

REACTIONS OF FURANS, THIOPHENES AND PYRROLES WITH ACTIVATED CARBONYL COMPOUNDS
UNDER THERMAL AND HIGH PRESSURE CONDITIONS

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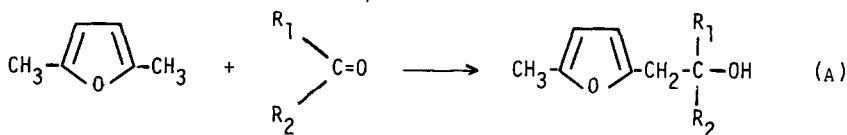
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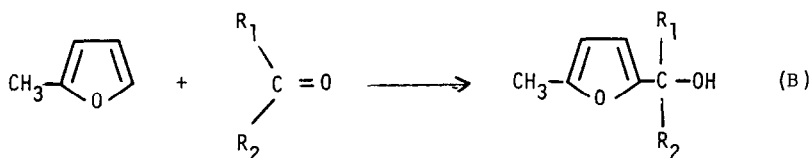
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Unsubstituted or α -methyl substituted five-membered heterocycles react under thermal and high pressure conditions with activated ketones affording electrophilic substitution products (B). 2,5-Dimethylfuran, -thiophene and pyrroles give substituted products (A). With dimethylpyrroles, β -substitution may occur leading to products (C). The reactions are supposed to proceed via ene-like reactions.

Recently, the unusual high pressure reaction of 2,5-dimethylfuran with carbonyl compounds affording the "ene-type" products (A), has been reported.



On the other hand, it is well known that furan and 2-methylfuran react with activated carbonyl compounds yielding normal electrophilic substitution products (B)²



Since our high pressure studies on reactivity of carbonyl compounds toward activated unsaturated hydrocarbons, we are prompted to report our new observations on reactions between activated ketocompounds and some five membered heterocycles (furan, thiophene and pyrrole) and their α -methyl substituted derivatives.

The thermal reactivity of ketones toward unsaturated³ or strained hydrocarbons⁴ is considerably enhanced when electron withdrawing substituents are attached to the carbonyl bond. Thus dialkyl mesoxalates have proved to be powerful dienophiles⁵ or enophiles⁶ allowing mild reaction conditions. When the C=O bond is substituted by only one activating group (e.g. alkyl pyruvate or phenylglyoxalate) reactivity is considerably lowered or nil, as exemplified in the reactions of 2-methyl or 2,5-dimethylfuran (cf. Table I).

TABLE I

Reactions of methylfurans with carbonyl compounds (in CH_2Cl_2 , 24h)

Furan	R_1	R_2	Conditions (a)		Product (yield)
			Pressure (MPa)	T (°C)	
2-methyl	CO_2CH_3	CO_2CH_3	0.1	50	B (25%)
			600	20	B (100%)
	CH_3	$\text{CO}_2\text{C}_2\text{H}_5$	0.1	70	no reaction
			850	70	B (80%)
2,5-dimethyl	CO_2CH_3	CO_2CH_3	0.1	20-50	no reaction
			850	20	A (100%)
	C_6H_5	CO_2CH_3	0.1	20-50	no reaction
			850	20	A (40%)

TABLE II

Reactions of thiophenes and pyrroles  with carbonyl compounds (a)

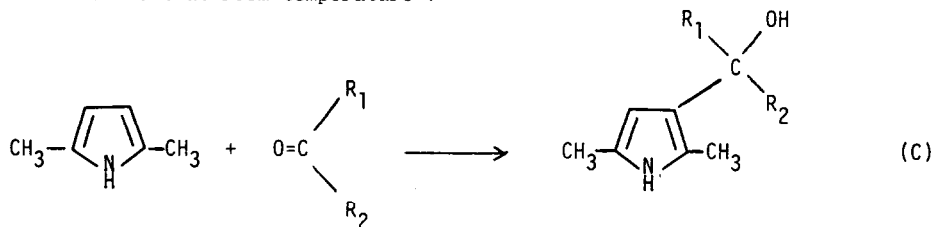
Entry	X	R	R_1	R_2	Pressure (MPa)	T (°C)	Product	Yield (%)
1	S	H	CO_2Et	CO_2Et	0.1	70	B	30
2	S	CH_3	CO_2Et	CO_2Et	800	40	A	85
3	S	CH_3	CO_2Me	C_6H_5	900	70	A	76
4	NH	H	CO_2Et	CO_2Et	0.1	20	B	75
5	NCH_3	H	CO_2Et	CO_2Et	0.1	60	B	87
					850	20	B	65
6	NCH_3	H	CO_2Me	C_6H_5	850	70	B	100
7	NH	CH_3	CO_2Et	CO_2Et	0.1	20	A or C	99
8	NCH_3	CH_3	CO_2Et	CO_2Et	0.1	20	C	100
9	NCH_3	CH_3	CO_2Et	C_6H_5	0.1	20	C	31
10	NCH_3	CH_3	CO_2Et	CH_3	0.1	20	C	46

(a) except in entry 7, the carbonyl compound is added to a CH_2Cl_2 solution of the heterocycle cooled at -60°C . Then the mixture is allowed to warm up to the desired temperature or is submitted to pressure where indicated. The reaction is stopped after 24 h or 48 h (entries 2, 3).

The reactions of 2-methylfuran with carbonyl compounds carried out under high pressure conditions lead to the α -substituted tertiary alcohol (B), whereas under normal pressure only dimethylmesoxalate gives the expected product. In case of 2,5-dimethylfuran, the high pressure reactions with carbonyl compounds afford the appropriate product (A).

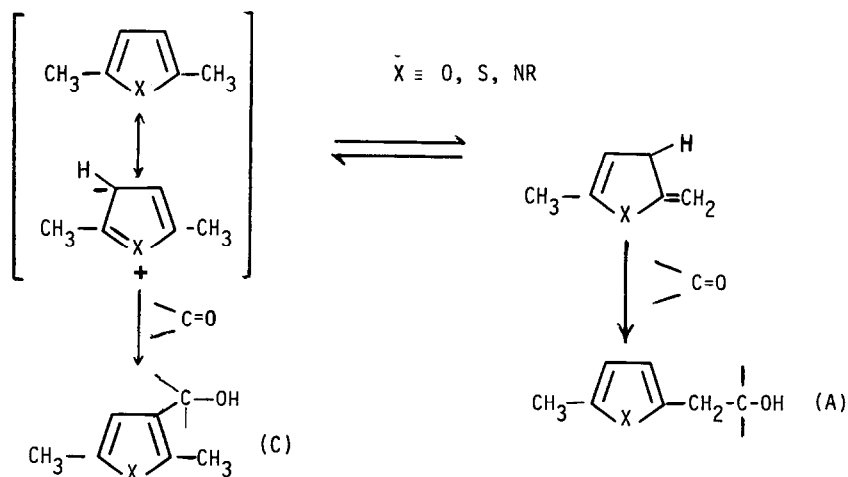
It was of interest to compare the behaviour of the corresponding thiophenes and pyrroles. The results are listed in Table II.

Unsubstituted thiophenes and pyrroles lead to the expected substitution product (B)⁷ under normal pressure conditions (entries 1, 4, 5, 6). 2,5-Dimethylthiophene affords an A-type adduct⁸ as it might have been expected from the corresponding reaction of 2,5-dimethylfuran, the reaction also needs high pressure assistance (entries 2, 3). With 2,5-dimethylpyrrole, the reaction proceeds smoothly under normal pressure and temperature (entry 7) leading to the reaction product in quantitative yield. However depending on conditions, either the A-type product, or the β -substituted (type C) derivative is obtained. It should be noted that under conditions of Table II (dilute CH_2Cl_2 solution of dimethylpyrrole) only product C is formed⁹, while compounds is the exclusive product when the reactants are mixed without solvent at room temperature :



Likewise reactions involving 1,2,5-trimethylpyrrole and carbonyl compounds (entries 8, 9, 10) afford a single product (C)¹⁰; interestingly the A-type adduct could not be formed.

The formation of the "ene-like" reaction product (A) may be explained according to our earlier suggestion¹, but this hypothesis can be extended for the interpretation of β -electrophilic substitution as shown in Scheme



The formation of the product (C) is observed only in case of pyrrole derivatives. This is in good agreement with polarized cannonic form which participation is more plausible than in case of 2,5-dimethylfuran and -thiophene.

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- 8) Adduct A (entry 2) NMR (CDCl₃, δ ppm|TMS) 6.50 (CH=C, d, 2), 4.25 (OCH₂, q, 4), 3.45 (CH₂, s, 2), 2.48 (CH₃-C=C, s, 3), 1.30 (CH₃-C, t, 6).
- 9) Adduct A (entry 7) NMR (CDCl₃, δ ppm|TMS), 8.05 (NH, s, 1), 5.80 (CH=C, d, 2), 4.25 (OCH₂, q, 4), 3.75 (OH, s, 1), 3.48 (CH₂, m, 2), 2.17 (CH₃-C=C, s, 3), 1.30 (CH₃-C, t, 6).
Adduct C (entry 7) NMR (CDCl₃, δ ppm|TMS), 8.02 (NH, s, 1), 5.80 (CH=C, s, 1) 4.35 (OCH₂, q, 4), 3.83 (OH, s, 1), 2.15 (CH₃-C=C, s, 6), 1.31 (CH₃-C, t, 6)
Mass and IR spectra are quite consistent with the assigned structures.
- 10) Adduct C (entry 8) NMR (CDCl₃, δ ppm|TMS), 5.85 (CH=C, s, 1), 4.20 (OCH₂, q, 4), 3.75 (OH, broad, 1), 3.36 (CH₃-N, s, 3), 2.17 (CH₃-C=C, s, 6), 1.30 (CH₃-C, t, 6).

N.B. The above spectroscopic data are given for representative products of type(A) and(C) All others are available upon request. The products are all new, except for some (B) methylfuran compounds formerly described (O. ACHMATOWICZ and B. SZECHNER, Rocz. Chem., 46, 513 (1972)

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