Preparatively Useful Method for the Synthesis of Diels-Alder Adducts between Furan and Methyl Acrylate

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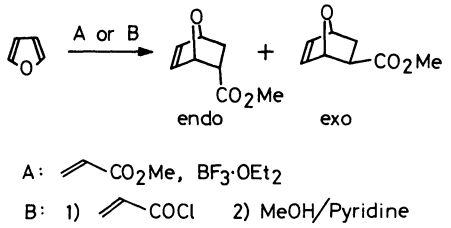
Synopsis. The Diels-Alder adducts of furan with methyl acrylate were successfully prepared by two methods on a preparative scale. The $BF_3 \cdot OEt_2$-catalyzed reaction of furan with methyl acrylate gave a 7:3 mixture of endo and exo adducts in 75.7% yield. When acryloyl chloride was used as a dienophile, after esterification with methanol, a 3:7 mixture of the same adducts was obtained in 76.5% overall yield.

The 7-oxabicyclo[2.2.1]heptyl system has been widely employed as a source of important intermediates in natural product syntheses.[1] The most straightforward approach to the construction of the 7-oxabicyclo[2.2.1]heptyl system takes advantage of the Diels-Alder reaction between furan and a suitable dienophile. However, the Diels-Alder reaction of furan with conventional dienophiles is usually sluggish because of the aromatic character of the furan ring (resonance energy *ca.* 25 kcal/mol).[2]

Previously, we have demonstrated the solution to this problem by the application of high-pressure technique.[3] Recently, however, it has been reported that some Lewis acid catalysts could provide an alternative approach to realize these Diels-Alder reactions.[4] These results prompt us to report our preliminary finding for a convenient preparation of Diels-Alder adducts between furan and methyl acrylate in preparatively useful amounts.



Firstly, the Lewis acid-catalyzed method is described. Among several Lewis acids, $BF_3 \cdot OEt_2$ was found to be a most effective catalyst for this reaction (Table 1). Thus, when the mixture of freshly distilled furan and methyl acrylate was catalyzed with 0.1 equiv of $BF_3 \cdot OEt_2$ *without solvent* at 5 °C for 10 h under nitrogen atmosphere , the desired endo and exo Diels-Alder adducts were obtained in 75.7% combined yields *with high endo selectivity* (endo:exo=7:3). For instance, the reported yield of the adducts is 55% using ZnI_2 as catalyst[4b] or 62% at 15 kbar pressure[3b] (endo:exo= 1:2 for the former or 6:4 for the latter). So the newly developed method considerably improves both the yield and the endo selectivity as the result of the kinetically controlled reaction.[5] Other Lewis acids such as $AlCl_3$, $SnCl_4$, and $ZnCl_2$ gave only resinous products and with other dienophiles such as methyl vinyl ketone, acrylonitrile, and dimethyl maleate either the reaction was not catalyzed or polymerization was predominant. Reaction with 2-methylfuran gave adducts in low yield and 2,5-dimethylfuran gave no adducts.

An alternative procedure is the use of a strongly reactive dienophile of acryloyl chloride. It has been known that acryloyl chloride reacts with furan in high yield.[6] However, the detailed experimental procedure has not been published. We found the reaction was greatly improved by addition of propylene oxide as a hydrogen chloride scavenger. Thus, the reaction of furan with acryloyl chloride in the presence of a few drops of propylene oxide gave adducts in high yield by ^1H NMR measurement. Esterification of the product with absolute methanol followed by purification gave the endo and exo adducts in 76.5% overall yield *in high exo selectivity* (endo:exo= 3:7), in contrast to the former case. This is probably due to the thermodynamic stability of the exo adduct. The reaction with 2-methylfuran gave the known Michael adduct[6,7] and 2,5-dimethylfuran gave no adducts.

By these two methods Diels-Alder adducts of furan with methyl acrylate have become available in large quantity. Both endo and exo stereoisomers are readily separable by column chromatography; for the preparation of the endo-isomer the first procedure is preferred and the second one is convenient for the exo-isomer.

TABLE 1. DIELS-ALDER REACTION OF FURAN WITH METHYL ACRYLATE

Catalyst	Solvent	Temp °C	Time h	Yield %	endo/exo ratio
—[a]	CH_2Cl_2	27	4	62[b]	6 : 4
ZnI_2[c]	—	40	48	55	1 : 2
$Cu(BF_4)_2$-HQ[d]	—	RT	2 weeks	33	ND[e]
$BF_3 \cdot OEt_2$[f]	—	5	10	75.7	7 : 3
$BF_3 \cdot OEt_2$[f]	CCl_4	5	14	41	7 : 3
$TiCl_4$[f]	CCl_4[g]	−20[g]	8	50	7 : 3

a) Ref. 3b. b) At 15 kbar pressure. c) Ref. 4b. d) Ref. 4c. e) Not described. f) 0.1 equiv based on methyl acrylate. g) Without solvent or at 0 °C only polymerization has occurred.

Experimental

^{1}H NMR spectra were obtained on a JEOL MH-100 spectrometer and the IR spectra were recorded on a JASCO IRA-1. All reactions were carried out in the presence of a catalytic amount of hydroquinone (HQ) under N_2 atmosphere. Furan and methyl acrylate were freshly distilled prior to use. $BF_3 \cdot OEt_2$ was fractionally distilled from CaH_2. Acryloyl chloride was prepared from acrylic acid according to the literature[8] and was freshly distilled prior to use. Column chromatography was performed with Wakogel C-200. Merck's precoated silica-gel 60 F-254 plates (0.25 mm) were used for monitoring the reactions.

Evaporation of the excess reagents or solvents was performed *in vacuo* below 35 °C. All the products were identified by comparing their spectral data with those of authentic samples.

Methyl 7-Oxabicyclo[2.2.1]hept-5-ene-2-carboxylate.
A) With $BF_3 \cdot OEt_2$ Catalyst: To a mixture of furan (24 g; 0.353 mol) and methyl acrylate (10 g; 0.116 mol) 1.5 ml of $BF_3 \cdot OEt_2$ was added *via* syringe at −20 °C with stirring. Thereafter, the reaction was allowed to proceed in the refrigerator (<5 °C) for 10 h. During the reaction, the solution color changed to pale yellow and a small amount of brown deposit formed. After evaporation of the excess reagents, the residue was poured into CH_2Cl_2 and washed successively with water, satd $NaHCO_3$, and satd NaCl, dried over $MgSO_4$, and concentrated. Purification of the oily product (14 g) by silica-gel column chromatography gave 9.86 g (55.1%) of endo-adduct and 3.69 g (20.6%) of exo-one. With hexane–AcOEt the endo-isomer was obtained from earlier fractions.

B) With Acryloyl Chloride: A mixture of furan (21.6 g; 0.32 mol), acryloyl chloride (10.2 g; 0.113 mol), and 3—4 drops of propylene oxide was stirred in the dark at room temperature for 48 h. After evaporation of the excess reagents, 15.6 g of the product was obtained as a dark yellow oil. The product was esterified conventionally with abs. MeOH (10 ml) using 3 equiv of pyridine at room temperature for 36 h and then quenched with ice-water. The excess MeOH was removed and the aqueous phase was extracted with AcOEt. The combined extracts were washed successively with water, 2M HCl (1 M=1 mol dm^{-3}), satd $NaHCO_3$, and satd NaCl, dried over $MgSO_4$, and concentrated. The yellowish product (14.16 g) was purified as above to afford 3.72 g (21.4%) of endo-adduct and 9.42 g (54.1%) of exo-one.

3-(5-Methyl-2-furyl)propanoyl Chloride. A mixture of 2-methylfuran (3 g; 37 mmol), acryloyl chloride (3 g; 33 mmol), and 2—3 drops of propylene oxide was stirred at room temperature for 24 h. Evaporation of the excess reagents gave an almost pure product (4.64 g; 81.5%), bp 95—100 °C/15 mmHg (lit,[7] 99 °C/15 mmHg; 1 mmHg=133.322 Pa).

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