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Synthesis and Antimicrobial Activity of New N-Methyl-N-(2-pyridyl) Aromatic and Heteroaromatic Hydrazones

RAJAB ABU-EL-HALAWA*, MOHAMED AL-NURI† and FOUAD MAHMOUD†
Chemistry Department, Al al-Bayt University, Mafraq, Jordan
E-mail: rajab@aabu.edu.jo

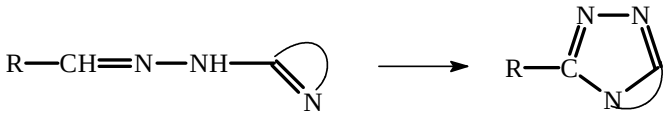
Aromatic and heteroaromatic N-methyl-N-(2-pyridyl)-hydrazones **3a-f** were synthesized and characterized by elemental analyses and spectral data. ^{1}H, ^{13}C NMR and mass spectra supported the formation of the E-isomer. N-Methyl-N-(2-pyridyl)hydrazone carboxaldehydes can be readily characterized by mass spectrometry. The new hydrazones **3a-h** have been screened for antimicrobial activity.

Key Words: Hydrazones, Antimicrobial activity.

INTRODUCTION

Hydrazones are compounds which contain a characteristic chain of atoms: C=N–N. A variety of substituents types are prepared to produce a range of hydrazones types. Hydrazones exhibited bactericidal, parasitical, leprosy, leukemia, malignant neoplasms and tuberculostatic antiactivity[1-6]. Pyridyl and pyrimidyl hydrazones are highly suitable for the protection of industrial materials against attack by microorganisms and animal pests[7-9]. Pyridazinyl hydrazones provide antiviral activity. Aryl and heteroaryl hydrazones are described as antifungal agent[10-13] as well as active substances for the treatment of malaria or malignant tumours[14].

Hydrozones have also found important applications as chromogenic reagents in the spectrophotometric determination of transition-metal ions (colorimetric agents) and metal extracts[15-23]. Aldehyde hydrazones with appropriately located heterocyclic ring **1** are readily cyclizes to fused 1,2,4-triazolo-heterocycles **2** and may be carried out with a variety of oxidizing agents[24-27].



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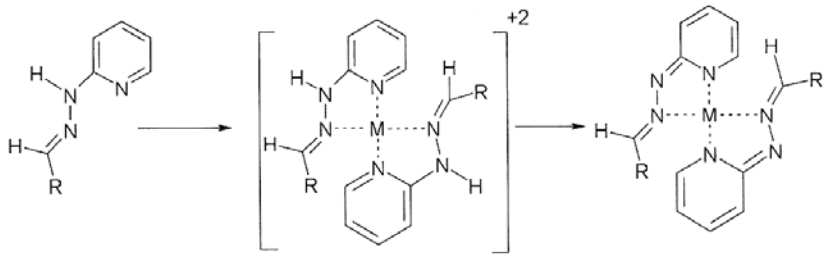
†Chemistry Department, An Najah University, Nablus, Palestine.

Hydrazones are easily converted to formzans upon the addition of diazonium salts. These type of compounds are used in analytical chemistry, pigments and in biological researches[28-33].

The sensitivity and selectivity of pyridylhydrazones towards metal ions are important for pharmaceutical samples, biological materials and in pharmacological applications[34-36].

Heterocyclic hydrazones have been shown to belong to an extensive group of compounds forming complexes with transition ions and possessing a hydrogen atom whose acidic character is strongly enhanced by the presence of the coordinated metals. This type of acidic hydrogen limited their use as potential analytical water soluble reagents in the basic solution due to the formation of uncharged complex as a conjugate base[37].



Recently the synthesis of metal complexes and the biological activities of 2-pyridinecarboxaldehyde N-methyl-N-(2-pyridyl)hydrazone have been reported[36]. This paper describes the preparation of new sensitive chemogenic reagents N-methyl heterocyclic hydrazones for determination of trace elements and their biological activities. The use of these multidentate ligands as selective spectrophotometric determination of transition metals are under investigation.

EXPERIMENTAL

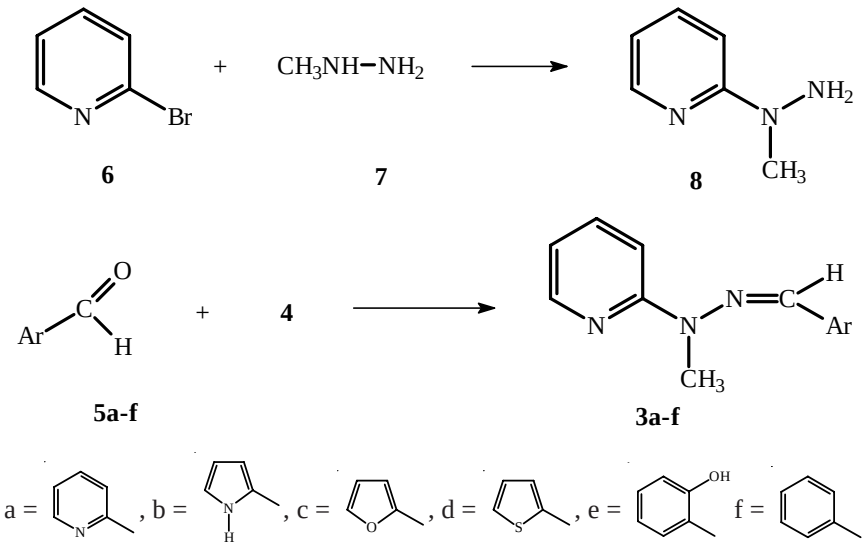
Starting materials were either purchased and purified. ^{1}H and ^{13}C NMR were recorded on Bruker WM 250 spectrometer using $CDCl_3$ solvent internal stanard TMS. Melting points were measured and uncorrected.

N-Methyl-N-(2-pyridylhydrazine) **4** was prepared by interaction of 2-bromopyridine **6** and N-methylhydrazine **7** as reported earlier[14].

Preparation of hydrazones 3a-f: The hydrazones were prepared by refluxing fairly concentrated ethanolic solution of stoichometrical portions of the corresponding aldehyde **5a-f** and N-methyl-N-(2-pyridyl)hydrazine **4** for 1 h. On cooling the solution, fine crystals appeared if not, water was added to enhance the precipitation of the product. The hydrazone was collected and crystallized from ethanol or ethanol/water.

RESULTS AND DISCUSSION

Hydrazones (**3a-c**) were prepared by the reaction of N-methyl-N-(2-pyridyl)hydrazine (**4**) with the appropriate salicyl-, or 2-heterocydic aldehyde (**5a-c**) in ethanol. N-methyl-2-pyridyl hydrazine (**4**) was obtained[38] by interaction of 2-bromopyridine (**6**) and N-methylhydrazine (**7**) (**Scheme-I**). Elemental analysis data are shown in Table-1.



Scheme-I Synthesis of hydrazones (**3a-f**)

TABLE-1
PHYSICAL AND ANALYTICAL DATA FOR COMPOUNDS (**3a-f**)

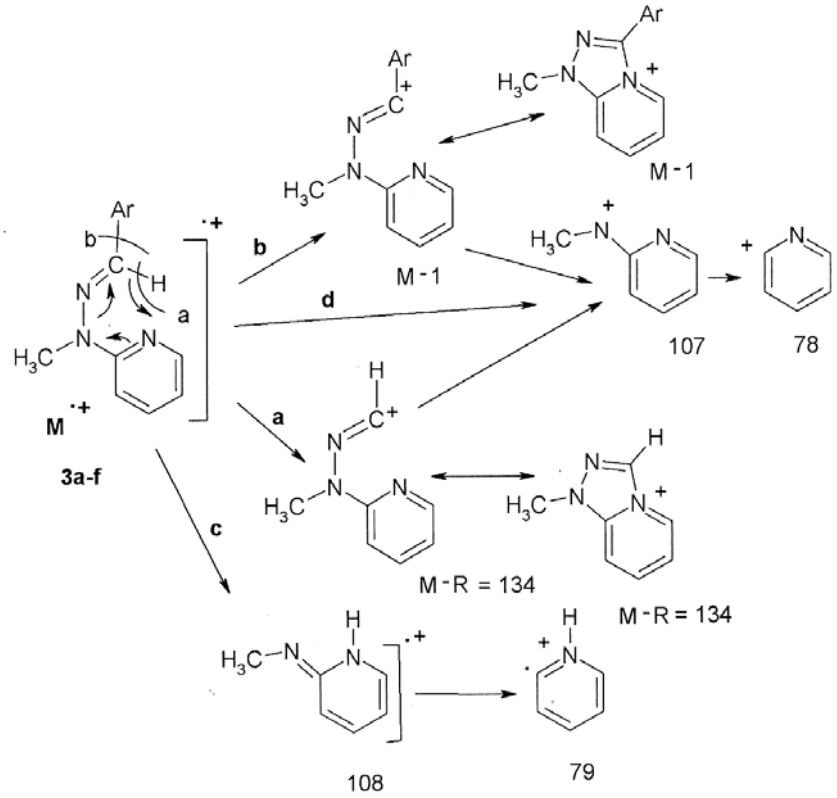
Comp. No.	Yield (%)	m.p. (ºC)	m.f.	$[M]^+$	Calcd. (found) %		
					C	H	N
3a	90	102-103	$C_{12}H_{12}N_4$	212	67.91 (67.82)	5.70 (5.69)	26.40 (26.60)
3b	92	112-115	$C_{11}H_{12}N_4$	200	65.98 (65.73)	6.04 (5.99)	27.98 (27.73)
3c	93	100-101	$C_{11}H_{11}N_3O$	201	65.66 (65.45)	5.51 (5.56)	20.88 (20.65)
3d	90	102-103	$C_{11}H_{11}N_3S$	217	60.80 (60.72)	5.10 (5.22)	19.34 (19.47)
3e	93	100-101	$C_{13}H_{13}N_3O$	227	68.71 (68.70)	5.77 (5.78)	18.49 (18.24)
3f	91	100-101	$C_{13}H_{13}N_3$	211	73.91 (73.72)	6.20 (6.34)	18.89 (18.68)

Mass spectra

Scheme-II display the main fragmentation pathways and the major fragment ions in the mass spectra of these compounds.

The spectra exhibit the molecular ions which eliminate (Ar) or hydrogen as principal fragmentation to give fragment ions **M-Ar** at m/z 134 and **M-1**, path **a** and **b**, respectively in **Scheme-II**. Intense peaks corresponding to ions 107 is observed in all the compounds and are formed *via* the loss of HCN or ArCN radical fragment followed by elimination of CH_3N radical fragment forming the fragtment 78. The fragment 107 can also be attributed to N–N bond cleavage as shown in path **d** is **Scheme-II**. The ions 108 is formed by the retro-Diels-Alder degradation follwed by elimination of CH_3N radical fragment forming the fragment 79 as shown in path c in **Scheme-II**[39-41].

The fragmentation pattern of N-methyl-2-pyridyl hydrazones of carboxyladehyde can be characterized by their diagnostic fragmentation pattern: m/z: $[M]^+$, $[M-1]^+$, $[M-R]^+$ (134), 108, 107, 79, 78 as shone in **Scheme-II**.



Scheme-II Main fragmentation pathways observed in the mass spectra of compounds (**3a-f**) in mass spectra

^{1}H and ^{13}C NMR spectra

^{1}H and ^{13}C NMR spectra of these compounds ($CDCl_3$) are in agreement with their suggested structure. The spectra also support that there is only one configurational isomer around the (C=N) double bond of the aldehyde derivatives. The chemical shifts of compounds **3a-f** are given[36,42,43] in Table-2.

TABLE-2
THE CHEMICAL SHIFT VALUES (δ) OF ^{1}H AND ^{13}C OF COMPOUND **3a-f** in $CDCl_3$

No.	^{1}H NMR	^{13}C NMR
3a	3.68 (s, N–CH_3), 6.80 (m, 1H), 7.21 (m, 1H), 7.75 (s, CH=N), 7.69 (m, 2H), 8.23 (m, 1H), 8.57 (m, 1H).	29.6 (N–CH_3), 110.1, 116.4, 119.3, 122.4, 134.6, 136.3, 137.5, 147.0, 149.2, 155.4, 157.4
3b	3.56 (s, N–CH_3), 6.23 (m, 1H), 6.35 (m, 1H), 6.77 (m, 1H), 6.80 (m, 1H), 7.54 (s, CH=N), 7.48 (m, 2H), 8.16 (m, 1H), 9.17 (br, 1H).	29.4 (N–CH_3), 109.3, 109.6, 110.7, 114.9, 119.7, 127.2, 129.6, 137.3, 147.0, 157.6
3c	3.63 (s, N–CH_3), 6.45 (q, 1H), 6.59 (d, 1H), 6.77 (m, 1H), 7.46 (d, 1H), 7.56 (q, 1H), 7.61 (d, 1H), 7.53 (s, CH=N), 8.21 (m, 1H)	29.6 (N–CH_3), 108.6, 110.0, 111.6, 115.7, 124.5, 137.5, 142.7, 146.9, 152.0, 157.6
3d	3.60 (s, N–CH_3), 6.99 (q, 1H), 7.12 (q, 1H), 7.21 (d, 1H) 7.53 (m, 1H), 7.63 (q, 1H), 7.76 (s, CH=N), 8.11 (m, 1H).	29.4 (N–CH_3), 109.8, 115.5, 125.4, 126.4, 127.3, 128.6, 137.5, 142.1, 146.8, 157.6
3e	3.66 (s, N–CH_3), 6.81 (m, 1H), 6.94 (m, 2H), 7.25 (m, 2H), 7.66 (m, 1H), 7.76 (s, CH=N), 8.24 (m, 1H), 11.20 (br, OH).	29.3 (N–CH_3), 108.5, 116.2, 116.5, 119.2, 119.5, 129.8, 130.0, 138.1, 138.2, 147.3, 156.4, 156.7
3f	3.66 (s, N–CH_3), 6.77 (q, 1H), 7.36 (m, 5H), 7.73 (m, 4H), 8.21 (m, 1H).	29.31 (N–CH_3), 109.9, 115.5, 126.3, 128.3, 128.6, 133.9, 136.3, 137.5, 146.9, 157.8

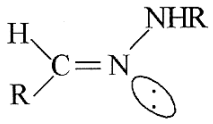
IR and electronic absorption spectra

The characteristic IR bands of (**3a-f**) isomethine ν(C=N) at 1595-1590 cm^{-1} as well as the band at 985 cm^{-1} assigned to ν(N–N) and the pyridine out-of-plane ring deformation the hydrazones which appears at around 777 cm^{-1}. **3b** and **3e** show NH and OH absorption[36].

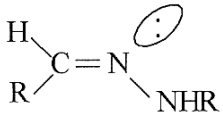
The electronic spectrum of the pyridylhydrazone exhibits three bands at 256, 272 and 340 nm ranges from $n\rightarrow\pi^*$, $n\rightarrow\sigma^*$ and $\pi\rightarrow\pi^*$[36].

Configuration of hydrazones

Two isomeric forms of hydrazones are possible, *anti*-(*E*-), **8a** and *syn*-(*Z*-) isomer **8b**[44-47]. Karabatoses *et al.*[47] have concluded that the *syn* isomer of a hydrazone is thermodynamically favoured over the *anti* isomers and it is well known that many hydrazones exist almost exclusively in the *syn* form[48].

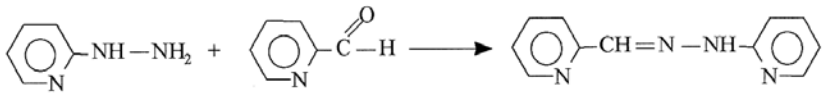


8 a

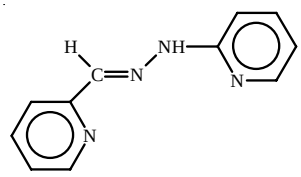


8 b

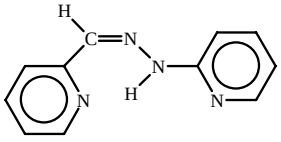
Chromatography, UV, IR and NMR spectroscopy and differences in the geometrical isomers of pyridine-2-carboxaldehyde pyridyl hydrazone PAPHY **10** as well as the chelating behaviour towards transition metals showed that the compound made by reaction between pyridine-2-carbaldehyde (**5a**) and 2-pyridylhydrazine (**9**) is the (E)- isomer (**10a**). The (Z)-isomer (**10b**) was prepared by heating the (E)-isomer at its melting point for 20 min or upon radiation with UV light in benzene solution[27,49-51].



9 **5a** **10**

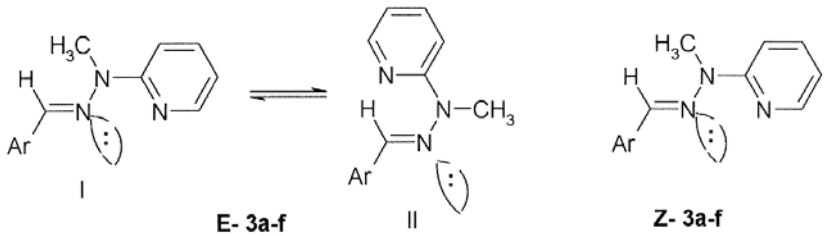


10a



10b

In the present work, ^{1}H and ^{13}C NMR spectroscopy (Table-2) supported the formation of only one isomer upon the reaction of N-methyl-N-(2-pyridylhydrazine) (**4**) with aldehydes (**5a-f**). In mass spectroscopy the formation of the intense peaks at m/s = 79 and 80 (Fragment **E** and **F Scheme-II**) supported the formation of E-isomer **II** (E) (**3a-f**). The formation of the intense fragment ion at m/z = 134 (fragment **A** and **B**), can be explained by the rotational isomerism **I** and **II** (E)-**3a-c** about the (N–N) single bond.



The rotational isomerism about the N–N single bond was proposed in N-methylphenylhydrazones of aldehydes.

In the E-isomer, the unshared electron pair orbital on the 2-pyridino nitrogen is parallel to and overlaps with the π-orbital of the (C=N) double bond, while in Z-isomer (as a result of nonbonded repulsions between R and N-methylpyridino) it would be orthogonal to the π-orbital. The ensuring loss of resonance stabilization in E-isomer might therefore be responsible for the presence of only the E-isomer.

Microbiological screening

In vitro screening tests were carried out to investigate the bactericidal and fungicidal activity of hydrazones **3a-h** are shown in Table-3. The tested bacteria were *E. coli*, *S. aureus* and *P. aeruginosa* while the fungus was *Candida albicans*. The culture media were Muller-Hinton agar supplemented with 1 g yeast. The antibacterial and antifungal activities of each compound was evaluated by the classical disk diffusion agar plates technique[52]. The biological screening data for the prepared hydrazones that all active against fungi *Candela albicans* in which **3e** and **3g** have similar activity potency to the reference Fluconazole used under the same conditions. These compounds show moderate activities against *E. coli*, *S. aureus* and *Ps. aeruginosa* compared to the reference streptomycine.

TABLE-3
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS IN DMF

Compound	Bacterial results			*C. albicans*
	E. coli (10 μg/disc)	*S. aureus* (10 μg/disc)	*Ps. aeruginosa* (10 μg/disc)	Sample result (10 μg/disc)
3a	+	–	–	–
3b	–	–	–	+
3d	+	+	+	+
3e	+	+	+	++
3f	++	++	+	++
3g	++	++	++	+++
3h	++	++	–	++
Streptomycin	+++	+++	+++	–
Fluconazole	–	–	–	+++

(i) DMF should not inhibition zones, (ii) Diameter of zone of inhibition (mm) - (0-5); + (6-10), ++ (11-20), +++ (21-30)

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