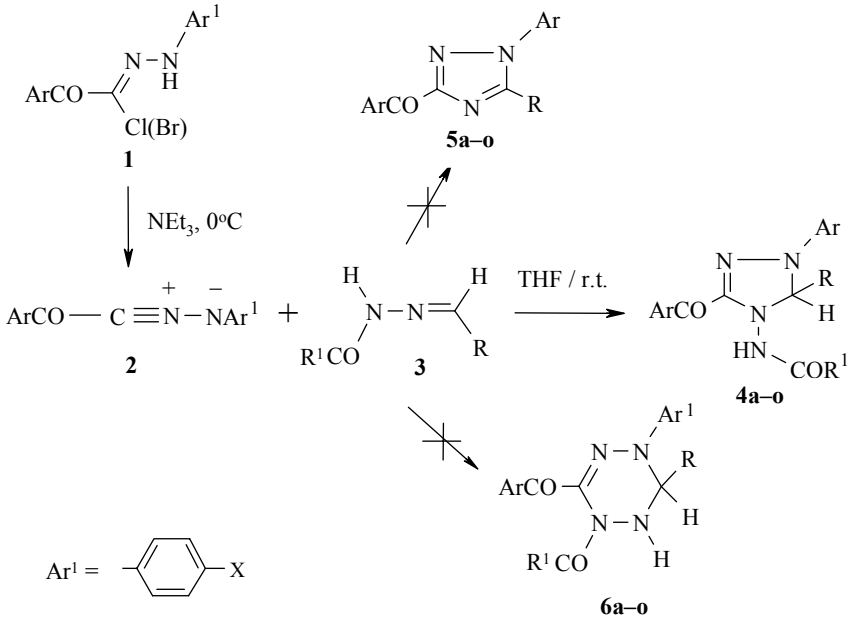
benzamide, or methyl carbamate occurred to get the aromatic 1,2,4-triazoles **5**. It is worth mentioning that the reaction of nitrile imines with acetaldoxime was found to give directly aromatic 1,2,4-triazoles *via* elimination of a water molecule [14]. The cyclocondensation adducts, 1,2,4,5-tetrazines **6a–o**, were not observed, apparently because of the low nucleophilicity of the nitrogen atom carrying the acetyl, benzoyl, and methoxycarbonyl group.



Entry	ArCO	R	R^1	X
a	2-Naphthoyl	Me	Me	H
b	2-Naphthoyl	Et	Ph	H
c	2-Naphthoyl	*n*-Hexyl	Ph	Cl
d	2-Naphthoyl	Cyclohexyl	Ph	Cl
e	2-Naphthoyl	Me	OMe	Me
f	2-Naphthoyl	Et	OMe	Me
g	Benzoyl	Me	Me	Cl
h	Benzoyl	Et	Ph	Cl
i	Benzoyl	Cyclohexyl	Ph	Cl
j	2-Furoyl	Me	Me	Cl
k	2-Furoyl	Et	Ph	Cl
l	2-Furoyl	Cyclohexyl	OMe	Cl
m	2-Thenoyl	Me	Ph	Cl
n	2-Thenoyl	Et	OMe	Cl
o	2-Thenoyl	Cyclohexyl	Me	Cl

The structures of the synthesized triazoles **4a–o** have been confirmed by elemental analysis, and their spectral data are depicted in the Experimental section. The IR spectra of the obtained compounds **4a-o** showed a strong absorption band in the region of 3350-3220 cm^{-1} that is assigned to NH and three groups of absorption bands at 1690-1675, 1675-1660, and 1735-1725 cm^{-1} for the N-acetyl, N-benzoyl, and carbamate carbonyl groups, respectively. The bands of NH and carbonyl of acetamide, benzamide, and carbamate groups characteristic of compounds **5** were not observed. In the ^1H NMR spectra, the signal of the proton at C-5 of the triazole ring was recorded between 5.5-5.3 ppm and the amide proton at 8.9-8.2 for compounds **4a**,**g**,**j**,**o**, 9.8-8.8 ppm for compounds **4b-d**,**h**,**i**,**k**,**m**, and 7.0-6.8 ppm for compounds **4e**,**f**,**l**,**n**. The ^{13}C NMR spectra showed the anticipated resonance signals of the different carbons, especially the signal of the C-5 of triazole ring around 84 ppm and for C=N carbon around 145 ppm.

TABLE 1. Physical Properties and Elemental Analysis Data of Compounds **4a-o**

Compound	Empirical formula (mw)	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
4a	$C_{22}H_{20}N_4O_2$	71.10 / 70.95	5.20 / 5.41	14.90 / 15.04	185-187	64
4b	$C_{28}H_{24}N_4O_2$	75.20 / 74.98	5.20 / 5.39	12.60 / 12.49	180-182	57
4c	$C_{32}H_{31}ClN_4O_2$	71.50 / 71.30	6.00 / 5.80	10.20 / 10.39	172-174	50
4d	$C_{32}H_{29}ClN_4O_2$	71.40 / 71.57	5.60 / 5.44	10.30 / 10.43	158-160	52
4e	$C_{23}H_{22}N_4O_3$	68.80 / 68.64	5.40 / 5.51	14.10 / 13.92	153-154	58
4f	$C_{24}H_{24}N_4O_3$	68.90 / 69.21	6.00 / 5.81	13.60 / 13.45	166-168	60
4g	$C_{22}H_{19}ClN_4O_2$	65.10 / 64.95	4.50 / 4.71	13.90 / 13.77	159-161	57
4h	$C_{24}H_{21}ClN_4O_2$	66.80 / 66.59	5.10 / 4.89	12.80 / 12.94	144-145	58
4i	$C_{28}H_{27}ClN_4O_2$	68.90 / 69.06	5.70 / 5.59	11.30 / 11.50	143-145	55
4j	$C_{16}H_{15}ClN_4O_3$	55.20 / 55.42	4.50 / 4.36	16.00 / 16.16	177-179	64
4k	$C_{22}H_{19}ClN_4O_3$	62.20 / 62.49	4.70 / 4.53	13.10 / 13.25	168-170	62
4l	$C_{21}H_{23}ClN_4O_4$	58.70 / 58.54	5.20 / 5.38	12.90 / 13.00	150-152	53
4m	$C_{21}H_{17}ClN_4O_2S$	59.50 / 59.36	3.90 / 4.03	13.30 / 13.19	165-167	60
4n	$C_{17}H_{17}ClN_4O_3S$	52.20 / 51.97	4.20 / 4.36	14.10 / 14.26	174-176	57
4o	$C_{21}H_{23}ClN_4O_2S$	58.30 / 58.53	5.50 / 5.38	12.80 / 13.00	146-148	55

This assignment is in good agreement with literature data for the carbon flanked by two nitrogens and the azomethine carbon in five-membered heterocycles [1, 15]. Again, if aromatic triazole **5** is formed, the C-5 would be observed over 150 ppm [14]. In conclusion, the results demonstrate that the reaction between nitrile imines and alkanal or cycloalkanal hydrazones containing electron-withdrawing groups is a clear 1,3-dipolar cycloaddition reaction.

EXPERIMENTAL

Melting points were determined in open capillaries on an Electrothermal Melting Temperature Apparatus and are uncorrected. The IR spectra were obtained using a Satellite 3000 Mid IR spectrometer in KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on a Brucker AM 300 spectrometer (300 and 75 MHz respectively) in $CDCl_3$ using TMS as internal reference. All chemical shifts were reported from internal TMS. Elemental analysis was performed at Cairo University, A.R.E. The hydrazonoyl halides **1** [17-20] and alkanalhydrazones **3** [21, 22] were prepared according to the known literature procedures.

Synthesis of compounds 4a-o (General procedure). Triethylamine (0.03 mol) in dioxane (5 ml) was added dropwise to a stirred solution of the appropriate hydrazonoyl halide **1** (0.005 mol) and the respective alkanal or cycloalkanal hydrazone **3** (0.01 mol) in dioxane (70 ml) at room temperature. Stirring was continued overnight, and the solvent was then evaporated under reduced pressure. The residue was washed several times with water to get rid of the triethylamine salt. The resulting crude solid was collected and recrystallized from ethanol or methanol to afford the desired products **4a-o**.

4-Acetylamino-5-methyl-3-(2-naphthoyl)-1-phenyl-4,5-dihydro-1H-1,2,4-triazole (**4a**). IR spectrum, ν, cm^{-1}: 3260 (NH); 1690 (N–C=O); 1654 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.50-7.02 (4H, m, arom. protons); 8.80 (1H, s, NH); 5.43 (1H, q, *J* = 9, CH); 2.0 (3H, s, CH_3CO); 1.58 (3H, d, *J* = 9, CH_3). ^{13}C NMR spectrum, δ, ppm: 184.3 (Ar–C=O); 177.5 (N–C=O); 145.35 (C=N); 141.34-115.51 (arom. carbons); 80.5 (C-5); 20.30 (CH_3); 20.00 (CH_3).

4-Benzoylamino-5-ethyl-3-(2-naphthoyl)-1-phenyl-4,5-dihydro-1H-1,2,4-triazole (**4b**). IR spectrum, ν, cm^{-1}: 3240 (NH); 1670 (N–C=O); 1640 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.55-7.01 (4H, m, arom. protons); 9.20 (1H, s, NH); 5.42 (1H, t, *J* = 9, CH); 1.86 (2H, m, CH_2); 0.95 (3H, t, *J* = 7, CH_3). ^{13}C NMR spectrum, δ, ppm: 184.10 (Ar–C=O); 168.8 (N–C=O); 145.40 (C=N); 141.34–115.51 (arom. carbons); 84.10 (C-5); 26.15 (CH_2); 6.60 (CH_3).

4-Benzoyl-1-(4-chlorophenyl)-5-*n*-hexyl-3-(2-naphthoyl)-4,5-dihydro-1H-1,2,4-triazole (**4c**). IR spectrum, ν, cm^{-1}: 3320 (NH); 1675 (N–C=O); 1645 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.50-7.04 (4H, m, arom. protons); 9.20 (1H, s, NH); 5.40 (1H, t, *J* = 9, CH); 1.82-0.60 (13H, m, *n*-hexyl protons). ^{13}C NMR spectrum, δ, ppm: 184.10 (Ar–C=O); 168.8 (N–C=O); 145.40 (C=N); 141.34-115.51 (arom. carbons); 84.50 (C-5); 26.65-4.60 (*n*-hexyl carbons).

4-Benzoylamino-1-(4-chlorophenyl)-5-cyclohexyl-3-(2-naphthoyl)-4,5-dihydro-1H-1,2,4-triazole (**4d**). IR spectrum, ν, cm^{-1}: 3230 (NH); 1660 (N–C=O); 1640 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.50-7.05 (4H, m, arom. protons); 9.30 (1H, s, NH); 5.41 (1H, d, *J* = 9, CH); 1.90–1.20 (11H, m, cyclohexyl protons). ^{13}C NMR spectrum, δ, ppm: 183.70 (Ar–C=O); 168.9 (N–C=O); 145.70 (C=N); 141.34–115.51 (arom. carbons); 87.50 (C-5); 40.30–24.20 (cyclohexyl carbons).

4-Methoxycarbonylamino-5-methyl-1-(4-methylphenyl)-3-(2-naphthoyl)-4,5-dihydro-1H-1,2,4-triazole (**4e**). IR spectrum, ν, cm^{-1}: 3280 (NH); 1730 (N–C=O); 1645 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.40-7.15 (4H, m, arom. protons); 6.90 (1H, s, NH); 5.45 (1H, q, *J* = 9, CH); 3.70 (3H, s, CH_3O); 2.30 (3H, s, CH_3); 1.59 (3H, d, *J* = 9, CH_3). ^{13}C NMR spectrum, δ, ppm: 183.5 (Ar–C=O); 156.50 (N–C=O); 145.10 (C=N); 141.34-115.51 (arom. carbons); 81.00 (C-5); 52.80 (O–CH_3); 20.70 (CH_3); 20.25 (CH_3).

5-Ethyl-4-methoxycarbonylamino-1-(4-methylphenyl)-3-(2-naphthoyl)-4,5-dihydro-1H-1,2,4-triazole (**4f**). IR spectrum, ν, cm^{-1}: 3280 (NH); 1735 (N–C=O); 1645 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.40-7.12 (4H, m, arom. protons); 6.90 (1H, s, NH); 5.43 (1H, t, *J* = 9, CH); 3.70 (3H, s, CH_3O); 2.30 (3H, s, CH_3); 1.85 (2H, m, CH_2); 0.93 (3H, t, *J* = 7, CH_3). ^{13}C NMR spectrum, δ, ppm: 183.20 (Ar–C=O); 156.50 (N–C=O); 145.20 (C=N); 141.34-115.51 (arom. carbons); 84.20 (C-5); 52.80 (O–CH_3); 26.15 (CH_2); 20.65 (CH_3); 6.60 (CH_3).

4-Acetylamino-3-benzoyl-1-(4-chlorophenyl)-5-methyl-4,5-dihydro-1H-1,2,4-triazole (**4g**). IR spectrum, ν, cm^{-1}: 3350 (NH); 1690 (N–C=O); 1640 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.10-7.15 (4H, m, arom. protons); 8.20 (1H, s, NH); 5.44 (1H, q, *J* = 9, CH); 1.98 (3H, s, CH_3CO); 1.56 (3H, d, *J* = 9, CH_3). ^{13}C NMR spectrum, δ, ppm: 183.8 (Ar–C=O); 168.8 (N–C=O); 145.40 (C=N); 141.34–115.51 (arom. carbons); 80.60 (C-5); 20.25 (CH_3); 19.80 (CH_3).

3-Benzoyl-4-benzoylamino-1-(4-chlorophenyl)-5-ethyl-4,5-dihydro-1H-1,2,4-triazole (**4h**). IR spectrum, ν, cm^{-1}: 3270 (NH); 1665 (N–C=O); 1640 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.15-7.15 (4H, m, arom. protons); 9.20 (1H, s, NH); 5.42 (1H, t, *J* = 9, CH); 1.87 (2H, m, CH_2); 0.94 (3H, t, *J* = 7, CH_3). ^{13}C NMR spectrum, δ, ppm: 183.80 (Ar–C=O); 168.9 (N–C=O); 145.40 (C=N); 141.34–115.51 (arom. carbons); 84.20 (C-5); 26.20 (CH_2); 6.60 (CH_3).

3-Benzoyl-4-benzoylamino-1-(4-chlorophenyl)-5-cyclohexyl-4,5-dihydro-1H-1,2,4-triazole (**4i**). IR spectrum, ν, cm^{-1}: 3245 (NH); 1665 (N–C=O); 1635 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.20-7.20 (4H, m, arom. protons); 9.80 (1H, s, NH); 5.40 (1H, q, *J* = 9, CH); 1.84-1.10 (11H, m, cyclohexyl protons). ^{13}C NMR spectrum, δ, ppm: 184.00 (Ar–C=O); 169.10 (N–C=O); 145.40 (C=N); 141.34-115.51 (arom. carbons); 87.40 (C-5); 40.20-24.20 (cyclohexyl carbons).

4-Acetylamino-1-(4-chlorophenyl)-3-(2-furoyl)-5-methyl-4,5-dihydro-1H-1,2,4-triazole (**4j**). IR spectrum, ν, cm^{-1}: 3290 (NH); 1680 (N–C=O); 1660 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.20-7.18 (4H, m, arom. protons); 8.80 (1H, s, NH); 5.46 (1H, q, *J* = 9, CH); 1.98 (3H, s, CH_3CO); 1.57 (3H, d, *J* = 9, CH_3). ^{13}C NMR spectrum, δ, ppm: 178.10 (N–C=O); 173.30 (Ar–C=O); 145.50 (C=N); 141.34-115.51 (arom. carbons); 80.50 (C-5); 20.35 (CH_3); 20.10 (CH_3).

4-Benzoylamino-1-(4-chlorophenyl)-5-ethyl-3-(2-furoyl)-4,5-dihydro-1H-1,2,4-triazole (**4k**). IR spectrum, ν, cm^{-1}: 3320 (NH); 1675 (N–C=O); 1660 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.20-7.20 (4H, m, arom. protons); 8.90 (1H, s, NH); 5.43 (1H, q, *J* = 9, CH); 1.84 (2H, m, CH_2); 0.95 (3H, t, *J* = 9, CH_3). ^{13}C NMR spectrum, δ, ppm: 173.50 (Ar–C=O); 169.20 (N–C=O); 145.40 (C=N); 141.34-115.51 (arom. carbons); 84.50 (C-5); 26.30 (CH_2); 6.70 (CH_3).

1-(4-Chlorophenyl)-5-cyclohexyl-3-(2-furoyl)-4-methoxycarbonylamino-4,5-dihydro-1H-1,2,4-triazole (**4l**). IR spectrum, ν, cm^{-1}: 3270 (NH); 1725 (N–C=O); 1650 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.25-7.15 (4H, m, arom. protons); 6.95 (1H, s, NH); 5.35 (1H, d, *J* = 9, CH); 1.80–1.10 (11H, m, cyclohexyl protons). ^{13}C NMR spectrum, δ, ppm: 173.60 (Ar–C=O); 156.6 (N–C=O); 145.75 (C=N); 141.34–115.51 (arom. carbons); 87.80 (C-5); 52.80 (O–CH_3); 40.90-24.20 (cyclohexyl carbons).

4-Benzoylamino-1-(4-chlorophenyl)-5-methyl-3-(2-thenoyl)-4,5-dihydro-1H-1,2,4-triazole (**4m**). ^{1}IR spectrum, ν, cm^{-1}: 3270 (NH); 1665 (N–C=O); 1655 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.30-7.20 (4H, m, arom. protons); 8.80 (1H, s, NH); 5.48 (1H, q, *J* = 9, CH); 1.56 (3H, d, *J* = 9, CH_3). ^{13}C NMR spectrum, δ, ppm: 174.20 (Ar–C=O); 169.20 (N–C=O); 145.45 (C=N); 141.34–115.51 (arom. carbons); 84.45 (C-5); 20.35 (CH_3).

1-(4-Chlorophenyl)-5-ethyl-4-methoxycarbonylamino-3-(2-thenoyl)-4,5-dihydro-1H-1,2,4- triazole (**4n**). IR spectrum, ν, cm^{-1}: 3260 (NH); 1735 (N–C=O); 1660 (Ar–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.25-7.16 (4H, m, arom. protons); 7.00 (1H, s, NH); 5.41 (1H, t, *J* = 9, CH); 3.67 (3H, s, CH_3O); 1.85 (2H, m, CH_2); 0.96 (3H, t, *J* = 7, CH_3). ^{13}C NMR spectrum, δ, ppm: 174.20 (Ar–C=O); 156.50 (N–C=O); 145.50 (C=N); 141.34–115.51 (arom. carbons); 84.40 (C-5); 52.90 (O–CH_3); 26.25 (CH_2); 6.65 (CH_3).

4-Acetylamino-1-(4-chlorophenyl)-5-cyclohexyl-3-(2-thenoyl)-4,5-dihydro-1H-1,2,4-triazole (**4o**). IR spectrum, ν, cm^{-1}: 3255 (NH); 1675 (N–C=O); 1655 (Ar–C=O) ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.30-7.20 (4H, m, arom. protons); 8.90 (1H, s, NH); 5.32 (1H, q, *J* = 9, CH); 1.96 (3H, s, CH_3CO); 1.81-1.20 (11H, m, cyclohexyl protons). ^{13}C NMR, δ, ppm: 178.30 (N–C=O); 174.40 (Ar–C=O); 145.70 (C=N); 141.34-115.51 (arom. carbons); 87.60 (C-5); 40.90-24.20 (cyclohexyl carbons).

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