Solvent-free Friedel-Crafts Reaction for Regioselective Synthesis of Ethyl (9-Anthryl)glyoxylate and Chiral Resolution of (±)-(9-Anthryl)hydroxyacetic Acid

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Z. Naturforsch. 2008, 63b, 77 – 82; received July 9, 2007

A green chemistry-based highly regioselective synthesis of ethyl (9-anthryl)glyoxylate was achieved by solvent-free Friedel-Crafts reaction at r. t. Several derivatives of ethyl (9-anthryl)glyoxylate were also synthesized. Ethyl (9-anthryl)hydroxyacetate was obtained almost quantitatively by reduction of ethyl (9-anthryl)glyoxylate with NaBH₄, and (9-anthryl)methoxyacetic acid was prepared by methylation of ethyl (9-anthryl)hydroxyacetate with CH₃I in the presence of Ag₂O and hydrolysis of ethyl (9-anthryl)methoxyacetate. The hydrolysis of ethyl (9-anthryl)hydroxyacetate gave racemic (9-anthryl)hydroxyacetic acid, and the racemate was successfully resolved by crystallization of the diastereomeric salts resulting from the reaction of (±)-(9-anthryl)hydroxyacetic acid with (−)-ephedrine. As a byproduct, crystals containing racemic (±)-(9-anthryl)hydroxyacetate and protonated (−)-ephedrine were isolated and their structures determined by X-ray diffraction.

Key words: Ethyl (9-Anthryl)glyoxylate, (9-Anthryl)hydroxyacetic Acid, Regioselectivity, Chiral Resolution, X-Ray Structure Analysis

Introduction

In the last decade, the interest in determining the absolute stereochemistry of chiral organic compounds stems from the widely recognized fact that the stereochemistry often determines important chemical, physical, biological, and pharmaceutical properties of the compounds [1]. Several instrumental methods exist for the determination of the absolute configuration of chiral organic compounds, such as X-ray crystallography and chiroptical methods etc. Due to appealing advantages based on NMR spectroscopy for these researches, the chiral recognition by NMR known as the “Mosher method” is widely used [2, 3]. The method uses α-methoxy-α-trifluoromethyl-α-phenylacetic acid as the chiral derivatizing reagent for the determination of the absolute configuration of secondary alcohols by NMR [4]. Many efforts to develop chiral derivatizing agents [5] that are useful to assign the absolute configuration of different substrates have been described [6, 7], and arylmethoxyacetic acids (see Fig. 1) containing naphthyl or anthryl systems [8 – 11] are widely used to assign the absolute configuration of chiral organic compounds by NMR with a modified Mosher method [12].

In general, all these compounds cause a larger magnetic shielding than α-methoxy-α-phenylacetic acid which was used as the chiral derivatizing reagent in the past [9, 13], thus better separation of the signals in ¹H NMR spectra is observed for the enantiomers of a substrate. This effect is particularly important when enantiomerically pure (9-anthryl)methoxyacetic acid (9AMAA(H)) or ethyl (9-anthryl)hydroxyacet-
Scheme 1. Synthesis of ethyl (9-anthryl)glyoxylate.

Results and Discussion
The synthesis of ethyl (9-anthryl)glyoxylate (1) and its derivatives 2–5

Ethyl (9-anthryl)glyoxylate is the precursor of 9AHA and 9AMAA(H). Though Riguera et al. have reported that 1 can be prepared from anthracene and ethyl oxalyl chloride [13], they have not described the procedure in detail and have not mentioned whether the reaction was conducted in solution or in the solid phase. We attempted to find a convenient and environmentally friendly way to prepare the precursor of these reagents. Initially, we synthesized 1 using the traditional liquid method. Due to low solubility of anthracene in most organic solvents, it was found that this synthesis method exhibited some drawbacks: the use of noxious organic solvents, such as CS₂ etc., a big reaction volume, the long reaction time and the low yield (< 10%). In addition, some byproducts, such as ethyl (1-anthryl)glyoxylate and ethyl (2-anthryl)glyoxylate, were found.

In the face of demands for green and ecologically friendly organic synthesis, solvent-free techniques hold a strategic position as solvents are very often toxic, expensive, problematic to use and to remove. In the absence of solvent, however, reaction pathways, as well as the products formed, may be modified significantly. Ghiacci et al. reported that a solvent-free reaction can shorten the reaction time and increase the yield [14]. In order to avoid the drawbacks of the traditional synthesis in liquid phase, our laboratory adopted the method of the solvent-free Friedel-Crafts acylation reaction of anthracene to prepare 1 (Scheme 1).

Initially, the yield (30–40%) was not as high as expected, but we found that when 0.2–0.5 equivalents of 1-methyl-2-pyrrolidone were added to the reaction system as an assistant catalyst, a highly regioselective synthesis of 1 was achieved in 92.5% yield without producing other isomers, such as ethyl (1-anthryl)glyoxylate and ethyl (2-anthryl)glyoxylate. In previous reports, most Friedel-Crafts acylation reactions were conducted in organic solvents. Our method is an efficient solvent-free Friedel-Crafts acylation reaction which can be performed successfully at r.t.

We used the reduction of 1 to obtain 9AHA (2), then transformed 9AHA to 9AMAA(H) (4) and 9AHAA(H) (5) by methylation and hydrolysis reactions (Scheme 2). Compound 1 was reduced almost quantitatively with NaBH₄ in EtOH at r.t. to give racemic 9AHA. Ethyl (9-anthryl)methoxyacetate was prepared by methylation of 9AHA(H) with CH₃I in the presence of Ag₂O. 9AMAA(H) and 9AHAA(H) were obtained by hydrolysis of their precursors. All these reactions were achieved in high yield.

Resolution of racemic 9AHAA (5) by crystallization with (−)-ephedrine

Several methods exist for the resolution of racemates, such as separation by chiral chromatography, enzymatic resolution and separation via diastereomeric adducts etc. [15]. We attempted to use inexpensive (−)-ephedrine, a natural chiral alkaloid, as a resolving agent to separate racemic 9AMAA(H) and racemic 9AHAA(H) via diastereomeric salts formed in the reactions of these racemates with (−)-ephedrine, respectively. Unfortunately, optically pure 9AMAA(H)
could not be obtained by this method, but racemic 9AHAA(H) was successfully isolated. When equivalents of racemic 9AHAA(H) and (−)-ephedrine were refluxed in ethanol and subsequently cooled to r.t., the salt of [(+)−9AHAA]− with [(−)-ephedrine(H)]+ could be precipitated as a yellow solid. The optically pure (+)−9AHAA(H) was obtained by acidification of the aqueous solution of the salt [(+)−9AHAA]− [(−)-ephedrine(H)]+ due to its water solubility. The successful resolution has been confirmed by chiral capillary electrophoresis. Though (+)−9AHAA(H) is not a new chiral compound, its specific rotation was not reported. We found its [α]20D to be +169° (c = 0.2197, methanol).

Crystal structure of [(±)-9AHAA]− [(−)-ephedrine(H)]+ · 0.5H2O

After filtering off the crystals of the salt [(+)−9AHAA]− [(−)-ephedrine(H)]+-, crystals containing racemic [9AHAA]− with [(−)-ephedrine(H)]+ were obtained from the mother liquid by slow evaporation of the solvent at r.t. These crystals were recrystallized from 95 % ethanol to give light-yellow single crystals of composition [(±)-9AHAA]− [(−)-ephedrine(H)]+ · 0.5H2O suitable for X-ray diffraction analysis. The structure determination revealed that racemic 9AHAA anions, two protonated ephedrine cations and a water molecule combine into a structural unit (Fig. 2). The compound crystallizes in the non-centrosymmetric space group P21 with Z = 4. The peculiar composition makes it necessary that there are two crystallographically independent anions of [(±)-9AHAA]− with opposite chirality while two independent homochiral [(−)-ephedrine(H)]+ cations are their counterparts. As Fig. 2 shows, these molecules are grouped together in a tight arrangement in which the heterochiral [(±)-9AHAA]− anions seem to be related by a non-crystallographical center of inversion whereas the homochiral ephedrine cations obviously are prohibitive for a center of inversion. This assembly is completed by the water molecule, also shown in Fig. 2, which only occurs once.

In the 9AHAA anion, both the plane of the carboxylate group and the plane of the anthracene ring form a dihedral angle of 68.8°. In the crystal, intermolecular H bonds together with the electrostatic interactions of 9AHAA anions and protonated ephedrine cations assemble anion, cation, and water molecules into a three-dimensional network. These H bond interactions are presented in Fig. 3, and the respective parameters are listed in Table 1.

Experimental Section

Reagents and techniques

Anthracene was bought from Alfa Aesar (98 %), the other chemicals were analytical grade reagents. The NMR spectra were recorded with a Bruker AVANCE300 spectrometer at 300 MHz for 1H and at 75 MHz for 13C.
Table 1. H bond geometry (Å, deg) in the crystal of [(±)-9AHAA]⁺ [((−)-ephedrine(H))⁻] · 0.5H₂O.

<table>
<thead>
<tr>
<th>D-H···A</th>
<th>D-H</th>
<th>H···A</th>
<th>D···A</th>
<th>D-H···A</th>
</tr>
</thead>
<tbody>
<tr>
<td>O4-H4O–O1’</td>
<td>0.82</td>
<td>2.05</td>
<td>2.82(3)</td>
<td>158.0</td>
</tr>
<tr>
<td>O4’-H4’O–O1’</td>
<td>0.82</td>
<td>2.08</td>
<td>2.77(2)</td>
<td>143.0</td>
</tr>
<tr>
<td>O3-H3O–O9’</td>
<td>0.82</td>
<td>2.00</td>
<td>2.79(3)</td>
<td>163.6</td>
</tr>
<tr>
<td>O2’-H2’O–O9’</td>
<td>0.90</td>
<td>1.93</td>
<td>2.74(4)</td>
<td>171.2</td>
</tr>
<tr>
<td>N–HOA–O1</td>
<td>0.90</td>
<td>1.86</td>
<td>2.75(3)</td>
<td>168.1</td>
</tr>
<tr>
<td>N–HOB–O2’</td>
<td>0.90</td>
<td>1.83</td>
<td>2.72(3)</td>
<td>172.5</td>
</tr>
<tr>
<td>N’–H’B–O1’</td>
<td>0.90</td>
<td>2.19</td>
<td>2.94(3)</td>
<td>148.6</td>
</tr>
<tr>
<td>N’–H’A–O2’</td>
<td>0.90</td>
<td>1.85</td>
<td>2.75(3)</td>
<td>178.1</td>
</tr>
<tr>
<td>O9’-H9OA–O2</td>
<td>0.839(10)</td>
<td>1.945(18)</td>
<td>2.758(3)</td>
<td>163(5)</td>
</tr>
<tr>
<td>O9’-H9OB–O2’</td>
<td>0.829(10)</td>
<td>2.28(3)</td>
<td>2.921(3)</td>
<td>135(4)</td>
</tr>
</tbody>
</table>

Fig. 3. Intermolecular H bonds in the crystal of [(±)-9AHAA]⁺ [((−)-ephedrine(H))⁻] · 0.5H₂O; the H bonds are indicated by dashed lines; some H atoms were omitted for clarity.

Table 2. Crystal and structure refinement data for [(±)-9AHAA]⁺ [((−)-ephedrine(H))⁻] · 0.5H₂O.

- **Empirical formula**: C₂₁H₂₈NO₄
- **Formula weight**: 426.49
- **Crystal size, mm**: 0.14 × 0.08 × 0.06
- **Volume, Å³**: 2242.9(6)
- **Z**: 4
- **Calculated density, Mg m⁻³**: 1.263
- **Absorption coefficient, mm⁻¹**: 0.086
- **F(000), e**: 908
- **Theta range for data collection, deg**: 1.86–28.25
- **Limiting indices**: 0 ≤ h ≤ 12, 0 ≤ k ≤ 29, −14 ≤ t ≤ 14
- **Reflections collected**: 6249
- **Independent reflections**: 5697
- **R indexes [I ≥ 2σ(I)]**: R1 = 0.037, wR2 = 0.058
- **R indices (all data)**: R1 = 0.079, wR2 = 0.064

**Ethyl (9-anthryl)glyoxylate (I)**

A mixture of anthracene (17.82 g, 0.10 mol), anhydrous AlCl₃ (26.67 g, 0.20 mol) and 1-methyl-2-pyrrolidone (1.98 g, 0.02 mol) was triturated in a porcelain mortar placed in an anhydrous operator chest with change-color silica gel for absorbing moisture and as a moisture indicator, and solid NaOH for absorbing the HCl gas released from the reaction process. To the mixture was added ethyl oxalyl chloride (20.48 g, 0.15 mol) at 3–6 drops per minute with adequate trituration. After allowing the dark green mixture to react for 4.5 h, crushed ice (130.00 g) was added. After the ice had thawed, the mixture was filtered to give a brown solid raw product 1. It was recrystallized from acetone to yield a yellow solid 1 (25.70 g, 92.5 % yield). M. p. 83.8 – 84.7 °C.

**Ethyl (9-anthryl)hydroxyacetate (9AHA, 2) and (9-anthryl)hydroxyacetic acid (9AHA(H), 5)**

To the ethanol solution (350 mL) of 1 (10.00 g) was added 1.00 g of NaBH₄ gradually with stirring in an ice-water bath until 1 was exhausted. The process was tracked by TLC. Then 10 mL of dilute hydrochloric acid was slowly added, and the mixture was stirred for 10 min. Ethanol was removed in vacuo and a yellow solid was obtained, which was dissolved in acetone and filtered. The acetone was removed in vacuo and a yellow solid was obtained, which was dissolved in acetone and filtered.
moved in vacuo. 9.81 g 9AHA was obtained as a straw yellow solid in 97.4 % yield. – 1H NMR (300 MHz, CDCl3): δ = 1.05 (t, 3 H), 3.71 (s, 1 H), 4.16 (m, 2 H), 6.61 (s, 1 H), 7.55 (m, 4 H), 8.03 (m, 2 H), 8.37 (m, 2 H), 8.51 (m, 1 H). – C19H18O3 (280.31): calcd. C 77.07, H 5.63.

9AHA(A) was obtained by the hydrolysis of 9AHA. To the ethanol solution (100 mL) of 9AHA (6.00 g) was added a 30 % aqueous solution of NaOH (20 mL) and the mixture was refluxed until the yellow solid was dissolved in vacuo. After acidification with dilute hydrochloric acid, 5.17 g of a straw yellow solid was filtered off (95 % yield). – 1H NMR (300 MHz, [D6]-DMSO): δ = 6.18 (s, 1 H), 6.55 (s, 1 H), 7.53 (m, 4 H), 8.11 (s, 1 H), 8.68 (m, 2 H). – C19H18O3 (280.31): calcd. C 77.07, H 5.63.

8.87 g of Ag2O was added. The mixture was refluxed until 9AHA was consumed (TLC). Ethanol was removed to give 13.30 g ethyl (9-anthryl)methoxyacetate as a yellow solid (90.5 % yield). – 1H NMR (300 MHz, CDCl3): δ = 0.94 (t, 2 H), 3.71 (s, 3 H), 4.16 (m, 2 H), 6.61 (s, 1 H), 7.48 (m, 4 H), 8.08 (t, 2 H), 8.53 (s, 1 H), 8.68 (m, 2 H). – C19H18O3 (280.31): calcd. C 77.07, H 5.63.

9.81 g 9AHA was dissolved in 82 mL of CH3I, and 1.41 g of (+)-9AHAA(A) was added, and the mixture was refluxed for 2 h. After cooling to r. t., 1.41 g of yellow ([±]-9AHAA(A)− ([±]-9AHAA(A))− was obtained at r. t. – 1H NMR (300 MHz, [D6]-DMSO): δ = 0.80 (d, 3 H), 2.46 (s, 3 H), 3.18 (m, 1 H), 5.06 (d, 1 H), 6.13 (s, 1 H), 7.30 (m, 5 H), 7.44 (d, 4 H), 8.01 (d, 2 H), 8.47 (s, 1 H), 8.60 (d, 2 H). – C28H27NO4 (417.50): calcd. C 74.80, H 6.52, N 3.35; found C 74.70, H 6.40, N 3.18.

The salt was dissolved in water, and acidified with dilute hydrochloric acid. Filtration gave 0.83 g of a straw yellow solid of (+)-9AHAA(A). – [α]D = 169° (c = 0.2197, methanol). – C16H12O3(252.26): calcd. C 77.07, H 5.63; found C 76.95, H 5.60.

Resolution of racemic 9AHAA(A)

4.00 g (20 mmol) of (+)-ephedrine hydrochloride was dissolved in 10 mL of H2O, and 5 mL of a 40 % aqueous solution of NaOH was added with stirring. The mixture was extracted twice with 10 mL of ethyl ether. The extract was dried with anhydrous Na2SO4, and the ethyl ether was removed to give 3.20 g of (+)-ephedrine. To a solution of (+)-ephedrine (3.20 g, 20 mmol) in 30 mL of ethanol, 5.04 g (20 mmol) of racemic 9AHAA(A) was added, and the mixture was refluxed for 2 h. After cooling to r. t., 1.41 g of yellow ([±]-9AHAA(A)− ([±]-9AHAA(A))− was obtained at r. t. – 1H NMR (300 MHz, [D6]-DMSO): δ = 6.18 (s, 1 H), 6.55 (s, 1 H), 7.53 (m, 4 H), 8.11 (d, 2 H), 8.57 (m, 3 H), 12.69 (s, 1 H). – 13CNMR(75MHz,[D6]-DMSO): δ = 67.4, 125.4, 125.6, 126.3, 128.1, 129.3, 130.0, 131.6, 132.7, 175.5. – C16H12O3 (252.26): calcd. C 77.07, H 5.63; found C 76.11, H 4.89.


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