

Synthesis of Isoquinoline-1, 3-Dicarboxylic Acid

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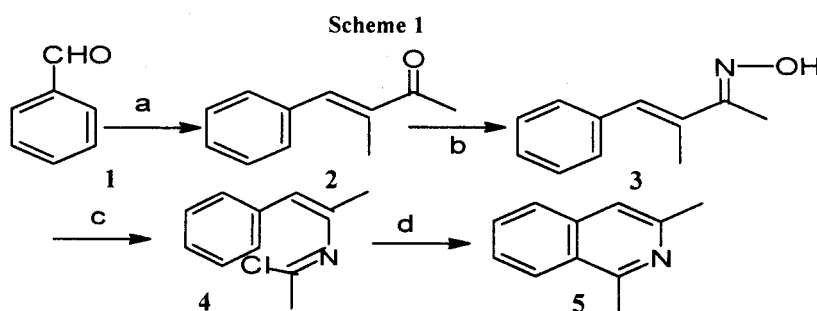
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Abstract: Two new compounds, isoquinoline-1, 3-dicarboxyaldehyde and (IDA) were synthesized *via* 6 or 7 steps starting from benzaldehyde, or prepared *via* 4 steps starting from allylbenzene.

Keywords: Beckman rearrangement reaction, intramolecular electrophilic substitution, 1,3-dimethyl-isoquinoline derivatives.

Chiroptical luminescence measurements¹ have been used for studying chirality-dependent molecular excited-state dynamic, for studying excited-state racemization kinetics associated with intermolecular chiral recognition processes in solution². In these processes, there are two molecular species, lanthanide complexes (luminophore) and resolved transition complexes (Δ or Λ , quencher). Many kinds of transition metal complexes have been used as quenchers to investigate influence of the intermolecular chiral recognition. However, the luminophores were only confined to Ln (DPA)₃³⁻ and Ln (CDA)₃³⁻ (Ln=Eu³⁺, Tb³⁺, DPA=dipicolinate dianion, CDA=chelidamate). In order to observe effects of different luminophores on the intermolecular chiral recognition processes, we have designed and successfully synthesized a new ligand IDA.



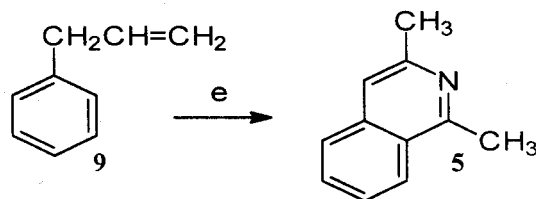
Reagents, conditions and yields: (a) 2-butanone, gaseous HCl, 0°C, 6h, 80%. (b) NH₂OH·HCl, NaOH, EtOH/H₂O(2:1), reflux, 1h, 85%. (c) PCl₅, decalin, N₂, 0°C, 5h. (d) P₂O₅, decalin, reflux, 1h, 62%.

We also tried to synthesize compound 2 (Scheme 1) from benzaldehyde by using conc. H₂SO₄ at room temperature in stead of gaseous HCl, but it failed to give 2 in good

yields. The possible reasons might be that conc. H_2SO_4 causes a lots of side reactions.

The oxime **3** exists only in the stable (E)-configuration³, and in the presence of phosphorus pentachloride, it underwent a Beckman rearrangement reaction to yield imidochloride **4**. The compound **4** without separation was subjected to cyclization reaction of intramolecular electrophilic substitution to give the isoquinoline **5**. The yield of the cyclization was higher at elevated temperatures, and highest at the boiling temperature of decalin. Decalin is a non-polar solvent and does not contain any nucleophilic centers. For these reasons, the side reactions of imidochloride **4** and solvent alkylation are suppressed.

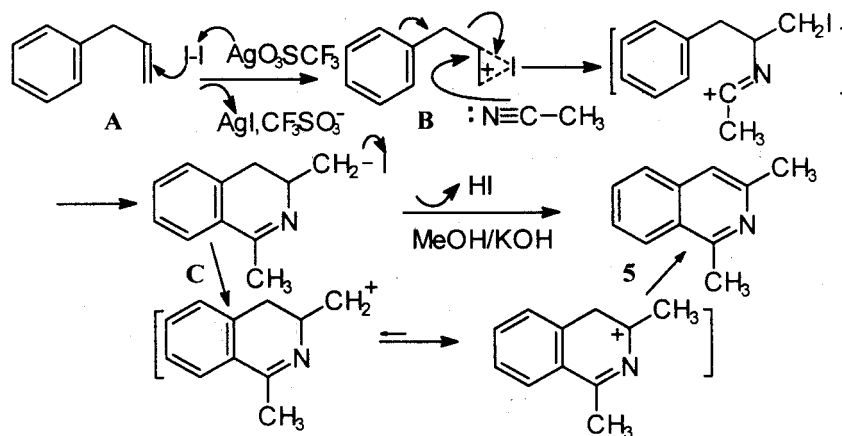
Scheme 2



Reagents, conditions and yields: (e) i. MeCN, AgO_3SCF_3 , I_2 , RT, overnight; ii. MeOH, KOH, 40°C , 72%.

1, 3-Dimethylisoquinoline **5** (Scheme 2) also was prepared under mild conditions from allylbenzene and acetonitrile using silver trifluoromethanesulfonate and iodine as catalyst.

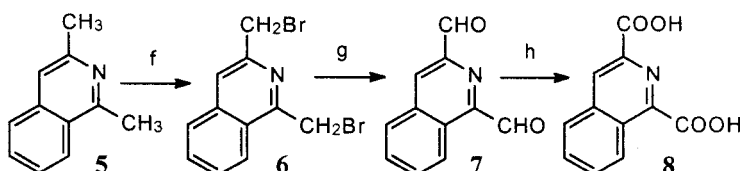
Scheme 3



In order to explain the catalytic function of AgO_3SCF_3 and find out the path how to produce isoquinoline **5**, the possible mechanism can be proposed (Scheme 3). Although silver triflate and iodine did not react with each other upon mixing in acetonitrile, the presence allylbenzene **A** in the mixture induced the precipitation of silver iodide and formation of positive iodonium ion **B**. The primary product in the solution was a

dihydroisoquinoline C produced from iodonium ion B by acetonitrile nucleophilic attack and ensuing cyclization of the resulted nitrilium ion through intramolecular electrophilic substitution. The compound C underwent a unimolecular elimination and rearrangement to give isoquinoline 5.

Scheme 4



Reagents, conditions and yields: (f) NBS, dibenzoylperoxide, CCl₄, reflux, 7h, 60%. (g) i. DMSO, NaHCO₃, N₂, 120°C, 2h. ii. silica gel(CH₂Cl₂), 18%. (h) 30%H₂O₂, CH₃COCH₃, 40 °C, 5h, 90%.

For preparing IDA 8 directly from 5, another two oxidizing agents were tested. One is KMnO₄, another is SeO₂, but they are all not successful. Benzoic acid was obtained by oxidizing with KMnO₄ and 3-methyl-isoquinoline-1-carboxyaldehyde was obtained by using SeO₂ as oxidizing agent.

1, 3-Dimethyl-isoquinoline and 1, 3-bis (bromomethyl) isoquinoline were prepared according the approach introduced by Mukkala *et.al*⁴. 1,3-Bis (bromomethyl) isoquinoline was converted into isoquinoline-1, 3-dicarboxyaldehyde by Kornblum's method⁵, although the product yield was low, but an oxidation to give isoquinoline-1, 3-dicarboxylic acid was successful⁶. All products were characterised by NMR, IR and MS⁷.

Acknowledgments

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References and Notes

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7. Compound **6**: ^1H NMR (90MHz, CDCl_3): δ 4.72 (s, 2H), 5.03 (s, 2H), 7.70 (dd, 1H), 7.73 (dd, 1H), 7.77 (s, 1H), 7.86 (d, 1H), 8.25 (d, 1H). IR (KBr): 3057, 2987, 1616-1496, 1384, 1342, 617, 751, 561 cm^{-1} . m/z (FAB): 315 (M^+ , 27%). Compound **7**: ^1H NMR (500MHz, CDCl_3): 7.91 (dd, 1H), 7.94 (dd, 1H), 8.11 (d, 1H), 8.59 (s, 1H), 9.40 (d, 1H), 10.35 (s, 1H), 10.47 (s, 1H). Compound **8**: ^1H NMR (500MHz, DMSO-D_6): δ 7.89 (dd, 1H), 7.91 (dd, 1H), 8.26 (d, 1H), 8.57 (d, 1H), 8.76 (s, 1H). m/z (FAB): 217 (M^+ , 46%). IR (KBr): ν (CO) 1714, 1651 cm^{-1} . ν (OH) 2550-3560 cm^{-1} . ^{13}C NMR (90MHz, DMSO-D_6): δ 166.77, 165.81, 150.14, 140.21, 136.46, 131.65, 131.06, 128.95, 126.27, 126.10, 126.01.

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