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Solvent-free synthesis of polymethoxy and dichloro p-nitrophenyl hydrazones

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ABSTRACT

A solvent-free method for the synthesis of novel p-nitrophenyl hydrazones was successfully developed. The condensation of the p-nitrophenyl hydrazine with aromatic aldehydes through this mechanochemical technique furnished three products **3a-c** with moderate to high yield. The developed method is eco-friendly, efficient, simple, and convenient, and indicated high reproducibility, short reaction time, catalyst-free, simple workup, and afforded pure and unsolvated products.

Keywords: Green synthesis, p-nitrophenyl hydrazine, solvent-free, mechanochemistry, p-nitrophenyl hydrazine

1. INRODUCTION

Over many decades now, enormous research has been innovated for the development of environmentally benign reactions with are both cost-effective and technologically feasible [1-2]. The green chemistry campaign started under pollution prevention legislation way back in 1990 [1], this legislation has given rise to the development of new technologies and techniques such as ultrasound, microwave, photochemical, and/or mechanical devices required in order to carry out ecologically beneficial reactions. In addition, this regulation has made organic compound synthesis in more environmentally friendly ways more visible. [1,5]. Environmentally sustainable synthetic techniques have lately received considerable attention, and a number of solvent-free procedures have been developed. Many other appealing characteristics of working without solvent have been described in the literature, with yields typically exceeding 90% and averaging around 95%. Because of the method's selectivity, it has resulted in fewer byproducts and the elimination during purification stages seen in pharmaceutical ingredients and treatments. Recently, the mechanochemistry approach has seen a boom of interest. The advantages of solvent-free or solid-state synthesis over traditional solvent-based synthesis comprise shorter reaction times, efficient reactions with minimum energy requirements, good to high yields, and easier work-up methods [6]. The use of volatile organic compounds (VOC) and other harmful substances in traditional solvent-based procedures results in the emission of

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hazardous effluents and the resulting environmental problems[1,3,4] and genetic mutations on public health and the implications disorders including cancers. Pierrick *et al*. reported the solvent-free synthesis of Boc-, Bz-, Fmoc-, and tosyl-hydrazones from aldehydes and their subsequent N-alkylation in a ball mill [7]. Mehtab *et al*. reported the development of the solvent-free synthesis of hydrazones catalyzed by Bronsted acid ionic liquid (BAIL) [Et_3NH][HSO_4] [8]. Oliveira *et al*. reported the synthesis of therapeutically active phenol hydrazones via a solvent-free mechanochemistry route [9]. Harith and Aymen reported the microwave-assisted synthesis of oxobenzotriazine hydrazides under solvent-free conditions [10]. Singh *et al*. reported the microwave-assisted synthesis of corrosion inhibitors series of thiophene hydrazones under solvent-free solvent-free conditions [11]. Crawford *et al*. reported the solvent-free and continuous flow synthesis of hydrazone-base active pharmaceutical ingredients using Twin-Screw Extrusion [12].

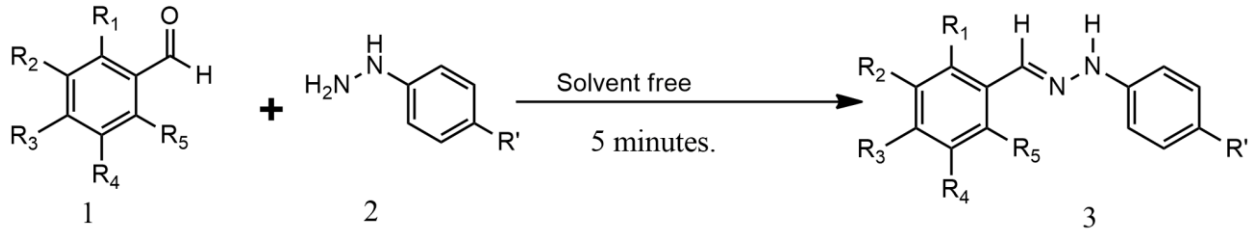
Hydrazones are topical in medicinal and bio-organic chemistry with intrinsic biological activities including anti-inflammatory [13-16], anti-cancer [17], anticonvulsant [21], antidepressant [22], analgesic [23], antioxidant [18], antimicrobial [19], antiviral [24], antimycobacterial [25], antimalarial [26], antiplatelet [27], vasodilator [28], cardioprotective [20], and the central nervous system [29] activities. Hydrazones are also useful as delivery agents in medical biotechnology applications. Hydrazones are useful as synthetic intermediates in the synthesis of medicinally significant heterocyclic compounds, and they have a wide range of applications in synthetic chemistry as ligands in complex formation.

2. EXPERIMENTAL

Sigma-Aldrich provided all of the chemicals, which were utilized without additional purification. Electrothermal Engineering LTD 9100 apparatus was used to measure the melting points. The FTIR spectra were acquired using Agilent technologies spectrophotometer model 543, and the ^1H and ^{13}C NMR spectra were derived with a Brucker AMX 400 MHz spectrometer operating at 400 MHz and 100 MHz respectively. Chemical shifts (d) are expressed in parts per million and are calculated using the NMR solvent peak as a reference point.

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

Equimolar quantities of p-nitrophenyl hydrazine **2** (1 mmol) and each of the aromatic aldehydes (1 mmol) were grounded in a universal tube with the aid of a glass rod for 5 minutes. The reactions were carried out at room conditions. The progress of the reaction was monitored using TLC. On completion, the mixture product was transferred into a beaker and 20 ml of cold 2 M hydrochloric acid was added and stirred to scavenge the possible unreacted p-nitrophenyl hydrazine **2**. The products were precipitated were filtered, dried, and subsequently washed with 30 ml of cold distilled water and 20 ml of cold 95% ethanol step-wisely to afford colored powdered products **3a-c** in moderate to high yield.



Scheme 1: Synthesis of p-nitrophenyl hydrazones.

Compound	R_1	R_2	R_3	R_4	R_5	R′
3a	Cl	H	Cl	H	H	NO_2
3b	H	OCH_3	OCH_3	OCH_3	H	NO_2
3c	H	Cl	H	Cl	H	NO_2

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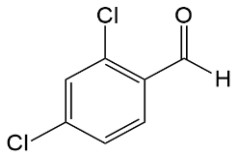
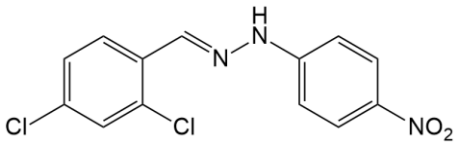
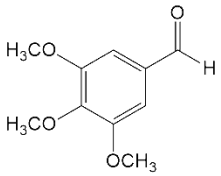
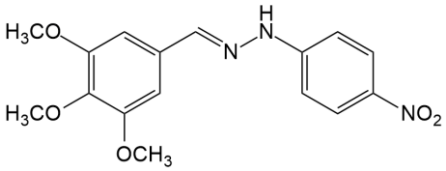
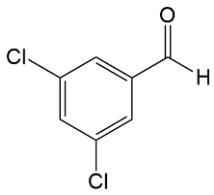
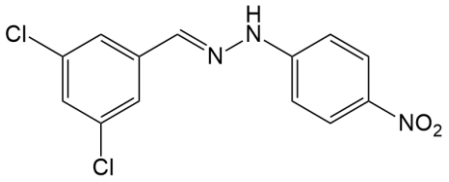
3. RESULTS

Table 1: Synthesis of compounds **3a-c** under solventless conditions.

Entry	Aldehyde	Product	Time (min)	Yield (%)	Mp (^{0}C)
1			5	57.28	226-228
2			5	30.51	198-201
3			5	32.69	257-259

1-(2,4-dichlorobenzylidene)-2-(4-nitrophenyl)hydrazine 3a. Yield 57.28%, chrome yellow powder, mp 226-228 °C. IR (KBr, cm^{-1}): 3265 (N-H), 3078 (C-H_{imine}), 1587 (C=N), 1498 (NO_2), 1461 (C=$C_{aromatic}$), 1300 (C-$N_{aniline}$), 1043 (C-Cl). H^1 NMR spectrum (400 MHz, DMSO-*d6*) δ, ppm: 7.18 d (2H_{arom}, *J* = 8.2 Hz), 7.47 d (1H_{arom}, *J* = 8.5 Hz), 7.65 d (1H_{arom}, *J* = 1.8 Hz), 8.05 d (1H_{arom}, *J* = 8.6 Hz), 8.13 d (2H_{arom}, *J* = 9.0 Hz), 8.29 s (1H_{imine}), 11.61 s (1H, NH). ^{13}C NMR spectrum (101 MHz, DMSO-*d6*), δ, ppm: 112.10, 126.54, 127.98, 128.29, 129.71, 131.39, 133.16, 134.36, 136.58, 139.43, 150.43.

1-(4-nitrophenyl)-2-(3,4,5-trimethoxybenzylidene)hydrazine 3b. Yield 30.51%, brick red powder, mp 198-201 °C. IR (KBr, cm^{-1}): 3283 (N-H), 2929 (C-H_{imine}), 2840 (C-$H_{methoxy}$), 1591 (C=N), 1494 (NO_2), 1412 (C=$C_{aromatic}$), 1125 (C-$N_{aniline}$). H^1 NMR spectrum (400 MHz, DMSO-*d6*) δ, ppm: 3.69 s (3H, OCH_3), 3.85 s (6H, OCH_3), 7.05 s (2H_{arom}), 7.19 d (2H_{arom}, *J* = 7.6 Hz), 7.97 s (1H_{imine}), 8.13 d (2H_{arom}, *J* = 8.7 Hz), 11.30 s (1H, NH). ^{13}C NMR spectrum (101 MHz, DMSO-*d6*), δ, ppm: 56.35, 60.54, 104.15, 111.69, 126.58, 130.65, 138.67, 139.02, 142.24, 150.98, 153.60.

1-(3,5-dichlorobenzylidene)-2-(4-nitrophenyl)hydrazine 3c. Yield 32.69%, bright yellow powder, mp 257-259 °C. IR (KBr, cm^{-1}): 3254 (N-H), 3075 (C-H_{imine}), 1580 (C=N), 1476 (NO_2), 1416 (C=$C_{aromatic}$), 1297 (C-$N_{aniline}$), 957 (C-Cl). H^1 NMR spectrum (400 MHz, DMSO-*d6*) δ, ppm: 7.25 d (2H_{arom}, *J* = 8.1 Hz), 7.59 s (1H_{arom}), 7.79 s (2H_{arom}), 7.98 s (1H_{imine}), 8.15 d (2H_{arom}, *J* = 9.1 Hz), 11.55 s (1H, NH). ^{13}C NMR spectrum (101 MHz, DMSO-*d6*), δ, ppm: 112.23, 124.96, 126.50, 128.38, 135.00, 138.80, 139.44, 145.24, 150.52.

4. DISCUSSION

We report the solvent-free synthesis of three novel para-nitrophenyl hydrazones cleanly and efficiently in short reaction times without using any acid catalyst under solventless conditions and at room temperature. 4-nitrophenyl hydrazine 1 was with condensed aromatic aldehydes having electron-withdrawing or electron-donating groups (2,4-dichloro benzaldehyde, 3,5-dichloro benzaldehyde, and 3,4,5-trimethoxy benzaldehyde). The hydrazones 3a-c were prepared by the reaction between the equimolar quantity of 4-nitrophenyl hydrazine and the said aromatic aldehyde 2a-c in solvent-free condition during 2-5 minutes at room condition. These reactions required no need for a solvent or an inert environment. Each of the compounds 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 step-wisely with moderate to high yields (30-57%). The results of these reactions are revealed in table 1 above.

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The spectroscopic spectra data of the new p-nitrophenyl hydrazones were elucidated for their chemical structures. In the FTIR spectra, the characteristic imine C=N and N-H stretching frequencies at υ 1580 – 1591 cm-1 and υ 3254 – 3283 cm-1 were noticed. In the H1 NMR spectra data, the imine proton and N-H were resonated at δ = 7.97 – 8.29 ppm and δ = 11.30 – 11.61 ppm respectively, the methoxy protons of compound 3b were resonated at δ = 3.85 – 3.69 ppm, aromatic hydrogens of the phenyl rings were resonated as singlets and multiplets at δ = 8.29 – 7.05 ppm. We have successfully established the synthesis of p-nitrophenyl hydrazones through a solvent-free approach that is rapid, easy, efficient, and uncatalyzed.

5. CONCLUSION

We devised a green chemistry technique for the synthesis of p-nitrophenyl hydrazones. The technique's generality and simplicity, catalyst-free conditions, lack of an organic solvent, fast reaction time, simple and efficient workup, and unsolvated pure products in significant yields are all environmental advantages. At the end of this experiment, we obtained a yield of 57.28%, 30.51% and 32.69% for the synthesis of (E)-1-(2,4-dichlorobenzylidene)-2-(4-nitrophenyl)hydrazine,(E)-1-(4-nitrophenyl)-2-(3,4,5-trimethoxy benzylidene) hydrazine and (E)-1-(3,5-dichloro benzylidene)-2-(4-nitrophenyl)hydrazine respectively.

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Conflict of Interest:

The authors declare that there are no conflicts of interests.

Ethical approval

Not applicable.

Data and materials availability:

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

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