UDC 547.77 + 542.95

RESEARCHES ON PYRAZOLES

L. Acylating Pyrazoles in the Presence of Traces of Sulfuric Acid*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 3, pp. 407-411, 1965

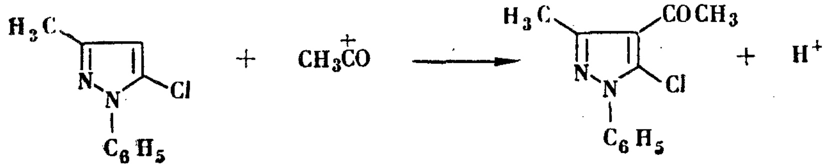
Alkyl and aryl pyrazoles are acylated at position 4 by the chloroanhydrides and anhydrides of the lowest fatty and aromatic acids in the presence of catalytic amounts of sulfuric acid. Reaction is readily effected because it is the neutral pyrazole molecule which is being acylated. In individual cases 1, 3, 5-trimethylpyrazole can be alkylated at position 4 by the Friedel-Crafts reaction.

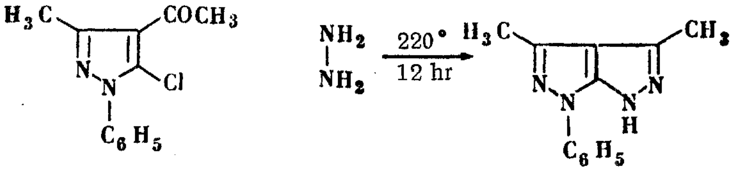
When previously studying the Friedel-Crafts reaction in the pyrazole series, it was found [1] that 1-alkyl- and 1-arylpyrazoles with only one electron-donating group at positions 3 and 5, can be acylated at position 4 using aluminum chloride, though 1-phenylpyrazole and 1-phenyl-3-methyl-5-chloropyrazole have so far not been found to react.

During a search for other acylation catalysts, it has been found that sulfuric or perchloric acid in catalytic quantities are excellent ones. Simply boiling n-alkyl- or aryl-substituted pyrazoles with excess acetic anhydride in the presence of 2 ml sulfuric acid per 0.1 mole pyrazole gave satisfactory yields of 4-acetylpyrazoles (see table). All the 4-acetylpyrazoles prepared here readily give the iodoform reaction, which is indirect evidence for the presence of the MeCO group.

Only monoacetyl derivatives were obtained when reaction was effected under the conditions developed, indicating that the acetyl group entered the pyrazole ring only, phenyl substituent present not being attacked. This was demonstrated by chromatography and comparison of constants for the structure 1-phenyl-3, 5-dimethyl-4-acetylpyrazole, which was completely identical with a specimen of known structure [1]. Indirect evidence of the presence of an acetyl group at precisely position 4 of the pyrazole was cyclization of 1-phenyl-3-methyl-5-chloro-4-acetylpyrazole by Rojahn's method [2] (but using more drastic conditions), with hydrazine, to the corresponding pyrazolopyrazole.

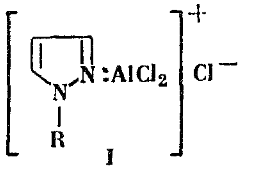
$$(CH_3CO)_2O + H_2SO_4 \rightarrow CH_3COOH + [CH_3COOSO_3H] \longleftrightarrow CH_3\overset{+}{C}O + \overset{-}{S}O_3OH$$





The most unexpected thing was that sulfuric acid (which, in the present work, always gave better results than perchloric acid) enabled acylation to be effected with chloroanhydrides of fatty and aromatic acids.

The table gives yields and constants for the 4-acylpyrazoles prepared. The method made it possible to introduce various acyl groups of fatty and aromatic acids into molecules, e.g., 1-phenyl- and 1-alkylpyrazoles, which could not be acylated by the Friedel-Crafts method [1]. Under those conditions, even a 3, 5-dimethylpyrazole unsubstituted at the nitrogen atom (actually 1-acetyl-3, 5-dimethylpyrazole) gave with benzoyl chloride a 25% yield of 4-benzoyl-3, 5-dimethylpyrazole, which it is rather a problem to prepare by an indirect method [3]; reaction of 4-acetyl-3, 5-dimethylpyrazole with acetic anhydride gives an even higher yield.



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Actually, it is the pyrazolonium cation I, which reacts in acylation by the Friedel-Crafts method and naturally this exhibits strongly depressed reactivity for electrophilic substitution, and additional influences (e.g., presence of electron-donating groups [1]) are needed to make the reaction take place. Under the conditions described above, sulfuric acid and a chloroanhydride or anhydride give a corresponding mixed anhydride which, decomposing

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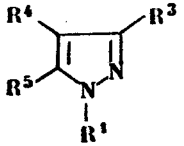
*For Part IL see [6].

4-Alkyl- and 4-Arylpyrazoles



No.	R^1	R^3	R^4	R^5	Bp, °C (pressure mm)	Mp, °C	Formula	Found, %				Calculated,%		Value of R_f on Al_2O_3		Yield, %
								C		H		C	H	Benzene-chloroform 1: 1	Benzene	
1	CH_3	CH_3	$COCH_3$	CH_3	133—137(11)	69—70[1]	—	—	—	—	—	—	—	0.29	0.13	54
2	C_6H_5	CH_3	$COCH_3$	CH_3	185—186,5(7)	59—59,5[1]		—	—	—	—	-	—	0,42	0.31	76
3	C_6H_5	CH_3	$COCH_3$	Cl	193—195(6)	76—77	$C_{12}H_{11}ClN_2O$	61,82	61.70	5.22	5.12	61,41	4.72	0.58	0,49	39
4	C_6H_5	Cl	$COCH_3$	H	192—194(6)	125	$C_{11}H_9ClN_2O$	59.66	59,50	4.44	4.25	59.68	4.13	—	—	49
5	C_6H_5	H	$COCH_3$	H	155—160(5)	128—128,5[4]	—	—	—	—	—	—	—	0.40	0,24	76
6	C_6H_5	C_6H_5	$COCH_3$	C_6H_5	—	123—124	$C_{23}H_{18}N_2O$	81.59	81.54	5.55	5.50	81.63	5.36	0.65	0,49	46
7	CH_3	CH_3	C_3H_7	CH_3	82—84(9)	n_D^{20} 1.4800	$C_9H_{16}N_2$	71,30	71,10	10.70	10,65	71,05	10.62	—	—	70
8	CH_3	CH_3	*i*-C_3H_7	CH_3	93—95(10)	n_D^{20} 1.4806	$C_9H_{16}N_2$	71.47	71.38	10,67	10.63	71.05	10.62	—	—	71
9	CH_3	CH_3	C_4H_9	CH_3	97—98(11)	n_D^{20} 1.4787	$C_{10}H_{18}N_2$	71.96	71.94	10,92	10.83	72.24	10,88	—	—	70
10	C_6H_5	CH_3	COC_3H_7	CH_3	198—205(7)	62.5—63	$C_{15}H_{18}N_2O$	74.07	73.93	7.24	7.49	74.35	7.49	0.49	0.41	25
11	CH_3	CH_3	COC_5H_{11}	CH_3	170—177(9)	36.5[1]	—	—	—	—	—	—	—	0.45	0.28	40
12	C_6H_5	H	COC_5H_{11}	H	199—205(7)	115.5—116	$C_{15}H_{18}N_2O$	74.26	74.40	7,56	7.64	74.34	7.48	0.58	0.39	27,1
13	C_6H_5	CH_3	COC_5H_{11}	CH_3	193—195(7)	*	$C_{17}H_{22}N_2O$	75,48	75.43	8.26	8.31	75.51	8.24	0.62	0.53	63
14	C_6H_5	CH_3	COC_5H_{11}	Cl	196—198(6)	56—57	$C_{16}H_{19}ClN_2O$	66.54	66.49	6.59	6.72	66.08	6.58	0.67	0.54	29
15	C_6H_5	H	COC_6H_5	H	191—193(5)	125—125.5[4]	—	—	—	—	—	—	—	0.47	0.35	66
16	C_6H_5	H	*p*-$CH_3OC_6H_4CO$	H	205—210(7)	171—172	$C_{17}H_{14}N_2O_2$	73.57	73.64	5.12	5.17	73.36	5.07	0.43	0.27	33,8
17	C_6H_5	H	$SO_2C_6H_5$**	H	235—236(10)	145.5—146	$C_{15}H_{12}N_2O_2S$	63.56	63.67	4.33	4.38	63.35	4.26	0.36	0.20	31

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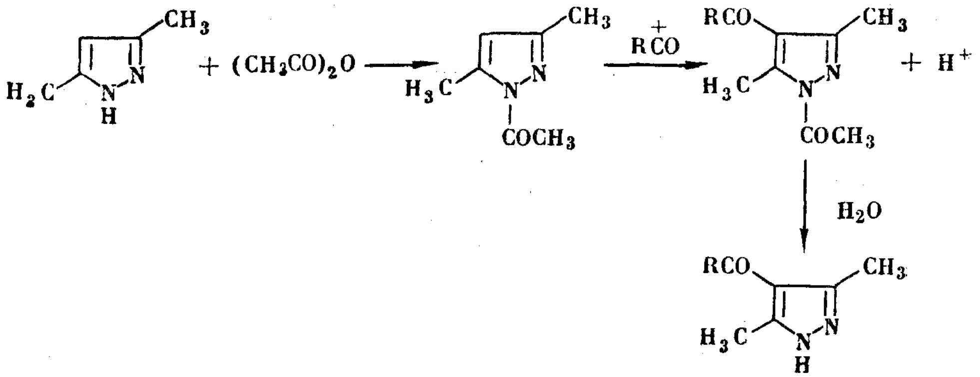
*n_D^{20} 1. 5520; d_4^{20} 1. 0485.

**Catalyst: p-toluenesulfonic acid.

on heating, is also the generator of the carbonium ion RCO. Then the carbonium ion attacks the neutral molecule of pyrazole (since with anhydrides and chloroanhydrides of acids pyrazoles give only unstable compounds) which is consequently more active. Under the drastic reaction conditions the hydrogen chloride which separates also does not add to the weakly basic pyrazole.



$$\begin{array}{c} RCOCl + HO{-}SO_3H \rightarrow [RCOOSO_3H] + HCl \\ \downarrow\!+\!\uparrow \quad - \\ \overset{+}{RCO} + \overset{-}{SO_4H} \end{array}$$

Under these conditions pyrazoles were not alkylated at position 4 by alkyl halides, but it proved possible, under Friedel-Crafts conditions (see experimental) to introduce propyl, isopropyl, and butyl groups at position 4 in the 1, 3, 5-trimethylpyrazole molecule. But under these conditions, and even in the presence of the more active $AlBr_3$, ethyl, isobutyl, amyl, and isoamyl chlorides, and also isoamyl bromide and iodide, did not react. Questions of possible isomerization of groups by $AlCl_3$ were ignored.

Experimental

Acylation with acetic anhydride. 0. 1 mole pyrazole was added to a mixture of 0. 4 mole acetic anhydride and 2 ml 96% sulfuric acid, and the whole heated in a flask for 10 hr under reflux. Excess acetic anhydride was distilled off in a vacuum on a water bath, the residue decomposed by heating for 30 min with 25 ml 20% sodium hydroxide, and the mixture then extracted with benzene. The benzene extract was vacuum-distilled. Yields and constants of the 4-acetylpyrazoles obtained are given in the table.

Acylation with chloroanhydrides of acids. 0. 1 mole pyrazole was added to a mixture of 0. 2 mole chloroanhydride of the acid and 2 ml 96% sulfuric acid, and the whole heated for 6 hr in an oil bath at 200° under reflux. After cooling 100 ml 20% sodium hydroxide was added to the reaction products, the whole refluxed for 30 min, and then extracted with benzene. The benzene extract was distilled in a vacuum. Yields and constants for the 4-acylpyrazoles are given in the table.

4-Acetyl-3, 5-dimethylpyrazole. 19. 2 g 3, 5-dimethylpyrazole with R_f[*] 0. 5 (Al_2O_3; benzene-acetone 3: 2); 0. 56 (Al_2O_3; ethyl acetate chloroform 3: 1), was added gradually to a mixture of 81. 6 g acetic anhydride and 4 ml 96% sulfuric acid, and the whole refluxed for 15 hr. Excess acetic anhydride was distilled off in a vacuum, heating being on a water bath. The residue was refluxed for 10 min with 80 ml concentrated hydrochloric acid plus 2 g active carbon, then cooled, then filtered to remove the carbon. The filtrate was evaporated to dryness in a vacuum on a water bath. The dry residue was dissolved in 20 ml water, and gradually made alkaline with 15 g sodium acetate trihydrate. The precipitate of 4-acetyl-3, 5-dimethylpyrazole (containing 1 molecule of water of crystallization) was separated off. Yield 12. 5 g (45. 3%) mp 111-112°. R_f 0. 55 (Al_2O_3; benzene-acetone 3: 2); 0. 58 (Al_2O_3; ethyl acetate-chloroform 3: 1). Picrate mp 145-146° (from alcohol). Both the pyrazole and its picrate are identical with specimens of known structure [3].

4-Benzoyl-3, 5-dimethylpyrazole. 9. 6 g 3, 5-dimethylpyrazole is added gradually to a mixture of 29. 5 g benzoyl chloride and 6 ml 96% sulfuric acid, and the mixture heated for 3 hr under reflux in an oil bath at 200°. The hot reaction products were poured into 200 ml water and rendered alkaline with concentrated ammonia solution. The alkaline solution was refluxed for 10 min with active carbon, and then filtered. The filtrate was acidified to pH 3 with acetic acid. To free the resultant tarry precipitate from tar, it was vacuum distilled, and the mixture of benzamide and 4-benzoylpyrazole obtained was boiled with 100 ml concentrated hydrochloric acid for 3 hr, cooled to 0°, and the benzoic acid filtered off using suction. The filtrate was evaporated to 50 ml and by adding ammonia brought to pH 5. The resultant precipitate of 4-benzoyl-3, 5-dimethylpyrazole was filtered off, and recrystallized from benzene-cyclohexane. Yield 5. 2 g (25%), mp 123-123. 5°. Mixed mp with an authentic specimen [3] undepressed. R_f 0. 65 (Al_2O_3; benzene-

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[*] Here and below results are given obtained by chromatographing using an unstabilized thin layer of aluminum oxide, activity II, visualizer: iodine vapor. Details of the conditions are given in [5].

acetone 3: 2); 0. 68 (Al_2O_3; ethyl acetate-chloroform 3: 1).

Alkylation of pyrazoles. 0. 1 mole 1, 3, 5-trimethylpyrazole was slowly added to a suspension of 0. 5 mole anhydrous aluminum chloride (activated by heating) in 200 ml dry carbon tetrachloride, and then at 0°, addition of 0. 6 mole of the appropriate alkyl chloride with good stirring was begun dropwise. The mixture was stirred for 4 hr, then decomposed with ice, made alkaline with 40% sodium hydroxide solution until the aluminum hydroxide dissolved, then carefully extracted with benzene. The benzene was distilled off, and the residue vacuum-distilled. The table gives the constants and yields for the compounds.

1-Phenyl-3, 3'-dimethylpyrazolo[4, 5-b]pyrazole. A mixture of 0. 01 mole 1-phenyl-3-methyl-4-acetyl-5-chloropyrazole and 0. 06 mole hydrazine hydrate was heated in an ampoule, in an autoclave, for 12 hr at 220°. After recrystallization from methanol, a 20% yield of pyrazolopyrazole, mp 210° was obtained. Found: C 68. 66; 68. 60; H 5. 93; 5. 85%, calculated for $C_{12}H_{12}N_4$: C 67. 93; H 5. 80%.

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24 July 1964

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