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Abstract

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ALKYLATION OF 4-FLUOROANISOLE BY OLEFINS IN THE PRESENCE OF THE CATALYSTS BF_3, $BF_3 \cdot H_3PO_4$, AND $BF_3 \cdot O(C_2H_5)_2$

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Continuing investigations in the field of the chemistry of alkylhalophenols and their alkyl ethers ([1]), we studied the alkylation reaction of 4-fluoroanisole with propylene, pseudobutylene, and cyclohexene in the presence of boron trifluoride and its molecular compounds with orthophosphoric acid and ethyl ether. There are no data in the literature on the alkylation of alkyl ethers of fluorophenols. As our investigations showed, 4-fluoroanisole is very readily alkylated by the indicated olefins (considerably more readily than phenol and anisole). A mixture of mono- and dialkylfluoroanisoles is thereby formed in almost quantitative yield. The strongest orienting group is the methoxy group; therefore the monosubstituted fluoroanisoles are 2-alkyl-4-fluoroanisoles, and the disubstituted ones are 2,6-dialkyl-4-fluoroanisoles. The reaction is not accompanied by polymerization of the olefins or by other side processes. The products are light-colored and, after appropriate treatment and drying, distil in vacuo completely, without any residue in the distillation flask. Separation of the products proceeds rather readily; the mono- and dialkylfluoroanisoles already during the first distillation of the alkylate distil within ranges of a few degrees.

In the reaction of 4-fluoroanisole with propylene in the presence of $BF_3 \cdot H_3PO_4$ at molar ratios equal to 2 : 1 : 0.4, the temperature in the range 40–80° does not affect the overall yield of mono- and diisopropylfluoroanisoles, which amounts to 95% of theoretical. However, at the lower temperature, diisopropylfluoroanisole is obtained in higher yield. Thus, the highest yield, 40% of theoretical, of 2,6-diisopropyl-4-fluoroanisole for the indicated ratios of reagents and catalyst is obtained at a temperature of 40°. The amount of $BF_3 \cdot H_3PO_4$ catalyst within the range 0.1–0.4 mole per 1 mole of propylene gives no sharp difference in the yields of the alkylation products. Somewhat higher yields of mono- and diisopropylfluoroanisoles are obtained when fluoroanisole is reacted with propylene and $BF_3 \cdot H_3PO_4$ at molar ratios equal to 2 : 1 : 0.3 at 60°. The molar ratios of the reagents exert a large influence on the composition of the alkylate. The greater the ratio of 4-fluoroanisole to propylene, the lower the yield of 2,6-diisopropyl-4-fluoroanisole. The highest yield (89%) of 2-isopropyl-4-fluoroanisole is obtained at molar ratios of fluoroanisole, propylene, and $BF_3 \cdot H_3PO_4$ equal to 5 : 1 : 0.6.

The yield of diisopropylfluoroanisole in this case is only 11% of theoretical.

4-Fluoroanisole with pseudobutylene in the presence of $BF_3 \cdot H_3PO_4$ likewise forms a mixture of 2-*tert*-butyl-4-fluoroanisole (III) and 2,6-di-*tert*-butyl-4-fluoroanisole (IV). The best conditions, under which (III) and (IV) are obtained in yields of respectively 76 and 20% of theoretical, are molar ratios of 4-fluoroanisole, pseudobutylene, and $BF_3 \cdot H_3PO_4$ equal to 4 : 1 : 0.4, a temperature of 60°, and a rate of introduction of pseudobutylene of 2.3 l/hr. With an increase in the molar ratio of 4-fluoroanisole from 2 to 4 moles per 1 mole of pseudobutylene, the yield of (III) increases and the yield remains practically unchanged.

(IV). In contrast to the reaction with propylene, in this case an amount of $BF_3 \cdot H_3PO_4$ of 0.1 mole per 1 mole of pseudobutylene is ineffective.

A very active catalyst for the alkylation of 4-fluoroanisole with pseudobutylene is free boron fluoride. Thus, when 4-fluoroanisole is reacted with pseudobutylene in the presence of BF_3 in molar ratios of 2 : 1 : 0.4, at 80° and with a pseudobutylene feed time of 1.5 l/hr, (III) and (IV) are obtained in yields of 65 and 35%, respectively, of theory. At 30° the yields of (III) and (IV) decrease and are, respectively, 50 and 18% of theory. Boron fluoride etherate proved to be a catalyst for the alkylation of 4-fluoroanisole with pseudobutylene that is 3–4 times less effective. Thus, when 4-fluoroanisole is reacted with pseudobutylene in the presence of $BF_3 \cdot O(C_2H_5)_2$ in molar ratios of 2 : 1 : 0.4, at 80° only one product, 2-*tert*-butyl-4-fluoroanisole, is obtained in a yield of 26% of theory. Upon repeated use of the catalyst $BF_3 \cdot H_3PO_4$ in this reaction, the total yield of the products remains the same, but their composition changes somewhat toward an increase in the yield of (IV) and a decrease in the yield of (III).

In the alkylation of 4-fluoroanisole with cyclohexene, liquid 2-cyclohexyl-4-fluoroanisole (V) and crystalline 2,6-dicyclohexyl-4-fluoroanisole (VI) are obtained. The total yield of products with the catalyst $BF_3 \cdot H_3PO_4$ ranges from 95 to 100%. The relative content of (V) and (VI) in the mixture depends on the molar ratios of the reactants, the amount of catalyst, and the temperature, but, as in the reaction with propylene and pseudobutylene, regardless of the conditions the mixture always contains predominantly 2-cyclohexyl-4-fluoroanisole. With an increase in the molar ratios of 4-fluoroanisole from 2 to 5 moles per 1 mole of cyclohexene and 0.4 mole of $BF_3 \cdot H_3PO_4$, the yield of (V) regularly increases from 63 to 86%, and the yield of (VI) decreases from 41 to 16% of theory. A temperature in the range 40–80° in this reaction likewise has almost no effect either on the total yield or on their composition. Amounts of the catalyst $BF_3 \cdot H_3PO_4$ from 0.2 to 0.4 mole per 1 mole of olefin at 60° make it possible to obtain (V) and (VI) in almost quantitative yield. 0.1 mole of $BF_3 \cdot H_3PO_4$ per 1 mole of cyclohexene and 2 moles of 4-fluoroanisole at 60° activates the reaction poorly. In this case the yields of (V) and (VI) are, respectively, 26 and 8% of theory. The most favorable conditions for the formation of (V) are: molar ratios of 4-fluoroanisole, cyclohexene, and

$BF_3 \cdot H_3PO_4$ equal to 5 : 1 : 0.4, temperature 60°, and cyclohexene addition time 0.1 mole/hr. Under these conditions (V) is obtained in a yield of 85% of theory. 2,6-Dicyclohexyl-4-fluoroanisole is obtained in the highest yield, 35–40%, when 4-fluoroanisole is reacted with cyclohexene and $BF_3 \cdot H_3PO_4$ in molar ratios of 2 : 1 : 0.4 and at a temperature of 60–80°.

Boron fluoride etherate, in comparison with $BF_3H_3PO_4$, is a catalyst half as active under analogous conditions.

Experimental Part

The 4-fluoroanisole required for the reaction was obtained by diazotization of *p*-anisidine and subsequent decomposition of *p*-methoxyphenyldiazonium tetrafluoroborate (2). It had b.p. 155–156°, d_4^{20} 1.1044; n_D^{20} 1.4878. Propylene was obtained by dehydration of isopropyl alcohol; pseudobutylene, cyclohexene, and the catalysts were obtained as described previously (3). Alkylation was carried out as follows. Into a round-bottom flask equipped with a mechanical stirrer, thermometer, and gas inlet tube (for alkylation with propylene and pseudobutylene) or a dropping funnel (for carrying out the reaction with cyclohexene), a weighed amount of anhydrous orthophosphoric acid was introduced and saturated with boron fluoride to a gain in weight corresponding to a 15–20% excess of BF_3 relative to the formula $BF_3H_3PO_4$. Then a definite amount of 4-fluoroanisole was added; the reaction mixture, in the form of a clear, almost colorless liquid (4-fluoroanisole mixes well with the cata-

(catalyst) was heated to the specified temperature, and, with vigorous stirring, the olefin was introduced. In the reaction with cyclohexene, the reaction mixture rather quickly became colored and by the end of the reaction had become dark brown. After the specified amounts of olefin had been introduced, the mixture was stirred for 2 hr at the experimental temperature, left to stand for 12 hr, mixed with benzene, and treated with water, a 5% soda solution, again with water, dried over calcium chloride, and distilled. After removal of the benzene and of the unreacted starting compounds, the mono- and dialkylfluoroanisoles were usually distilled over within a narrow temperature range. No other products remained in the flask. In the case of the cyclohexyl derivatives, only monocyclohexylfluoroanisole was distilled off from the reaction mixture, while dicyclohexylfluoroanisole remained in the distillation flask. At room temperature it quickly crystallized in the form of colorless or pale-yellow needles. For each experiment, 0.1 mole of olefin and the corresponding amounts of 4-fluoroanisole and catalysts were taken. The most characteristic experiments are summarized in Table 1.

Table 1

Alkylation of 4-fluoroanisole with olefins

Olefin	Catalyst	Molar ratios of fluoroanisole, olefin, and catalyst	Reaction temperature, °C $±$2°	Yield, % of theory: monoalkyl product	Yield, % of theory: dialkyl product
Propylene	$BF_3 \cdot H_3PO_4$	1:1:0,4	80	63,9	22,4
Propylene	$BF_3 \cdot H_3PO_4$	2:1:0,1	60	57,7	32,6
Propylene	$BF_3 \cdot H_3PO_4$	2:1:0,2	60	61,0	29,7
Propylene	$BF_3 \cdot H_3PO_4$	2:1:0,3	60	64,3	33,7
Propylene	$BF_3 \cdot H_3PO_4$	2:1:0,4	40	55,3	39,7
Propylene	$BF_3 \cdot H_3PO_4$	2:1:0,4	60	63,2	32,0
Propylene	$BF_3 \cdot H_3PO_4$	2:1:0,4	80	62,7	31,6
Propylene	$BF_3 \cdot H_3PO_4$	3:1:0,3	60	61,7	25,1
Propylene	$BF_3 \cdot H_3PO_4$	3:1:0,4	60	71,7	23,3
Propylene	$BF_3 \cdot H_3PO_4$	3:1:0,4	60	73,0	26,1
Propylene	$BF_3 \cdot H_3PO_4$	3:1:0,5	60	71,1	28,2
Propylene	$BF_3 \cdot H_3PO_4$	4:1:0,4	60	68,7	23,4
Propylene	$BF_3 \cdot H_3PO_4$	4:1:0,5	60	84,6	14,8
Propylene	$BF_3 \cdot H_3PO_4$	5:1:0,4	60	70,7	19,9
Propylene	$BF_3 \cdot H_3PO_4$	5:1:0,6	60	88,8	11,0
Pseudobutylene	$BF_3 \cdot H_3PO_4$	1:1:0,4	80	53,0	16,2
Pseudobutylene	$BF_3 \cdot H_3PO_4$	1:1:0,4*	80	48,5	22,0
Pseudobutylene	$BF_3 \cdot H_3PO_4$	2:1:0,1	80	traces	traces
Pseudobutylene	$BF_3 \cdot H_3PO_4$	2:1:0,2	80	57,5	18,9
Pseudobutylene	$BF_3 \cdot H_3PO_4$	2:1:0,3	80	56,9	30,8
Pseudobutylene	$BF_3 \cdot H_3PO_4$	2:1:0,4	80	58,7	18,8
Pseudobutylene	BF_3	2:1:0,4	80	64,7	35,3
Pseudobutylene	$BF_3 \cdot O(C_2H_5)_2$	2:1:0,4	80	25,9	–
Pseudobutylene	$BF_3 \cdot H_3PO_4$	2:1:0,4	60	55,2	30,8
Pseudobutylene	BF_3	2:1:0,4	30	49,7	17,8
Pseudobutylene	BF_3	2:1:0,5	80	45,3	31,6
Pseudobutylene	$BF_3 \cdot H_3PO_4$	3:1:0,4	80	70,3	21,4
Pseudobutylene	$BF_3 \cdot H_3PO_4$	3:1:0,4	60	69,4	23,7
Pseudobutylene	$BF_3 \cdot H_3PO_4$	4:1:0,4	60	75,7	20,1
Pseudobutylene	$BF_3 \cdot H_3PO_4$	5:1:0,4	60	67,6	14,0
Pseudobutylene	$BF_3 \cdot H_3PO_4$	5:1:0,5	60	72,4	22,8
Pseudobutylene	$BF_3 \cdot H_3PO_4$	5:1:0,6	60	72,0	17,6
Cyclohexene	$BF_3 \cdot H_3PO_4$	2:1:0,1	60	25,6	8,2
Cyclohexene	$BF_3 \cdot H_3PO_4$	2:1:0,2	60	64,9	32,5
Cyclohexene	$BF_3 \cdot H_3PO_4$	2:1:0,3	60	62,0	34,3
Cyclohexene	$BF_3 \cdot H_3PO_4$	2:1:0,3	80	56,4	39,1
Cyclohexene	$BF_3 \cdot H_3PO_4$	2:1:0,4	40	61,2	37,9
Cyclohexene	$BF_3 \cdot H_3PO_4$	2:1:0,4	60	63,4	36,6
Cyclohexene	$BF_3 \cdot H_3PO_4$	2:1:0,4	80	64,3	34,3
Cyclohexene	$BF_3 \cdot O(C_2H_5)_2$	2:1:0,4	80	31,3	17,5

Olefin	Catalyst	Molar ratios of fluoroanisole, olefin, and catalyst	Reaction temperature, °C $\pm$2°	Yield, % of theory: monoalkyl product	Yield, % of theory: dialkyl product
Cyclohexene	$BF_3 \cdot H_3PO_4$	3:1:0,4	60	71,1	29,4
Cyclohexene	$BF_3 \cdot H_3PO_4$	4:1:0,4	60	80,4	19,6
Cyclohexene	$BF_3 \cdot H_3PO_4$	5:1:0,4	60	85,8	14,2
Cyclohexene	$BF_3 \cdot H_3PO_4$	5:1:0,6	60	81,5	16,8

* Catalyst from the preceding experiment. *R* is isopropyl, sec-butyl, or cyclohexyl.

The alkylation products were purified by repeated distillation (dicyclohexylfluoroanisole—by recrystallization from ethyl alcohol). The monoalkylfluoroanisoles were demethylated to the corresponding 2-alkyl-4-fluorophenols. Table 2 gives the physicochemical constants of the mono- and dialkylfluoroanisoles obtained, as well as of the 2-alkyl-4-fluorophenols obtained by demethylation of the corresponding monoalkylfluoroanisoles.

Table 2

No.	Compound	B.p., °C/mm	d_4^{20}	n_D^{20}
I	2-Isopropyl-4-fluoroanisole	67°/5	1.0624	1.4880
II	2,6-Diisopropyl-4-fluoroanisole	95°/7	1.0363	1.4865
III	2-sec-Butyl-4-fluoroanisole	73–74°/3	1.0234	1.4870
IV	2,6-Di-sec-butyl-4-fluoroanisole	104–105°/3	0.9660	1.4830
V	2-Cyclohexyl-4-fluoroanisole	123°/5	1.0741	1.5142
VI	2,6-Dicyclohexyl-4-fluoroanisole	m.p. 98–99°		

No.	Compound	B.p., °C/mm	d_4^{20}	n_D^{20}
VII	2-Isopropyl-4-fluorophenol	75-77°/4 (m.p. 42°)	1.0944	1.5048
VIII	2-sec-Butyl-4-fluorophenol	92°/4	1.1076	1.5022
IX	2-Cyclohexyl-4-fluorophenol	104-105°/2	1.1231	1.5300

The absence of side processes in the reaction studied, the high yields of the products, and the ease of isolating them in pure form allow us to recommend the alkylation of 4-fluoroanisole with olefins in the presence of $BF_3 \cdot H_3PO_4$ as a convenient preparative method for obtaining 2-alkyl- and 2,6-dialkyl-4-fluoroanisoles.

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Note: Figure translations are in progress. See original paper for figures.

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