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Synthesis and characterization of new *p*-substituted aromatic hydrazones

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ABSTRACT

A three series of *p*-substituted aromatic hydrazones have been synthesized by condensation of benzhydrazide/*p*-substituted benzhydrazides (–CH_3, –OCH_3, –Cl and –OH) with benzaldehyde/*p*-substituted benzaldehydes (–OCH_3 and –NO_2). Initially, *p*-substituted esters were prepared from benzoic acid, *p*-substituted benzoic acid and methanol. In the second step, *p*-substituted hydrazides were prepared from the previously synthesized esters and hydrazine hydrate. Finally, *p*-substituted aromatic hydrazones were obtained from hydrazides and benzaldehyde or *p*-substituted benzaldehyde. The identity of the synthesized hydrazones was confirmed by the following techniques: ^{1}H NMR, ^{13}C NMR, IR and UV spectroscopy and element analysis (CNH). The proposed method of synthesis resulted in excellent yield and purity of the prepared hydrazones. Using three conventional LFER models based on mono and the dual substituent parameters, quantitative assessment of the substituent effects on the substituent chemical shifts (SCS) was made. In order to obtain the correlation models for investigated series the IR ($\nu_{C=O}$, $\nu_{C=N}$ and $\nu_{NHC=O}$), $^1H_{NH}$, $^1H_{=CH}$, $^{13}C_{=CH-}$ and $^{13}C_{C=O}$ peaks were used.

KEYWORDS

p-substituted aromatic hydrazones;
Synthesis;
NMR;
IR;
Substituent effects.

INTRODUCTION

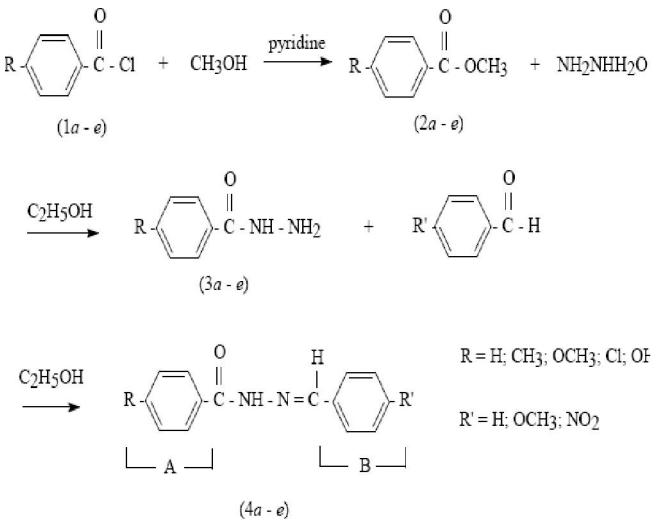
Hydrazones and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity[1]. The changes in this activity depend on its substituents. The use of the hydrazones in medicine is due to their anticonvulsant, antidepressant, analgesic, antiinflammatory, antiplatelet, antimicrobial, antitumoral, antischistosomiasis and antiviral activity[2-11]. On the other hand, hydrazones possessing an *azometine proton* (-NHN=CH-) constitute an important class of compounds for new drug development.

The wide palette of the useful medical properties has attracted considerable scientific interest for their synthesis[2-14]. There are a large number of methods known from the literature that have been developed for the synthesis of hydrazones[15, 16]. Aromatic hydrazones are also important for a number of synthetically useful transformations of carbonyl compounds and characterization of aldehydes and ketones[17].

Some of the hydrazones are used as chelating

agents, and their complexes with transition metals are used in various fields, including analytical, clinical and biological[18]. Additionally, hydrazones are group of the most useful spectrophotometric reagents[19]. Combining appropriate starting materials such as carbonyl compounds and hydrazine, the sensitivity as analytical reagents could be improved and they could be used as analytical reagents for transition metal analysis and as catalyst for epoxidation of olefins. Hydrazones and their metal complexes exhibit a wide spectrum of physiological and pharmacological activities[20]. Due to their physiological activity, they are used as herbicides, insecticides, and plant growth stimulants[21]. Some aromatic hydrazones are potent inhibitors of DNA synthesis and therefore their metal complexes are useful as therapeutic agents[22]. Furthermore, the hydrazones are used in industry as plasticizers, polymer stabilizers, antioxidants, polymerization initiators[23].

Considering these applications we have synthesized and characterized some *p*-substituted aromatic hydrazones with the interest towards their biological activity. In this work an efficient method for the preparation of hydrazides starting from esters and followed hydrazine hydrate reaction was developed. Then, the hydrazones were prepared by condensation of the hydrazides either with benzaldehyde or *p*-substituted benzaldehyde. The proposed method resulted in excellent yield and purity of hydrazones. Presentation of the mechanism for synthesis of the obtained *p*-substituted aromatic hydrazones is as follows:



Additionally, using the spectral data, an attempt to investigate the substituent effect of the synthesized hydrazones was made. According to the literature data, structure parameter correlations have recently become popular to follow transition state study of reaction mechanisms, biological activities and normal coordinate analysis[24, 25]. Dhami and Stothers[26] have extensively studied the ^{1}H NMR spectra of a large number of acetophenones and styrenes with an aim to establish the validity of the additivity of substituent effects in aromatic shieldings, first observed by Lauterber[27]. Nowadays scientists pay more interest to correlate the group frequencies of spectral data with Hammett substituent constants to explain the substituent effect of organic compounds.

The single and multi substituent effects by spectral data of biphenyl and 9*H*-fluorenyl chalcones were also investigated[28]. Within the above view there was no information available in the literature referring to substituted styryl 4-methoxy-1-naphthyl ketones. Hence, the authors have synthesized thirteen chalcones of the above type using microwave irradiation technique. The substituent effects of these compounds were investigated from IR and NMR spectra. A substituent effect of the substituted styryl 4-methoxy-1-naphthyl ketones was investigated by Nadar et al[29].

In this work, the substituent effects of the synthesized series of hydrazones have been studied using IR and NMR substituent chemical shifts (SCS). The intention of the present investigation was to monitor the effects of substituents at the A-benzene ring on the characteristic IR signals ($\nu_{C=O}$, $\nu_{C=N}$ and $\nu_{NHC=O}$) and ^{1}H and ^{13}C NMR chemical shifts. The SCS were correlated using a few different linear free energy relationship (LFER) models, based on the mono and the dual substituent parameter (MSP and DSP, respectively) treatments.

EXPERIMENTAL

All chemicals for the synthesis with reagent grade supplied from Merck and Alkaloid were used without further purification. Melting points of synthesized hydrazones were determined in Büchi B-540. UV-vis spectra were obtained on a Varian Cary 50 spectrophotometer. IR spectra were collected on PerkinElmer

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Interferometer 2000 system (KBr pellet method). NMR (^{1}H and ^{13}C) were collected on a BRUKER ADVANCE DRX500 NMR spectrometer in DMSO-d_6. Element analyses were performed on an Analyzer elemental Carlo Erba model CHNS EA 1108.

General procedure of synthesis of *p*-substituted aromatic hydrazones

Synthesis of methyl esters of substituted arylchlorides (2a-e)

The esters were synthesized by reaction of esterification from benzoylchloride, *p*-methyl, *p*-methoxy, *p*-chloro and *p*-hydroxybenzoyl chloride and excess methanol in the presence of pyridine[30].

Synthesis of hydrazides and p-substituted hydrazides (3a-e)

The hydrazides were synthesized by reactions of the corresponding methyl esters of benzoic acid (2*a-e*) with hydrazine hydrate following the literature methods[30].

Synthesis of p-substituted aromatic hydrazones (4a-e)

By condensation of the *p*-substituted hydrazides and benzaldehyde, *p*-methyl benzaldehyde and *p*-metoxy benzaldehyde, the hydrazones were prepared.[30] The structure of the hydrazones was confirmed by element analysis, UV, IR, ^{1}H NMR, ^{13}C NMR spectra and element analysis. The element analysis data, molecular formulas/molecular weights, melting points and yields of the synthesized hydrazones are given in TABLE 1.

The results of element analysis are in good agreement with the proposed formulas (See TABLE 1). The synthesized hydrazones are white or yellow colored crystalline solids, insoluble in water, but soluble in or-

TABLE 1 : Physical and analytical data of hydrazones (4*a-e*)

Comp.	R	R'	Mol. formula mol. wt	Melting point/°C	Yield/%	Element analysis (calculated/found)		
						C(%)	H(%)	N(%)
4*a*	H	H	$C_{14}H_{12}ON_2$ 224	212-214	74.10	75.00 75.87	5.36 5.54	12.50 12.55
4*b*	CH_3	H	$C_{15}H_{14}N_2O$ 238	246.5-249	89.91	75.63 75.96	5.88 6.11	11.76 11.94
4*c*	OCH_3	H	$C_{15}H_{14}O_2N_2$ 254	204.5-207	78.74	70.86 71.32	5.51 5.53	11.02 11.00
4*d*	Cl	H	$C_{14}H_{11}ON_2Cl$ 258	240-242	94.57	65.12 66.11	4.26 4.32	10.85 11.06
4*e*	OH	H	$C_{14}H_{12}O_2N_2$ 240	237-239	93.33	70.00 71.31	5.00 5.11	11.66 11.43
4*f*	H	OCH_3	$C_{15}H_{14}O_2N_2$ 254	163-166	93.70	70.86 69.35	5.51 5.69	11.02 10.09
4*g*	CH_3	OCH_3	$C_{16}H_{16}O_2N_2$ 268	217-219	95.52	71.64 71.67	5.97 6.03	10.44 9.83
4*h*	OCH_3	OCH_3	$C_{16}H_{16}O_3N_2$ 284	176-178.5	95.77	67.60 67.14	5.63 5.71	9.85 9.02
4*i*	Cl	OCH_3	$C_{15}H_{13}O_2N_2Cl$ 288	200-202	84.02	62.50 63.24	4.51 4.51	9.72 9.07
4*j*	OH	OCH_3	$C_{15}H_{14}O_3N_2$ 260	230-233	67.70	69.23 67.17	5.38 5.19	10.76 9.59
4*k*	H	NO_2	$C_{14}H_{11}O_3N_3$ 269	236-239	81.78	62.45 62.60	4.08 4.06	15.61 14.74
4*l*	CH_3	NO_2	$C_{15}H_{13}O_3N_3$ 283	246-248.5	96.81	63.60 61.57	4.59 4.83	14.84 13.75
4*m*	OCH_3	NO_2	$C_{15}H_{13}O_4N_3$ 299	243-245.5	76.25	60.20 58.88	4.35 4.54	14.04 13.25
4*n*	Cl	NO_2	$C_{14}H_{10}O_3N_3Cl$ 303	253-255	87.78	55.44 52.78	3.30 3.70	13.86 12.63
4*o*	OH	NO_2	$C_{14}H_{11}O_4N_3$ 285	328.5-330	93.66	58.95 59.02	3.86 3.80	14.74 13.78

TABLE 2 : IR, ^{1}H NMR and ^{13}C NMR spectral data of hydrazones (4*a-e*)

Comp.	IR spectra (in cm^{-1})	^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) H_2O: 3.33 ppm, DMSO: 2.50 ppm	^{13}C NMR (400 MHz, DMSO-d_6, δ ppm) DMSO: 39.52±0.06 ppm
4*a*	3181-3207 [*v*(N–H)], 3025-3061 [*v*(aromatic CH)], 1643 [*v*(C=O)], 1604 [*v*(C=N)], 1552 [*v*(NH–C=O)]	δ = 7.95 (1H, –NH), 8.48 (1H, =CH–), 7.52-8.03 (10H, –CH (Ar))	δ = 148.30 (=CH–), 163.64 (>C=O) 127.56-134.82 (C and –CH (Ar))
4*b*	3172-3200 [*v*(N–H)], 3026-3066 [*v*(aromatic CH)], 1639 [*v*(C=O)], 1610 [*v*(C=N)], 1552 [*v*(NH–C=O)]	δ = 2.39 (3H, $–CH_3$), 7.85 (1H, –NH), 8.47 (1H, =CH–), 7.33-7.85 (9H, –CH (Ar))	δ = 21.5 ($–CH_3$), 148.00 (=CH–), 163.43 (>C=O) 127.51-142.27 (C and –CH (Ar))
4*c*	3194 [*v*(N–H)], 3029-3068 [*v*(aromatic CH)], 1630 [*v*(C=O)], 1600 [*v*(C=N)], 1542 [*v*(NH–C=O)]	δ = 3.83 (3H, $–OCH_3$), 7.95 (1H, –NH), 8.48 (1H, =CH–), 7.17-7.92 (9H, –CH (Ar))	δ = 55.90 ($–OCH_3$), 147.65 (=CH–), 163.03 (>C=O) 125.93-134.94 (C and –CH (Ar))
4*d*	3182-3204 [*v*(N–H)], 3022-3058 [*v*(aromatic CH)], 1636 [*v*(C=O)], 1607 [*v*(C=N)], 1552 [*v*(NH–C=O)]	δ = 7.97 (1H, –NH), 8.47 (1H, =CH–), 7.46-7.97 (9H, –CH (Ar))	δ = 148.62 (=CH–), 162.55 (>C=O) 127.61-137.07 (C and –CH (Ar))
4*e*	3224-3254 [*v*(N–H)], 3025-3065 [*v*(aromatic CH)], 1617 [*v*(C=O)], 1591 [*v*(C=N)], 1552 [*v*(NH–C=O)], 1509 [*v*(C–O) Phenolic], 3444 [*v*(OH)]	δ = 6.88 (1H, –OH), 7.84 (1H, –NH), 8.44 (1H, =CH–), 7.42-7.84 (9H, –CH (Ar))	δ = 147.32 (=CH–), 163.26 (>C=O) 124.36-135.00 (C and –CH (Ar))
4*f*	3201 [*v*(N–H)], 2935-3068 [*v*(aromatic CH)], 1639 [*v*(C=O)], 1604 [*v*(C=N)], 1548 [*v*(NH–C=O)], 3419 [*v*(OCH_3)]	δ = 3.83 (3H, $–OCH_3$), 7.92 (1H, –NH), 8.48 (1H, =CH–), 7.06-8.03 (9H, –CH (Ar))	δ = 55.77 ($–OCH_3$), 148.19 (=CH–), 163.44 (>C=O) 127.37-134.07 (C and –CH (Ar))
4*g*	3165-3201 [*v*(N–H)], 2997-3029 [*v*(aromatic CH)], 1636 [*v*(C=O)], 1601 [*v*(C=N)], 1548 [*v*(NH–C=O)]	δ = 2.38 (3H, $–CH_3$), 3.82 (3H, $–OCH_3$), 7.86 (1H, –NH), 8.41 (1H, =CH–), 7.02-7.84 (8H, –CH (Ar))	δ = 21.3 ($–CH_3$), 55.8 ($–OCH_3$), 146.80 (=CH–), 163.20 (>C=O) 114.40-130.20 (C and –CH (Ar))
4*h*	3178-3211 [*v*(N–H)], 3039 [*v*(aromatic CH)], 1643 [*v*(C=O)], 1608 [*v*(C=N)], 1548 [*v*(NH–C=O)]	δ = 3.83 (6H, 2–OCH_3), 7.90 (1H, –NH), 8.41 (1H, =CH–), 7.06-7.92 (8H, –CH (Ar))	δ = 55.75 (2–CH_3), 147.57 (=CH–), 161.21 (>C=O) 114.15-129.92 (C and –CH (Ar))
4*i*	3289 [*v*(N–H)], 3026-3074 [*v*(aromatic CH)], 1659 [*v*(C=O)], 1604 [*v*(C=N)], 1542 [*v*(NH–C=O)]	δ = 3.83 (3H, $–OCH_3$), 7.95 (1H, –NH), 8.40 (1H, =CH–), 6.99-7.95 (8H, –CH (Ar))	δ = 55.78 ($–OCH_3$), 148.53 (=CH–), 162.36 (>C=O) 127.27-136.92 (C and –CH (Ar))
4*j*	3162 [*v*(N–H)], 3025-3065 [*v*(aromatic CH)], 1637 [*v*(C=O)], 1591 [*v*(C=N)], 1552 [*v*(NH–C=O)], 1506 [*v*(C–O) Phenolic], 3444 [*v*(OH)]	δ = 3.83 (3H, $–OCH_3$), 5.35 (1H, –OH), 8.00 (1H, –NH), 8.48 (1H, =CH–), 6.88-7.86 (8H, –CH (Ar))	δ = 55.80 ($–OCH_3$), 146.80 (=CH–), 163.20 (>C=O) 114.40-130.20 (C and –CH (Ar))
4*k*	3175 [*v*(N–H)], 3003-3026 [*v*(aromatic CH)], 1649 [*v*(C=O)], 1604 [*v*(C=N)], 1552 [*v*(NH–C=O)], 1509 [*v*(NO_2)]	δ = 7.99 (1H, –NH), 8.56 (1H, =CH–), 7.53-8.31 (8H, –CH (Ar))	δ = 146.80 (=CH–), 163.20 (>C=O) 124.54-129.00 (C and –CH (Ar))
4*l*	3191 [*v*(N–H)], 3029 [*v*(aromatic CH)], 1639 [*v*(C=O)], 1602 [*v*(C=N)], 1542 [*v*(NH–C=O)], 1513 [*v*(NO_2)]	δ = 2.34 (3H, $–CH_3$), 8.00 (1H, –NH), 8.48 (1H, =CH–), 7.41-8.33 (8H, –CH (Ar))	δ = 21.3 ($–CH_3$), 146.80 (=CH–), 163.20 (>C=O) 124.00-150.20 (C and –CH (Ar))
4*m*	3185-3221 [*v*(N–H)], 3029 [*v*(aromatic CH)], 1649 [*v*(C=O)], 1607 [*v*(C=N)], 1552 [*v*(NH–C=O)], 1509 [*v*(NO_2)], 1012 [*v*(N–N)]	δ = 3.84 (3H, $–OCH_3$), 7.98 (1H, –NH), 8.54 (1H, =CH–), 7.17-8.33 (8H, –CH (Ar))	δ = 55.92 ($–OCH_3$), 148.21 (=CH–), 163.25 (>C=O) 114.24-145.04 (C and –CH (Ar))
4*n*	3185-3221 [*v*(N–H)], 3032 [*v*(aromatic CH)], 1649 [*v*(C=O)], 1597 [*v*(C=N)], 1568 [*v*(NH–C=O)], 1513 [*v*(NO_2)]	δ = 8.00 (1H, –NH), 8.48 (1H, =CH–), 7.67-8.33 (8H, –CH (Ar))	δ = 146.80 (=CH–), 163.20 (>C=O) 124.00-150.20 (C and –CH (Ar))
4*o*	3162 [*v*(N–H)], 3003-3026 [*v*(aromatic CH)], 1656 [*v*(C=O)], 1604 [*v*(C=N)], 1552 [*v*(NH–C=O)], 1509 [*v*(NO_2)], 1509 [*v*(C–O) Phenolic], 3340 [*v*(OH)]	δ = 5.35 (1H, –OH), 8.00 (1H, –NH), 8.48 (1H, =CH–), 6.88-8.33 (8H, –CH (Ar))	δ = 146.80 (=CH–), 163.20 (>C=O) 116.00-150.20 (C and –CH (Ar))

ganic solvents. The obtained solutions are stable for several months. The position of the characteristic bands in the electronic absorption spectra in water (or ethanol) is discussed (See chapter Results and discussion), whereas the most important IR and NMR (^{1}H and ^{13}C) spectral bands are presented in TABLE 2.

The prepared hydrazones were recrystalized using either ethanol or diluted ethanol. The above described method of synthesis resulted in excellent yield of the corresponding hydrazones (See TABLE 1) and high purity which was confirmed by constancy of the melting points.

Investigation of substituents effects

Given the need to follow the quantitative assessment of the substituent effects on the substituent chemical shifts (SCS) in *4a-o*, three conventional LFER models, based on mono and the dual substituent parameter (MSP and DSP, respectively) treatment were used. All the substituent constants were taken from the literature[31, 32]. The first LFER model is MSP equation, named, simple *Hammett* equation" which was used in the following form:

$$SCS(X) = \rho\sigma_p + h \quad (1)$$

Where SCS(X) is the change in chemical shift (IR or NMR) induced by the substituent X, and σ_p is the substituent parameter reflecting the electronic effects. Parameters *h* (the intercept on the ordinate) and ρ (measure of the sensitivity of the chemical shift to the electronic effects of the substituents), were obtained by the regression analysis.

The second one is the DSP equation, so called, extended *Hammett* equation" which was used in the following form:

$$SCS(X) = \rho_R\sigma_R + \rho_I\sigma_I + h \quad (2)$$

Where, σ_I and σ_R are substituent parameters reflecting the polar and resonance electronic effects, respectively. Parameters ρ_I and ρ_R (measure of the sensitivity of the chemical shift to the polar and resonance electronic effects of the substituents, respectively), were obtained by the regression analysis.

The third one is the DSP equation, so called, *Swain-Lupton* equation" (3), which was used in the following form:

$$SCS(X) = fF + rR + h \quad (3)$$

Where *F* and *R* are substituent parameters reflecting the field and resonance electronic effects, respectively. Parameters *f* and *r* (measures of the sensitivity of the chemical shift to the field and resonance electronic effects of the substituents, respectively), were obtained by the regression analysis. Substituent parameters: σ_p, σ_R, σ_I, F and R used in this investigation are presented in TABLE 3.

TABLE 3 : Substituent parameters: σ_p, σ_R, σ_I, *F* and *R*

Substitutents	σ_p	σ_R	σ_I	*F*	*R*
-H	0.00	0.00	0.00	0.000	0.000
-CH_3	-0.17	-0.11	-0.05	-0.052	-0.141
-OCH_3	-0.27	-0.51	0.17	0.413	-0.500
-Cl	0.23	-0.24	0.47	0.690	-0.161
-OH	-0.37	-0.60	0.25	0.487	-0.643

RESULTS AND DISCUSSION

Synthesis and characterisation of *p*-substituted aromatic hydrazones

As mentioned before, here, an efficient method for synthesis of the hydrazones starting from esters was developed. First, the hydrazides were prepared and finally the hydrazones were prepared by condensation of the esters and hydrazides. Three series of *p*-substituted aromatic hydrazones were synthesized in three steps.

Step I: Initially esters were prepared from acylchlorides of benzoic acid, *p*-methylbenzoic acid, *p*-metoxybenzoic acid, *p*-chlorobenzoic acid, *p*-hydrohybenzoic acid and methanol. The refluxion of these acylchlorides with absolute methanol and pyridine formed corresponding methyl substituted benzoates. The pyridine was used in order to achieve higher yield. These compounds were characterized by their similarity of physical constants with those reported in the literature[33]. The prepared esters were recrystalized using diluted ethanol.

Step II: *p*-substituted hydrazides were prepared from the previously synthesized esters and hydrazine hydrate in excess (1:5). The methyl esters on refluxing in water bath (about 2.5 hours) with hydrazine hydrate dissolved in ethanol, formed corresponding benzhydrazides. These hydrazides were recrystalized using diluted ethanol and characterized by their similar-

ity of physical constants[33].

Step III: *p*-substituted aromatic hydrazones were prepared by condensation of hydrazides and benzaldehyde, *p*-metoxybenzaldehyde and *p*-nitrobenzaldehyde. This reaction was performed on water bath about 3 hours. Some of the hydrazones presented in this paper (4*a*, 4*d*, 4*e*, 4*i*, 4*j* and 4*f*) are already synthesized by Rajput et al[34]. They used general process of synthesis, involving esters or amides by reaction with hydrazine for the preparation of hydrazides. Furthermore, they performed the synthesis at different conditions and there are no spectroscopic data that confirmed the structure of the synthesized hydrazones. The method used here, resulted in excellent yield and purity of the synthesized hydrazones with satisfactory duration of the synthesis.

The structure of hydrazones (4*a-e*) was established using UV, IR, ^{1}H NMR and ^{13}C NMR spectra. UV spectra were recorded in water (4*a-j*) and in diluted ethanol (4*k-o*). Two bands were noticed in the spectra, first one positioned at 195 nm as a result of $\pi>\pi^*$ electron transitions and second one placed in the wavelength region from 295 to 340 nm due to $n>\pi^*$ electron transitions[35]. All absorption bands were characterized with high values of the molar absorption coefficients.

The IR absorptions due to stretching C=O, C=N and N-H groups appeared at 1660-1620, 1610-1590 and 3250-3160 cm^{-1}, respectively. The absorption bands associated with other functional groups (NH–C=O, N-N, C-H aromatic, O-H and C-O phenolic) appeared in the expected regions. The absorption band as a result of N-N bending vibration appeared at 1012 cm^{-1} for all synthesized hydrazones. The positions of the IR absorption bands are in accordance with literature data[36].

The ^{1}H NMR spectra of compounds (4*a-o*) (in DMSO-d_6) exhibited a multiplet in the aromatic region accounting for aromatic protons at 6.88-8.33 ppm due to strong deshielding effect of the aromatic ring system. The singlets were observed at the 7.85-8.00, 8.50 ppm region accounting for protons of N–H and =CH– group, respectively. The positions of the signals obtained from H_2O and DMSO were in accordance with literature data[37]. The ^{1}H NMR spectra of hydrazones 4*b*, 4*g* and 4*l* also exhibited signals at 2.40 ppm as a result of –CH_3 group in their molecule, the hydrazones 4*c*, 4*f-j* and 4*m* have signals at 3.80 ppm for –OCH_3 protons, and finally the signals positioned between 5.35-6.88 ppm due to the presence of –OH group in the 4*e*, 4*j* and 4*o* hydrazone molecule.

The ^{13}C NMR spectra of (4*a-o*) exhibited (=CH, C=O, C and –CH aromatic) signals at around 148.00, 163.00 and 114.15-150.20 ppm, respectively. The hydrazones 4*b*, 4*g* and 4*l* hade signals in the ^{13}C NMR spectra with position at 21.3 ppm as a result of presence of –CH_3 group in their molecule, while the signals at around 55.8 ppm appeared due to –OCH_3 group of the hydrazones 4*c*, 4*h* and 4*m*.

In addition, a prediction of the NMR (^{1}H and ^{13}C) spectra using the computer program ChemBioDraw Ultra 12 was carried out and the obtained results were in excellent agreement with the experimental counterparts. Next step, as a continuation of this study will be investigation of biological activity of synthesized hydrazones such as their zone of inhibition against selected strains of microorganisms.

Investigation of substituent effects

MSP analysis

IR signals: For MSP analysis were used the C=O, C=N and NH=CO stretching frequencies (cm^{-1}) of compounds 4*a*-4*o*, given in TABLE 2. The frequencies were separately analyzed through classical Hammett sigma constants (σ_p). The statistically relevant results from that correlation are presented in the following Figure.

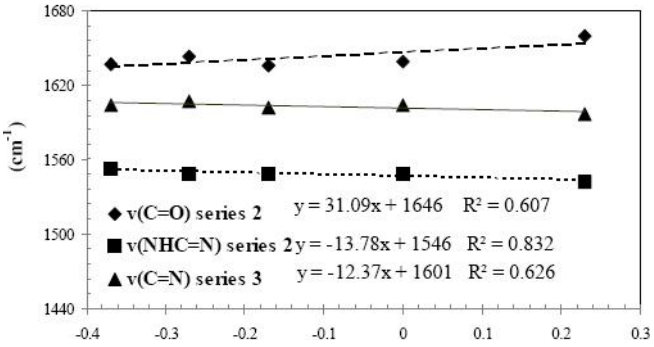

Figure : Statistically relevant correlation between Hammett sigma constants and ν(C=O), ν(C=N) and ν(NHC=O)

The statistical analysis showed that there was no significant correlation obtained with Hammett sigma constants and ν(C=O) for series 1 and 3 (R^2 = 0.046 and 0.206); ν(C=N) for series 1 and 2 (R^2 = 0,013 and 0.218) and ν(NHC=O) for series 1 and 3 (R^2 = 0.499 and

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TABLE 5 : Results of the correlations of SCS(IR) and SCS(NMR) with Eq. (3)

	R^a	F^a	h^b	R^c	SD^d	F^e
SCS(IR)						
ν(C=O) Series 1	-0.0226 (±0.01)	0.0198 (±0.01)	1639.7 (±2.53)	0.9071	0.814	9.7678
ν(C=N) Series 2	0.0061 (±0.0048)	0.0264 (±0.0046)	1605.50 (±1.23)	0.9507	0.9014	19.2787
ν(NHC=O) Series 1	-0.0361 (±0.0119)	0.04451 (±0.0112)	1556.47 (±3.0142)	0.9647	0.9294	27.3451
SCS(NMR)						
^{1}H (NH) Series 1	0.132 (±0.111)	0.172 (±0.132)	7.921 (±0.045)	0.7138	0.061	1.037
^{13}C (CH=)						
Series 1	0.924 (±0.092)	2.215 (±0.110)	148.333 (±0.037)	0.9975	0.051	201.835
Series 2	1.968 (±2.787)	0.983 (±1.170)	147.778 (±0.399)	0.8742	0.541	3.242
(C=O)						
Series 1	-1.372 (±0.401)	-0.524 (±0.478)	163.452 (±0.163)	0.9273	0.221	6.138
Series 3	0.906 (±0.147)	0.783 (±0.176)	163.277 (±0.060)	0.9758	0.0815	19.9127

0.471). As it can be seen from Figure, there was significant correlation obtained (R^2 = 0.995) between σ_p constants and ν(C=O) for series 2, ν(C=N) for series 3 and ν(NHC=O) for series 2.

TABLE 4 : Results of the correlations of SCS(IR) and SCS(NMR) with Eq. (2)

		ρ_R^a	ρ_I^a	h^b	R^c	SD^d	F^e
SCS(IR)							
ν(C=O)	Series 1	17.206 (±10.14)	-42.834 (±12.48)	1641.42 (±3.42)	0.9271	0.854	12.720
	Series 2	19.069 (±9.223)	48.483 (±11.36)	1640.22 (±3.11)	0.9011	0.802	9.113
ν(C=N)	Series 1	8.229 (±8.74)	-31.642 (±10.76)	1606.92 (±1.85)	0.8848	0.769	7.682
	Series 3	-11.247 (±5.48)	-16.020 (±6.75)	1602.21	0.7724	0.545	3.394
ν(NHC=O)	Series 1	64.660 (±32.85)	16.336 (±40.72)	1557.54	0.6772	0.3544	2.098
	Series 2	1.092 (±5.46)	-12.645 (±6.730	1548.04 (1.843)	0.7130	0.4264	2.487
	Series 3	14.456 (±7.34)	48.589 (9.05)	1549.26 (±2.48)	0.9358	0.8713	14.591
				SCS(^{13}C NMR)			
^{13}C(CH=)	Series 1	2.176 (±0.30)	1.699 (±0.37)	148.32 (±0.10)	0.9643	0.928	27.078
	Series 2	2.377 (±1.42)	1.699 (±1.75)	147.76 (0.48)	0.6656	0.331	1.990
^{13}C(C=O	Series 1	-0.333 (±0.59)	-2.355 (±0.73)	163.44 (±0.20)	0.8508	0.701	5.704
	Series 3	0.595 (±0.19)	1.382 (±0.24)	163.27	0.9447	0.889	17.086

^{1}H and ^{13}C NMR Spectra: The ^{1}H NMR spectral signals of NH and =CH protons in all investigated *p*-substituted aromatic hydrazones were assigned (See TABLE 2). The chemical shifts of =CH protons are at higher field (8.40-8.56) than those of NH protons (7.84-8.00) for the investigated hydrazones. All attempted correlations involving substituent parameters (σ_p) and NMR signals gave statistically unreliable results (R<0.5). The observed ^{13}C chemical shifts of $C_{(=CH-)}$ and the $C_{(C=O)}$ carbons from the ^{13}C NMR spectra are presented in TABLE 2. These chemical shifts were correlated with the classical Hammett substituent constants (σ_p). The results of statistical analysis of the substituent effects on $C_{(=CH-)}$ and $C_{(C=O)}$ carbons are presented in Eqs. (4) and (5). The attempted correlations involving classical Hammett substituent parameters gave positive ρ values indicating that normal substituent effects is operates for all the hydrazones.

Series 1

$$\mathbf{SCS(^{13}C_{=CH-}) = 2.121\sigma_p \pm (0.26) + 148.22(\pm 0.06)} \quad \mathbf{(4)}$$

$$\mathbf{R = 0.9774\ SD = 0.125}$$

Series 3

$$\mathbf{SCS(^{13}C_{C=O}) = 0.891(\pm 0.38)\sigma_p + 163.43(\pm 0.09)} \quad \mathbf{(5)}$$

$$\mathbf{R = 0.8005\ SD = 0.182}$$

The chemical shifts observed for $^{13}C_{=CH-}$ and the $^{13}C_{C=O}$ in the present investigation were satisfactory

correlated with Hammett sigma constants. In some cases correlation of ^{13}C with σ values was slightly better Eq. (4).

DSP analysis

In view of the inability of some σ constants to produce individually satisfactory correlations, it was thought worthwhile to seek multiple correlations involving σ_R and σ_I and *Swain-Lupton*'s *F* and *R* parameters (*F* and *R* are substituent parameters reflecting the field and resonance electronic effects).

Much better correlation for SCS(IR) and SCS(NMR) was obtained with DSP Eqs. (2) and (3), presented in the Experimental section. The relationships that are shown in TABLEs 4 and 5 were statistically satisfactory. The pattern of the weighting factors (ρ_I, ρ_R and *F*, *R*) indicated generally a dominant inductive effect for both SCS(IR) and SCS(NMR).

It is known that *Swain-Luptons* substituent parameters (*F* and *R*) have the qualitative characteristic of σ_R and σ_I, respectively. They have the added virtues, however, of being independent of position in the aromatic ring, reaction, solvent, and temperature[38]. Our results confirmed those findings in most of the cases and coefficient *F* has the larger values.

CONCLUSION

The simple method for synthesis of some *p*-substituted aromatic hydrazones from aromatic aldehydes and hydrazides was developed. Their structure was confirmed by element analysis and three spectroscopic techniques: UV, IR and NMR (^1H and ^{13}C). The proposed method of synthesis resulted in excellent yield and purity of the prepared hydrazones. The procedure is also simple and clean.

Using the IR stretching frequencies for C=O, C=N and NH=CO bands, statistically significant MSP correlation were obtained only for series 2 (νC=O and νNHC=N) and for series 3 (νC=N). Statistically unreliable results were obtained from MSP correlation using characteristical ^1H proton signals. Correlations involving classical Hammett substituent parameters and $^{13}C_{(=CH-)}$ and $^{13}C_{(C=O)}$ signals for series 1 and 3, gave positive ρ values.

Much better correlation for SCS(IR) and SCS(NMR) was obtained with DSP analysis using σ_R, σ_I, *F* and *R* parameters confirming that in most of the cases coefficients ρ_I and *f* has the larger values.

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