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Kneading Ball-Milling and Stoichiometric Melts for the Quantitative Derivatization of Carbonyl Compounds with Gas–Solid Recovery

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An effective methodology of kneading with a ball mill under temperature control was used for the stoichiometric quantitative preparation of synthetically versatile oximes and 2,4-dinitrophenylhydrazones from low-melting aldehydes and ketones. Also, a large number of phenylhydrazones are obtained by safe stoichiometric quantitative melt reactions. Advantages of this technique are short reaction times, eco-friendliness, and ease of handling under solvent-free conditions, as no waste-producing purifying workup is necessary. The different reactivities of aldehydes and ketones allow for easy separation of mixtures containing aldehydes and ketones. Furthermore, a new effective, gas–solid deprotection methodology for oximes was developed, using nitrogen dioxide as the reagent under solvent-free conditions to recover the aldehydes or ketones. The corresponding aldehydes were obtained free of overoxidized acids in quantitative yields.

Introduction

Waste-free sustainable syntheses require quantitative yields of products without solvent-consuming, waste-producing workup procedures.[1] Organic solid–solid syntheses by ball-milling with controlled cooling or heating are most useful in this aim, and already hundreds of examples of waste-free procedures, including industrial scale-up processes, are available.[2] Also, reviews on the topic have appeared recently.[1–4] These solid–solid reactions are comparable to melt reactions at higher temperatures, although there is a risk of inferior results because the benefit of self-assembled packing is lost.[5] Nevertheless, there is also an urgency for solvent-free reactions under efficient kneading conditions[6] in the absence of solvents, because many useful reagents do not have sufficiently high melting points and many melt reactions at high viscosity suffer from inefficient mixing of the reaction partners. Important targets are the versatile oximes and arylhydrazones because of their high synthetic potential for transformations to nitriles, nitro compounds, nitrones, amines, amides, nitrile oxides, and others,[7–8] or heterocycles such as pyrazoles, triazoles, formazanes, or hydrazines, nitrile imines, and others.[7–8] Recently reported "solvent-free" routes for the preparation of oximes required the use of a little organic solvent, solid supports, catalysts, or microwave irradiation but did not give quantitative yields and suffered difficulties with recycling of the auxiliaries.[9–12] A claim of up to quantitative yields of products upon grinding aldehydes and ketones with hydroxylamine hydrochloride, sodium hydroxide, and silica[13] could not be reproduced beyond yields of 45 % (4-hydroxybenzaldehyde) or 20 % (acetophenone) in our hands. Oximes, phenylhydrazones, and 2,4-dinitrophenylhydrazones are often used for the characterization,[14] isolation, and purification of carbonyl compounds. The latter application requires recovery of the aldehydes and ketones by an efficient deprotection technique. As a consequence, there has been a growing interest in the development of appropriate methods for such deprotection, and more than 30 hydrolytic or oxidative techniques have been reported. However, all previous methods suffer from one or more disadvantages such as the use of expensive organic or inorganic reagents, low yields, overoxidization of aldehydes to the carboxylic acids, long reaction times, difficulties in the product isolation, and production of toxic waste. Also, the use of N_2O_4 at $-40\,^{\circ}$C in dangerous aprotic solvents such as CH_3CN, THF, $CHCl_3$, or CCl_4 for the deprotection of oximes and hydrazones afforded the parent carbonyls only with 65–95 % yield.[15] We report herein quantitative syntheses under solvent-free conditions[16–19] that provide superior results by kneading ball-milling or stoichiometric melt reaction, and the deprotection of the carbonyl derivatives to isolate the parent carbonyl compounds simply with gaseous NO_2. All of these quantitative reactions avoid the production of dangerous wastes.

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