

Reaction of Nitrilimines with Aromatic and Heterocyclic Ketoximes, Part 3: Synthesis of Substituted 1,2,4-Triazoles and 1,2,4,8-Tetraazaspiro[4,5]dec-2-enes

ABDEL-RAHMAN S. FERWANAH*, ADEL M. AWADALLAH† and
NEVEEN A. KHAFAJA

Chemistry Department, Faculty of Science, Al-Azhar University of Gaza
P.O. Box 1277, Gaza, Palestine
e-mail: awada@mail.iugaza.edu.

Nitrilimines (**2a–g**) react with acetophenone oxime (**3**) to afford 3-acyl-1-aryl-4,5-dihydro-5-methyl-5-phenyl-1H-1,2,4-triazoles (**4a–g**). Similarly, the reaction of nitrilimines (**2**) with 1-methyl-4-piperidone oxime (**6**) gives 3-acyl-1-aryl-8-methyl-1,2,4,8-tetraazaspiro[4,5]dec-2-enes (**7**). Spectral data of the title compounds are discussed.

INTRODUCTION

Substituted 1,2,4-triazoles have been receiving an important interest in recent years. The synthesis and applications of these heterocycles were reviewed by Polya.¹ One of the most practical applications of this heterocyclic system is in the synthesis of different polymers.² Recently, 3,5-disubstituted 1,2,4-triazoles were used for the synthesis of peptidomimetics.³

Cycloaddition reactions of nitrilimines with dipolarophiles containing (C=N) represents an important synthetic route to substituted 1,2,4-triazoles.¹ The synthesis of 3-acyl-1-aryl-5,5-disubstituted-1H-1,2,4-triazoles from the reaction of nitrilimines with aliphatic⁴ and cyclic⁵ ketoximes was recently reported by our group.

In continuation of our project for the synthesis of substituted 1,2,4-triazoles, we now investigate the reaction of nitrilimines with acetophenone and 1-methyl-4-piperidone oximes.

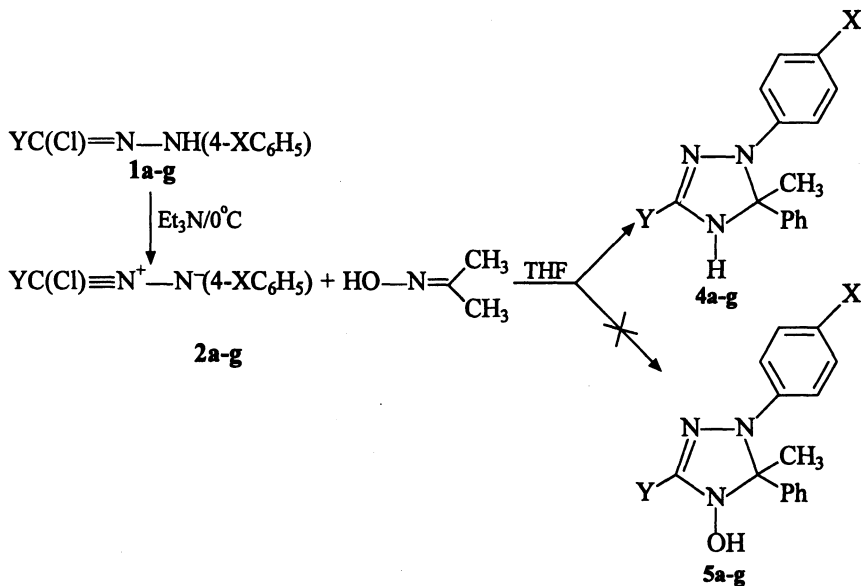
The precursors of nitrilimines hydrazoneyl halides (**1a–g**) employed in this study were prepared using Japp-Klingmann reaction.^{6,7} Acetophenone oxime⁸ and 1-methyl-4-piperidone oxime⁹ were prepared from direct reaction of the respective ketone with hydroxylamine hydrochloride in presence of sodium acetate.

EXPERIMENTAL

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer (KBr discs). ¹H and ¹³C-NMR spectra were recorded on a JEOL

†Chemistry Department, Faculty of Science, Islamic University of Gaza, Gaza, Palestine.

JNM-LA300 MHz instrument for solutions in CDCl_3 at 21°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. Elemental microanalyses were performed at H. Kolbe Microanalytische Laboratorium, Muelheim an der Ruhr, Germany. Hydrazonoyl halides (**1a–f**)⁶, and (g)⁷, acetophenone oxime (**3**)⁸ and 1-methyl-4-piperidone oximes⁹ (**6**) were prepared as described in the literature.

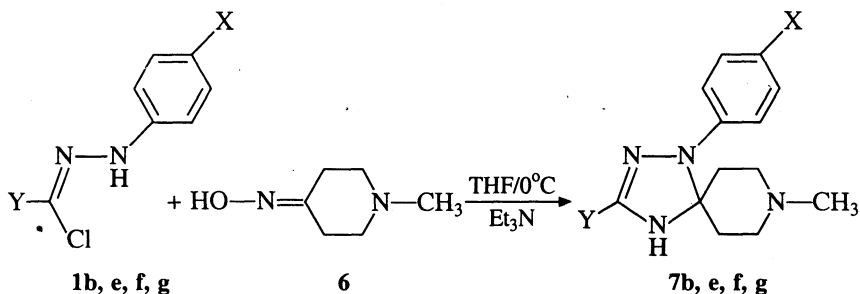


Entry	a	b	c	d	e	f	g
Y	Ac	Ac	Ac	Ac	Ac	benzoyl	2-naphthoyl
X	H	Cl	Br	CH_3	NO_2	Cl	Br

Scheme 1

Synthesis of the title compounds (4 and 7)

Triethylamine (5 g, 0.05 mol) in absolute tetrahydrofuran (10 mL) was added dropwise to a stirred solution of hydrazonoyl halides (**1a–g**) (0.015 mol) and the respective oximes (**3** or **6**) (0.03 mol) in tetrahydrofuran (100 mL) at $0\text{--}10^\circ\text{C}$. The temperature of the reaction mixture was then allowed to rise slowly to room temperature and stirring was continued for 3 days. The solvent was then evaporated *in vacuo*, and the residual solid was washed with water to get rid of the triethylamine salt. The crude product was recrystallized from ethanol. Compounds (**7**) were purified on preparative TLC plates, using silica gel as an adsorbent and CH_2Cl_2 as a developing solvent. The following compounds were prepared using this method:



Scheme 2.

3-Acetyl-4,5-dihydro-5-methyl-1,5-diphenyl-1H-1,2,4-triazole (4a)

$^1\text{H NMR}$ (CDCl_3): $\delta/\text{ppm} = 7.58\text{--}6.82$ (m, 10H, aromatic protons), 5.01 (s, 1H, NH), 2.53 (s, 3H, CH_3CO), 1.96 (s, 3H, $\text{C}_5\text{--CH}_3$); $^{13}\text{C NMR}$: $\delta/\text{ppm} = 189.33$ ($\text{C}=\text{O}$), 146.24 ($\text{C}=\text{N}$), 143.06, 141.99, 129.09, 128.96, 126.39, 121.16, 116.00, 114.65 (aromatic carbons), 86.23 (C-5 ring carbon), 25.11 ($\text{CH}_3\text{C}=\text{O}$), 23.35 (CH_3); IR $\text{cm}^{-1} = 3334$ (NH), 1661 ($\text{C}=\text{O}$).

3-Acetyl-1-(4-chlorophenyl)-4,5-dihydro-5-methyl-5-phenyl-1H-1,2,4-triazole (4b)

$^1\text{H NMR}$ (CDCl_3): $\delta/\text{ppm} = 7.55\text{--}6.87$ (m, 9H, aromatic protons), 5.08 (s, 1H, NH), 2.52 (s, 3H, CH_3CO), 1.94 (s, 3H, $\text{C}_5\text{--CH}_3$); $^{13}\text{C NMR}$: $\delta/\text{ppm} = 189.13$ ($\text{C}=\text{O}$), 146.19 ($\text{C}=\text{N}$), 142.40, 140.41, 128.98, 128.94, 128.73, 126.17, 125.79, 116.78 (aromatic carbons), 86.01 (C-5 ring carbon), 24.95 ($\text{CH}_3\text{C}=\text{O}$), 23.00 (CH_3); IR (cm^{-1}) 3355 ν (NH), 1670 ν ($\text{C}=\text{O}$).

3-Acetyl-1-(4-bromophenyl)-4,5-dihydro-5-methyl-5-phenyl-1H-1,2,4-triazole (4c)

$^1\text{H NMR}$ (CDCl_3): $\delta/\text{ppm} = 7.96\text{--}6.55$ (m, 9H, aromatic protons), 5.19 (s, 1H, NH), 2.50 (s, 3H, CH_3CO), 1.94 (s, 3H, $\text{C}_5\text{--CH}_3$); $^{13}\text{C NMR}$: $\delta/\text{ppm} = 189.16$ ($\text{C}=\text{O}$), 146.23 ($\text{C}=\text{N}$), 142.35, 140.86, 131.62, 128.98, 128.93, 126.16, 117.12, 113.13 (aromatic carbons), 85.94 (C-5 ring carbon), 24.98 ($\text{CH}_3\text{C}=\text{O}$), 22.98 (CH_3); IR (cm^{-1}) 3352 ν (NH), 1670 ν ($\text{C}=\text{O}$).

3-Acetyl-4,5-dihydro-5-methyl-5-phenyl-1-(*p*-tolyl)-1H-1,2,4-triazole (4d)

$^1\text{H NMR}$ (CDCl_3): $\delta/\text{ppm} = 7.59\text{--}6.85$ (m, 9H, aromatic protons), 4.96 (s, 1H, NH), 2.52 (s, 3H, CH_3CO), 2.22 (s, 3H, Ph--CH_3), 1.93 (s, 3H, $\text{C}_5\text{--CH}_3$); $^{13}\text{C NMR}$: $\delta/\text{ppm} = 189.05$ ($\text{C}=\text{O}$), 145.96 ($\text{C}=\text{N}$), 143.07, 139.46, 130.68, 129.33, 128.85, 128.69, 126.25, 116.15, (aromatic carbons), 86.31 (C-5 ring carbon), 24.88 ($\text{CH}_3\text{C}=\text{O}$), 23.06 (CH_3); 20.54 (Ph--CH_3), IR (cm^{-1}) 3339 ν (NH), 1656 ν ($\text{C}=\text{O}$).

3-Acetyl-4,5-dihydro-5-methyl-1-(4-nitrophenyl)-5-phenyl-1H-1,2,4-triazole (4e)

^1H NMR (CDCl_3): $\delta/\text{ppm} = 8.01\text{--}6.95$ (m, 9H, aromatic protons), 5.28 (s, 1H, NH), 2.57 (s, 3H, CH_3CO), 2.17 (s, 3H, C5-CH_3); ^{13}C NMR: $\delta/\text{ppm} = 189.27$ (C=O), 147.24 (C=N), 146.24, 140.96, 140.09, 129.55, 129.39, 125.97, 125.39, 113.61 (aromatic carbons), 85.33 (C-5 ring carbon), 25.26 ($\text{CH}_3\text{C=O}$), 23.65 (CH_3). IR (cm^{-1}) 3360 $\nu(\text{NH})$, 1672 $\nu(\text{C=O})$.

3-Benzoyl-4,5-dihydro-5-methyl-1-(4-nitrophenyl)-5-phenyl-1H-1,2,4-triazole (4f)

^1H NMR (CDCl_3): $\delta/\text{ppm} = 8.40\text{--}6.89$ (m, 12H, aromatic protons), 5.41 (s, 1H, NH), 2.02 (s, 3H, C5-CH_3); ^{13}C NMR: $\delta/\text{ppm} = 181.86$ (C=O), 146.16 (C=N), 142.50, 140.49, 135.69, 133.18, 130.27, 129.08, 129.02, 128.82, 128.31, 126.30, 125.95, 116.97 (aromatic carbons), 84.84 (C-5 ring carbon), 23.21 (CH_3); IR (cm^{-1}) 3352 $\nu(\text{NH})$, 1618 $\nu(\text{C=O})$.

1-(4-Bromophenyl)-4,5-dihydro-5-methyl-3-(2-Naphthoyl)-5-phenyl-1H-1,2,4-triazole (4g)

^1H NMR (CDCl_3): $\delta/\text{ppm} = 9.06\text{--}6.87$ (m, 16H, aromatic protons), 5.65 (s, 1H, NH), 2.02 (s, 3H, Ph-CH_3), ^{13}C NMR: $\delta/\text{ppm} = 181.62$ (C=O), 146.38 (C=N), 142.37, 140.88, 135.60, 132.87, 132.59, 132.38, 131.69, 129.95, 129.01, 128.95, 128.58, 127.96, 127.72, 126.64, 126.26, 125.46, 117.18, 113.17 (aromatic carbons), 84.76 (C-5 ring carbon), 23.06 (CH_3); IR (cm^{-1}) 3360 $\nu(\text{NH})$, 1607 $\nu(\text{C=O})$.

3-Acetyl-1-(4-chlorophenyl)-8-methyl-1,2,4,8-tetraazaspiro[4,5]dec-2-ene (7b)

^1H NMR (CDCl_3): $\delta/\text{ppm} = 7.21\text{--}7.14$ (4H, aromatic protons), 5.22 (s, 1H, NH), 2.40 (s, 3H, CH_3CO), 2.23 (s, 3H, N-CH_3), 3.65–1.54 (m, 8H, piperidone moiety protons). ^{13}C NMR: $\delta/\text{ppm} = 189.54$ (C=O), 147.75 (C=N), 141.02, 128.97, 128.24, 120.61 (aromatic carbons), 85.97 (C-5 spiro carbon), 52.56, 35.20 (piperidone carbons), 45.96 (NCH_3), 24.91 ($\text{CH}_3\text{C=O}$); IR (cm^{-1}) 3379 $\nu(\text{NH})$, 1670 $\nu(\text{C=O})$.

3-Acetyl-8-methyl-1-(4-nitrophenyl)-1,2,4,8-tetraazaspiro[4,5]dec-2-ene (7e)

^1H NMR (CDCl_3): $\delta/\text{ppm} = 8.14\text{--}7.38$ (4H, aromatic protons), 5.62 (s, 1H, NH), 2.52 (s, 3H, CH_3CO), 2.37 (s, 3H, N-CH_3), 3.01–1.22 (m, 8H, piperidone moiety protons). ^{13}C NMR: $\delta/\text{ppm} = 189.64$ (C=O), 147.88 (C=N), 147.17, 140.24, 125.48, 114.30 (aromatic carbons), 84.62 (C-5 spiro carbon), 52.37, 34.24 (piperidone carbons), 45.94 (NCH_3), 25.15 ($\text{CH}_3\text{C=O}$); IR (cm^{-1}) 3421 $\nu(\text{NH})$, 1693 $\nu(\text{C=O})$.

3-Benzoyl-1-(4-chlorophenyl)-8-methyl-1,2,4,8-tetraazaspiro[4,5] dec-2-ene (7f)

^1H NMR (CDCl_3): $\delta/\text{ppm} = 8.34\text{--}7.22$ (9H, aromatic protons), 5.68 (s, 1H, NH), 2.41 (s, 3H, N—CH₃), 3.00—1.23 (m, 8H, piperidone moiety protons). ^{13}C NMR: $\delta/\text{ppm} = 182.26$ (C=O), 147.57 (C=N), 140.98, 135.54, 133.24, 130.81, 130.29, 129.05, 128.29, 120.45 (aromatic carbons), 84.46 (C-5 spiro carbon), 52.53, 34.90 (piperidone carbons), 45.71 (NCH₃), IR (cm^{-1}) 3377 ν (NH), 1668 ν (C=O).

1-(4-Bromophenyl)-8-methyl-3-(2-naphthoyl)-1,2,4,8-tetarazaspiro [4,5] dec-2-ene (7g)

^1H NMR (CDCl_3): $\delta/\text{ppm} = 9.00\text{--}7.25$ (11H, aromatic protons), 5.74 (s, 1H, NH), 2.36 (s, 3H, N—CH₃), 2.98—1.22 (m, 8H, piperidone moiety protons). ^{13}C NMR: $\delta/\text{ppm} = 182.03$ (C=O), 147.77 (C=N), 141.53, 135.65, 132.73, 132.38, 131.94, 131.85, 129.98, 128.64, 127.99, 127.72, 126.66, 125.43, 120.54, 115.49 (14 aromatic carbons), 84.59 (C-5 ring carbon), 52.58, 35.02 (piperidone carbons), 45.90 (NCH₃), IR (cm^{-1}) 3375 ν (NH), 1612 ν (C=O).

RESULTS AND DISCUSSION

In the present work, it was found that nitrilimines (2)—generated *in situ* from the action of triethylamine on the respective hydrazoneoyl halides (1)—react with acetophenone oxime (3) and 1-methyl-4-piperidone oxime (6) to give the substituted triazoles (4) and (7), respectively. These compounds show hydrogen rather than an OH group at position 4.

Structural assignment of the triazoles (4) and (7) is based on elemental microanalysis and spectral data.

The IR spectra (KBr) indicates a strong N—H absorption band in the range 3441—3321 cm^{-1} and a strong C=O absorption band at *ca.* 1670 cm^{-1} (acetyl C=O), *ca.* 1618 cm^{-1} (benzoyl C=O) and *ca.* 1610 cm^{-1} (naphthoyl C=O).

The ^1H NMR of (4) show singlets for the CH₃ of the acetyl group (δ *ca.* 2.5 ppm) and the N—CH₃ (δ *ca.* 2.5 ppm) compounds (a–e). The NH signal appears at (δ *ca.* 5.1 ppm) in addition to the signals resulting from the aromatic rings and those of the piperidone moiety (δ *ca.* 3.6—1.54 ppm). The detailed ^1H NMR data is shown in the experimental part.

The ^{13}C NMR spectra display the characteristic signals of the suggested structure. Thus, compounds (a–e) exhibit a signal for the methyl carbon of the acetyl group at about 25 ppm. The C=O signal appears at about 190 ppm for compounds (a–e) containing an acetyl group, and at about 182 ppm for compounds (f, g) containing the benzoyl or 2-naphthoyl groups. The C-5 (spiro carbon) appears at about 85 ppm, and this is similar to reported values of spiro

carbons flanked by two heteroatoms in five-membered heterocycles.¹⁰ The signal at about 147 ppm is attributed to the C-3 carbon of the ring.

TABLE-1
PHYSICAL DATA FOR COMPOUNDS 4, 7

Compd.	m.p. (°C)	Yield (%)	m.f. (m.w.)	% Analysis, found (Calcd.)		
				C	H	N
4a	140–141	52	C ₁₇ H ₁₇ N ₃ O (279.34)	73.10 (72.91)	6.13 (5.78)	15.04 (14.73)
4b	130–132	47	C ₁₇ H ₁₆ N ₃ OCl (313.79)	65.07 (64.75)	5.14 (5.19)	13.39 (13.24)
4c	137–138	44	C ₁₇ H ₁₆ N ₃ OBr (358.24)	57.00 (56.70)	4.50 (4.59)	11.73 (11.71)
4d	82–83	46	C ₁₈ H ₁₉ N ₃ O (293.37)	73.70 (73.25)	6.53 (6.35)	14.32 (14.24)
4e	139–140	43	C ₁₇ H ₁₆ N ₄ O ₃ (324.34)	62.95 (63.40)	4.97 (4.96)	17.27 (17.29)
4f	130–131	47	C ₂₂ H ₁₈ N ₃ OCl (375.86)	70.30 (70.19)	4.83 (4.81)	11.18 (11.00)
4g	150–151	44	C ₂₆ H ₂₀ N ₃ OBr (470.37)	66.39 (66.44)	4.29 (4.90)	8.93 (8.56)
7b	126–127	55	C ₁₅ H ₁₉ N ₄ OCl (306.80)	58.73 (57.47)	6.24 (6.77)	18.26 (18.01)
7e	205–206	56	C ₁₅ H ₁₉ N ₅ O ₃ (317.35)	56.77 (56.85)	6.03 (6.02)	22.07 (22.13)
7f	80–81	40	C ₂₀ H ₂₁ N ₄ OCl (368.87)	65.12 (65.00)	5.74 (5.51)	15.19 (14.85)
7g	117–118	41	C ₂₄ H ₂₃ N ₄ OBr (463.38)	62.21 (61.81)	5.00 (5.10)	12.09 (11.83)

The electron impact (EI) spectra of these compounds display the correct molecular ions in accordance with the suggested formulas. The base peak in compounds (4) is always the ($M^{+}-15$) peak. The ($M^{+}-71$) is a major peak in compounds (7).

The ¹⁵N NMR of 3-acetyl-4,5-dihydro-1-phenyl-5,5-dimethyl-1H-1,2,4-triazole was recently reported in our first communication about this reaction to support the suggested structure, where it displays a doublet for the NH at 284.26 ppm relative to nitromethane (¹J_{N-H} = 85 Hz, ³J_{N-CH₃} = 2.5 Hz).⁴

It is worth mentioning that the reaction of nitrile oxides with oximes is reported to give the cycloaddition products 4-hydroxy- Δ^2 -1,2,4-oxadiazolines.¹⁰

ACKNOWLEDGEMENT

The authors wish to thank Dr. L. Gossen and Dr. W. Schrader, Max-Planck Institute fuer Kohlenforschung, Muelheim, Germany for obtaining elemental analyses, NMR and mass spectra.

REFERENCES

1. J.B. Polya, in A.R. Katritzky and C.W. Rees (Eds.), *Comprehensive Heterocyclic Chemistry*, Vol. 5, Pergamon Press, p. 733 (1984).
2. Jr. C. Temple, *Chem. Heterocycl. Compd.*, **37**, 575 (1981).
3. J. Cesar and M. Sollner, *Synth. Commun.*, **30**, 4147 (2000).
4. A.R.S. Ferwanah, *Asian J. Chem.*, **11**, 480 (1999).
5. A.R.S. Ferwanah, N.G. Kandile, A.M. Awadallah and O.M. Miqdad (unpublished work).
6. M.M. El-Abadelah, A.Q. Hussein and B.A. Thaher, *Heterocycles*, **10**, 1879 (1991).
7. N.M. Abu Nada, Ph.D. Thesis, University of Cairo, p. 79 (1992).
8. R.L. Shriner, R.C. Fuson, D.Y. Curtin and T.C. Morrill, *The Systematic Identification of Organic Compounds*, 6th Edn., John Wiley & Sons, New York, p. 181 (1980).
9. M.M. El-Abadelah, A.Q. Hussein and A.M. Awadallah, *Heterocycles*, **29**, 1957 (1989).
10. S. Morrocchi and A. Ricca, *Chim. Ind. (Milan)*, **49**, 629 (1967).

(Received: 27 March 2001; Accepted: 4 May 2001)

AJC-2343