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Synthesis and Spectroscopic Studies of Dichloro p-Nitrophenyl Hydrazones: A Comparative Study

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ABSTRACT

We conducted a comparative study on the development of two synthetic methods. The current study is the reaction of 4-nitrophenyl hydrazine with dichloro benzaldehydes (2,4-dichlorobenzaldehyde and 3,5-dichlorobenzaldehyde) under acid catalyzed solvent-based condition and solvent-free condition at room temperature. These reactions proceeded well under both conditions to give the corresponding hydrazone products in good to excellent yield (68%-72%) and in moderate to good yield (33%-57%) respectively without further column chromatography purification. Both methods had high atom economy (94.50%-94.84%). The solvent-free synthesis which is considered to be greener method developed in a bid to ameliorate the environmental adverse effects of the conventional solvent-based synthesis had lower E-factor (0.85-2.24 g/g) and higher effective mass yield (30.89%-54.13%) compared to those of conventional method's (52.34-55.85 g/g) and (15.00%-16.42%). Conversely, the conventional method had higher but comparable reaction mass efficiency (63.83%-68.02%) to those of solvent-free method's (30.89%-54.13%) but rather with better process mass intensity (91.09-97.33 g/g) in relation to those of solvent-free method's (413.69-724.98 g/g) due to higher yields. The structures of the synthesized compounds were confirmed by FTIR, 1D, and 2D-NMR analyses. Universality and simplicity, catalyst-free conditions, non-use of an organic solvent, rapid reaction time, fast and efficient workup, and un-solvated pure products are only a few of the advantages of the developed solvent-free method.

Keywords: solvent-free synthesis, green synthesis, mechanochemistry, dichloro p-nitrophenyl hydrazone, structure elucidation.

1. INTRODUCTION

The importance of new chemical entities is to leverage the drawbacks in drug discovery research. This gives synthetic chemists the impetus to discover novel molecules with improved properties or novel methodologies to access these molecules with high efficiency. Organic synthesis can result in major or minor modifications to form new compounds, or modifications to the existing synthetic

methodology to form new molecules with improved yield. Traditional synthetic techniques that involve heating reactants with specific heat energy sources have disadvantages such as low yield, high energy requirements, and extended reaction times [1].
Several research strategies for the creation of environmentally friendly reactions that are both cost-effective and technologically possible have been developed for a long time [2,3]. The green chemistry campaign began in 1990 as a result of pollution prevention legislation [2], and this legislation has sparked the development of new technologies and techniques such as ultrasound, microwave, photochemical, and/or mechanical devices that are required to perform environmentally friendly reactions. Furthermore, this law has made organic compound synthesis more greener [2-6]. Environmentally friendly synthetic techniques have lately received a lot of attention, and certain solvent-free procedures have been developed [7]. The method's selectivity has led to fewer by-products and their ease of removal during the purification stages in medicinal ingredients and therapies.

The benefits of solvent-free or solid-state synthesis over conventional solvent-based synthesis, such as faster reaction times, efficient reactions with minimum energy requirements, high to exceptional yield, and easier work-up methods, have boosted the appeal of mechanochemistry [7]. Traditional solvent-based procedures use volatile organic compounds (VOCs) and other harmful chemicals, resulting in hazardous effluents and associated environmental concerns [2,4,5] as well as genetic changes in humans, leading to illnesses such as cancer.

Chlorobenzaldehydes have found usefulness in the pharmaceutical industry, especially in the synthesis of active pharmaceutical ingredients (API). The formation of the C-N bond is of importance as it allows the incorporation of nitrogen into organic compounds such as heterocycles. However, the formation of this bond remains a major challenge to organic chemists due to unfavorable reaction conditions and the cost of catalysts [8].

Hydrazones have a wide range of uses in synthetic chemistry, including as synthetic intermediates in the synthesis of medicinally important heterocyclic compounds and as ligands in the formation of complexes. Because of their nucleophilic and electrophilic properties, compounds containing the hydrazone functional group have found important roles in organic synthesis as intermediates in Mannich type reactions, Wolf-Kishner reactions, asymmetric hydro-cyanation, Mitsunobu reactions, and allylation. [9].

Until recently, the majority of hydrazones were made using classical methods, which entailed combining hydrazine with a carbonyl molecule in diluted medium at reflux. In a 1:1 aqueous ethanol environment catalyzed by meglumine, Mo *et al*. synthesized a variety of hydrazones. Some hydrazones were synthesized in good to excellent yields by condensation of phenylhydrazine with benzaldehydes substituted with electron-withdrawing or electron-donating groups [10]. Noor *et al*. reported the synthesis of novel hydrazones derivatives by refluxing an equimolar quantity of 2-Amino-3-formyl chromone and hydrazide derivatives in acetic acid. The reaction gave high to excellent yields of hydrazone products [11]. In methanol, Jana *et al*. synthesized hydrazones by condensation of dihydroxybenzaldehyde with hydrazide derivatives. The products of the reactions were produced in excellent yields. [12].

Also in the literature, only a few solvent-free hydrazone synthesis methods have been published. Pierrick *et al*. used a ball mill to synthesize Boc-, Bz-, Fmoc-, and tosyl-hydrazones from aldehydes in a solventless condition [13]. Mehtab *et al*. reported the development of a solvent-free hydrazone synthesis catalyzed by Bronsted acid ionic liquid (BAIL) $[Et_3NH][HSO_4]$. [14]. Oliveira *et al*. also report a solvent-free mechanochemistry synthesis of a series of therapeutically active phenol hydrazones [15]. Harith and Aymen investigated the microwave-assisted synthesis of oxobenzotriazine hydrazides in solvent-free conditions [16]. The microwave-assisted synthesis of corrosion inhibitors series of thiophene hydrazones under solvent-free solvent-free conditions were described by Singh *et al*. [17]. Crawford et al. employed Twin-Screw Extrusion in a solvent-free, continuous flow method to synthesis hydrazone-base active medicinal agents [18].

Hydrazone derivatives have a wide range of biological properties and are commonly used as medicines. The possible applications of hydrazones as anti-diuretic, antioxidant, anti-inflammatory, anti-sepsis, anti-parkinsonism, anti-tuberculosis agents, analgesic, anti-ulcer, vasodilators for hypertension therapy, anti-aging, central nervous system diseases, anticancer agents, anti-neoplastic, antimicrobial, anti-depressant, anti-convulsant, antiviral, anti-arrhythmic, antimycobacterial, antimalarial, antiplatelet, anti-histaminic are some of the conceivable applications of hydrazones which demonstrate that the hydrazone class is essential for new drug development [19-34]. The discovery of hydrazone drugs such as levosimendan, dantrolene, nitrofurantoin, nitrofurazone, furazolidone, and nifuroxazide etc., indicate that hydrazone moiety is a privileged scaffold. Here, we report the synthesis, and spectroscopic studies of dichloro p-nitrophenyl hydrazones, highlighting its comparative studies on solvent-based and solvent-free methods.

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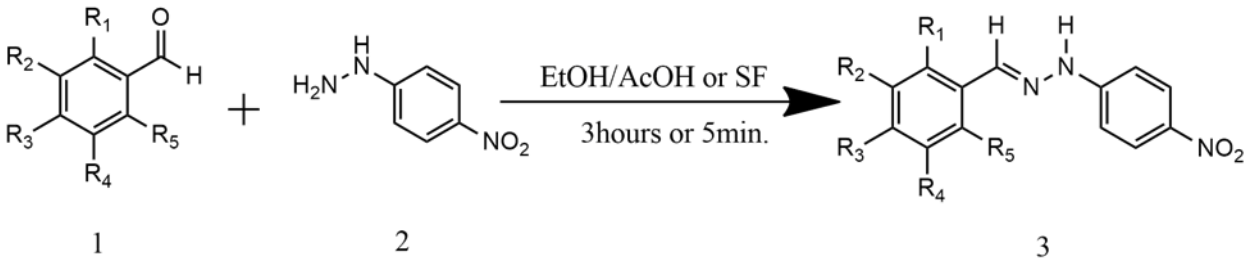
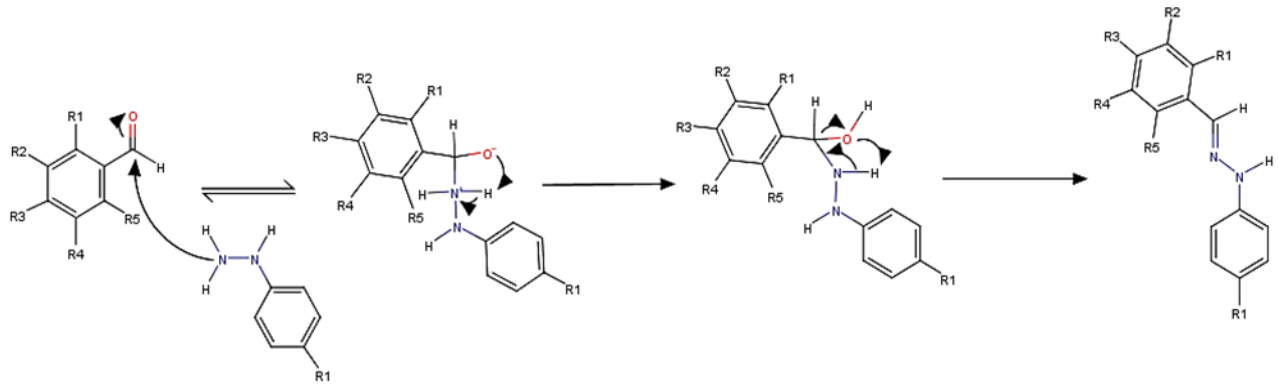
2. RESULTS AND DISCUSSION

2.1. Condensation reaction methods



Scheme 1: Synthesis of p-nitrophenyl hydrazones.

Compound	R_1	R_2	R_3	R_4	R_5
3a	Cl	H	Cl	H	H
3b	H	Cl	H	Cl	H



Scheme 2: Solvent-free mechanism of the reaction.

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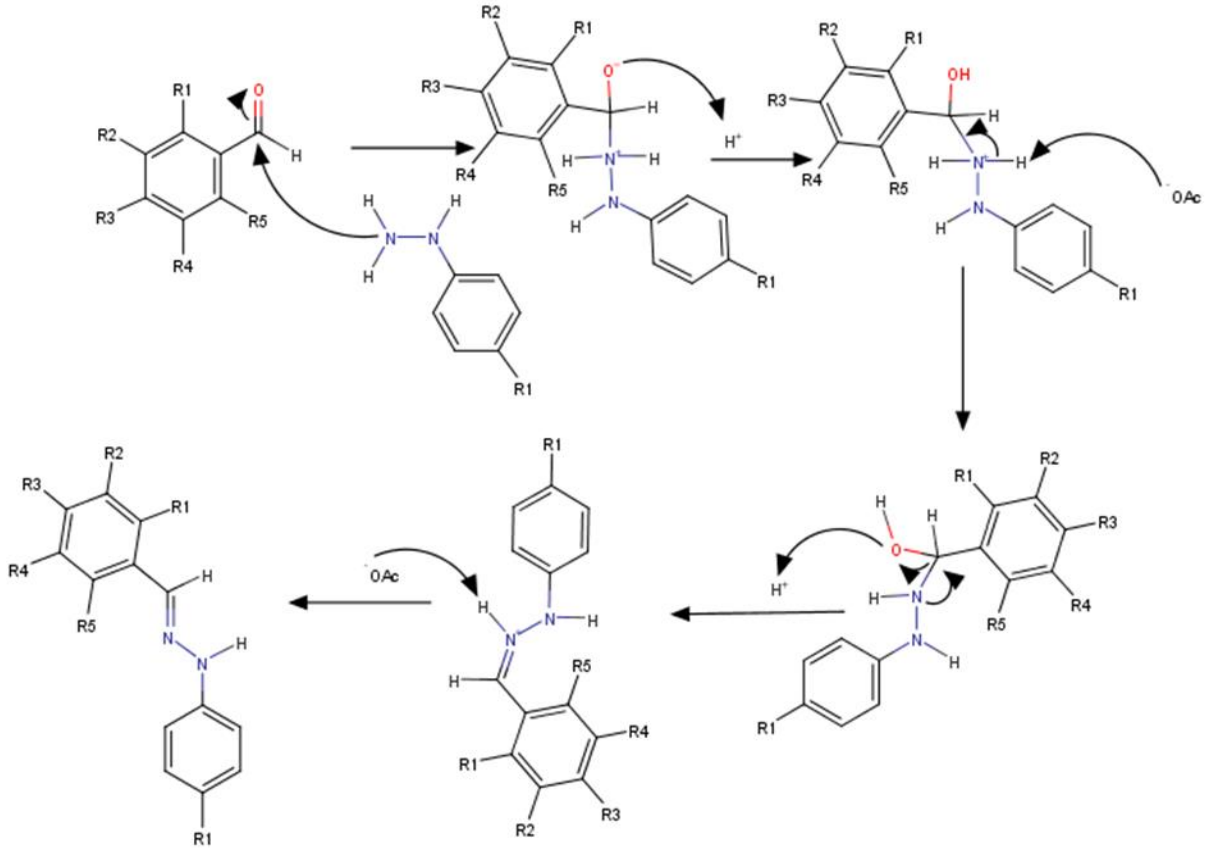

Scheme 3: Solvent-based reaction mechanism.

Table 1: Solvent-based and solvent-free synthesis of compounds **3a-b** results comparison under room conditions.

	Solvent-free			Solvent-based		
Compd	Time	Yield (%)	Mp (°C)	Time (h)	Yield (%)	Mp (°C)
3a	5 min	57	226-228	3	68	226-228
3b	5 min	33	257-259	3	72	257-259

Table 2: Green Chemistry metrics.

	Solvent-based					Solvent-free				
Compd	AM (%)	EMY(%)	RME(%)	E-factor	PMI	AM (%)	EMY(%)	RME (%)	E-factor	PMI
3a	94.50	15.00	63.83	55.85	97.33	94.50	54.13	54.13	0.85	413.69
3b	94.50	16.42	68.02	52.34	91.09	94.50	30.89	30.89	2.24	724.98

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2.2. Spectroscopy analysis results

Table 3: FTIR data of the synthesized hydrazones (cm^{-1}).

Compound	N-H	C-H_{imine}	C=N	NO_2	C-$N_{aniline}$	C-Cl	C=C_{arom}	C-H_{arom}
3a	3265	3078	1587	1498	1300	1043	1461	1271
3b	3254	3075	1580	1476	1297	957	1416	1271

Table 4: 1D and 2D NMR data for **3a** (ppm).

Position	δ_H (*J* in Hz)	δ_C, type	COSY	HSQC	HMBC
1	---	131.39, C---	---		3,5,7
2	---	134.36, C	---	---	3
3	7.65, d (1.8)	129.71, CH 5	3		1,2,5
4	---	133.16, C---	---		6
5	7.47, d (8.5)	128.29, CH	3,5	5	1,3
6	8.05, d (8.6)	127.98, CH	5	6	4,7
7	8.29, s	136.58, CH	N-H	7	1,6,N-H
N-H	11.61, s	---	7	---	(2′,6′),7
1′	---	139.43, C---	---		(2′,6′),(3′,5′)
2′	7.18, d (8.2)	112.10, CH	(3′,5′)	(2′,6′)	N-H,1′,(2′,6′),(3′,5′)
3′	8.13, d (9.0)	126.54, CH	(2′,6′)	(3′,5′)	1′, (2′,6′), (3′,5′), 4′
4′	---	150.43, C ---	---		(3′,5′)
5′	8.13, d (9.0)	126.54, CH	(2′,6′)	(3′,5′)	1′, (2′,6′), (3′,5′), 4′
6′	7.18, d (8.2)	112.10, CH	(3′,5′)	(2′,6′)	N-H,1′,(2′,6′),(3′.5′)

Table 5: 1D and 2D NMR data for **3b** (ppm).

Position	δ_H (*J* in Hz)	δ_C, type	COSY	HSQC	HMBC
1	---	135.00, C ---	---		(2,6)
2	7.79, s	124.96, CH	4	(2,6)	1,(2,6),4,7
3	---	139.44, C ---	---	---	
4	7.59, s	128.38	(2,6)	4	(2,6)
5	---	139.44, C ---	---	---	
6	7.79, s	124.96, CH	4	(2,6)	1,4,7
7	7.98, s	138.80, CH	N-H	7	N-H, (2,6), 7
N-H	11.55, s	---	7	---	(2′,6′), 7
1′	---	135.00, C ---	---	---	
2′	7.25, d (8.1)	112.23, CH	(3′,5′)	(2′,6′)	N-H, (2′,6′)
3′	8.16, d (9.1)	126.50	(2′,6′)	(3′,5′)	(3′,5′), 4′
4′	---	150.52	---	---	(3′,5′), 4′
5′	8.16, d (9.1)	126.50	(2′,6′)	(3′,5′)	(3′,5′), 4′
6′	7.25, d (8.1)	112.23, CH	(3′,5′)	(2′,6′)	N-H, (2′,6′)

3. DISCUSSION

We present a comparative analysis of p-nitrophenyl hydrazone synthesis using solvent-free and solvent-based condensation of p-nitrophenyl hydrazine with dichloro benzaldehydes containing at ambient temperature.

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3.1 Solvent-free

Under solventless circumstances and at room temperature, the synthesis of two dichloro para-nitrophenyl hydrazones was carried out cleanly and effectively in short reaction periods without the need of an acid catalyst. Aromatic aldehydes (2,4-dichloro benzaldehyde and 3,5-dichloro benzaldehyde) 2 were used to condense 4-nitrophenyl hydrazine 1. The hydrazones 3a and 3b were made by reacting an equimolar amount of 4-nitrophenyl hydrazine with the aromatic aldehydes 2a-b in a solvent-free environment for 2-5 minutes at room temperature.

3.2 Solvent-based

The solvent-based synthesis investigates the condensation of the equimolar quantity of p-nitrophenylhydrazine 1 with each of the benzaldehydes 2 (2,4-dichlorobenzaldehyde and 3,5-dichlorobenzaldehyde) in 30 ml of ethanol catalyzed by five drops of glacial acetic acid at room conditions. The reaction was allowed for three hours. Surprisingly, the products were formed within the first hour of the reactions. The ability of electron-withdrawing groups to boost the reactivity of aldehydes in hydrazone synthesis has long been known. The reaction with 2,4-dichlorobenzaldehyde was the fastest due to the inductive effect and the resultant increased electrophilic strength of the carbonyl carbon. The reaction with 3,5-dichlorobenzaldehyde was slower although with a better yield than that of 2,4-dichlorobenzaldehyde due to the reduced electrophilic character of the carbonyl carbon. It was observed that the reactivity trend favored electron-deficient aldehyde over electron-rich counterparts [35].

All the reactions with p-nitrophenyl hydrazine afforded powdered products with slight color variation. The solvent-based method gave better yields compared to the solvent-free method in this case. However, the solvent-free method had a faster reaction time with less energy requirement. Both methods required no need for an inert environment and had the same selectivity and purity. Each compound was purified and isolated from the reaction mixture by washing with freshly prepared cold 2 M hydrochloric acid, followed by cold distilled water and cold 95 % ethanol, in that order, with high to excellent yields (68 % - 72 %) for the solvent-based method and moderate to high yields (33 % -57 %) for the solvent-free method. Table 1 below shows the results of these reactions.

Mechanistically, the rate-limiting step is the formation of tetrahedral addition carbinolamine. The first two steps are concerted which involved the formation of a carbon-nitrogen bond and the addition of a proton to the oxygen atom via an acid-catalyzed hydrazine attack on the carbonyl carbon. Unlike the uncatalyzed solvent-free method, this step leads to the formation of zwitterion intermediate form of carbinolamine whose stability is pH and hydrazine basicity dependent. There could be intramolecular proton abstraction from the possibly formed zwitterion quaternary ammonium center in the solvent-free mechanism akin to acid protonation of the carbonyl oxygen in the solvent-based method. This aided the rapid intramolecular dehydration of the carbinolamine intermediate formed in the solvent-free method contrary to acid-catalyzed dehydration of the kinetically significant carbinolamine intermediate in the solvent-based method.

3.3 Green Chemistry metrics

Atom economy (AM) is a green chemistry concept aimed at minimizing waste to the molecular level by overviewing how materials from the starting materials or reagents are maximally incorporated into the products. It is a concept used in evaluating reaction efficiency beyond the traditional concept of percentage yield. It is used to determine how much of the starting materials end up in the product. The atom economy is a means of waste prevention in synthesis. The two synthetic methods gave similar results according to the results in table 2. The equal atom economy for each compound with both synthetic methods is due to the same molar mass of the compounds as atom economy calculates reaction efficiency and waste at the molecular level. The ideal atom economy score is 100%. The atom economy of the two dichloro p-nitrophenyl hydrazone compounds stands at 94.50%-94.80%. This high values demonstrate the efficient conversion of nearly all the atoms from the reactants into the products with minimal by-products, in this case, water.

Reaction mass efficiency (RME) is a green chemistry metric that measures the efficiency with which reactant mass ends up in the desired product. It does not include catalysts, solvents, or other reagents not specifically in the balanced chemical equations for the process/reactions. This metric is an analogy for percentage yield. However, this metric only takes into account the proportion of the mass of the product and the total mass of the reactants, unlike percentage yield. In this case, the conventional method indicated superior efficiency due to the higher yield of products with the most mass of the reactants converted to products compared to the solvent-free method. The ideal RME score is 100%. The RME for the conventional methods was recorded between 63.83%-68.02% for the conventional method whereas 30.89% - 54.13% was recorded for the solvent-free method as revealed in table 2. This is glaringly due to the low yield of the solvent-free method.

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Environmental factor (E-factor): This green chemistry measure emphasizes the amount of waste generated per unit of product mass. It also exposes the relative wastefulness of a chemical reaction/process. In this case, the conventional or solvent-based method products substantial was compared to the solvent-free method. This includes the medium of reaction, unrecovered catalyst, and side products. Unlike solvent-free, with no use of solvent medium nor catalyst minimizing the waste output of the reaction. The ideal E-factor score is 0. The E-factor value of the reaction for solvent-free according to table 2 ranges between 0.85 – 2.46 compared to 52.34 – 55.85 for the conventional method. This indicates that the conventional method is less benign and generates more waste which may be harmful to the environment.

Effective mass yield (EMY) is an attempt to describe yield in terms of the percentage of a product's mass that is made from non-toxic ingredients. The introduction of reagent and reactant toxicity is a critical concern that is sometimes overlooked in yield discussions. It is defined as the mass of the intended product as a percentage of the total mass of all non-beneficial ingredients employed in the synthesis. The solvent-free method demonstrated higher efficiency compared to the conventional method with EMY values ranging between 54.13% - 30.89% and 15.00% - 16.42% respectively. The ideal EMY is 100%. The solvent-free method had fewer non-benign materials in its setup compared to the solvent-based method. Therefore, this tells on its effective mass yield.

The total mass of materials utilized to generate a certain mass of product is defined as Process Mass Intensity (PMI). Reactants, reagents, solvents used for the reaction and purification solvents, and catalysts are among these materials. This metric is useful in determining total waste in a chemical reaction process including the purification process to determine the overall waste materials produced during the reaction and the workup process in the production of a particular chemical substance. The wastes produced in synthetic produce are always largely from the purification (workup) process. This tends to exponentially increase the PMI of reaction processes. In table 2, the PMI values of solvent-free products are substantially higher 413.69 – 724.98 than those of conventional method products as illustrated in the table 2.

3.4 Spectroscopic studies

Tables 3, 4, and 5 revealed detailed elucidation of FTIR, 1D NMR: 1H-NMR, and 13C-NMR and 2D NMR: COSY, HSQC, and HMBC spectra of the synthesized dichloro and methoxy p-nitrophenyl hydrazones.

3.4.1 Structure elucidation of compound 3a (chrome yellow powder)

1-(2,4-dichlorobenzylidene)-2-(4-nitrophenyl)hydrazine

For compound 1-(2,4-dichloro benzylidene)-2-(4-nitrophenyl) hydrazine (3a), the disappearance of characteristic aldehyde signals on proton and carbon-13 NMR spectra and the emergence of a singlet peak at 8.29 ppm integrating for one proton on the proton NMR spectrum and a peak at 136.58 ppm on carbon-13 NMR spectrum which was coupled to each other (8.31, 136.54) ppm on HSQC spectrum suggest the synthesis of a new bond. FTIR absorption signals at 3078 cm^{-1} and 1587 cm^{-1} in table 3 correspond to azomethine (imine) C-H bond and azomethine (imine) C=N bond stretchings confirming the formation of new azomethine bond.

The singlet peak at 11.61 ppm integrating for one hydrogen on proton NMR spectrum in table 3 was noticed to couple with no carbon on HSQC spectrum which illustrated the presence of secondary amino N-H bond as suggested by the observed FTIR absorption signal at 3254 cm^{-1} in table 3 characteristics of secondary amino N-H bond. Additionally, this singlet peak signal at 11.61 ppm on the proton NMR spectrum in was coupled with a corresponding imine hydrogen singlet peak at 8.29 ppm on the COSY spectrum (11.63, 8.26) ppm indicating the formation of hydrazone functional group. Further, the correlation between a carbon-13 peak at 136.28 ppm and with proton peak at 11.61 ppm on the HMBC spectrum (11.61, 136.28) ppm confirmed the formation of the hydrazone functional group.

The upfield doublet peak at 7.18 ppm integrating for two hydrogens and the downfield doublet peak at 8.13 ppm integrating for two hydrogens on the proton NMR spectrum were coupled on COSY cross peak spectrum (8.14, 7.18) ppm which implies that four neighboring protons are on a di-substituted benzene ring. Their coupling constants 8.2 Hz and 9.0 Hz respectively suggest that each of the two hydrogens is ortho coupled. Furthermore, it was noticed that the upfield doublet proton peak at 7.18 ppm integrating for two hydrogens was found coupled with carbon-13 signal at 112.04 ppm on HSQC spectrum (7.18, 112.04) ppm which suggests that the two equivalent hydrogens are on two equivalent carbons. Also, the downfield doublet proton peak at 8.14 ppm integrating for two hydrogens was observed to couple to carbon-13 peak at 126.46 ppm on the HSQC spectrum (8.14, 126.46) ppm indicating that these two equivalent hydrogens are also directly attached to the two equivalent carbons.

The carbon-13 signal at 150.43 ppm was found to correlate with the proton signal at 8.14 ppm (8.14, 150.43) ppm, and another carbon-13 signal at 139.43 ppm was also found to correlate with proton signals at 7.18 ppm (7.18, 139.43) ppm and 8.14 ppm (8.14, 139.43) ppm on HMBC spectrum. Furthermore, the peaks at 150.43 ppm and 139.43 ppm on the carbon-13 spectrum were observed to couple with no hydrogens on the HSQC spectrum which suggests that they are substituted aromatic carbons. Additionally, there

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is a correlation between the proton signal at 7.18 ppm and the carbon-13 signal at 126.21 ppm (7.18, 126.21), and another correlation between the amino hydrogen at 11.61 ppm and carbon signal at 111.81 ppm (11.61, 111.81) ppm on the HMBC spectrum. Also, the FTIR absorption signal at 1300 cm-1 corresponded to C-N bond stretching as indicated in table 3. All taken together and on careful analysis of these correlated HMBC signals together with HSQC and COSY correlations conform with ring B (hydrazine ring) of the synthesized compound and are numbered accordingly. The upfield signals (7.18, 112.04) suggests that the two aromatic C-H are at position 2′ and 6′ and are neighbor to another aromatic carbon that is directly attached to an electron-donating group, this was confirmed by (11.61, 111.81) ppm i.e N-H and C-2′, 6′ correlation indicates that the amino group is directly attached to the carbon with 139.43 signal and it is assigned C-1′.

The downfield signals (8.14, 126.46) ppm indicates that the two aromatic C-H are at position 3′ and 5′ and are neighbor to another aromatic carbon directly attached to a strong electron-withdrawing group (the most deshielded carbon on the spectrum), this was also confirmed by (8.14, 150.43) ppm correlation. The presence of a strongly electron-withdrawing group was further proven by the FTIR absorption band at 1498 cm^{-1} in table 3 characteristic of nitro group (NO_2) asymmetric stretching. Therefore carbon-13 peak at 150.43 ppm was assigned to C-4′ for that reason. This conforms to the structure of ring B within the compound structure.

The three doublet signals on the proton NMR spectrum; 8.05 ppm integrating for one hydrogen, 7.65 ppm integrating for one hydrogen, and 7.47 ppm integrating for one proton as well were found coupled in COSY cross-peaks (8.05, 7.43) ppm and (7.66, 7.46) ppm respectively. The coupling constant for a peak at 8.05 ppm and 7.47 ppm were 8.5 Hz and 8.6 Hz suggesting that these hydrogens are ortho to each other. Moreso, the coupling constant for a peak at 7.65 ppm was 1.8 Hz which also suggests that this proton is meta coupled with another proton. These protons peaks were found to be directly attached to respective carbon-13 peaks on the HSQC spectrum as follows (7.66, 129.65) ppm, (7.47, 128.22) ppm, and (8.08, 127.93) ppm. It only makes sense to say signals at (7.66, 129.65) ppm are meta to signals at (7.47, 128.22) ppm. As such are assigned as C-H at position 3, C-H at position 5, and C-H at position 6 respectively. Moreover, carbon-13 peaks at 134.36 ppm, 133.16 ppm, and 131.39 ppm are coupled to no proton signals on the HSQC spectrum which indicates that they are substituted aromatic carbons.

A correlation between imine proton at 8.27 ppm and carbon-13 peak at 131.19 ppm was observed on the HMBC spectrum, also imine proton at 8.27 ppm and carbon-13 peak at 127.74 ppm for C-6 was observed, proton 6 at 8.04 ppm and imine carbon-13 peak at 136.30 ppm on HMBC spectrum all indicated a direct linkage between the imine group and ring A. It can be deduced that the hydrazone functional group is the bridge linking the two benzene rings. Hence carbon-13 peak at 131.19 ppm was assigned C-1. The FTIR absorption signal at 1043 cm^{-1} has been characterized by aromatic C-Cl stretching. Therefore the downfield carbon-13 peaks at 134.34 ppm and 133.16 ppm are directly attached to chloro groups. A careful examination of the compound structure revealed that C-2 is more deshielded due to the cumulative inductive effect from imine group nitrogen and C-4 chlorine which are each three bonds away compared to C-4 which is only weakly deshielded by C-2 chlorine. Therefore, the carbon-13 peak at 134.34 ppm is assigned to C-2 while the carbon-13 peak at 133.16 ppm is assigned to C-4 respectively. Accordingly, this agrees with the compound's ring A of compound 3a.

3.4.2 Structure elucidation of compound 3b (bright yellow powder)

1-(3,5-dichlorobenzylidene)-2-(4-nitrophenyl)hydrazine

For compounds 1-(3,5-dichlorobenzylidene)-2-(4-nitrophenyl) hydrazine (3b). The FTIR absorption signals at 3254 cm^{-1}, 3075 cm^{-1}, and 1580 cm^{-1} suggested the stretchings of the secondary N-H bond, C-H bond, and C=N bond respectively in table 3. The emergence of these bonds was confirmed by the non-occurrence of carbonyl proton and carbon diagnostic peaks and the appearance of singlet proton peaks at 11.55 ppm, and 7.98 ppm, with carbon-13 peak at 139.44 ppm on 1H and 13C NMR spectra respectively. The proton peak at 7.94 ppm was found to couple with the carbon-13 peak at 138.66 ppm on the HSQC spectrum confirming the formation of the azomethine C-H bond. More so, the two protons were coupled at (11.47, 7.87) ppm on the COSY spectrum indicating that they are neighboring protons to each other. This further substantiates the formation of the hydrazone functional group. Also, the proton at a peak of 11.18 ppm was observed to couple to no carbon on HSQC, this implies that it is bonded to a heteroatom which is consistent with the FTIR absorption signal for the N-H bond. These indicated the formation of a new hydrazone bond. Finally, HMBC correlation between N-H proton and azomethine carbon at (11.51, 138.84) ppm was noticed on the HMBC spectrum affirming the synthesis of the hydrazone functional group.

Absorption signals at 1416 cm^{-1} and 1271 cm^{-1} in tale 3 correspond to aromatic C=C stretching and C-H in-plane bending which suggests the presence of aromatic ring(s) in the compound. The presence of doublet and singlet proton peaks within the aromatic chemical shift on the proton spectrum. The carbon-13 spectrum indicated nine peaks within the aromatic chemical shift which indicates that there is more than one aromatic ring in the structure of the compound. HSQC spectrum showed coupling between

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peaks at (8.12, 126.35) ppm, (7.53, 128.25) ppm, (7.73, 124.83) ppm, and (7.21, 112.11) ppm which indicates aromatic C-H bonds present in the compound. Additionally, the doublet proton peaks at 8.15 ppm and 7.25 ppm are each resonating for two hydrogens. This suggests that their respective carbon-13 peaks at 126.35 ppm and 112.11 ppm are each resonating for two equivalent carbons as well. The two proton peaks were noticed to couple at (8.14, 7.18) ppm on the COSY spectrum which indicates that they are neighboring protons to each other, the coupling constant of the two protons peaks are 9.1 Hz and 8.1 Hz respectively suggesting that each of the peaks is resonating for two protons that are ortho to each other.

The HMBC correlation at (11.53, 113.00) ppm involving N-H proton suggested that the four aromatic C-H at (8.12, 126.35) ppm and (7.21, 112.11) ppm are on ring B (hydrazine ring). Carbon-13 peaks at 150.46 ppm and 142.24 ppm were noticed to couple to no hydrogen on the HSQC spectrum indicating that they are substituted aromatic carbons. Also, the HMBC correlation at (8.12, 150.46) ppm indicates that the carbon-13 peak at 150.46 ppm is also on ring B. Furthermore, absorption signals at 1476 cm^{-1} and 1297 cm^{-1} corresponded to NO_2 asymmetric stretching and amino C-N stretching respectively in table 3. Hence, the carbon-13 peak at 150.46 ppm is assigned to position 4′ of the ring while 142.24 ppm is assigned to position 1′ of the ring as well. Similarly, the downfield coupled peaks at (8.12, 126.35) ppm on the HSQC spectrum are assigned to the equivalent C-H at positions 3′ and 5′ of the ring. The upfield coupled peaks at (7.21, 112.11) ppm are assigned to the equivalent C-H at positions 2′ and 6′ of the ring. These analyses conform to the structure of ring B and hence its presence is confirmed.

On the other hand, the HMBC spectrum in figure 4.28 revealed the correlation of imine carbon at 138.79 ppm to proton peak at 7.79 ppm which suggests that the protons responsible for the signal are on ring A. The two singlet proton peaks were coupled to their respective carbons as follows (7.53, 128.25) ppm, (7.73, 124.83) ppm on the HSQC spectrum. The singlet proton peak at 7.79 ppm was found to integrate for two hydrogens suggesting that each of the equivalent aromatic hydrogens is coupled to equivalent aromatic carbons. As such, the two equivalent C-H are assigned to positions 2 and 6 of ring A. Also, C-H at (7.53, 128.25) ppm is assigned to position 4 of ring A. These assignments were further confirmed by the meta coupling of the two proton peaks at (7.69, 7.50) on the COSY spectrum. Their meta coupling was also confirmed by the HMBC correlations between their protons and carbons at (7.55, 124.86) for H-4 and C-2,6 and (7.76, 128.38) ppm for H-2,6 and C-4 respectively.

The position 2 and 6 protons were correlated to another carbon at (7.79, 134.70) ppm. This carbon at 134.70 ppm was noticed to be substituted aromatic carbon on the HSQC spectrum as it does not couple with any proton. Therefore, it is assigned to carbon at position 1. Also, the downfield carbon-13 peak at 139.44 ppm was observed coupled with no proton on the HSQC spectrum which suggests that it is a substituted aromatic carbon as well. FTIR absorption signal at 957 cm^{-1} corresponds to aromatic C-Cl stretching confirming the presence of chloro groups on substituted carbons at 139.44 ppm which is more deshielded compared to C-1 at 134.70 ppm. Also, the carbon-13 peak at 139.44 ppm has equal intensity to those of C-2,6 and C-2′,6′ which indicates that it is resonating for two carbons as those of the latter. Thus, a ^{13}C peak at 139.44 ppm is assigned to carbon 3 and 5 of ring A. These analyses are consistent with the structure of compound 3b. Therefore, its synthesis is confirmed successfully.

4. MATERIALS AND METHODS

All of the reagents used were bought from Sigma Aldrich and utilized without additional purification. The melting points of the produced compounds were determined using an Electrothermal Engineering LTD 9100 device. The 1H and 13C NMR spectra were acquired using a Brucker AMX 400 MHz spectrometer running at 400 MHz and 101 MHz, respectively, with dimethyl sulfoxide (DMSO) as the solvent using an Agilent technologies spectrometer model 543. Chemical shifts (δ) are expressed in parts per million and are calculated using the NMR solvent peak as a reference.

General procedure: Synthesis of p-nitrophenyl hydrazones 3a-b

4.1 Solvent-based procedure

In 30 ml of ethanol, 5.09mmol of each of the benzaldehydes 1a-b and p-nitrophenyl hydrazine 2 were dissolved. Following that, five drops of glacial acetic acid were added as a catalyst. For three hours, the liquid was magnetically stirred. The reactions were performed under room condition. TLC was used to track the reaction's development. The crude products were then filtered, dried, and placed into a beaker.

4.2 Solvent-free procedure

A glass rod was used to grind equimolar amounts of p-nitrophenyl hydrazine 2 (1 mmol) and each of the aromatic aldehydes 1a-b (1 mmol) in a universal tube for 5 minutes. The reactions were performed under room condition. TLC was used to monitor the reaction's progress.

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4.3 Purification (work-up)

To scavenge any possibly unreacted p-nitrophenyl hydrazine 2, 20 ml of cold 2 M hydrochloric acid was added and stirred. The product precipitate was filtered off, dried, and washed with 30 ml cold distilled water and 20 ml cold 95 % ethanol in a step-wise manner to obtain colored powdered products 3a-b which were recrystallized in ethyl acetate in high to excellent yield.

5. CONCLUSION

Summarily, we have successfully synthesized novel dichloro p-nitrophenyl hydrazones using a solvent-free method and the modified existing solvent-based method of condensation. Easy and efficient workups, and unsolvated pure products with high to excellent yields are the advantages of this modified method. At the end of this experiment, all the compounds were obtained at high to excellent yield using the solvent-based method which was superior to solvent-free yields. The generality and simplicity of the technique, catalyst-free conditions, non-use of an organic solvent, the short reaction time, and the easy and efficient workup, unsolvated pure products in moderate to high yields are all the advantages of the developed solvent-free method.

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Conflicts of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Singh A.K., Thakur S., Pani B., B. Chugh B., Lgaz H. *et al*. Solvent-free microwave-assisted synthesis and corrosion inhibition study of a series of hydrazones derived from thiophene derivatives: Experimental, surface, and theoretical study. J. Mol. lipids (2019). doi: 10.1016/j.molliq
2. Sainath Zangade and Pravinkumar Patil. A Review on Solvent-free Methods in Organic Synthesis. Current Organic Chemistry, 23, (2019) 2295-2318.
3. Hossein Naeimi, Hashem Sharghi, Fariba Salimi, and Khadijeh Rabiei. Facile and Efficient Method for Preparation of Schiff Bases Catalyzed By P2O5/SiO2 under Free Solvent Conditions. Heteroatom Chemistry Volume 19, Number 1 (2008).
4. V. Koteswara Rao, S. Subba Reddy, B. Satheesh Krishna, K. Reddi Mohan Naidu, and C. Naga Raju. Synthesis of Schiff's bases in aqueous medium: a green alternative approach with effective mass yield and high reaction rates. Green Chemistry Letters and Reviews Vol. 3, No. 3, September 2010, 217-223.
5. Duha Adnan, Bijender Singh, Surinder Kumar Mehta, Vinod Kumar, and Ramesh Kataria. Simple and solvent-free practical procedure for chalcones: An expeditious, mild and greener approach. Current Research in Green and Sustainable Chemistry 3, (2020) 100041.
6. Sunita Bhagat, Nutan Sharma, and Tejpal Singh Chundawat. Synthesis of Some Salicylaldehyde-Based Schiff Bases in Aqueous Media. Journal of Chemistry, Volume, Article ID 909217, (2013) 4 pages. doi: 10.1155/2013/909217.
7. Abbas Shockravi, Mahdieh Sadeghpour, and Abolfazl Olyaei. Simple and Efficient Procedure for the Synthesis of Symmetrical Bis-Schiff Bases of 5,5′-Methylenebis(2-aminothiazole) Under Solvent-free Conditions. Synthetic Communications 1, (40) (2010). 2531–2538. Taylor & Francis Group, LLC.
8. Mehtab Parveen, Shaista Azaz, Ali Mohammed Malla, Faheem Ahmad, and Pedro Sidonio Pereira da Silva *et al*. Solvent-free, [Et3NH][HSO4] catalyzed facile synthesis of hydrazone derivatives. RSC (2014). DOI: 10.1039/c4nj01666a
9. Pierrick Nun, Charlotte Martin, Jean Martinez, Frédéric Lamaty. Solvent-free synthesis of hydrazones and their subsequent N-alkylation in a Ball-mill. Tetrahedron, Elsevier, 67 (42), (2011) pp. 8187-8194. doi: 10.1016/j.tet.2011.07.056. hal-00623809
10. Mo Zhang, Ze-Ren Shang, Xiao-Tang Li, Jia-Nan Zhang, Yong Wang *et al*. An International Journal for Rapid

Communication of Synthetic Organic Chemistry Volume 47, (2017). doi: 10.1080/00397911.2016.1258476

11. Noor ul Ain, Tariq Mahmood Ansari, M. Rehan H. Shah Gilani, Guobao Xu, Gaolin Liang. Facile and straightforward synthesis of Hydrazone derivatives. Hindawi Journal of Nanomaterials. Volume (2022), Article ID 3945810, 6 pages doi: 10.1155/2022/3945810
12. Jana Pisk, Ivica Đilovic, Tomica Hrenar, Danijela Cvijanovic, Gordana Pavlovic *et al*. Effective methods for the synthesis of hydrazones, quinazolines, and Schiff bases: reaction monitoring using a chemometric approach. RSC Adv., (2020), 10, 38566
13. Pierrick Nun, Charlotte Martin, Jean Martinez, Frédéric Lamaty. Solvent-free synthesis of hydrazones and their subsequent N-alkylation in a Ball-mill. Tetrahedron, Elsevier, 67 (42), (2011) pp. 8187-8194. 10.1016/j.tet.2011.07.056. hal-00623809
14. Mehtab Parveen, Shaista Azaz, Ali Mohammed Malla, Faheem Ahmad, Pedro Sidonio Pereira da Silva et al. Solvent-free, [Et3NH][HSO4] catalyzed facile synthesis of hydrazone derivatives. Royal Society of Chemistry (2014). doi: 10.1039/c4nj01666a
15. Oliveira P. F. M., Baron M., Chamayou A., Andre-Barr`es C., Guidettib B. and Baltas M. Solvent-free mechanochemical route for green synthesis of pharmaceutically attractive phenol hydrazones. RSC Advances, Royal Society of Chemistry, (2014), 4 (100), p.56736-56742. doi: 10.1039/c4ra10489g. hal-01625025
16. Harith M. Al-Ajely and Aymen N. Yassen. Microwave Synthesis of some Substituted Hydrazones under Solvent-Free Conditions. International Journal of Scientific & Engineering Research Volume 8, Issue 5, (2017) 1854 ISSN 2229-5518
17. Singh A.K., Thakur S., Pani B., B. Chugh B., Lgaz H. et al. Solvent-free microwave-assisted synthesis and corrosion inhibition study of a series of hydrazones derived from thiophene derivatives: Experimental, surface, and theoretical study. Journal of Molecular lipids (2019). doi: 10.1016/j.molliq. 03.126
18. Crawford, D. E., Porcheddu, A., McCalmont, A. S., Delogu, F., James, S. L. et al. Solvent-free, Continuous Synthesis of Hydrazone-Based Active Pharmaceutical Ingredients by Twin-Screw Extrusion. ACS Sustainable Chemistry & Engineering, 8(32), (2020) 12230-12238. doi: 10.1021/acssus chemeng.0c03816
19. Hayder M. Abdulhamza and Muthanna S. Farhan. Synthesis, Characterization and Preliminary Anti-inflammatory Evaluation of New Fenoprofen Hydrazone Derivatives. Iraqi J Pharm Sci, Vol. 29 (2) (2020).
20. Wang Shi-Meng, Gao-Feng Zha, K. P. Rakesh et al. Synthesis of benzo[d]thiazole-hydrazone analogs: molecular docking and SAR studies of potential H^+/K^+ ATPase inhibitors and anti-inflammatory agents. MedChem Comm. Royal Society of Chemistry (2017).
21. A.L.V. Kumar Reddy and Niren E Kathale. Synthesis and Anti-inflammatory Activity of Hydrazide-Hydrazones Bearing Anacardic Acid and 1,2,3-Triazole Ring Based Hybrids. Orient. J. Chem., Vol. 33(6), (2017) 2930-29 36.
22. Abadi, A.H.; Eissa, A.A.H.; Hassan, G.S. Synthesis of novel 1,3,4-trisubstituted pyrazole derivatives and their evaluation as antitumor and antiangiogenic agents. Chem. Pharm. Bull. 51, (2003) 838-844.
23. Ziad Moussa, Mohammed Al-Mamary, Sultan Al-Juhani et al. Preparation and biological assessment of some aromatic hydrazones derived from hydrazides of phenolic acids and aromatic aldehydes. Heliyon 6; (2020). e05019.
24. Lee Y. J., Jeong W. K., Shin S., Lee U. J. and Kim Y. Discovery of novel selective inhibitors of Staphylococcus aureus β- ketoacyl acyl carrier protein synthase III, Eur. J. Med. Chem., 47, (2012) 261-269.
25. El-Sabbagh OI., Shabaan MA., Kadry HH. And Al-Din ES. New octahydroquinazoline derivatives: Synthesis and hypotensive activity, Eur. J. Med. Chem., 45, (2010) 5390-5396.
26. Ragavendran, J.; Sriram, D.; Patel, S.; Reddy, I. and Bharathwajan, N. et al. Design and synthesis of anticonvulsants from a combined phthalimide-GABA-anilide and hydrazone pharmacophore. Eur. J. Med. Chem. 42, (2007) 146-151.
27. Ergenç, N.; Günay, N.S. Synthesis and antidepressant evaluation of new 3-phenyl-5-sulfonamidoindole derivatives, Eur. J. Med. Chem. (1998), 33, 143-148.
28. Nawaf A. Alsaif, Mashooq A. Bhat, Mohamed A. Al-Omar, Hanaa M. Al-Tuwajiri, Ahmed M. Naglah et al. Synthesis of Novel Diclofenac Hydrazones: Molecular Docking, Anti-Inflammatory, Analgesic, and Ulcerogenic Activity. Journal of Chemistry (2020). Hindawi doi: 10.1155/2020/4916726
29. Abdel-Aal, M.T.; El-Sayed, W.A.; El-Ashry, E.H. Synthesis and antiviral evaluation of some sugar arylglycinoylhydrazones and their oxadiazoline derivatives. Arch. Pharm. Chem. Life Sci. (2006), 339, 656-663.
30. Bukowski L.; Janowiec, M. 1-Methyl-1H-2-imidazo[4,5-b]pyridinecarboxylic acid and some derivatives with suspected antituberculotic activity. Pharmazie, 51, (1996) 27-30.
31. Gemma, S.; Kukreja, G.; Fattorusso, C.; Persico, M.; Romano, M.; Altarelli, M.; Savini, L.; Campiani, G.; Fattorusso, E.; Basilico, N. Synthesis of N1-arylidene-N2-quinolyl- and N2-acrydinylhydrazones as potent antimalarial agents active against CQ-resistant P. falciparum strains. Bioorg. Med. Chem. Lett. (2006), 16, 5384-5388.

32. Jordao A. K., Sathler PC., Ferreira VF., Campos VR., de Souza MCBV, et al. Synthesis, antitubercular activity, and SAR study of N-substituted phenylamino-5-methyl-1H-1,2,3-triazole-4-carbohydrazides, Bioorg. Med. Chem., 19, (2011), 5605-5611.
33. Silva, A.G.; Zapata-Suto, G.; Kummerle, A.E.; Fraga, C.A.M.; Barreiro, E.J. et al. Synthesis and vasodilatory activity of new N-acyl hydrazone derivatives, designed as LASSBio-294 analogs. Bioorg. Med. Chem. 13, (2005) 3431-3437.
34. Gage JL., Onrust R., Johnston D., Osnowski A., MacDonald W. N-Acylhydrazones as inhibitors of PDE10A, Bioorg. Med. Chem. Lett., 21, (2011) 4155-4159.
35. Babalola SA, Idris AY, Sani YM, Hamza A, Igie N, Muhammad H, Erumiseli OG, Bakare LO. Solvent-free synthesis of polymethoxy and dichloro p-nitrophenyl hydrazones. Drug Discovery, 2022, 16(37), 63-67

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