

One-Pot Synthesis of Hydrazones by Mechanochemistry

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Introduction:-

To design and conduct chemical reactions with “green” experimental protocol is an enormous challenge that chemists have to confront to improve the quality of the environment for present and future generations. Target areas for achieving this goal are the exploration of alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimized by-products or waste, and elimination of the use of conventional organic solvents, wherever possible. Traditional chemical syntheses or transformations generally require volatile and often hazardous organic solvents as reaction media to facilitate mass and heat transfer, and to isolate and purify desired product from reaction mixtures. Over the past several years, chemists have been aware of the environmental implications of their chemistry. Nowadays, they are trying to develop new synthetic methods, reaction conditions, and uses of chemicals that reduce risks to humans and the environment. Organic solvents are high on the list of damaging chemicals because they are employed in huge amounts and are usually volatile liquids that are difficult to store. In recent years, solid-state organic reactions have caused great interest. They have many advantages such as high efficiency and selectivity, easy separation and purification, and mild reaction conditions and benefit industry as well as the environment [1]. Many articles about solid-state reactions with grinding have been reported, such as the Grignard reaction [2], Aldol condensations [3] and other reactions [4].

Hydrazones are used not only to characterize aldehydes and ketones by derivatization with appropriate hydrazine's [5] but they have also emerged as important synthons for several organic transformations [6] the most remarkable being the Fischer indole synthesis [7]. Hydrazones are of interest also because of their importance in analytical chemistry, medicine and industry. Especially, isonicotinhydrazide and its N-isopropyl acylhydrazone have been used as effective drugs in curing human tuberculosis in the past few years [8]. They have been studied as chelating ligands for spectroscopic and fluorometric determination of trace elements [9]. The chelation of several classes of aryl and hetaryl hydrazones with metals, especially iron [10], has lead to their study as antiproliferative active agents against tumor cells [11]. Recently some hydrazones have been found useful in treating sexual dysfunction [12]. Hydrazones derivatives possessing anti-inflammatory,[13] Analgesic [14] antipyretic [15] and antibacterial [16] activities are also reported in the literature. Carbazole-based hydrazones have been investigated for their optoelectronic and high hole motilities [17]. Several substituted aryl hydrazones have been tested for their nonlinear optical properties[18].

Hydrazones synthesis from various precursors is well documented [6]. Recently, some hydrazones have been prepared from carbonyl compounds and hydrazine hydrate in ethylene glycol[19] and toluene[20] by the application of MW irradiation. Some examples on supported reactions using silica gel/sodium hydroxide [21] and solvent-free synthesis of heterocyclic hydrazones under microwave irradiation conditions [22] and room temperature ionic liquid known [23]. Very recently Verma *et al.* reported aqueous protocol for the synthesis of cyclic, bi-cyclic, and heterocyclic hydrazones using polystyrene sulfonic acid (PSSA) as a catalyst[24].

Result And Discussion:-

We are increasingly aware of the environmental impact of human activity, and consequently of the need to develop cleaner and more energy-efficient technologies. It has long been

recognized that the large-scale use of volatile organic solvents has important implications for environmental contamination [25]. Approaches to the problems presented by organic solvents include the use of more benign solvents (especially water and supercritical CO₂), or solvents with negligible vapour pressures (ionic liquids). It has also been said that ‘the best solvent is no solvent’[26.] Despite the power of this statement, our use and understanding of solvent-free synthesis, especially where solid starting materials are concerned, has remained undeveloped in comparison to solvent based methods. the use of grinding to promote reactions between solid reactants is known as mechanochemistry and whilst its usefulness appears to have been recognized for a long time it has become neglected in comparison to solvent based methods.

In continuation of our work on the mechanochemistry here we decided to synthesize the hydrazone under solvent free conditions.

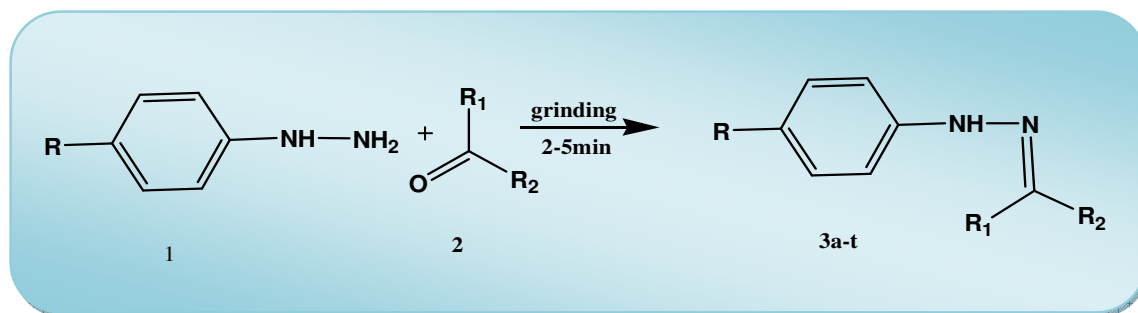
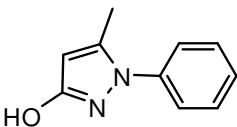
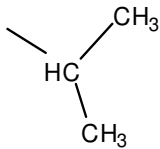
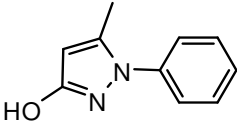
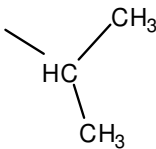
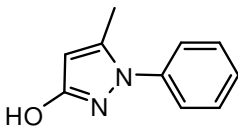
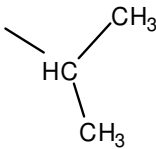


Table 1:- Synthesis of arylhydrazone(3)

Entry	Hydrazones 3	R	R ₁	R ₂	Time(min)	Yield (%)
1	3a	H	H	n-C ₅ H ₁₁	3	90
2	3b	H	H		5	92
3	3c	H	CH ₃	Ph	5	91
4	3d	H	CH ₃		4	94
5	3e	H	H	Ph	3	95
6	3f	NO ₂	H	n-C ₅ H ₁₁	5	91
7	3g	NO ₂	H		5	93

8	3h	NO ₂	CH ₃	Ph	6	94
9	3i	NO ₂	CH ₃		4	91
10	3j	Cl	H	n-C ₅ H ₁₁	3	92
11	3k	Cl	H		5	91
12	3l	Cl	CH ₃	Ph	3	93
13	3m	Cl	CH ₃		5	92

^a: Reaction Condition; phenyl hydrazine's(1) benzaldehyde (1 mmol), RT

^b: Isolated yield after column chromatography.

Typical Procedure:-

Phenyl hydrazine or substituted phenyl hydrazine's(1) were grind with a variety of carbonyl compounds (2) (alkyl, aryl and heteroaryl) at room temperature in solvent free condition (scheme 1). All the reactions proceed to completion in just 2-5 min. at room temperature without any organic solvent or any added catalyst. The respective hydrazones could be isolated in excellent yields in all the cases (Table 1). The hydrazones 3a-l are known compounds and were well characterized by melting point, IR, ¹HNMR and mass spectra.[21]. The methodology tolerates both electron withdrawing and electron donating substituents on the phenylhydrazines. The reactions wherein both 1 and 2 are liquids (Entries 2-4) when carried out neat required 2 h for complete conversion under similar conditions. Likewise, all the reactions when carried out in a molecular solvent such as methanol under similar conditions required 2 h for complete conversions. In summary, we have developed a efficient, solvent free synthesis of hydrazones at ambient conditions in near quantitative yields using mechanochemistry. The excellent isolated yield, high reaction rate. Absence of organic solvent and any acid or base catalyst makes this an environment friendly methodology amenable for scale up.

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