

# Chlorodinitrophenylhydrazine, a useful crystalline agent for absolute configuration determination of various chiral ketones

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**Abstract**—For the determination of absolute configuration of various chiral ketones, we examined some hydrazines having a heavy atom as crystalline auxiliaries, and found that 2-chloro-4,6-dinitrophenylhydrazine is a useful crystalline agent for carbonyl compounds. Chiral hydrazones prepared from the hydrazine and various chiral ketones gave suitable single crystals for X-ray crystallographic analysis. The absolute configurations of the hydrazones were determined by X-ray crystallographic analysis using anomalous dispersion effect of the chlorine atom. The hydrazine is a useful crystalline agent for absolute configuration determination of various chiral ketones.

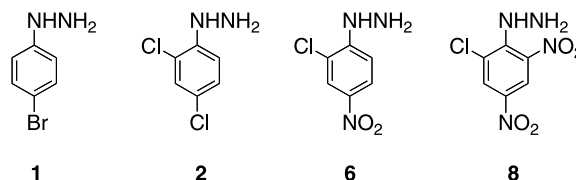
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## 1. Introduction

Optically active  $\alpha$ -substituted ketones ( $\alpha$ -chiral ketones) are versatile intermediates for the synthesis of natural products, especially in pheromone synthesis.<sup>1</sup> A number of methods for the synthesis of  $\alpha$ -chiral ketones have been reported, for example, stereoselective  $\alpha$ -alkylation<sup>2</sup> and enantioselective protonation of enolates and enols.<sup>3</sup> Enzymatic transformations to obtain  $\alpha$ -chiral ketones have also been reported, for example, hydrolysis of enol esters<sup>4</sup> and reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds (enones).<sup>5</sup> The enantioselective protonation of enol esters<sup>6</sup> and enol ethers<sup>7</sup> using a catalytic antibody has also been reported. We have developed the method for the asymmetric synthesis of  $\alpha$ -chiral ketones by the reduction of enones with baker's yeast<sup>8</sup> or a carbon–carbon double bond reductase purified from baker's yeast.<sup>9</sup> However, few studies are found in the literature for the direct method to determine the absolute configurations of these chiral ketones. They have been determined by derivation to the known compounds<sup>2g,6</sup> or assumed from empirical rules.<sup>2f,4c,10</sup>

X-ray crystallographic analysis is the only method to determine the absolute configuration of a molecule. The anomalous dispersion effect of a heavy atom must be used for the determination of the absolute configuration. However, in most cases, the chiral ketones reduced from

the corresponding enones are oily substances and contain no heavy atom, so that single crystals must be prepared with a certain crystalline auxiliary having a heavy atom. Hydrazines are well-known to be good crystalline agents for ketones. It is easy that a halogen atom as a heavy atom is introduced into a phenyl ring in the phenylhydrazine. Thus, a phenylhydrazine derivative having (a) halogen atom(s) is employed as a crystalline agent (Scheme 1). Recently, we reported some preliminary results on the determination of absolute configuration of chiral ketones.<sup>11</sup> This paper will describe the details and application of this method.



Scheme 1.

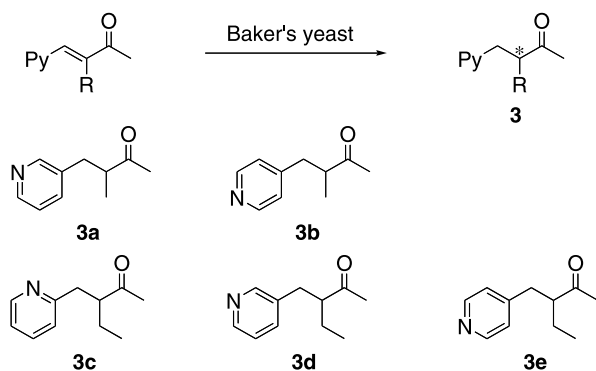
## 2. Results and discussion

### 2.1. Design and synthesis of crystalline agents

At first, commercial 4-bromophenylhydrazine (**1**) and 2,4-dichlorophenylhydrazine (**2**) were used as crystalline agents, and hydrazones of chiral ketones were prepared with them under acidic conditions. All chiral ketones here studied (**3a–e**) were obtained by baker's yeast reduction of enones (Scheme 2).<sup>8c</sup> The yields of hydrazone (**4**, **5c,e**) are

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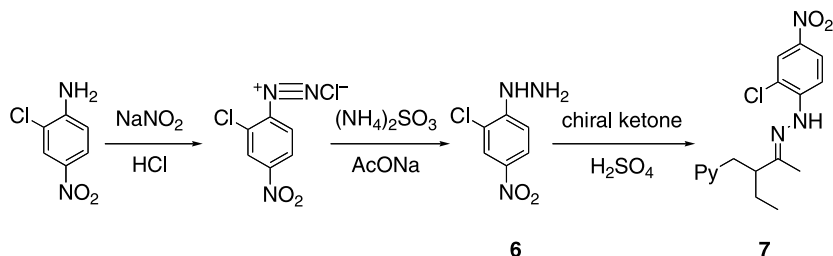
Scheme 2.

listed in Table 1. Unfortunately, these hydrazones did not give suitable single crystals for X-ray crystallographic analysis.

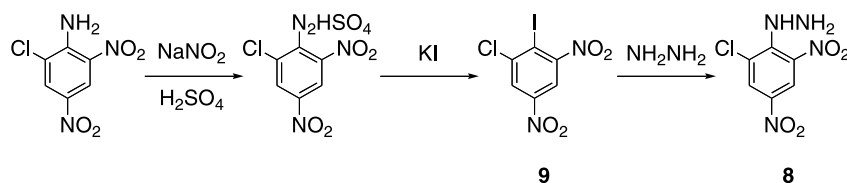
Table 1. Yields (%) of hydrazone

Ketone	Hydrazone			
	1	2	6	8
3a	4 (70)			10a (64)
3b				10b (75)
3c		5c (63)	7c (40)	10c (31)
3d			7d (61)	10d (80)
3e		5e (35)	7e (24)	10e (86)
11				14 (91)
12				15 (59)
13				16 (80)

Since, a nitro group is also known to have a good crystallinity, introduction of a nitro group into the hydrazone is expected for more crystallinity. Therefore, 2-chloro-4-nitrophenylhydrazine (**6**) was designed and synthesized. It has a chlorine atom as a heavy atom and a nitro group for a crystallinity. Its synthesis was carried out in the conventional method (Scheme 3). 2-Chloro-4-nitrophenylhydrazones (**7**) were prepared from the corresponding hydrazine **6** and various chiral ketones (Table 1), but they did not give good single crystals as in the cases of **4** and **5**.



Scheme 3.



Scheme 4.

2-Chloro-4,6-dinitrophenylhydrazine (**8**) having two nitro groups was designed with the hope of more crystallinity.<sup>12</sup> 2-Chloro-4,6-dinitroaniline is a weak base because of two nitro groups and a chlorine atom, so that diazotization does not occur with a conventional way. Therefore, the aniline dissolved in hot acetic acid was diazotized with nitrosyl sulfate prepared from sodium nitrite and sulfuric acid,<sup>13</sup> and iodinated with potassium iodide to afford 1-chloro-2-iodo-3,5-dinitrobenzene (**9**). It was stirred with hydrazine monohydrate in methanol at room temperature to give the desired hydrazine **8** (Scheme 4).<sup>14</sup>

## 2.2. Determination of the absolute configuration of chiral ketones

The reaction of hydrazine **8** with chiral ketones in the presence of an acid catalyst gave chiral hydrazones **10** in good yields as shown in Table 1. The ketone **3a** and **3b** having a methyl group at the  $\alpha$ -position of carbonyl group were racemized slowly under a strong acidic condition. The conditions to prevent the racemization were studied and found that ee of the chiral ketone kept with a catalytic amount of sulfuric acid. Therefore, syntheses of hydrazone with chiral ketones **3a** and **3b** having a methyl group at the  $\alpha$ -position of carbonyl group were carried out under that condition (condition A). Syntheses with other ketones were done under a strong acid condition (condition B). Synthesized 2-chloro-4,6-dinitrophenylhydrazone derivatives (**10a–e**) were recrystallized from various solvents to obtain single crystals. Single crystals of the hydrazone were subjected to X-ray crystallographic analysis in order to elucidate their absolute configurations using the anomalous dispersion effect of a chlorine atom. The ORTEP drawings of **10a–e** are shown in Figures 1–5, respectively. Crystallographic data of the above analysis are listed in Table 2.

Except for **10c**, the structures of hydrazones exhibit (*E*)-forms at the carbon–nitrogen double bond, and the production of single isomer was confirmed by <sup>1</sup>H NMR experiments. As judged by <sup>1</sup>H NMR experiment, hydrazone **10c** consisted of two isomers, which should be (*E*)- and (*Z*)-forms. The ratio of isomers was about 1/1 estimated by

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