

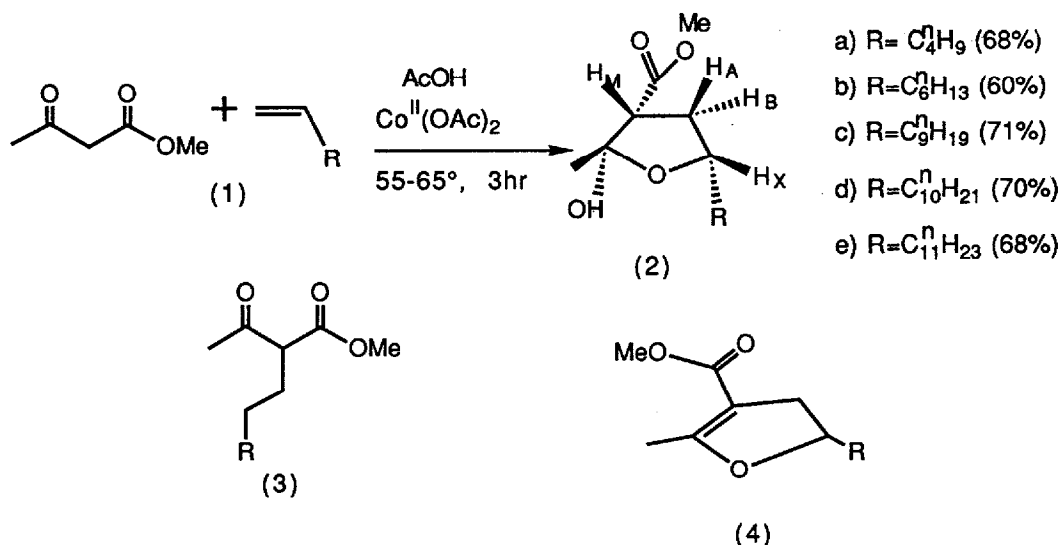
COBALT(II) ACETATE PROMOTED ADDITION OF ACETOACETATE TO TERMINAL OLEFINS: A HIGHLY STEREOSELECTIVE SYNTHESIS OF 5-ALKYL-2-HYDROXY 2 METHYL-3-METHOXYCARBONYL TETRAHYDROFURANS

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Summary: Methylacetoacetate and terminal olefins react in presence of Cobalt(II) acetate and Oxygen to give the titled compound(2) in a highly stereoselective manner and the structure of this compound is elucidated by ¹H NMR simulation studies .

In a study directed towards the synthesis of tetrahydrofuranoid natural products, we required substituted dihydrofurans and envisioned that such a molecule can be synthesized by a metal promoted oxidative addition of acetoacetate to olefins. Manganese(III) acetate promoted¹ addition of acetoacetate to activated olefins, has been shown to be a very efficient route to dihydrofurans and other cyclic organic molecules. The Manganese(III) acetate promoted oxidative cyclisation is quite efficient in an intramolecular reaction, however, the intermolecular reaction of acetoacetate with olefins like 1-hexene normally results in poor yields of dihydrofurans. In order to overcome this problem, we explored the possibility of using Cobalt(II) complexes for mediating such a reaction. A Cobalt(II) acetate promoted addition of acetoacetate to terminal olefins under the atmosphere of nitrogen mainly gave unchanged starting materials, however, we were pleasantly surprised to find that if the reaction is carried out without the atmosphere of nitrogen, a high yield of the titled compound (2) is obtained. A preliminary account of these findings are given below.

Anhydrous cobalt(II) acetate (10 mmol), methylacetoacetate (10 mmol) and 1-hexene (15 mmol) are dissolved in glacial acetic acid (60 ml) and the resulting solution is heated to 55-65°C for 3 hours. The reaction mixture is then poured into diethyl ether (100 ml) and the ether layer is washed with saturated solution of sodium bicarbonate, water and dried over anhydrous sodium sulphate. Removal of ether gave a viscous liquid which on addition of n-hexane and cooling yielded compound (2a) as fluffy solid (68%). This reaction is facile with terminal olefins and in all the cases, after the work up of the reaction the product (2) crystallised out as one diastereomer¹ (Scheme). A careful study of the mother liquor revealed the presence of alkylated product (3) and the dihydrofuran(4) in minor amounts (~ 10%). Surprisingly the other diastereomers of compound (2) were not present in the mother liquor. A careful exclusion of oxygen (by degassing) from the solvent and reagent did not yield the compound (2) and the starting material remained largely unchanged. On the other hand, the compound (2) is obtained in good yields if the reaction mixture is purged with oxygen. However, no noticeable change in the yield of product (2) was observed under the conditions where the reaction mixture is neither degassed nor purged with oxygen. Passing a stream of oxygen throughout the reaction resulted in the formation of a complex mixture. Non terminal olefins, cyclohexene and cyclopentene gave a complex mixture of products under these reaction conditions.



The relative stereochemistry of compounds (2a-e) were assigned from $^1\text{H-NMR}$ simulation studies.³ The four protons form an ABMX spin system and the coupling constant J_{BM} (12.0 Hz) and J_{BX} (11.80 Hz) for compound (2a) are of similar magnitude indicating that H_{M} and H_{X} form nearly the same dihedral angle with H_{B} and are cis to each other. The small coupling constant J_{AM} (5.10 Hz) and J_{AX} (2.60 Hz) also indicates the cis arrangement of H_{M} , H_{A} and H_{X} . The relative stereochemistry of CH_3 group at C-2 is assigned by different NOE spectra of compound (2a) at 270 MHz. It showed a 5% NOE at H_{M} irradiating the CH_3 protons, indicating that CH_3 is cis to H_{M} .

Thus Cobalt(II) acetate mediated addition of acetoacetate to terminal olefin is an extremely useful route to a highly stereoselective synthesis of substituted tetrahydrofurans. We are currently probing the role of oxygen in these reactions.

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References and Notes

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- Satisfactory elemental analyses were obtained for Compound (2a-e) and their structure were conclusively proved by $^1\text{H-NMR}$ and Mass.
- The actual values of chemical shifts and coupling constants were extracted using the iterative computer program LAOCON.

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