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# On the Use of $CeCl_3.7H_2O$ as a Catalyst for the Synthesis of Hydrazones Derived from Aromatic Aldehydes and Ketones †

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**Abstract:** Hydrazonation of acetophenones and benzaldehydes under $CeCl_3$ assistance was evaluated. The transformations entailed the use of the respective hydrazines ($H_2N–NH_2.HCl$, $Me_2N–NH_2$, or $Ph_2N–NH_2.HCl$) and $CeCl_3.7H_2O$ (2–5 mol %). The use of different solvents in a model reaction between 3,4-dimethoxybenzaldehyde and *N*,*N*-dimethylhydrazine was studied.

**Keywords:** hydrazonation; hydrazones; $CeCl_3$-assisted reaction

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## 1. Introduction

Hydrazones are a class of organic compounds with the structure $R^1R^2C=N–NR^3R^4$ (Figure 1). These prominent compounds have been widely used in the bioconjugation and functionalization of polymers, due to the ease of introducing these functions into biomolecules and probes [1]. Hydrazones have exerted a dominant influence in many other research areas as well. For example, these compounds have been used extensively in materials science for the synthesis of molecular switches [2], hydrogels [3], sensors, and fluorophores [4].

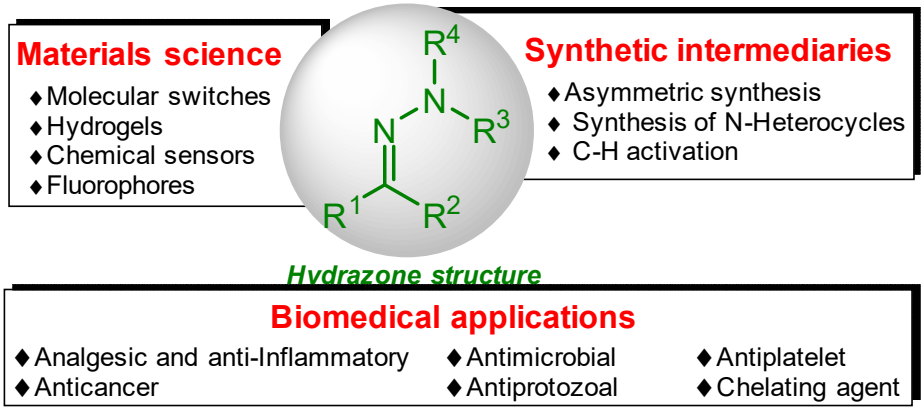
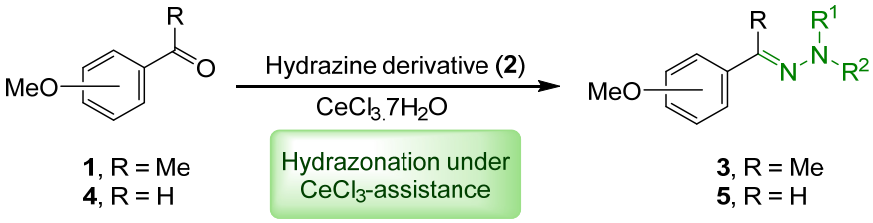



**Figure 1.** General structure and applications of hydrazones.

Other characteristics of the hydrazones are their diverse biomedical applications [5,6] and their utility as high-value synthetic intermediates in asymmetric synthesis [7], synthesis of N-heterocycles [8], and C–H activation [9]. Indeed, these types of scaffolds are key intermediaries in a variety of chemical transformations, and can be classified as versatile building blocks for organic synthesis. Therefore, the development of new synthetic approaches to such compounds is considered of high relevance.

On the other hand, the synthesis of hydrazones is mainly carried out by a reaction between hydrazine derivatives and aldehydes/ketones under the promotion of Brønsted acids [10,11] in a protic solvent, or through the use of a Dean–Stark trap [12,13], which usually requires long heating times. In particular, Lewis acids have been seldom employed for their preparation [14,15].

Recently, our group reported the use of oximes as synthetic intermediates for the total synthesis of natural isoquinolines [16–18]. The formation of these oximes was carried out through the use of $CeCl_3.7H_2O$ as an efficient and eco-friendly promoter, as developed by Cortés et al. [19]. Against this background, we have studied $CeCl_3$-assisted hydrazonation of acetophenones and benzaldehydes, in order to explore a new eco-friendly approach to this reaction (Scheme 1).

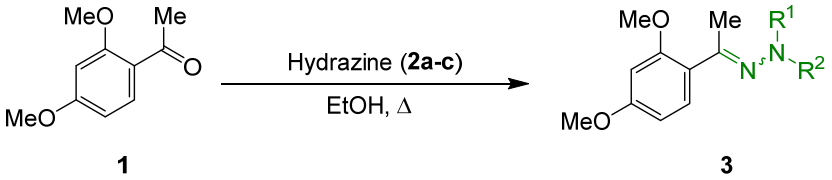



**Scheme 1.** $CeCl_3$-assisted hydrazonation of acetophenones and benzaldehydes.

## 2. Results and Discussion

In the synthesis of 6-*O*-methyl anciscochine, an alkaloid isolated from *Ancistrocladus tectorius*, it was projected to use hydrazone **3** as a potential ortho-directing substrate in the C($sp^2$)-H activation reaction [13]. For the preparation of these compounds, 2,4-dimethoxyacetophenone (**1**) was subjected to hydrazonation with hydrazine hydrochloride **2a** ($H_2N$–$NH_2$.HCl), *N*,*N*-dimethylhydrazine **2b** ($Me_2N$–$NH_2$), and *N*,*N*-diphenylhydrazine hydrochloride **2c** ($Ph_2N$–$NH_2$.HCl) in EtOH at reflux for 24 h, to provide good isolated yields (63–80%) of the expected hydrazones **3a–c** (Table 1, entries 1, 3, and 5).

**Table 1.** Preparation of acetophenone-derived hydrazones (**3a–c**).



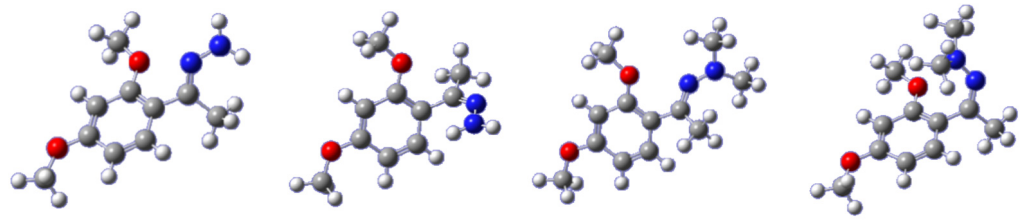

| Entry | $R^1$ | $R^2$ | Hydrazine (Equiv.) | Additive (Equiv.) | *t* (h) | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | H | H | $H_2NNH_2$.HCl (2.0) | NaOAc (2.5) | 24 | 74 |
| 2 | H | H | $H_2NNH_2$.HCl (2.0) | NaOAc (2.5), $CeCl_3.7H_2O$ (0.05) | 12 | 20 |
| 3 | Me | Me | $Me_2NNH_2$ (2.5) | AcOH (1.5) | 24 | 63 |
| 4 | Me | Me | $Me_2NNH_2$ (2.5) | $CeCl_3.7H_2O$ (0.05) | 12 | 15 |
| 5 | Ph | Ph | $Ph_2NNH_2$.HCl (2.0) | NaOAc (2.5) | 24 | 80 |
| 6 | Ph | Ph | $Ph_2NNH_2$.HCl (2.0) | NaOAc (2.5), $CeCl_3.7H_2O$ (0.05) | 12 | 58 |

[a] These compounds were obtained as mixtures of *E* and *Z* isomers. *t*: time.

In this same work, we were interested in evaluating the assistance of $CeCl_3 \cdot 7H_2O$ in these reactions (Table 1, entries 2, 4, and 6). Interestingly enough, application of the cerium(III)-assisted protocol to the preparation of the acetophenone hydrazones proved to be an unsuitable alternative, since hydrazones **3a–c** were obtained with lower yields of 20%, 15%, and 58%, respectively. This decrease in yield could be related to the hydrolytic instability of hydrazones derived from acetophenone with respect to the $H_2O$ molecules from the Ce(III) salt, as well as the assistance of $CeCl_3$ in their hydrolysis [20].

On the other hand, *E*/*Z* geometric isomers of hydrazones **3a–c** were determined by $^1H$ NMR analysis, and Nuclear Overhauser Effect (NOE) experiments on the hydrazones revealed signal enhancement between the protons of the methyl (**3b**) and *o*-phenyl (**3c**) substituents and H-6, suggesting a plausible *Z*-configuration for their major stereoisomers [21,22].

The unexpected geometry observed could be attributed to electronic factors of the substituents at both ends of the N–N bond [17]. Therefore, in order to validate our hypothesis, a computational study of the conformations of the hydrazones was carried out. The conformational analysis of *E* and *Z* isomers of hydrazones **3a–c** revealed the most stable conformer; fully optimized structures of *E* and *Z* isomers are shown in Figure 2.



***E*-3a** −649.34387008 a.u.

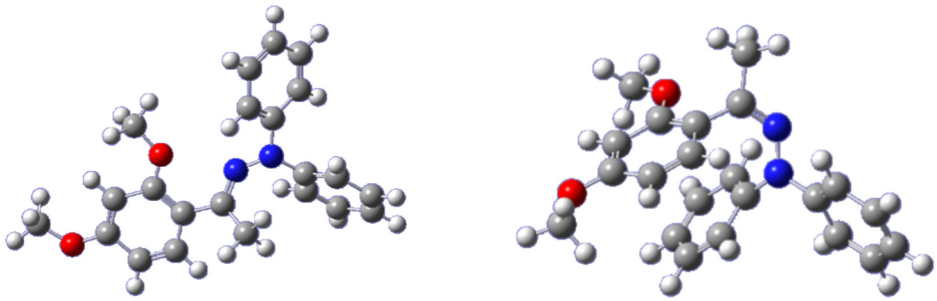
***Z*-3a** −649.34639697 a.u.

***E*-3b** −727.94187800 a.u.

***Z*-3b** −727.98909115 a.u.

ΔE = 1.58 kcal/mol

ΔE = 29.62 kcal/mol



***E*-3c** −1111.40635828 a.u.

***Z*-3c** −1111.40708154 a.u.

ΔE = 0.45 kcal/mol

**Figure 2.** Optimized geometrical structures and calculated total energies (Hartree) of hydrazones **3a–c** at the B3LYP/6-31G(d) level of theory.

The lowest energy conformers presented a twisted geometry to avoid steric repulsions between the phenyl ring and the =N–$NR_2$ group. In all three cases, the results of energy analysis showed that the *Z* isomers (i.e., the conformers with the lowest total energy resulting from the B3LYP/6-31G(d) calculations for the gas phase) are more stable than the corresponding lowest-energy *E* isomers.

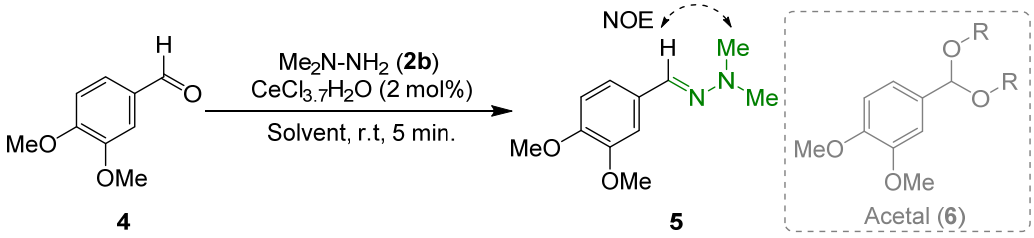
The energy differences between the *E* and *Z* isomers found for hydrazones **3a** and **3b** were 1.58 and 29.62 kcal/mol, respectively. Nevertheless, for hydrazone **3c**, the difference was smaller (0.45 kcal/mol). Thus, the density functional theory (DFT) calculations predicted a higher stability for the *Z*-isomers compared to the corresponding *E*-isomers,

which is in agreement with the NOE experiments performed on acetophenone hydrazones **3a–c** [18].

On the other side, the performance of the reaction between 3,4-dimethoxy benzaldehyde (**4**) and *N*,*N*-dimethylhydrazine (**2b**) under $CeCl_3.7H_2O$-assistance (2 mol %) for the formation of *N*,*N*-dimethylhydrazone **5** was also evaluated (Table 2). The hydrazonation was carried out in different solvents at room temperature, affording (*E*)-**5** with 14–97% yield after stirring for only 5 min [23,24].

In some cases, minor amounts of the starting material and the formation of acetals (**6**) as undesired products were detected (Table 2, entries 1–3) as an unfavorable effect of the solvent, related to its nucleophilicity and the possible assistance of cerium(III) in the acetalization reaction. For example, the diethyl acetal (R = Et) was isolated with a yield of 22% (Table 2, entry 2), and its structure was confirmed by $^1$H NMR analysis, where it exhibited a characteristic singlet corresponding to the methine hydrogen [-C*H*(OEt)] at δ = 5.42 ppm. Rewardingly, the best condition found for this transformation was when *tert*-butanol was employed as a solvent (Table 2, entry 4).

**Table 2.** Screening conditions for the formation of *N*,*N*-dimethylhydrazone (**5**).




| Entry | Solvent | 5 (%) | 4 (%) | Acetal (%) |
|---|---|---|---|---|
| 1 | MeOH | 79 | 6 | traces |
| 2 | EtOH | 71 | 4 | 22 |
| 3 | *i*-PrOH | 81 | 16 | traces |
| 4 | *t*-BuOH | 97 | 0 | 0 |
| 5 | THF | 14 | 63 | 0 |
| 6 | MeCN | 31 | 53 | 0 |

Furthermore, this protocol was tested for the formation of the *N*,*N*-dimethylhydrazone hydrazone of an acetophenone (Scheme 2). Initially, 3,4-dimethoxyacetophenone (**7**) was subjected to hydrazonation with *N*,*N*-dimethylhydrazine (**2b**) and $CeCl_3{\cdot}7H_2O$ (2 mol %) in methanol at room temperature for up to 24 h without showing product formation. After heating at 60 °C for 12 h, only 20% of *N*,*N*-dimethylhydrazone **8** was isolated; however, with the use of *tert*-butanol, the yield increased to 63%.


| Solvent | **8** (%) | **7** (%) |
|---|---|---|
| MeOH | 20 | 60 |
| *t*-BuOH | **63** | 20 |

**Scheme 2.** Preparation of acetophenone hydrazone **8**.

In general, the results suggest that this protocol could be an advantageous alternative for the formation of aldehyde hydrazones, while the preparation of acetophenone derivatives may require more drastic conditions and the use of specicific solvents like *t*-BuOH.

## 3. Experimental Section

### *3.1. General Experimental Details*

The reactions were monitored by TLC, using silica gel $GF_{254}$ plates supported on aluminum and run with different hexane–EtOAc solvent mixtures containing $Et_3N$ (1% *v*/*v*). The chromatographic spots were detected by exposure of the plates to 254 nm UV light, and by spraying with an ethanolic *p*-anisaldehyde/sulfuric acid reagent. The flash column chromatographies were run with silica gel 60 H (particle size < 55 μm), eluting with hexane–EtOAc mixtures under positive pressure, and employing gradient of solvent polarity techniques.

The nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 NMR spectrometer at 300.13 ($^1$H) and 75.48 ($^{13}$C) MHz. $CDCl_3$ was used as solvent, and the chemical shifts are informed in parts per million (ppm) in the δ scale. TMS was used as the internal standard (resonances of $CHCl_3$ in $CDCl_3$: δ 7.26 and 77.0 ppm for $^1$H and $^{13}$C NMR, respectively).

### *3.2. General Procedure for the Preparation of* N,N-*Dimethylhydrazones*

A mixture of the corresponding carbonyl compound (0.2 mmol), *N*,*N*-dimethyl hydrazine (0.25 mmol) and $CeCl_3{\cdot}7H_2O$ (0.004 mmol) in *tert*-butanol (1 mL), was stirred or heated until complete consumption of the starting material was observed. The solvent was then evaporated and the residue was purified by column chromatography, in order to produce the corresponding *N*,*N*-dimethylhydrazones.

### *3.3. Computational Details*

Initially, a conformational search was performed using the corresponding module of HyperChem v. 8.0 with the MM+ method. Then the selected structures were used as input geometries for the Gaussian-09 program package, and successively re-optimized by using the density functional theory (DFT) at the B3LYP/6-31G(d) level of theory. The selected geometries of these rotamers correspond to the energy minima in the gas state.

## 4. Conclusions

An efficient method for the preparation of *N*,*N*-dimethylhydrazones was developed. We have collected evidence on the assistance of $CeCl_3.7H_2O$ in the hydrazonation of 3,4-dimethoxybenzaldehyde with *N*,*N*-dimethylhydrazine, which resulted in a shortened reaction time when compared with previous protocols. A visible solvent effect was observed during the preparation of *N*,*N*-dimethylhydrazones derived from benzaldehyde. On the other hand, this protocol was not so efficient when acetophenones like 3,4-dimethoxyacetophenone were reacted with *N*,*N*-dimethylhydrazine.

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