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6-Chloro-2,4-dinitrophenylhydrazine as a useful crystalline agent for the determination of absolute configuration

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Abstract—For the determination of absolute configuration, we designed and synthesized some hydrazines as crystalline auxiliaries having a heavy atom, and found that 6-chloro-2,4-dinitrophenylhydrazine is a useful crystalline agent for chiral carbonyl compounds. The absolute configurations of chiral hydrazones prepared from the hydrazine and chiral ketones were determined by X-ray crystallographic analysis. © 2002 Elsevier Science Ltd. All rights reserved.

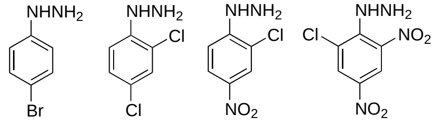
Chiral carbonyl compounds (chiral ketones) are versatile starting materials for the synthesis of various chiral compounds.[1,2] We have developed the method for the asymmetric synthesis of chiral ketones by the reduction of α,β-unsaturated carbonyl compounds (enones) with baker's yeast or carbon–carbon double bond reductases purified from baker's yeast.[3–5] 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[6,7] or assumed from empirical rules.[8–10]

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, the chiral ketones reduced from the corresponding enones are oily substances and contain no heavy atom, so that single crystals must be prepared with the crystalline auxiliary. Since hydrazines are known to be good crystalline agents for ketones, we designed and synthesized some hydrazines suitable for the crystallographic analysis.

Phenylhydrazine derivatives used as crystalline agents were listed in Scheme 1. All these hydrazines have (a) heavy atom(s). First, hydrazones derived from commercially available hydrazines **1** and **2** were prepared, but they did not give suitable single crystals for X-ray crystallographic analysis. We designed and synthesized hydrazine **3** having a nitro group with the hope of more crystallinity, but its derivatives did not give good single crystals as in the cases of **1** and **2**. Hydrazine **4** was synthesized from commercial 6-chloro-2,4-dinitroaniline in three steps and the total yield was 58%.[11] Since 6-chloro-2,4-dinitroaniline is a weak base, diazotization does not occur with a conventional method. Therefore, the aniline dissolved in hot acetic acid was diazotized with nitrosyl sulfate,[12] and iodinated with potassium iodide to afford 5-chloro-4-iodo-1,3-dinitrobenzene. It was stirred with hydrazine monohydrate at room temperature to give the desired hydrazine.[13]

The chiral ketones here studied were obtained from the stereoselective reduction of the carbon–carbon double bond in the corresponding enones with baker's yeast.[14,15]

Hydrazones **6** were synthesized from hydrazine **4** and chiral ketones **5** in the presence of an acid catalyst. Their yields were shown in Table 1. Since chiral ketones, **5a** and **5b**, were racemized slowly under a strong acid condition, syntheses of their hydrazones are carried out with catalytic amount of sulfuric acid. On recrystallization under various conditions, hydrazones **6**



1 **2** **3** **4**

Scheme 1. Phenylhydrazine derivatives.

Keywords: phenylhydrazine; chiral ketones; X-ray crystallography; absolute configuration.

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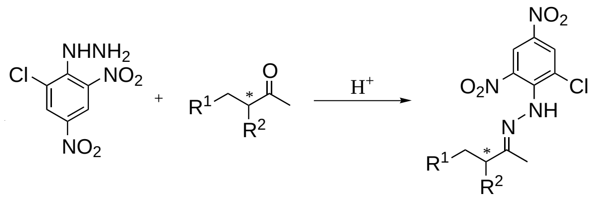
Table 1. Yields of hydrazone



4 **5a-f** **6a-f**

	R^1	R^2	Yield (%)	Conditions
a	3-Py	Me	65	A
b	4-Py	Me	75	A
c	2-Py	Et	31	B
d	3-Py	Et	80	B
e	4-Py	Et	86	B
f	Me	Me	91	A

Reaction conditions: (A) Hydrazine **4**, 0.43 mmol; chiral ketone **5**, 0.43 mmol; H_2SO_4, 5 drops; H_2O, 1 mL; EtOH, 17 mL. (B) Hydrazine **4**, 0.23 mmol; chiral ketone **5**, 0.23 mmol; H_2SO_4, 0.25 mL; H_2O, 0.37 mL; EtOH, 2 mL.

derived from all ketones **5a–f** gave suitable single crystals. Consequently, we found that hydrazine **4** is the useful crystalline agent.

Single crystals of the hydrazones were subjected to X-ray crystallographic analysis in order to elucidate their absolute configurations using the anomalous dispersion effect of a chlorine atom.[16] The ORTEP drawing of **6a** is shown in Fig. 1. The structure of **6a** exhibits (*E*)-form at a carbon–nitrogen double bond, and the production of single isomer was confirmed by ^{1}H NMR experiment. These phenomena are similar to those observed for other hydrazones except for **6c**. As judged by ^{1}H NMR experiment, hydrazone **6c** consisted of two isomers, which should be (*E*)- and (*Z*)-forms. The ORTEP drawing of (*Z*)-**6c** illustrated in Fig. 2 shows that there exists a hydrogen bond between N in the pyridine ring and NH in the hydrazone moiety, the length of which is 2.91 Å. Because of the hydrogen bond, the (*Z*)-form should be stabilized. Furthermore, this method was applied to a ketone without any aromatic ring, i.e. **5f**. Hydrazone **6f** also gave single crystals, and the ORTEP drawing of **6f** is shown in Fig. 3.

The absolute configurations of all hydrazones **6a–f** were determined to be *S* by Flack parameters[17] and intensities comparisons of Bijvoet pairs. These configurations were determined by the anomalous dispersion effect of a chlorine atom in the crystalline auxiliary. Therefore, the absolute configurations of the chiral ketones obtained by baker's yeast reduction determined to be *S*.

It should be noted that 6-chloro-2,4-dinitrophenylhydrazine (**4**) is a useful crystalline agent to determine the absolute configuration of chiral ketones. This method can be applied to both of aromatic and aliphatic ketones, and is helpful for the determination the absolute configuration of chiral ketones. Further application of this hydrazine **4** to determine the absolute configurations of various chiral carbonyl compounds is currently in progress.

Crysrallographic data (including structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 172429 for **6a**, CCDC 172430 for **6b**, CCDC 172427 for **6c**, CCDC 172428 for **6d**, CCDC 172432 for **6e**, and CCDC 172431 for **6f**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road,

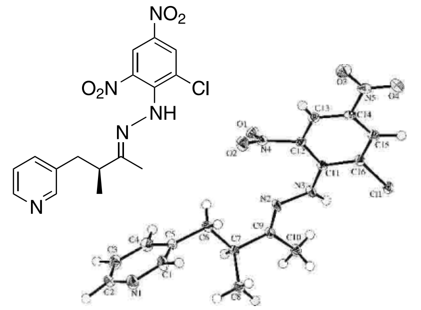


Figure 1. ORTEP drawing of **6a** with displacement ellipsoids at 50% probability level.

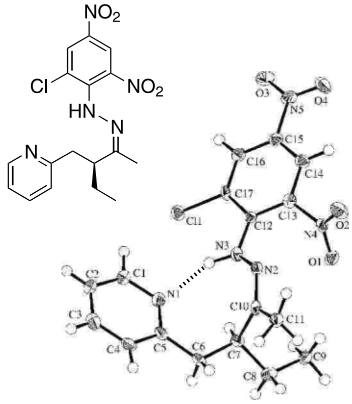


Figure 2. ORTEP drawing of (*Z*)-**6a** with displacement ellipsoids at 50% probability level. The hydrogen bond is indicated by a broken bond.

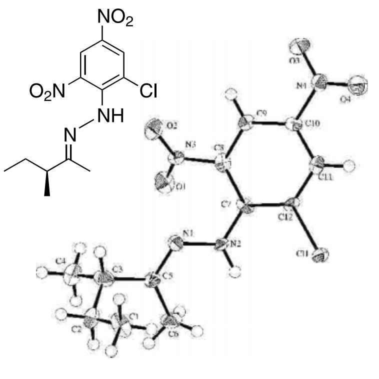


Figure 3. ORTEP drawing of **6f** with displacement ellipsoids at 50% probability level.

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References

1. For a review, see: Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298 and references cited therein.
2. Kan, K.; Miyama, A.; Hamaguchi, S.; Ohashi, T.; Watanabe, K. *Agric. Biol. Chem.* **1985**, *49*, 207–210.
3. Kawai, Y.; Saitou, K.; Hida, K.; Ohno, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2143–2144.
4. Kawai, Y.; Saitou, K.; Hida, K.; Dao, D. H.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2633–2638.
5. Kawai, Y.; Hayashi, M.; Inaba, Y.; Saitou, K.; Ohno, A. *Tetrahedron Lett.* **1998**, *39*, 5225–5228.
6. Mayers, A. I.; Williams, D. R.; White, S.; Erickson, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 3088–3093.
7. Fujii, I.; Lerner, R. A.; Janda, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 8528–8529.
8. Mayers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081–3087.
9. Kume, Y.; Ohta, H. *Tetrahedron Lett.* **1992**, *33*, 6367–6370.
10. Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1063–1066.
11. ^{1}H NMR (DMSO-d_6/$CDCl_3 = 1/2$, TMS): δ 4.54 (1H, br), 4.57 (1H, br), 8.23 (1H, br), 8.32 (1H, br), 8.59(1H, br). Anal. calcd for $C_6H_5ClN_4O_4$: C, 30.98; H, 2.17; N, 24.09. Found: C, 30.76; H, 2.23; N, 23.86%.
12. Hodgson, H. H.; Walker, J. *J. Chem. Soc.* **1933**, 1620–1621.
13. Borsche, W. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 669–684.
14. Kawai, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron: Asymmetry*, in press.
15. Chiral alkyl ketone **5f** was supplied by Daicel Chemical Industries, Ltd.
16. Kawai, Y.; Hayashi, M.; Tokitoh, N. Crystallographic data will be published elsewhere.
17. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.