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A HIGHLY EFFICIENT SOLVENT FREE SYNTHESIS OF HYDRAZIDES USING GRINDING TECHNIQUE

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Abstract
A highly efficient eco-friendly synthesis of hydrazides directly from carboxylic acids is described under solvent-free conditions using grinding technique.

Keywords: Grinding technique, Hydrazides, Solvent-free, eco-friendly reaction.

Introduction

Hydrazides constitute an important class of biologically active organic compounds and their therapeutic uses are well documented in the literature[i-vii]. Hydrazides and their condensation products are reported to possess a wide range of biological activities including antibacterial activity[i-iii], tuberculostatic properties[iv], HIV inhibitors[v], pesticidal[vi], antifungal[vii] and many more. Some of the hydrazides and corresponding hydrazones are psychopharmacological agent, eg, monoamine oxidase (MAO) inhibitor and serotonin antagonists[viii].

Hydrazides have also been used as important intermediates in synthesis of various heterocyclic compounds[ix-xii] such as 1,2,4-triazoles, 1,3,4-thiadiazoles, 1,3,4-oxadiazoles, 1,2,4,5-tetrazines, which are known to possess diverse pharmacological properties.

A variety of methods have been used to prepare hydrazides, by reaction of acids or their derivatives with hydrazine hydrate, acid chlorides and acyl anhydrides were used to prepare hydrazides[xiii]. The reaction of acid chlorides and acyl anhydrides with hydrazine often leads to the formation of diacyl derivatives due to their high reactivity. Hydrazides are commonly prepared by the hydrazinolysis of esters with hydrazine hydrate[xiv]. Esters being less reactive are not converted into diacyl derivatives but require longer periods for conversion to hydrazides which vary from hours to several days. The use of inclusion complexes of hydroquinone and hydrazine in solid state hydrazinolysis of esters[xv] and MW irradiation technique[xvi] has also been reported.

In a recent report[xvii], synthesis of hydrazides from acids has been reported under MW irradiations, but it involves tedious workup procedure including lympholisation of the solution at -50°C.

Results and Discussion

Today much emphasis is being laid on the development of synthetic procedures which avoid toxic and hazardous chemicals and solvents[xviii]. In continuation of our work to develop simple and eco-friendly procedures for the synthesis of organic compounds, we wish to report a highly efficient synthesis of hydrazides directly from acids under solvent free conditions using grinding technique. The carboxylic acids on grinding with hydrazine hydrate in a mortar by a pestle at room temperature set into a solid mass after some time which on crystallization from ethanol gives the hydrazine hydrazide directly (Scheme 1). Due to the mild nature of the reaction conditions, the formation of the diacyl hydrazides is avoided and the workup procedure is also simple and avoids the addition of water as the recovery of the hydrazide from aqueous solution is tedious due to its high solubility. The identity of the compounds (Table 1) was confirmed from their IR, ^{1}H-NMR spectra and melting point comparison with literature value.

Experimental

All the melting points were determined in open capillary tubes using liquid paraffin bath and are uncorrected. IR spectra were recorded in Perkin-Elmer Spectrophotometer and ^{1}H-NMR on Bruker Avance II 400 MHz Spectrometer using TMS as an internal standard.

General experimental procedure

The carboxylic acids (3.0 mmol) was ground with hydrazine hydrate (80 %, 3.75 mmol) by a pestle in a mortar for 3-5 minutes and left for digestion (10 minutes) when the reaction mixture set into a solid mass. The completion of the reaction was checked by thin layer chromatography. The solid mass was crystallized from ethanol to give hydrazides.

Scheme 1. Synthesis of hydrazides

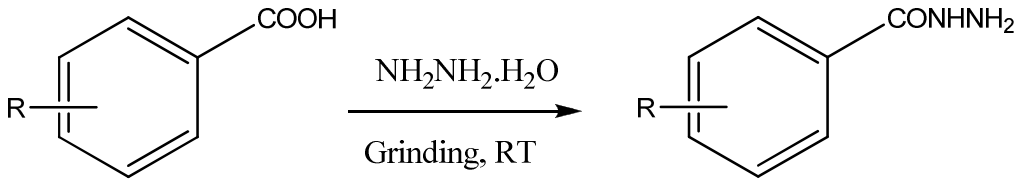

Table 1. Physical data of acid hydrazides synthesizd (1-11).

Compound	R	Time (min)[a]	M.P. (^{o}C)	Lit. M.P. (^{o}C)	Yield (%)[b]
1	H	12	110-11	112[xix]	82
2	2-Cl	13	108-10	110[xix]	85
3	4-Cl	13	160-62	163[xix]	87
4	4-Br	12	165-67	164[xix]	82
5	4-OH	15	260-62	264-65[xxi]	85
6	4-OCH_3	12	163-65	160-64[xx]	90
7	4-NH_2	14	222-23	225-27[xxii]	87
8	4-NO_2	15	117-18	120-21[xix]	80
9	2-CH_3	12	122-23	124[xix]	90
10	3-CH_3	12	95-98	97[xix]	92
11	4-CH_3	12	116-17	117[xix]	92

[a]Grinding + Digestion time [b]Yield after crystallization

Spectral data of compounds

1. IR (KBr): 3205 cm^{-1} (NH_2), 1672 cm^{-1} (C=O).
^1H NMR ($CDCl_3$): δ 4.64 (s, 2H, NH_2), 7.45-7.94 (m, 5H, H-2, H-3, H-4, H-5, H-6), 8.74 (bs, 1H, CONH).

3. IR (KBr): 3309 cm^{-1} (NH_2), 1662 cm^{-1} (C=O).
^1H NMR ($CDCl_3$): δ 4.27 (s, 2H, NH_2), 7.39 (d, 2H, H-3, H-5), 7.85 (d, 2H, H-2, H-6), 9.77 (bs, 1H, CONH).

5. IR (KBr): 3321 cm^{-1} (OH), 3209 cm^{-1} (NH_2), 1678 cm^{-1} (C=O).
^1H NMR ($CDCl_3$): δ 1.5 (s, 2H, NH_2), 4.2 (s, 1H, OH), 7.52 (d, 2H, H-3, H-5), 7.89 (d, 2H, H-2, H-6), 8.85 (bs, 1H, CONH).

6. IR (KBr): 3325 cm^{-1} (NH_2), 1664 cm^{-1} (C=O).
^1H NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.92 (s, 2H, NH_2), 6.90 (d, 2H, H-3, H-5), 7.83 (d, 2H, H-2, H-6), 9.25 (bs, 1H, CONH).

11. IR (KBr): 3210 cm^{-1} (NH_2), 1685 cm^{-1} (C=O).
^1H NMR: ($CDCl_3$): δ 4.84 (s, 2H, NH_2), 7.48 (d, 2H, H-3, H-5), 7.62 (d, 2H, H-2, H-6), 8.83 (bs, 1H, CONH).

Conclusion

In conclusion, it can be said that the present method developed for the synthesis of hydrazides is simple, highly efficient and eco-friendly and avoids the use of organic solvents during the reaction.

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