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Synthesis of aryl-hydrazones via ultrasound irradiation in aqueous medium

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Abstract

The synthesis of aryl-hydrazones from aromatic aldehydes/ketones and hydrazides (semicarbazide, thiosemicarbazide and aminoguanidine) is described using aqueous medium (acid conditions) under ultrasound irradiation with short reaction times (20–30 min), the reactions occurring at room temperature and giving rise to good to excellent yields of the products, along with the diastereoselectivities. The procedure is also simple and clean.

Keywords: Hydrazones; Aqueous medium; Ultrasound irradiation; Condensation

Aryl-hydrazones, such as semicarbazones, thiosemicarbazones and guanyl hydrazones, are important compounds for drug design,[1] as possible ligands for metal complexes,[2] organocatalysis[3] and also for the preparation of heterocyclic rings.[4]

At present a broad range of methods for synthesizing imines[5] in the presence of catalysts are available: $ZnCl_2$,[6] $TiCl_2$,[7] K-10,[8] $MgSO_4$-PPTL,[9] $Mg(ClO_4)_2$[10] and also SiO_2–$NaHSO_4$ (under MW irradiation condition).[11] More recently, ultrasound irradiation has been used to give rise to the formation of a series of Schiff bases (aryl–aryl and aryl–alkyl), under solvent-free conditions[12] or using SiO_2 as a catalyst in ethanol,[13] with short reaction times (10–20 min) and high yields.

For aryl-hydrazones, most reaction methods described to date involve the use of methanol as a solvent without catalysts at reflux, although ethanol and acid catalysis (or *p*-toluenesulfonic acid in dried toluene) are required if the carbonyl compounds bear a strong electron-withdrawing group.[14] Improvements in yields of the aryl-hydrazones synthesis have been achieved when MW-irradiation at solvent-free conditions were used.[15] In some cases, a mixture of isomers (*Z* and *E*) is reported, mainly for reaction procedures that are only possible at high temperatures or for prolonged reaction periods.[16]

At the same time, many addition/condensation reactions have been demonstrated to occur in aqueous media (such as: Barbier and Mannich-type reactions, Diels–Alder cycloaddition, and Knoevenagel condensation).[17] Water is the cheapest and safest solvent available, and in the presence of reactive functional groups, protection and deprotection processes are often unnecessary. In fact, total solubility is required for efficient reaction in water, and thus, either organic co-solvents or heating are almost always employed.[18] Although Schiff and colleagues have reported that the presence of water is a disadvantage in imine synthesis, three works have shown that such reactions can be effective in completely aqueous media under mild conditions.[19] More recently, a protocol for the synthesis of aryl- and heterocyclic-hydrazones from aryl-hydrazine

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and aldehydes/ketones has been described with excellent yields using polystyrene sulfonic acid as a catalyst under MW irradiation (100 °C) in water.[20] However, the literature does not report the general synthesis of aryl-hydrazones (such as thiosemicarbazones, semicarbazones, or guanyl hydrazones) in aqueous media using ultrasound irradiation, nor the diastereoselectivities for these compounds.

Taking into account its application to studies of medicinal chemistry and its use for obtaining metal complexes, we describe here an efficient and rapid aryl-hydrazone synthesis process using ultrasound irradiation in an aqueous medium (Scheme 1).

The reactions were carried out in parallel on a microscale: 2 mL of water, 1 mmol of amine, 1 mmol of aryl-aldehyde/ketone and irradiated with ultrasound (low intensity) for 20–30 min at rt (30 °C), and the precipitate was then filtered and washed (in H_2O or EtOH).

First, the reaction of *p*-methoxybenzaldehyde (**1a**) and thiosemicarbazide (**2a**) was used as the model reaction in the simplest manner, by mixing the amines and the aldehydes directly in water, without adding any co-solvent or catalyst, at rt and irradiating for 20–30 min with ultrasound (Table 1). However, the yield was only 45% under these conditions (entry 1). When the reaction was run between 40 and 60 °C, the yields only improved to 55% and 65%, respectively (entries 2 and 3), and no improvement was observed in the case of solid aldehydes/ketones.

The effect of acidity is very important in this reaction, as it protonates the carbonyl carbon in the first step to produce the formation of imines.[5] Subsequently, acetic acid and inorganic salts were tested. $KHSO_4$ and NH_4Cl showed good yields comparable to acetic acid, and thus the use of acid conditions proved to be crucial, because of the effect of acidity and also in helping to produce total solubility of the carbonyl compounds. By contrast, under basic conditions, only a moderate yield was detected (entry 11). The addition of water-miscible co-solvents (0.5 mL, MeOH or EtOH) brought about a considerable improvement, mainly in the case of more lipophilic aldehydes/ketones.

When activated SiO_2 was used as catalyst[13] in water or ethanol (Table 1, entry 12), the yield was comparable with that produced using acetic acid, but generated more problems due to the precipitation accompanying the product, and, in this case, it was necessary to use toluene or ethyl acetate to separate aryl-hydrazone (**3a**) of the SiO_2. We observed that the application of ultrasound irradiation significantly increased the reaction rates and yields

Table 1
Aqueous medium-promoted condensation of 4-methoxybenzaldehyde (**1a**) with thiosemicarbazide (**2a**) via ultrasound irradiation

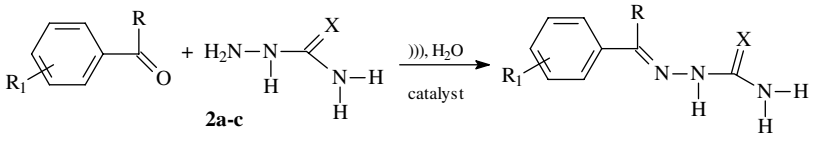
Entry	Catalyst	Co-solvent	Temp (°C)	Yield[a] (%)
1	None	None	30	45[b]
2	None	None	40	55[b]
3	None	None	60	65[b] (68)[g]
4	HOAc[c]	None	30	98
5	HOAc	None	60	98
6	None	EtOH[d]	60	75 (78)[g]
7	HOAc	EtOH[d]	30	98
8	NH_4Cl[e]	None	60	90
9	NH_4Cl	EtOH[d]	30	95
10	$KHSO_4$[f]	None	60	85
11	NaOAc	None	30	65
12	SiO_2 (5 equiv)	None	30	80 (85)[h]

[a] Determined as isolated products after 20 min.
[b] The starting materials were mostly recovered.
[c] Five drops (0.1 mL).
[d] A mixture (5:1) of water and co-solvent.
[e] Saturated solution (pH 5.0).
[f] Solution at 10% wt (pH 4.5).
[g] After 30 min.
[h] Using ethanol.

(20–30 min) compared to the traditional stirring for 4–6 h for the reaction between aldehyde **1a** and hydrazide **2a** (at rt).

The reaction can be carried out effectively with a wide variety of aldehydes/ketones and hydrazides using the optimal condition described in entry 4. Excellent results were obtained in most cases, with the formation of crystalline products and the same diastereoselectivity (only one isomer isolated).[21] Aromatic ketones proved to be less reactive and did not furnish the best yields, these being only moderate to good. Low yield (>20%) was obtained in the condensation reaction with benzophenone (showing reduced electrophilicity of the carbonyl carbon under powerful resonance) under the conditions of entry 5 (Table 1), even after 1 h. In the case of cinnaldehyde and arylthioacetaldehyde the use of a co-solvent (0.5 mL EtOH) or a large amount of acetic acid (0.5 mL) provided better results than the use of a complete aqueous medium. Furthermore, cinnaldehyde derivatives did not precipitate at the end of reaction, and had to be isolated by freezing them overnight and then filtering.

Similarly, the use of semicarbazide (chloridrate) or aminoguanidine [22] (carbonate) also furnished the desired products under the reaction conditions at good to excellent yields



2a: X=S thiosemicarbazide
2b: X = O semicarbazide
2c: X = NH aminoguanidine

Scheme 1. Synthetic route for aryl-hydrazones.