SUBSTITUTION IN A NUMBER OF FIVE-MEMBERED HETEROCYCLES WITH ONE HETEROATOM

CATALYTIC ALKYLATION OF N-METHYLPYRROLE AND THIOPHENE WITH OLEFINS

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UDC 547.732.742:542.953.97:543.422.25.4

It has been found that a decrease in the yield of α-substituted products during alkylation with olefins is observed in a number of five-membered heterocycles (furan, thiophene, and N-methylpyrrole). The change in the α-orienting effect depends not only on the nature of the heteroatom but also on the type of reaction and on the conditions of the process. In the case of N-methylpyrrole, the possibility of C-alkylation of the pyrrole ring with olefins was demonstrated for the first time.

It is known that in electrophilic substitution processes of benzoheterocycles one observes a tendency for weakening of the α-orienting effect of the heteroatoms in the order benzofuran > benzothiophene > indole, while primarily α-substituted products* [1] are formed in the electrophilic substitution of furan, thiophene, and pyrrole [1]. The decrease in the yield of the α isomer in the benzoheterocycle series is associated with the effect of a number of factors, including the nature of the heteroatom. Since this sort of regularity exists in a number of condensed heterocycles, we assumed that in five-membered heterocycles one should also observe a similar weakening of the α-orienting effect of the heteroatoms: furan > thiophene > pyrrole.

We confirmed this assumption in the case of alkylation of five-membered heterocycles with one heteroatom by olefins in the presence of zinc chloride.

By taking into account the negative action of halogen salts of Group III, IV, and V elements and the relative stability of furan in the presence of halides of Group II metals, we were able to show that zinc chloride catalyzes the alkylation of furan by olefins. It was established that 10-17% β-monoalkylfuran is formed along with the α-substituted furans [6].

There is practically no information in the literature regarding the alkylation of the pyrrole ring with olefins. Considering the similarity in the chemical properties of five-membered heterocycles, we assumed that pyrrole and its derivatives, like furan, would also react with olefins in the presence of zinc chloride. N-Methylpyrrole was used in place of pyrrole in a study of the conditions for alkylation of the pyrrole ring in order to avoid reaction at the imine hydrogen, since it has been shown that pyrrole and 1-methylpyrrole undergo identical substitution – exclusively in the α position – in metallation, acylation, and formylation [7]. In the present paper we demonstrate that a mixture of 1-methyl-2-tert-butylpyrrole and 1-methyl-3-tert-butylpyrrole is formed in the alkylation of N-methylpyrrole with isobutylene in the presence of zinc chloride. In contrast to furan, more 3-alkyl-substituted N-methylpyrroles are formed

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*The principal exception to this is the alkylation of thiophene, in which up to 30% of the β isomer is formed [2]. In the nitration of thiophene and pyrrole, 5-7% of the β isomer is formed [3, 4]. The β isomer was found by qualitative means in attempts to alkylate furan with propylene. However, in subsequent studies involving alkylation with butenes and amylenes the β isomer was not isolated [5].

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 502-506, April, 1973. Original article submitted July 3, 1970; revision submitted April 24, 1972.

TABLE 1. Catalytic Alkylation of N-Methylpyrrole with Isobutylene

Amount of catalyst, g	Methylpyrrole–isobutylene ratio	Time, h	Temperature, °C	Degree of conversion of methylpyrrole, %	Degree of conversion of isobutylene, %	Yield of monoalkylated product, %						Ratio of 2- and 3-alkyl isomers
						2- and 3-alkyl-substituted		2-alkyl-substituted		3-alkyl-substituted		
						with resp. to conv. isobutylene	with resp. to conv. methylpyrrole	with resp. to conv. isobutylene	with resp. to conv. methylpyrrole	with resp. to conv. isobutylene	with resp. to conv. methylpyrrole	
3	1 : 1	3	200	35,3	17,9	45,0	22,6	14,0	6,8	31,5	15,5	0,3 : 0,7
5	1 : 1	3	150	21,2	19,6	8,1	8,0	3,1	2,9	5,5	5,1	0,36 : 0,64
3	1 : 1	1	200	23,2	23,2	12,7	12,4	2,8	2,7	9,9	9,7	0,22 : 0,78
3	1 : 1	1	250	34,0	27,6	28,3	22,6	3,3	2,7	25,0	19,9	0,12 : 0,88
3	1 : 1	5	200	40,0	36,6	46,5	42,0	11,7	10,4	34,8	31,6	0,25 : 0,75
3	1 : 1	7	200	38,4	34,0	40,5	35,2	12,1	9,5	28,4	25,7	0,27 : 0,73
3	1 : 1	5	250	53,7	38,0	46,5	33,0	4,0	3,0	42,5	30,0	0,09 : 0,91
3	1 : 1	5	150	24,6	20,6	45,0	41,5	12,5	11,5	32,5	30,0	0,28 : 0,72
3	1 : 1	5	225	44,0	37,6	40,0	33,7	4,8	4,4	35,2	29,3	0,12 : 0,88
3	1 : 1,5	5	200	46,0	60,5		50,2		10,7		39,5	0,21 : 0,79
3	1 : 1,75	5	200	54,0	61,5		65,7		12,0		53,7	0,18 : 0,82
3	1 : 2	5	200	61,0	69,0		67,0		10,4		56,6	0,15 : 0,85
5	1 : 2	5	200	70,0	80,5		55,5		5,0		50,5	0,09 : 0,91
1	1 : 2	5	200	22,8	26,0		73,0		25,2		47,8	0,34 : 0,66
0,5	1 : 2	5	200	11,1	23,2		85,5		32,0		53,5	0,37 : 0,63

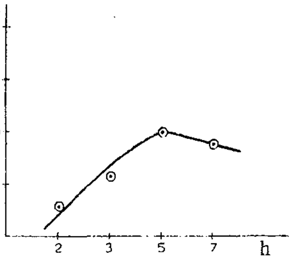

Fig. 1

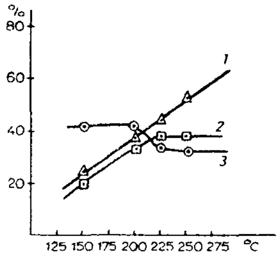

Fig. 2

Fig. 1. Effect of the reaction time on the yield of butyl-N-methylpyrrole.

Fig. 2. Effect of the temperature on the alkylation: 1) degree of conversion of N-methylpyrrole; 2) degree of conversion of isobutylene; 3) yield of butyl-N-methylpyrrole.

than 2-alkyl-substituted derivatives. It must be noted that the ratio of the isomeric 2- and 3-alkyl-substituted N-methylpyrroles depends on the reaction conditions and is ~ 10 : 90; this figure differs sharply from the corresponding ratios of isomers obtained in the alkylation of furan (90 : 10). We investigated the effect of reaction temperature, reaction time, reagent ratio, and amount of catalyst (Table 1) on the yield of monobutyl derivatives.

The study of the effect of reaction time (Fig. 1) was carried out at 200°. It was shown that the yield of butyl derivative increases from 12.4 to 42% as the reaction time increases from 1 h to 5 h. The yield of the butyl derivative falls to 35.2% when the reaction time is subsequently increased to 7 h. The effect of temperature was studied in the 150-250° range (Fig. 2). It was found that while the conversion of N-methylpyrrole is proportional to the temperature, the conversion of isobutylene above 200° is stabilized. The maximum yield of the butyl derivative (42%) is achieved at 200°.

The effect of the reagent ratio was studied at 200° (Fig. 3). It was shown that the yield of the butyl derivative increases from 42% to 67% when the N-methylpyrrole–isobutylene ratio changes from 1 : 1 to 1 : 2. An investigation of the dependence of the yield of the butyl derivative on the amount of catalyst showed (Fig. 4) that the yield of the monoalkylated compound decreased, respectively, from 85.5% to 55.5% as the amount of catalyst was increased from 0.5 g to 5 g. However the highest yield of the monoalkylated compound (85.5%) is reached for the lowest value of the degree of conversion of N-methylpyrrole (11.1%). The yield in the presence of 3-5 g of catalyst can therefore be considered to be the optimum value. We note that at 150-250°, the percentage of the β isomer in the monoalkylate reaches 72-91%.

TABLE 2. Alkylation of Thiophene with Isobutylene*

Temp., °C	Reaction time, h	Deg. of conversion of thiophene, %	Deg. of conversion of isobutylene, %	Yield of alkylthiophene, %			Ratio of 2- and 3-alkylthiophenes
				monosubstituted	2-alkyl-substituted	3-alkyl-substituted	
225	3	40,0	65,0	37,0	27,0	10,0	0,73 : 0,27
200	1	33,3	58,0	35,0	26,2	8,8	0,75 : 0,25
250	1	37,0	60,0	33,6	23,9	9,7	0,71 : 0,29
150	1	24,4	43,7	25,0	19,8	5,2	0,79 : 0,21
300	1	65,0	62,0	30,0	28,7	1,3	0,96 : 0,04

*Thiophene – isobutylene ratio 2 : 1, 3 g of $ZnCl_2$.

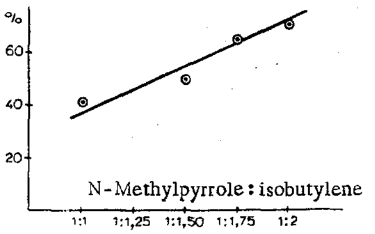

Fig. 3

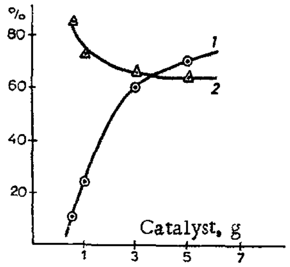

Fig. 4

Fig. 3. Effect of the reagent ratio on the yield of butyl-N-methylpyrrole.

Fig. 4. Dependence of the yield of butyl-N-methylpyrrole on the amount of catalyst: 1) degree of conversion of N-methylpyrrole; 2) yield of butyl-N-methylpyrrole.

In the present study we have for the first time demonstrated that zinc chloride catalyzes the alkylation of thiophene with olefins (Table 2). A study of the effect of temperature showed that the maximum yield is reached at 200°. The monoalkylation products proved to be a mixture of α and β isomers. At 150-300°, the amount of the β isomer in the mixture of monoalkyl derivatives reaches 29%.

Thus an analysis of the results obtained in the alkylation of furan, thiophene, and N-methylpyrrole in the presence of zinc chloride confirmed our assumption that, as in the benzoheterocycle series, in the five-membered heterocycle series one observes weakening of the α-orienting effect of the heteroatom: furan > thiophene > N-methylpyrrole (Fig. 6). However, one apparently cannot explain this sort of dependence only by the effect of the nature of the heteroatom. The type of reaction and the reaction conditions probably also have a definite effect here. The effect of the type of reaction can be demonstrated satisfactorily on comparison of the alkylation reactions, on the one hand, with the acylation, sulfonation, and halogenation reactions of heterocycles, on the other. While all three heterocycles give a mixture of the α and β isomers (the ratio of which changes in the various heterocycles) in the case of alkylation, substitution proceeds primarily at the α position [1] in the acylation, sulfonation, and halogenation of furan, thiophene, and pyrrole. An investigation of the effect of temperature, reagent ratio, amount of catalyst, and reaction time in the alkylation of furan with isobutylene in the presence of an H_3PO_4/kieselguhr catalyst showed that under more severe conditions the α-orienting effect of the heteroatom drops sharply [8]. Similar results are obtained in the alkylation of N-methylpyrrole in the presence of zinc chloride. It was found that the yield of α-alkyl isomers falls sharply (Fig. 5) as the amount of catalyst, the N-methylpyrrole–isobutylene ratio, and the temperature are increased. The temperature has a considerable effect on the change in the ratio of α and β isomers formed. A comparison of the results of the alkylation of furan, thiophene, and N-methylpyrrole showed (Fig. 6) that at 150-300° a general decrease in the yield of the α isomer is observed as the temperature rises.

The fact of the formation of not only the α- but also the β-alkyl-substituted compounds in the products of alkylation of furan compelled us to have doubts about the correctness of the opinion that only the α isomers are formed in the electrophilic substitution of benzofuran [1]. There is no information in the literature concerning the alkylation of benzofuran with olefins. We were able to show that benzofuran

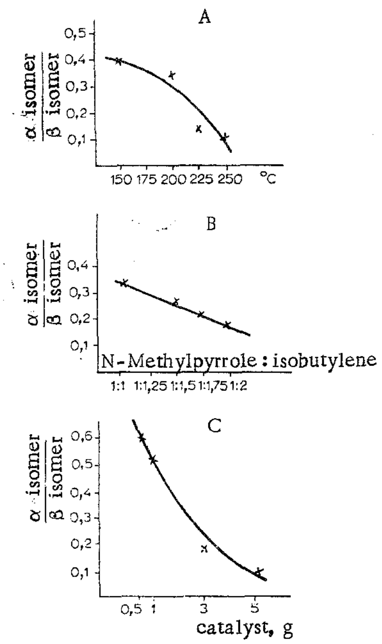

Fig. 5. Change in the ratio of the alkyl isomers of N-methylpyrrole as a function of the temperature (A), reagent ratio (B), and amount of catalyst (C).

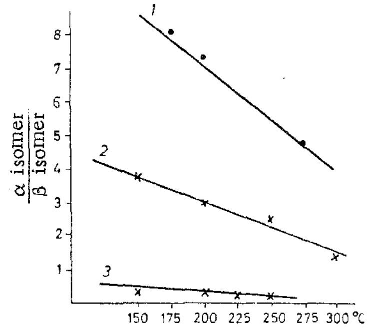

Fig. 6. Change in the ratio of the alkyl isomers formed in the alkylation of furan (1), thiophene (2), and N-methylpyrrole (3) in the presence of zinc chloride at 150-300°C.

reacts with olefins in the presence of H_3PO_4/kieselguhr. We worked out a preparative method for the production of monoalkylbenzofurans in yields up to 77% [9]. Despite the prevailing opinion, it was found that substitution in the β position is also observed along with α substitution of the furan ring, and the β isomer is formed in greater amounts than the α isomer. In addition, it must be noted that substitution in the benzene ring is observed along with substitution in the furan ring.

EXPERIMENTAL

The experiments were carried out in a 0.25-liter steel autoclave with 0.4 mole of the heterocycle. Reactive anhydrous zinc chloride was used as the catalyst. The resulting alkylate was fractionally distilled and analyzed by gas–liquid chromatography: the pyrroles were analyzed with an LKhM-4 chromatograph with a thermal-conductivity detector (with helium as the carrier gas and polyethylene glycol adipate as the liquid phase; l = 2 m), while the thiophenes were analyzed with a chromatograph with a microflame detector (with hydrogen as the carrier gas and tricresyl phosphate as the liquid phase; l = 2 m). The individual substances, which were isolated from the combined alkylate by column fractionation, were analyzed by GLC and IR and PMR spectroscopy. The PMR spectra were recorded with an RS-60 spectrometer. The chemical shifts were measured relative to hexamethyldisiloxane, the shift of which on the δ scale was taken as 0.05 ppm. The following alkylation products were isolated by fractionation of the catalyzate with a column with 40 theoretical plates.

1-Methyl-2-tert-butylpyrrole. This compound had bp 67° (8 mm) n_D^{20} 1.4885, and d_4^{20} 0.8828. Found: C 78.6; 78.9; H 10.6; 10.8; N 10.4; 10.6%. $C_9H_{15}N$. Calculated: C 78.8; H 11.0; N 10.2%.

1-Methyl-3-tert-butylpyrrole. This compound had bp 65° (10 mm), n_D^{20} 1.4770, and d_4^{20} 0.8715. Found: C 78.6; 78.9; H 10.6; 10.8; N 10.4; 10.5%. $C_9H_{15}N$. Calculated: C 78.8; H 10.0; N 10.2%.

The ring structure, the site of the substituent, and the degree of branching of the side chain were proved by IR and PMR spectroscopy. Two groups of lines were observed in the spectra of the α and β protons of 1-methyl-3-tert-butylpyrrole. One, centered at δ 5.95 ppm, belongs to the β proton; the other, at δ 6.35 ppm, belongs to the α proton. The relative integral intensity is, respectively, 1 : 2; this confirms the indicated character of the substitution. In the spectrum of 1-methyl-2-tert-butylpyrrole, the lines from the β protons at 5.85 ppm have an integral intensity that corresponds to two protons. The line from the α proton at δ 6.25 ppm has an integral intensity that corresponds to one proton. The indicated ratio of the integral intensities made it possible to confirm the structure of the α-alkyl derivative of N-methylpyrrole.

Workup of the catalyzate from the alkylation of thiophene gave 2-tert-butylthiophene with bp 163°, n_D^{20} 1.4933, and d_4^{20} 0.9525, and 3-tert-butylthiophene with bp 163°, n_D^{20} 1.5021, and d_4^{20} 0.9585 (the physical constants were in agreement with the literature values [2]).

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