THE SEQUENTIAL LITHIATION OF 1-PHENYLPYRAZOLES

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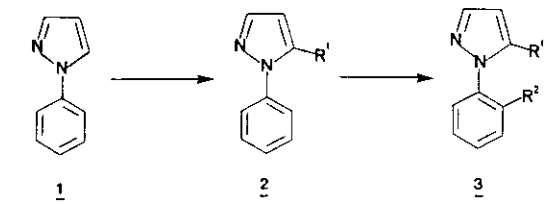
Abstract - 1-Phenylpyrazole is lithiated exclusively at the C-5 position. Suitable 5-substituted 1-phenylpyrazoles undergo lithiation at the ortho position of the phenyl ring. 5-Thiomethyl-1-(o-tolyl) pyrazole is laterally lithiated at the ortho methyl group. In the case of 5-methoxymethyl-1-phenylpyrazole, lithiation occurs at both the C-5 methylene group and the ortho position of the phenyl ring with n-butyllithium, but essentially exclusive lithiation occurs at the C-5 methylene group with LDA.

In continuing work on the synthesis of novel heterocyclic compounds with potential biological activity, we have extended our studies on the lithiation reactions of heteroaromatic compounds[2-7]. This paper summarises the results of our work on the sequential lithiation reactions of 1-phenylpyrazole, as a method of preparing 1-phenylpyrazole substituted at specific positions by various functional groups.

Various publications (mainly patents) exist on pyrazole carboxylic acids and pyrazole acetic acids, in which the -COOH or $-CH_2COOH$ moiety is directly linked to the pyrazole ring. Such compounds are reported to possess antiinflammatory, analgesic and antipyretic activity. Pyrazolebenzoic acids, such as 2-(3-p-methoxyphenyl-5-pyrazolyl)benzoic acid, its esters and amides are reported to be plant growth regulators[8]. p-(3-Pyrazole)phenylacetic acids[9] and p-(1-pyrazole)phenylacetic acids[10], have been patented as antiinflammatory agents. 1-Phenylpyrazole, 1, is reported to lithiate at both the C-5 position and the ortho position of the phenyl ring in a ratio of about 4:1[11]. We found that by careful control of the reaction conditions (dry THF as solvent and a reaction temperature of -65°C or

lower) exclusive lithiation at the C-5 position occurs. The pure C-5 methyl, thiomethyl, methoxymethyl, and carboxylic acid derivatives, 2, were prepared in better than 80% yields, by reacting the lithio-compound with methyl iodide, dimethyl disulfide, chloromethyl methyl ether, and carbon dioxide respectively. Table 1 summarizes the data on the 1-phenyl-5-substituted pyrazoles.



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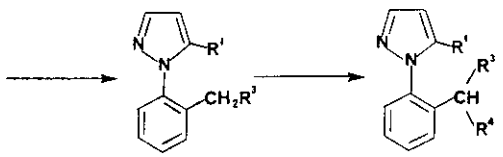

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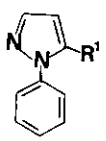
Table 1

5-Substituted 1-Phenylpyrazoles



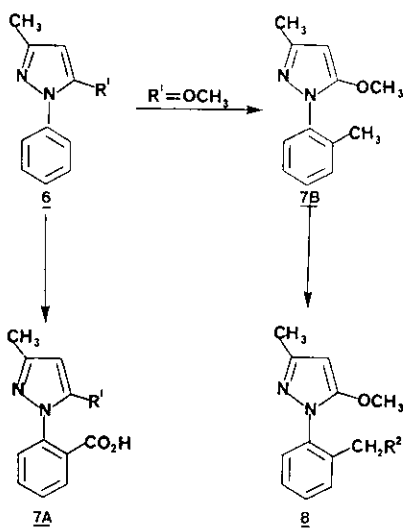
No	R^1	Yield %	bp °C/mm	nmr spectrum 60 MHz ($CDCl_3$), δ
2a	CH_3	99	87-88/0.9	2.25(s,3H,CH_3), 6.05(d,1H,J=2.0Hz,C=CH), 7.32(s,5H, C_6H_5), 7.48(d,1H,J=2.0Hz,N=CH).
2b	SCH_3	95	102-103/0.6	2.10(s,3H,SCH_3), 6.15(d,1H,J=2.0Hz,C=CH), 7.10-7.42 (m,5H,C_6H_5),7.52(d,1H,J=2.0Hz,N=CH).
2c	CH_2OCH_3	80	86-88/0.2	3.22(s,3H,OCH_3), 4.27(s,2H,CH_2O), 6.28(d,1H,J=2.0Hz, C=CH), 7.1-7.55(m,5H,C_6H_5), 7.48(d,1H,J=2.0Hz,N=CH).
2d	COOH	80	183-184 (mp)	7.03(d,1H,J=2.0Hz,C=CH), 7.52(s,5H,C_6H_5), 7.70(d,1H, J=2.0Hz,N=CH)*
2e	$SOCH_3$	90	148-150/0.09	2.83(s,3H,$SOCH_3$), 6.95(d,1H,J=2.0Hz,C=CH), 7.52(s,5H, C_6H_5), 7.75(d,1H,J=2.0Hz,N=CH).
2f	SO_2CH_3	87	140-141 (mp)	2.87(s,3H,SO_2CH_3), 7.05(d,1H,J=2.0Hz,C=CH), 7.56(s,5H C_6H_5), 7.68(d,1H,J=2.0Hz,N=CH).

*Acetone - d_6 as solvent

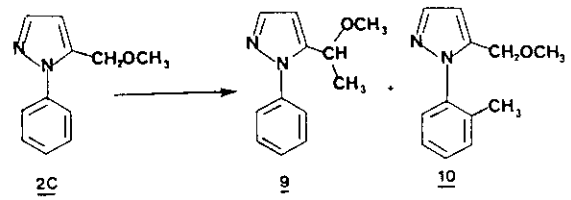
When compounds 2 (R^1= CH_3 or SCH_3) were separately treated with n-butyllithium, exclusive lithiation at the ortho position on the phenyl group occurred, and compounds 3 (R^1= CH_3 or SCH_3 ; R^2= CH_3, SCH_3, CH_2OCH_3 and COOH) were obtained by using appropriate reagents. The compound 3 (R^1= SCH_3, R^2= CH_3) underwent lateral lithiation cleanly at the ortho methyl group to give compounds 4 (R^1= SCH_3, R^3= CH_3, SCH_3 and COOH) after reaction with methyl iodide, dimethyl disulfide and carbon dioxide respectively.

In the case of compound 4 (R^1= SCH_3, R^3= SCH_3) further lithiation with n-butyllithium followed by reaction with dimethyl disulfide gave the thioacetal 5 (R^1= R^3= R^4= SCH_3).

We have previously reported the preparation of the ortho-benzoic acids 7A by the lithiation of 1-phenyl-3,5-dimethylpyrazole, 6 (R^1= CH_3) and 1-phenyl-3-methyl-5-methoxypyrazole, 6 , (R^1= OCH_3), followed by reaction with carbon dioxide[3]. As expected, the 1-(o-tolyl)-3-methyl-5-methoxypyrazole 7B (obtained from the lithio derivative of 6 (R^1= OCH_3) with methyl iodide) gave the ortho lithiomethyl derivative 8 (R^2= Li), with n-butyllithium, and provided the compounds 8 (R^2= CH_3 or COOH) with methyl iodide or carbon dioxide.



1-Phenyl-5-methoxymethylpyrazole, 2c, with n-butyllithium, followed by methyl iodide gave a 1:1 mixture of compounds 9 and 10 (as determined from the nmr spectrum of the product). When lithium diisopropylamide was used as the lithiating agent, almost exclusive formation of compound 9 occurred.

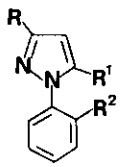


2C 9 10

Table 2 summarizes the data on the 1-(o-substituted phenyl)-5-substituted pyrazoles prepared.

Table 2

1-(o-Substituted phenyl)-5-substituted Pyrazoles



No	R	R^1	R^2	Yield %	bp °C/mm	nmr spectrum 60 MHz ($CDCl_3$), δ
3a	H	CH_3	SCH_3	92	118-120/0.5	2.17(s,3H,C$\underline{H}_3$), 2.33(s,3H,SC$\underline{H}_3$), 6.13(broad s, 1H,C=C$\underline{H}$), 7.10-7.47(m,4H,$C_6\underline{H}_4$), 7.58(broad s, 1H,N=C$\underline{H}$).
3b	H	CH_3	$SOCH_3$	80	143-144/0.4	2.26(s,3H,C$\underline{H}_3$), 2.73(s,3H,SOC$\underline{H}_3$), 6.23(d,1H, J=2.0Hz,C=C$\underline{H}$) 7.37-8.40(m,5H,$C_6\underline{H}_4$ and N=C$\underline{H}$).
3c	H	CH_3	SO_2CH_3	81	123-125 (mp)	2.20(s,3H,C$\underline{H}_3$), 3.20(s,3H,$SO_2C\underline{H}_3$), 6.28(d,1H, J=2.0Hz,C=C$\underline{H}$), 7.37-8.40(m,5H,$C_6\underline{H}_4$ and N=C$\underline{H}$).
3d	H	CH_3	COOH	85	169-170 (mp)	2.18(s,3H,C$\underline{H}_3$), 6.20(broad s,1H,C=C$\underline{H}$), 7.27-8.12(m,5H,$C_6\underline{H}_4$ and N=C$\underline{H}$), 9.43(s,1H,COO$\underline{H}$).
3e	H	SCH_3	CH_3	86	109-110/0.6	2.13(s,3H,C$\underline{H}_3$), 2.37(s,3H,SC$\underline{H}_3$), 6.38(d,1H, J=2.0Hz,C=C$\underline{H}$), 7.40(s,4H,$C_6\underline{H}_4$), 7.72(d,1H, J=2.0Hz,N=C$\underline{H}$).
3f	H	SCH_3	SCH_3	77	161-163/1.0	2.35(s,3H,SC$\underline{H}_3$), 2.38(s,3H,SC$\underline{H}_3$), 6.43(d,1H, J=2.0Hz,C=C$\underline{H}$), 7.27-7.50(m,4H,$C_6\underline{H}_4$), 7.75(d, 1H,J=2.0Hz,N=C$\underline{H}$).
3g	H	SCH_3	CH_2OCH_3	55	123-124/0.8	2.35(s,3H,SC$\underline{H}_3$), 3.33(s,3H,OC$\underline{H}_3$), 4.28(s,2H, $C\underline{H}_2O$), 6.38(d,1H,J=2.0Hz,C=C$\underline{H}$), 7.30-7.67(m,

Table 2 (contd)

						4H, C_6H_4), 7.70(d,1H,J=2.0Hz,N=CH).
3h	H	$SOCH_3$	CH_2OCH_3	82	167/0.05	2.80(s,3H,$SOCH_3$), 3.27(s,3H,OCH_3), 4.26(s,2H, CH_2O), 6.97(d,1H,J=2.0Hz,C=CH), 7.33-7.67(m, 4H,C_6H_4), 7.80(d,1H,J=2.0Hz,N=CH).
3i	H	SO_2CH_3	CH_2OCH_3	80	171-172/0.07	2.88(s,3H,SO_2CH_3), 3.27(s,3H,OCH_3), 4.25(s,2H, CH_2O), 7.08(d.1H,J=2.0Hz,C=CH), 7.43-7.62(m, 4H,C_6H_4), 7.78(d,1H,J=2.0Hz,N=CH).
3j	H	SCH_3	COOH	56	147-149 (mp)	2.32(s,3H,SCH_3), 6.47(d,1H,J=2.0Hz,C=CH), 7.38 -8.08(m,5H,C_6H_4 and N=CH).*
3k	CH_3	OCH_3	CH_3	91	88-90/0.1	2.17(s,3H,CH_3), 2.30(s,3H,CH_3),3.75(s,3H,OCH_3), 5.42(s,1H,C=CH), 7.27(s,4H,C_6H_4).
4a	H	SCH_3	C_2H_5	83	115-116/0.6	1.06(t,3H,J=7.0Hz,CH_2CH_3), 2.25(s,3H,SCH_3), 2.38(q,2H,J=7.0Hz,CH_2CH_3), 6.28(d,1H,J=2.0Hz, C=CH), 7.20-7.38(m,4H,C_6H_4), 7.65(d,1H,J=2.0Hz, N=CH).
4b	H	SCH_3	CH_2SCH_3	65	135-137/0.7	1.90(s,3H,CH_2SCH_3), 2.33(s,3H,SCH_3), 3.57(s,2H, CH_2SCH_3), 6.35(d,1H,J=2.0Hz,C=CH), 7.33-7.60 (m,4H,C_6H_4),7.70(d,1H,J=2.0Hz,N=CH).
4c	H	SCH_3	CH_2COOH	65	83-85 (mp)	2.43(s,3H,SCH_3), 3.50(s,2H,CH_2COOH), 6.35(d,1H, J=2.0Hz,C=CH), 7.33-7.53(m,4H,C_6H_4), 7.68(d,1H, J=2.0Hz,N=CH), 10.41(broad s,1H,COOH).
4d	H	SCH_3	CH_2COOCH_3	95	184-185/1.0	2.35(s,3H,SCH_3), 3.53(s,2H,CH_2COOCH_3), 3.65(s, 3H,OCH_3), 6.36(d,1H,J=2.0Hz,C=CH), 7.35-7.52 (m,4H,C_6H_4), 7.70(d,1H,J=2.0Hz,N=CH).
4e	H	$SOCH_3$	CH_2COOCH_3	75	197-199/0.6	2.87(s,3H,$SOCH_3$), 3.61(s,5H,CH_2COOCH_3 and CH_2COOCH_3), 6.98(d,1H,J=2.0Hz,C=CH), 7.20(s,4H, C_6H_4), 7.83(d,1H,J=2.0Hz,N=CH).
4f	H	SO_2CH_3	CH_2COOCH_3	86	87-88 (mp)	2.97(s,3H,SO_2CH_3), 3.55(s,2H,CH_2COOCH_3), 3.68 (s,3H,CH_2COOCH_3), 7.18(d,1H,J=2.0Hz,C=CH), 7.63(s,4H,C_6H_4), 7.85(d,1H,J=2.0Hz,N=CH).
4g	CH_3	OCH_3	C_2H_5	84	88-90/0.1	1.11(t,3H,J=8.0Hz,CH_2CH_3), 2.32(s,3H,CH_3), 2.48(q,2H,J=8.0Hz,CH_2CH_3), 3.85(s,3H,OCH_3), 5.46(s,1H,C=CH), 7.35(s,4H,C_6H_4).
4h	CH_3	OCH_3	CH_2COOH	85	122-123 (mp)	2.35(s,3H,CH_3), 3.63(s,2H,CH_2COOH), 3.98 (s,3H,OCH_3), 5.66(s,1H,C=CH), 7.38(s,4H,C_6H_4),

Table 2 (contd)

						11.0 (broad s,1H,COOH).
5a	H	SCH_3	$CH(SCH_3)_2$	70	165-167/0.1	2.05(s,6H,$CHSCH_3$), 2.40(s,3H,SCH_3), 4.66(s, 1H,$CHSCH_3$), 6.35(d,1H,J=2.0Hz,C=CH), 7.23-7.53(m,4H,C_6H_4), 7.68(d,1H,J=2.0Hz,N=CH).

* Acetone - d_6 was used as a solvent

The methyl ester 4d, was made by treating the acetic acid 4c, with diazomethane; and the sulfoxides 2e, 3b, 3h and 4e. and the sulfones 2f. 3c, 3i and 4f, were prepared by the usual method by reaction with m-chloroperbenzoic acid and the appropriate stoichiometry. Many of these compounds showed biological activity and this activity (antiinflammatory, analgesic and antipyretic), will be described in a later publication.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover "UniMelt" capillary melting point apparatus, and are uncorrected. Nmr spectra were recorded as $CDCl_3$ solutions using a Varian EM-360 spectrometer, with TMS as the internal reference, and are recorded as δ units. Representative experiments are described. The elemental analyses of all compounds are within acceptable limits.

5-Thiomethyl-1-phenylpyrazole, (2b)

n-Butyllithium (96 ml of a 2.1 molar solution in n-hexane, 0.202 mole) was added over 15 min to a stirred, cold (dry ice-acetone bath) solution of 1-phenylpyrazole (28.8g, 0.2 mole) in dry THF (500 ml) in a nitrogen atmosphere, maintaining the temperature below -70°C. The reaction mixture was stirred for an additional hour at -75°C, and dimethyl disulfide (20.6g, 19.4 ml, 0.22 mole) was added at such a rate as to keep the reaction temperature below -70°C. The reaction mixture was stirred an additional 15 min at -75°C and then allowed to reach ambient temperature. The reaction mixture was stirred under nitrogen overnight, and concentrated on a rotary evaporator. The residue was stirred with dilute (10%) hydrochloric acid, and extracted with ethyl acetate (three times). The combined organic extracts were dried ($MgSO_4$) filtered, and concentrated. The residue was distilled under reduced pressure to give 36 g (95%) of compound 2b, as a yellow oil, bp 102-103°C/0.6mm.

5-Thiomethyl-1-o-tolylpyrazole, (3e)

n-Butyllithium (275 ml of a 1.6 molar solution in n-hexane, 0.44 mole) was added slowly to a stirred, cold (dry ice-acetone bath) solution of 5-thiomethyl-1-phenylpyrazole (76g, 0.4

mole) in dry THF (800 ml), in a nitrogen atmosphere, maintaining the temperature below -70°C. The lithio compound precipated from solution. After stirring for 1 h at -70°C, methyl iodide (68.16g, 30 ml, 0.48 mole) was added slowly, when an exothermic reaction occurred. The reaction mixture was stirred at -50°C for 15 mins, then allowed to warm to room temperature, and stirred overnight. The reaction mixture was concentrated on a rotary evaporator, the residue taken up in ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was distilled under vacuum to give 70.5g (86%) of a pale yellow oil, bp 109-110°C/0.6mm.

5-Thiomethyl-1-(o-phenylacetic acid)pyrazole, (4c)

n-Butyllithium (85.6 ml of a 1.6 molar solution in n-hexane, 0.137 mole) was added slowly to a stirred, cold (dry ice-acetone bath) solution of 5-thiomethyl-1-o-tolylpyrazole (25.5g, 0.125 mole) in dry THF (250 ml) in a nitrogen atmosphere, maintaining the temperature below -70°C. After stirring for 1 h at -70°C, the reaction mixture was poured with vigorous stirring into excess powdered dry ice, and the mixture stirred and allowed to reach room temperature. The reaction mixture was concentrated on a rotary evaporator, and the residue triturated with excess ether. The lithium salt was separated by filtration, and washed well with ether. The salt was dissolved in water and the solution cooled in an ice-bath and acidified with conc. hydrochloric acid, and extracted with ethyl acetate (three times). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residual oil was dissolved in warm ether (300 ml) and then concentrated to about 70 ml, and stirred in an ice bath, when the acid, 20g (65%) crystallised, mp 83-85°C.

5-Methoxymethyl-1-phenylpyrazole, (2c)

n-Butyllithium (100 ml of a 2.22 molar solution in n-hexane, 0.22 mole) was added slowly to a stirred, cold (dry ice-acetone bath) solution of 1-phenylpyrazole (28.8g, 0.2 mole) in dry THF (750 ml), in a nitrogen atmosphere, maintaining the temperature below -70°C. After stirring for 1 h at -70°C, the reaction mixture was added slowly to a cold (-75°C), stirred solution of chloromethyl methyl ether (32.2g, 0.4 mole) in dry THF (150 ml), in a nitrogen atmosphere, maintaining the temperature at -75°C. The reaction mixture was stirred at -70°C for 1 h and then allowed to reach room temperature. Stirred at room temperature for 3 h and then concentrated on a rotary evaporator. The residue was dissolved in methylene chloride (500 ml), washed with brine (three times), dried ($MgSO_4$), filtered and concentrated. The residue was distilled under reduced pressure to give 30g (80%) of a colourless oil, bp 86-88°C/0.2mm.

Reaction of 2c with n-butyllithium and methyl iodide

n-Butyllithium (13.2 ml of a 1.6 molar solution in n-hexane, 0.021 mole) was added slowly to a stirred, cold (dry ice-acetone bath) solution of 5-methoxymethyl-1-phenylpyrazole (3.76g, 0.02 mole) in dry THF (100 ml), in a nitrogen atmosphere, maintaining the temperature below -70°C. After stirring for 1 h at -70°C, a solution of methyl iodide (2.98g, 0.021 mole) in dry THF (20 ml) was added over 30 min. There was an exothermic reaction and the temperature rose to -35°C. The reaction mixture was allowed to reach room temperature and stirred for an additional 2 h. The reaction mixture was concentrated, the residue taken up in methylene chloride, washed with brine (three times), dried ($MgSO_4$), filtered and concentrated to give 4.33g of an oil, whose nmr spectrum showed a 1:1 mixture of 9 and 10. Distillation under reduced pressure gave 2.6g (64%) of a clear oil, bp 86-88°C/0.08mm, whose nmr spectrum showed the same 1:1 mixture of 9 and 10. The nmr ($CDCl_3$) spectrum : δ 1.43(d,3H,$CHCH_3$ of 9), 2.04 (s,3H,phenyl CH_3 of 10), 3.16 and 3.20(s,s,3H,3H,OCH_3 of 9 and 10), 4.23(s,2H,CH_2OCH_3 of 10), 4.38(q,1H,$CHCH_3$ of 9), 6.43(d,1H,pyrazole H), 7.27 to 7.43(m,phenyl H), and 7.63(d,1H, pyrazole H).

Reaction of 2c with LDA and methyl iodide

n-Butyllithium (45 ml of a 2.22 molar solution in n-hexane, 0.1 mole) was added to a stirred solution of diisopropylamine (10.62g, 0.105 mole) in dry THF (100 ml) in a nitrogen atmosphere, maintaining the temperature at 0°C. The reaction mixture was stirred at 0°C for 1 h, and then cooled to -70°C. The prepared solution of LDA was then added in a nitrogen atmosphere to a stirred, cooled (dry ice-acetone bath) solution of 5-methoxymethyl-1-phenyl-pyrazole (9.4g, 0.05 mole) in dry THF (300 ml), maintaining the temperature below -70°C. The reaction mixture was stirred at this temperature for 1 h and a solution of methyl iodide (14.9g, 0.105 mole) in dry THF (100 ml),then added, while maintaining the temperature at -70°C. The reaction mixture was stirred at -70°C for 1 h, then at room temperature for 3 h, and concentrated under vacuum. The residue was dissolved in methylene chloride, washed with brine (three times), dried ($MgSO_4$), and concentrated, to give 10.5g of an oil, whose nmr spectrum showed that it was mainly compound 9. Distillation under reduced pressure gave 10g (47%) of a colourless oil, bp 90-92°C/0.1mm ; nmr ($CDCl_3$): δ 1.40(d,3H,$CHCH_3$), 3.13(s,3H,OCH_3), 4.42(q,1H,$CHCH_3$), 6.40(d,1H,pyrazole H), 7.40(s,5H,phenyl H), 7.60 (d,1H,pyrazole H).

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