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SYNTHETIC CONTROL BASED ON 2-HALOPYRIDINIUM SALTS I. THE PREPARATION OF (R)- AND (S)-2-CHLORO-1-(1-CYCLOHEXYLETHYL)-3-ETHYL-6-METHYLPYRIDINIUM FLUOROBORATE

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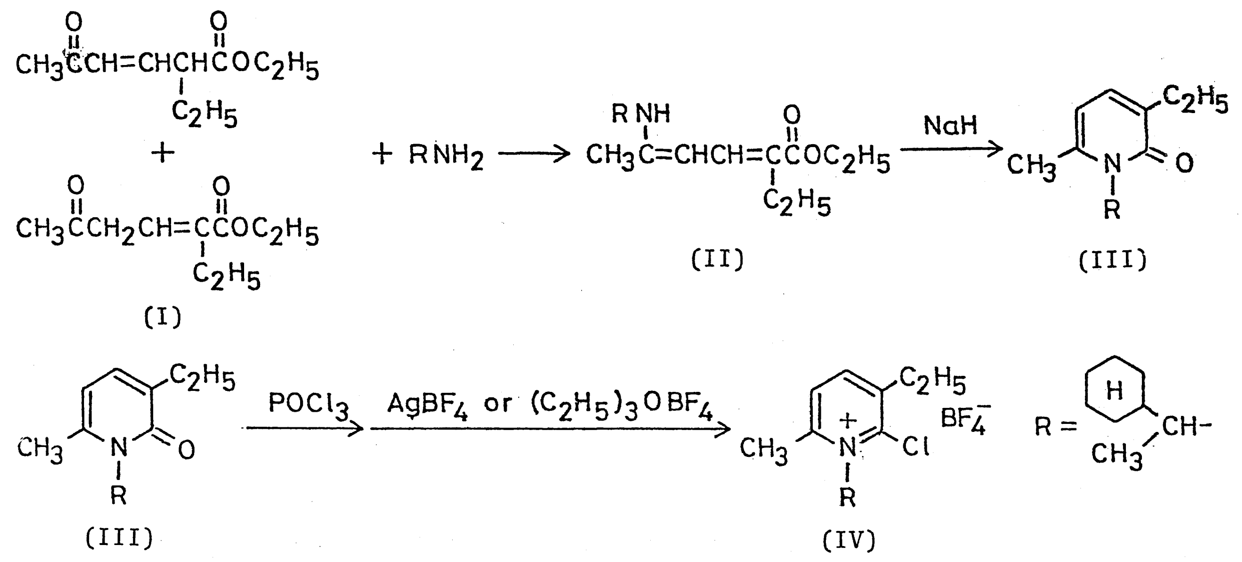
Optically active (R)- and (S)-2-chloro-1-(1-cyclohexylethyl)-3-ethyl-6-methylpyridinium fluoroborate were prepared by a new and versatile method.

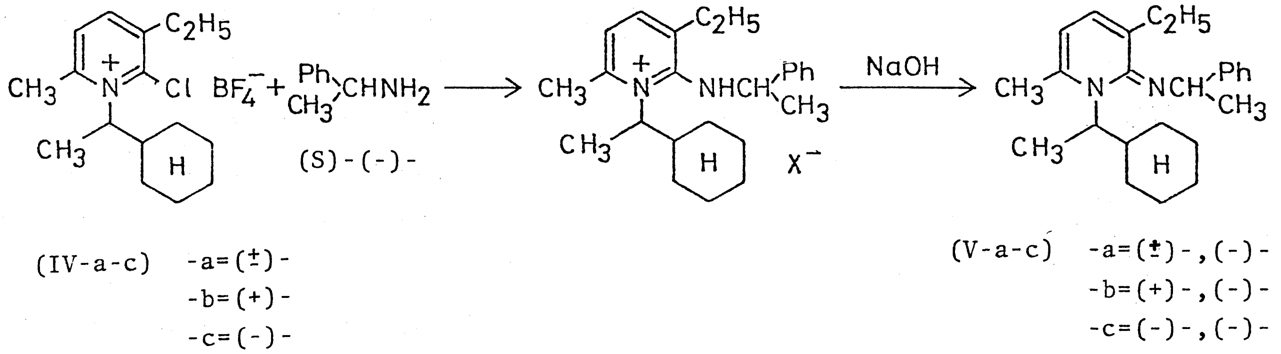
In the course of our study on "Synthetic Control" based on 2-halopyridinium salts, it became necessary to prepare optically active 2-halopyridinium salts. Concerning with the synthesis of 2-halopyridinium salts, there have been known two principal methods, namely, 1-alkylation of 2-halopyridine[1)] or of 2-pyridone followed by quaternization[2)], and the cyclization to 1-alkyl-2-pyridone and following quaternization. Of these two methods, the former was not suitable for the preparation of optically active pyridinium salts because of the possibility of the racemization during quaternization. In the latter, the preparation of only 1-aryl- or 1-small alkyl-2-pyridones using the Knoevenagel reaction[3)] or reaction between α-pyrones and amines[4)] has been known. We first examined the synthesis of optically active 2-pyridones by these methods, but the desired pyridones could not prepared.

Then, we established a new method for the preparation of optically active 2-pyridones by the cyclization of dienaminoester as explained below. The mixture (I) of ethyl 2-ethyl-5-oxo-2-hexenoate and ethyl 2-ethyl-5-oxo-3-hexenoate, prepared from ethyl α-ethylacetoacetate and β-halovinyl methyl ketone, was converted to the corresponding enamines (II) by the treatment with (1-cyclohexylethyl)amine. The enamines (II) thus obtained were cyclized to the corresponding 2-pyridones (III) by the treatment with sodium hydride.



The pyridone (III) was converted into 2-chloropyridinium salt by the treatment with phosphorus oxychloride and then with silver tetrafluoroborate or triethyloxonium fluoroborate. 2-Fluoropyridinium salt was also prepared by the treatment of 2-chloropyridinium salt with cesium fluoride in DMF.

It was confirmed that no racemization took place during these processes by the following experiments. The pyridinium salt (IV-a) derived from (±)-(1-cyclohexylethyl)amine reacted with (S)-(-)-(1-phenylethyl)amine and afforded diastereomers (V-a), which were easily separated to (V-b) and (V-c) by silica gel chromatography, after treatment with sodium hydroxide.



On the other hand, the reaction of pyridinium salt (IV-b) derived from (S)-(+)-(1-cyclohexylethyl)amine with (S)-(-)-(1-phenylethyl)amine gave only a single product, one diastereomer(V-b), and the other isomer(V-c) was also obtained as a single product by the reaction of pyridinium salt (IV-c) derived from (R)-(-)-(1-cyclohexylethyl)amine with (S)-(-)-(1-phenylethyl)amine. Similar results were obtained in the case of the reaction of (S)-(-)-(1-phenylethyl)amine with 2-fluoropyridinium salt.

The following procedure is representative for the preparation of optically active 2-chloropyridinium salt. The mixture of ethyl 2-ethyl-5-oxo-3-hexenoate and ethyl 2-ethyl-5-oxo-2-hexenoate were prepared by modified Kochetkov's[5] method. The above mixture (9.4 g) and (S)-(+)-(1-cyclohexylethyl)amine (6.48 g) were dissolved in 50 ml of toluene and heated for 2 hr under argon atmosphere. Liberated water was distilled as azeotrope with toluene and toluene was removed in vacuo. The resulting residue, ethyl 5-[(1-cyclohexylethyl)amino]-2-ethyl-2,4-hexadienoate, was dissolved in 70 ml of dry toluene and NaH (content 55%) (2.24 g) was added to the solution. The mixture was refluxed for 2 hr, poured into cold water, acidified with dil. hydrochloric acid, and then extracted with ether. The ethereal extract was washed with aq. $NaHCO_3$ solution and then with water, and dried over Na_2SO_4. After evaporation of solvent, distillation of residue under diminished pressure afforded 9.1 g (72% yield) of (S)-(+)-1-(1-cyclohexylethyl)-3-ethyl-6-methyl-2-pyridone, bp 131-134°C/0.9 mmHg, $[\alpha]_D^{24}$ = +106° (c=3.86, CH_2Cl_2). By the similar procedure, (R)-(-)-pyridone was obtained, $[\alpha]_D^{22}$ = -97° (c=0.63, CH_2Cl_2). (S)-(+)-Pyridone (1.036 g) was dissolved in 3 ml of $POCl_3$, and heated at 80°C with stirring for 8 hr. After evaporation of excess $POCl_3$, the resulting residue was dissolved in 4 ml of dry acetone, and added dropwise into the solution of $AgBF_4$ (1.70 g) in 4 ml of dry acetone. After stirring for 2 hr, the mixture was filtered, and yellow powder was washed with acetone. The filtrate and washings were evaporated in vacuo, and resulting residue was washed with ether, dissolved in dry CH_2Cl_2, washed with cold water, and then dried over Na_2SO_4. After evaporation of solvent, the residue was solidified by addition of ether, and filtered. The brown mass obtained was dissolved in dry CH_2Cl_2 and recrystallized by adding dry ether to give 0.787 g (53%) of (S)-(+)-2-chloro-1-(1-cyclohexylethyl)-3-ethyl-6-methylpyridinium fluoroborate as colorless crystals, mp 131°C, $[\alpha]_D^{24}$ = +36.2° (c=7.14, CH_2Cl_2).

Similarly, (R)-(-)-pyridinium salt was obtained, mp 128°C, $[\alpha]_D^{26}$ = -37.6° (c=0.335, CH_2Cl_2).

The typical procedure for the reaction of 2-halopyridinium salts with optically active amines is mentioned below. To (S)-(+)-2-chloro-1-(1-cyclohexylethyl)-3-ethyl-6-methylpyridinium fluoroborate (0.177 g, 0.5 mmol) was added the solution of (R)-(+)-(1-phenylethyl)amine (0.061 g, 0.5 mmol) and triethylamine (0.051 g, 0.5 mmol) in CH_3CN. The mixture was refluxed for 4 hr and then evaporated. Sodium hydroxide (0.200 g) in 2 ml of H_2O and 40 ml of MeOH was added to the residue and the mixture was stirred for 1 hr. After evaporation of MeOH, the residue was extracted with CH_2Cl_2. The extract was washed with H_2O and dried over Na_2SO_4. There was obtained 1-(1-cyclohexylethyl)-3-ethyl-6-methyl-2-[(1-phenylethyl)imino]-1,2-dihydropyridine by thin layer chromatography on silica gel, 0.124 g (71% yield); $[\alpha]_D^{22} = -83.2°$ (c=2.2, CH_2Cl_2).

The present method provides a new and versatile method for the preparation of optically active 2-pyridones and their 2-halopyridinium salts, both of which are difficult to prepare by conventional methods. Furthermore, the optically active 2-halopyridinium salts obtained here are useful reagents to perform "Synthetic Control" which involves kinetic resolution and asymmetric synthesis. We now investigate interesting reactions using these optically active pyridinium salts.

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