Crystal and molecular structure of N-(S)-α-bromophenylacetyl-(S)-proline methyl ester, C_{14}H_{16}NO_{3}Br

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Abstract

The structure of the title compound, C_{14}H_{16}NO_{3}Br, was determined by X-rays. \( M_r = 326.19 \), tetragonal, space group \( P4_3 \), \( a = 9.2030(6) \), \( c = 16.9979(9) \) Å, \( V_c = 1439.6 \) Å\(^3\), \( Z = 4 \), \( D_x = 1.51 \) Mg m\(^{-3}\). Cu K\(\alpha\) radiation (graphite crystal monochromator, \( \lambda = 1.54184 \) Å), \( \mu(\text{Cu } K\alpha) = 39.49 \) cm\(^{-1}\), \( T = 290 \) K. Final conventional \( R \)-factor = 0.039, \( R_w = 0.052 \) for 2566 unique reflections and 204 variables. The structure was solved using MULTAN and DIRDIF. The presence of bromine in the structure enabled the unambiguous assignment of the space group. The synthesis to prepare the title compound yields only one stereoisomer with the S-configuration, caused by the chirality of the S-proline methyl ester.

Introduction

The preparation of enantiomerically pure compounds is an increasingly important challenge in modern organic synthesis. The use of chiral catalysts offers one of the most promising approaches. The most innovative advancements have been made in the applications of metalloorganic chemistry in which
the central metal atom together with a coordinated chiral ligand is used to guide, control, and orient the stereochemical course of a reaction.

Our aim was to investigate some chiral hydroxamic acids for their ability to induce chirality in various transition metal-catalyzed reactions.

Hydroxamic acids 1 (see scheme 1) are compounds characterized by one or more oxidized amide bonds. They have been isolated mainly from microbial sources (Neilands, 1967, 1973; Maehr, 1971). However, recently they were also found in human and animal tumors (Neunhoeffer, 1970; Herscheid et al., 1986).

The natural products featuring 1 act variously as potent growth factors, antibiotics, antibiotic antagonists, tumor inhibitors, or cell-division factors (Neilands, 1967, 1973; Maehr, 1971). With regard to their physical properties, it is worth mentioning that hydroxamic acids are relatively weak acids; pKₐ 7–12 (Exner and Simon, 1965; Chatterjee, 1978; Agrawal, 1979); they form stable complexes with a great number of transition metals (Chatterjee, 1978; Agrawal, 1979; Fritz and von Stetten, 1973; Raymond et al., 1984).

In this respect we became intrigued by the potential usefulness of chiral hydroxamic acids as ligands in asymmetric, metal-catalyzed reactions. One of the ligands we have selected is 5 (see scheme 2), an anhydride of S-proline and N-hydroxyphenylglycine. This target compound was chosen because of its rigidity and the presence of an aromatic side chain. It was our aim to study the influence of the chirality at C(6) on the inductive power of 5.

The synthesis of 5 (Smits et al., 1986) starts with N-acylation of S-proline methyl ester 2 with α-bromophenylacetyl bromide 3. As racemic 3 was used, we expected the acylated product 4 to consist of a mixture of 4a and 4b. However, to our surprise only one stereoisomer—of unknown chirality at C(α)—was isolated in 88% yield. Obviously, the chirality of proline methyl ester causes selective formation of one stereoisomer. This inductive process must involve heterolysis or homolysis of either the C(α)–H or C(α)–Br bond. In order to study the mechanism of this asymmetric transformation (Zeegers and Otten-