

COMMUNICATIONS TO THE EDITOR

A Facile Synthesis of Dihydrobenzofuran and Benzofuran Derivatives

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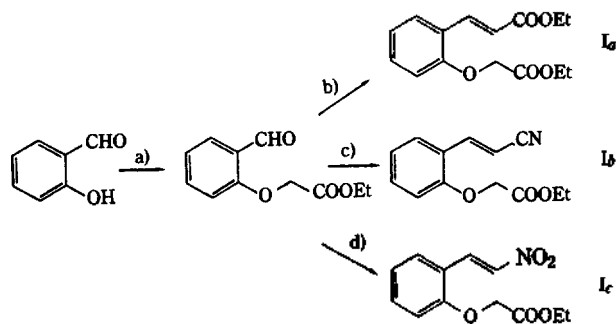
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Dihydrobenzofuran and benzofuran are important heterocyclic ring systems in organic and medicinal chemistry. For our research programs we need various 2,3-dialkyl substituted dihydrobenzofuran and benzofuran derivatives. Most of the existing methods for the preparation of the dihydrobenzofuran and benzofuran systems are not suitable for the preparation of the 2,3-dialkyl substituted system.¹ Herein we would like to report a new synthetic methodology which involves the internal Michael reaction as a key step for the preparation of the 2,3-dialkyl substituted dihydrobenzofuran and benzofuran systems.

When the cinnamic acid derivative, Ia,² prepared according to Figure 1, was treated with a catalytic amount of sodium ethoxide, the desired dihydrobenzofuran derivative, II, was formed in high yield. The reaction gave a mixture of the trans and cis isomers in 9:1 ratio. The stereochemistry of two isomers was determined by the coupling constants between the protons at 2,3 positions. Namely the major and minor isomer have coupling constants of 6.9 and 9.1 hz respectively. The dihedral angles of protons at 2,3 positions were estimated by the molecular mechanics calculation and found to be 156° and -0.55° for trans and cis isomer respectively.⁵ From these angles and the Karplus equation, the major isomer was assigned as a trans and the minor isomer as a cis isomer respectively (Figure 2).

Likewise cinnamionitrile and nitrostyrene derivatives also gave the corresponding dihydrobenzofuran derivatives in high yield (Figure 1 & Table 1).

The oxidation of the dihydrobenzofuran to the benzofuran



a) NaH, BrCH₂COOEt, DMF, 16hr, 89%. b) P(Ph)₃=CHCOOEt, benzene, reflux, 2hr, 84%. c) (EtO)₂P(=O)CH₂CN, EtN(i-pr)₂ LiCl, THF, rt, 16r, 87%. d) CH₃NO₂, pyrrolidine, benzene, reflux, 4Hr, 73%.

Figure 1.

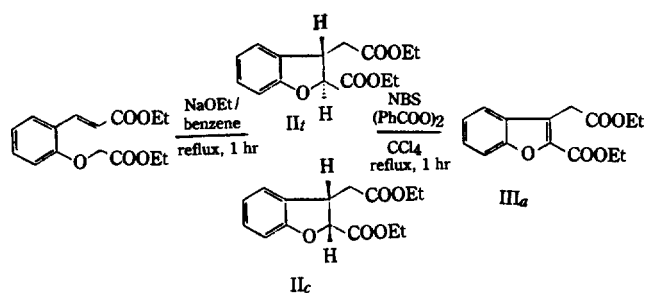


Figure 2.

Table 1.

W	Yield ⁴
-COOEt	92%
-CN	86%
-NO ₂	84%

system was achieved by the benzylic bromination followed by the elimination of HBr which occurred spontaneously under the reaction condition.

Acknowledgement. We thank the Ministry of Science and Technology for financial support.

References and Footnotes

- Katritzky, A. R., Handbook of Heterocyclic Chemistry, Pergamon Press.
- The Wittig reaction gives ~15% of the cis isomer. The cis isomer also undergoes the cyclization to give the same compound. Thus it is not necessary to separate two isomers.
- Masamune, S & Roush, W. R. *et al.*, Tetrahedron Letters, **25**, 2183 (1984).
- In all cases ~10% of the cis isomer was obtained.
- According to the molecular mechanics calculation (using mm2 '77 (Allinger-QCPE 395)) the minimum energy of IIc is 2.2 kcal less than that of IIc. This energy difference is well consistent with the ratio of the two isomers.