LITHIATION REACTIONS OF 5-ALKOXYMETHYL-, 5-ALKYLTHIOMETHYL-, AND 5-DIALKYLAMINOMETHYLISOXAZOLES

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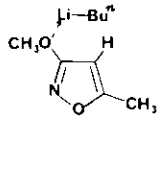
Abstract - The 5-alkoxymethyl- and 5-alkylthiomethylisoxazoles undergo exclusive lateral lithiation at the C-5 methylene, the products reacting separately with methyl iodide, dimethyl disulfide, and carbon dioxide to give after work up the respective 5α-alkoxyethyl, 5α-alkylthioethyl, the mixed acetal, the thio-acetal, the α-alkoxy acid and the α-thioalkoxy acid of the isoxazoles. This reaction can be repeated to give the mixed ortho ester, the thio ortho ester, the mixed α-ketal acid, and the mixed -thioketal acid. This method provides a very convenient route to these classes of compounds. The 5-dialkylaminomethylisoxazole is lithiated at the C-4 position.

The preceding paper describes the preparation of various 5-alkoxymethyl-, 5-alkylthiomethyl-, and 5-dimethylaminomethylisoxazoles. Our studies on the lithiation of these compounds using n-butyllithium as reagent, are described in this publication. This work, which is a follow-up to our previous research in this area[2,3], complements the studies of Gainer and co-workers on the 3- and 3,4-substituted 5-methylisoxazoles.[4]

An earlier publication by Bowden and co-workers reported that the lithiation of 3-methoxy-5-methylisoxazole with n-butyllithium gave a mixture of the 4-lithio- and 5-lithiomethylisoxazoles in a ratio of 17:83.[4] These results were explained by the formation of the complexes, 1, and 2, which direct the lithiation to the adjacent sites, resulting in the observed mixture of products.



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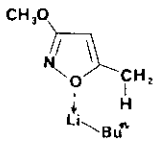

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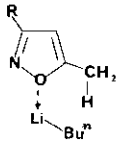

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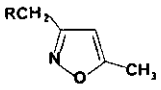
By contrast, 3,5-dimethylisoxazole, 3-phenyl-5-methylisoxazole, and other 5-methylisoxazoles substituted at C-3 or C-4 by groups that do not complex with butyllithium, undergo exclusive lateral lithiation at the C-5 methyl group[3,6-8], the reaction being directed by the formation of the intermediate complex, 3.

Gainer and co-workers found that 3-hydroxymethyl-5-methylisoxazole, 4a, is lithiated exclusively at the C-5 methyl group (65%) on treatment with two equivalents of n-butyllithium.[4] By contrast, 3-methoxymethyl-5-methylisoxazole, 4b, and 3-dimethylaminomethyl-5-methylisoxazole, 4c, with n-butyllithium gave a mixture of the C-4 ring metalated and C-3 lateral metalated products.[4] These



4a R = OH
4b = OCH_3
4c = $N(CH_3)_2$

results can again be explained by formation of an initial complex between the butyllithium and the appropriate heteroatom on the C-3 substituent (as in 1), or the isoxazole oxygen (as in 2). Greater selectivity in the lithiation is reported with the use of lithium diisopropylamide, when exclusive lateral lithiation of the C-5 methyl group of 4b and 4c occurs.[4] Co-ordination of this reagent with heteroatoms does not occur, so that the site of lithiation is entirely dependent on the "acidity" of the proton.[9]

Exclusive lateral lithiation of the C-5 methyl group occurs with 3,5-dimethyl-4-dimethylaminomethyl-isoxazole (high yield), and 3,5-dimethyl-4-hydroxymethylisoxazole (low yield)[4].

The lithiation of the 5-methoxymethylisoxazoles, 5 (R = CH_3 or 2,6-dichlorophenyl, XR^1 = OCH_3) and the 5-methylthiomethylisoxazoles, 5 (R = CH_3 or 2,6-dichlorophenyl, XR^1 = SCH_3), with n-butyllithium proceeds smoothly and in high yields to the 5 -lithiomethyl compounds, 6 (R = CH_3 and 2,6-dichlorophenyl, XR^1 = OCH_3 and SCH_3, and R^2 = Li), which react with methyl iodide to give the 5α-methoxy or 5α-methylthioethylisoxazoles, 6, (R = CH_3 and 2,6-dichlorophenyl, XR^1 = OCH_3 and SCH_3, and R^2 = CH_3); with dimethyldisulfide to give the 5-mixed acetals, 6 (R = CH_3 and 2,6-dichlorophenyl, XR^1 = OCH_3 and SCH_3, and R^2 = SCH_3), or 5-thioacetals, 6 (R = CH_3 and 2,6-dichlorophenyl, XR^1 = R^2 = SCH_3); and with carbon dioxide to give the isoxazole-5 -methoxyacetic acids, 6, (R = CH_3 and

2,6-dichlorophenyl, XR^1 = OCH_3, R^2 = COOH) and the isoxazole-5 -methylthioacetic acids, 6, (R = CH_3 and 2,6-dichlorophenyl, XR^1 = SCH_3, R^2 = COOH). Table 1 summarizes the data on the compounds made.

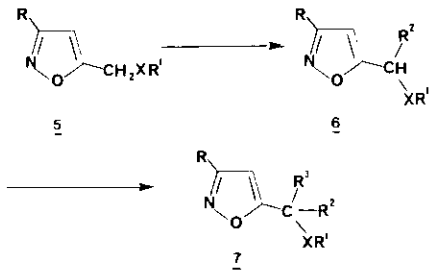


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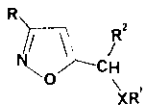
Table 1



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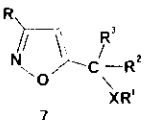
No.	R	XR^1	R^2	bp°C/mm	Yield %	pmr spectrum, 60 MHz ($CDCl_3$)
6a	CH_3	OCH_3	COOH	145/0.5	50	2.32(s,3H,CH_3); 3.48(s,3H,OCH_3); 5.05(s,1H,$CHOCH_3$); 6.33(s,1H,=CH); 8.88(s,1H,exchangeable with D_2O, COOH).
6b	CH_3	SCH_3	CH_3	62/0.6	65	1.63(d,J=8.0Hz,3H,$CHCH_3$); 2.13(s,3H,SCH_3); 2.33(s, 3H,CH_3); 4.00(q,J=8.0Hz,1H,$CHCH_3$); 6.03(s,1H,=CH).
6c	CH_3	SCH_3	SCH_3	mp 40-41	62	2.20(s,6H,SCH_3); 2.27(s,3H,CH_3); 5.03(s,1H, $CH(SCH_3)_2$); 6.13(s,1H,=CH).
6d	CH_3	SCH_3	COOH	mp 92-94	60	2.23(s,3H,SCH_3); 2.35(s,3H,CH_3); 4.68(s,1H,CH); 6.38(s,1H,=CH); 11.16(s,1H,COOH).
6e	DCP	Oφ	CH_3	mp 84-85	76	1.8(d,J=8.0Hz,3H,$CHCH_3$); 5.63(q,1H,$CHCH_3$); 6.37(s, 1H,=CH); 6.93-7.50(m,8H,C_6H_5 and $C_6H_3Cl_2$).
6f	DCP	SCH_3	CH_3	152-4/0.5	91	1.73(d,J=7.0Hz,3H,$CHCH_3$); 2.17(s,3H,SCH_3); 4.13(q, J=7.0Hz,1H,$CHCH_3$); 6.27(s,1H,=CH); 7.43(s,3H, $C_6H_3Cl_2$).
6g	DCP	SCH_3	$CH_2φ$	198-200/0.07	84	2.13(s,3H,SCH_3); 3.27(d,J=8.0Hz,2H,$CHCH_2Ph$); 4.20 (t,J=8.0Hz,$CHCH_2Ph$); 6.10(s,1H,=CH); 7.22-7.38(m, 8H,$C_6H_3Cl_2$ and C_6H_5).
6h	DCP	SCH_3	OCH_3	156-158/0.1	92	2.02(s,3H,SCH_3); 3.88(s,3H,OCH_3); 5.65(s,1H,CH); 6.38(s,1H,=CH); 7.40(s,3H,$C_6H_3Cl_2$).
6i	DCP	Oφ	COOH	mp 45-47	85	5.97(s,1H,$CHOPh$); 6.00(s,1H,=CH); 7.07-7.43(m,8H, $C_6H_3Cl_2$ and C_6H_5); 9.68(s,1H,COOH).
6j	DCP	SCH_3	COOH	mp 179-180	88	2.32(s,3H,SCH_3); 5.10(s,1H,CH CH_3); 6.77(s,1H,=CH); 7.65(s,3H,$C_6H_3Cl_2$); 10.13(broad s,1H,COOH).
6k	DCP	SCH_3	SCH_3	183-184/0.4	65	2.23(s,6H,SCH_3); 5.07(s,1H,$CH(SCH_3)_2$); 6.36(s,1H, =CH); 7.37(s,3H,$C_6H_3Cl_2$).

This process of lithiation followed by reaction with methyl iodide, dimethyl disulfide or carbon dioxide can be repeated with compounds, 6, to produce compounds, 7, (R = CH_3 or 2,6-dichlorophenyl, XR^1 = OCH_3 or SCH_3, R^2 and R^3 can be the same or different and each can be CH_3 or SCH_3 or COOH). Table 2 summarizes the data on the compounds prepared.

Table 2



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No	R	XR^1	R^2	R^3	bp°C/mm	Yield %	pmr Spectrum 60 MHz ($CDCl_3$)
7a	CH_3	SCH_3	CH_3	CH_3	48-52/0.2	70	1.68(s,6H,C$\underline{CH_3}$); 1.98(s,3H,S$\underline{CH_3}$); 2.25(s,3H, $\underline{CH_3}$); 5.98(s,1H,=$\underline{CH}$).
7b	CH_3	SCH_3	SCH_3	SCH_3	109-110/0.4	78	2.20(s,9H,S$\underline{CH_3}$); 2.32(s,3H,$\underline{CH_3}$); 6.27(s,1H, =$\underline{CH}$).
7c	CH_3	SCH_3	SCH_3	COOH	mp 112-113	65	2.13(s,6H,S$\underline{CH_3}$); 2.30(s,3H,$\underline{CH_3}$); 6.43(s,1H, =$\underline{CH}$); 8.48(broad s,1H,$\underline{COOH}$).
7d	DCP	OCH_3	SCH_3	SCH_3	mp 100-102	77	2.03(s,6H,S$\underline{CH_3}$); 3.57(s,3H,O$\underline{CH_3}$); 6.50(s,1H, =$\underline{CH}$); 7.43(s,3H,$C_6\underline{H_3}Cl_2$).
7e	DCP	SCH_3	CH_3	COOH	mp 155-157	95	2.03(s,3H,C$\underline{CH_3}$); 2.20(s,3H,S$\underline{CH_3}$); 6.62(s,1H, =$\underline{CH}$); 7.47(s,3H,$C_6\underline{H_3}Cl_2$).
7f	DCP	SCH_3	OCH_3	COOH	mp 140-141	89	2.03(s,3H,S$\underline{CH_3}$); 3.48(s,3H,O$\underline{CH_3}$); 6.73(s,1H, =$\underline{CH}$); 7.60(s,3H,$C_6\underline{H_3}Cl_2$); 8.20(broad s,1H, $\underline{COOH}$).
7g	DCP	SCH_3	SCH_3	SCH_3	*159-170 / 0.08	84	2.20(s,9H,S$\underline{CH_3}$); 6.43(s,1H,=$\underline{CH}$); 7.37(s,3H, $C_6\underline{H_3}Cl_2$).
7h	DCP	SCH_3	SCH_3	COOH	mp 127-128	92	2.18(s,6H,S$\underline{CH_3}$); 6.58(s,1H,=$\underline{CH}$); 7.40(s,3H, $C_6\underline{H_3}Cl_2$); 9.57(s,1H,$\underline{COOH}$).

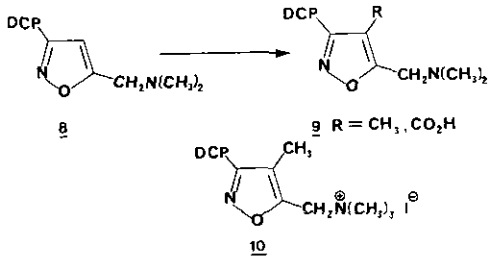
*Kugelrohr distillation. Air bath temperature.

This method is particularly useful for preparing the isoxazole-5-thioacetals, the isoxazole-5-α-methoxyacetic acids, the isoxazole-5 -methylthioacetic acids, and the isoxazole-5-orthothioesters.

The process also can be utilised to prepare the unknown isoxazole mixed acetals, 6, [in which XR^1 and R^2 can each represent a different thio function (SR and SR^1), or can represent an oxo and a thio function (OR^3 and SR^2)], and isoxazole mixed ortho esters, 7, [in which XR^1, R^2 and R^3 can each represent a different thio function (SR, SR^1 and SR^2), or can represent an oxo and thio functions (OR, SR^1 and SR^2)]. The scope and limitation of the method have not been fully studied.

In the case of 3-(2,6-dichlorophenyl)-5-dimethylaminomethylisoxazole, 8, lithiation occurred exclusively at the C-4 position. There was no evidence for the formation of the 5α-lithiomethyl compound. Reaction of the lithio-derivative with carbon dioxide gave 9 (R = COOH), while treatment

of the lithio-compound with methyl iodide gave 9 (R = CH_3), mixed with the quart-ammonium iodide, 10.



There is thus a considerable difference in the effect of the $-OCH_3$ and $-SCH_3$ groups when compared to the $-N(CH_3)_2$ moiety in the 5-substituted methylisoxazoles. The observed results can be explained by coordination of the n-butyllithium with the ring oxygen of compounds 5 (XR^1 = OCH_3 or SCH_3) predominating and directing reaction to the 5α-position. Also, the 5α-protons are probably the most "acidic" and this would again favour 5α-lithiation. *In the case of compound 8, coordination of the* n-butyllithium with the C-5 $N(CH_3)_2$ function would appear to predominate and direct lithiation to the C-4 position.

EXPERIMENTAL

Representative examples are described. Melting points were taken on a Thomas Hoover "UniMelt" capillary melting point apparatus, and are uncorrected. Pmr spectra were run on a Varian EM360 spectrometer. Elemental analyses of all compounds were within accepted levels.

3-Methyl-5-bis(methylthio)methylisoxazole, 6c

n-Butyllithium (128 ml of a 1.6 molar solution in n-hexane, 0.205 mole) was added dropwise under a nitrogen atmosphere, to a stirred solution of 3-methyl-5-methylthiomethylisoxazole (28.6 g, 0.2 mole) in dry THF (250 ml), cooled in a dry ice-acetone bath, the reaction temperature being kept below -65°C. The reaction mixture was stirred for an additional hour at about -70°C, and a solution of dimethyldisulfide (22.6 g, 0.24 mole) in THF (250 ml) added at such a rate as to maintain the temperature below -65°C. The reaction mixture was stirred at about -70°C for 1 h and the temperature then allowed to rise. *The reaction mixture was stirred at ambient temperature overnight* and the THF then removed on a rotary evaporator. The solid residue was shaken with ether (500 ml) and water. The ether layer was washed with water, then brine, dried ($MgSO_4$), filtered and concentrated. Distillation gave a fraction, 25.5 g, bp 114-116°C/0.7 mm, which crystallized from hexane as a white solid, 23.4 g (62%), mp 40-41°C.

3-(2,6-Dichlorophenyl)isoxazole-5α-phenoxyacetic acid, 6i.

n-Butyllithium (23.45 ml of a 1.6 molar solution in n-hexane, 0.0375 mole) was added dropwise, under a nitrogen atmosphere, to a stirred solution of 3-(2,6-dichlorophenyl)-5-phenoxymethylisoxazole (10 g, 0.0312 mole) in dry THF (100 ml), cooled in a dry ice-acetone bath, the reaction temperature being kept below -70°C. The reaction mixture was stirred for an additional hour at -70°C, and then poured onto an excess of crushed dry ice, after which the stirred mixture was allowed to warm to room temperature. The resulting solution was concentrated, ether added and the resulting lithium salt filtered. The resulting cake was dissolved in water and ethyl acetate and acidified with concentrated hydrochloric acid, and the layers separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers dried over $MgSO_4$, filtered and concentrated. The residue was crystallized from carbon tetrachloride to give 9.7 g (85%) of white crystals, mp 45-47°C.

3-Methyl-5-tri(methylthio)methylisoxazole, 7b.

n-Butyllithium (313 ml of a 1.6 molar solution in n-hexane, 0.5 mole) was added dropwise, under a nitrogen atmosphere, to a stirred solution of 3-methyl-5-bis(methylthio)methylisoxazole (94.66 g, 0.5 mole) in dry THF (500 ml), cooled in a dry ice-acetone bath, the reaction temperature being kept below -65°C. The reaction mixture was stirred for an additional hour at about -70°C, and a solution of dimethyldisulfide (55 ml, 0.6 mole) in THF (500 ml) added. The reaction mixture was stirred at -70°C for a further 30 min, then allowed to reach ambient temperature and stirred for 3 h. The solution was concentrated on a rotary evaporator and dissolved in ether (1 litre), washed with water (three times), dried ($MgSO_4$), and concentrated. The residue was distilled under reduced pressure giving 91.6 g (78%) of an oil, bp 109-110°C/0.4 mm.

3-(2,6-Dichlorophenyl)isoxazole-5α-methoxy-5α-thiomethyl-5-acetic acid, 7f.

n-Butyllithium (9 ml of a 1.6 molar solution in n-hexane, 0.014 mole) was added dropwise, under a nitrogen atmosphere, to a stirred solution of 3-(2,6-dichlorophenyl)-5α-methoxy-5-methylthiomethyl-isoxazole (3.95 g, 0.013 mole) in dry THF (35 ml), cooled in a dry ice-acetone bath, the reaction temperature being kept below -70°C. The reaction mixture was stirred for 30 min at -75°C, and then stirred with excess of crushed dry ice. The reaction mixture was allowed to warm to room temperature, and the resulting yellow solution concentrated. The residue was taken up in water and extracted with ether (twice). The aqueous layer was cooled in an ice-bath, layered with ethyl acetate, and then acidified with conc. hydrochloric acid. The layers were separated and the aqueous layer extracted again with ethyl acetate. The combined ethyl acetate layers were dried ($MgSO_4$), filtered, and concentrated to give 4 g (89%) of a pale yellow solid, mp 140-141°C (with gas evolution).

3-(2,6-Dichlorophenyl)-5-(dimethylaminomethyl)isoxazole-4-carboxylic acid, 9, (R = COOH)

n-Butyllithium in hexane (3 ml of a 2.1 molar solution, 6.3 mmole) was added dropwise to a stirred solution of 3-(2,6-dichlorophenyl)-4-(dimethylaminomethyl)isoxazole (1.63 g, 6 mmole) in dry THF (20 ml), *under a nitrogen atmosphere and at a temperature of -70°C.* The reaction mixture was stirred an additional 40 min at -70°C, and carbon dioxide then bubbled through the dark red solution. The colour changed to light yellow. The cooling bath was removed and the reaction mixture stirred until it attained room temperature. On concentration, a yellow foam resulted. This foam was taken up in ice water and extracted twice with ether. The water layer was concentrated to about 10 ml, cooled in an ice-bath and acidified to a pH 6.5 with hydrochloric acid. The resulting white solid was filtered, washed with ether and dried overnight to give 1.35 g (71%) of the desired compound, mp 228-230°C dec; pmr ($DMSOd_6$) spectrum: δ 2.45(s,6H,$N(CH_3)_2$), 4.30(s,2H,CH_2N), 7.50(s,3H, $C_6H_3Cl_2$), 10.30(s,br,1H,COOH). There was no indication in the pmr spectrum of the singlet at about δ 6.30 ($CDCl_3$) due to the isoxazole C-4 proton.

3-(2,6-Dichlorophenyl)-5-(dimethylaminomethyl)-4-methylisoxazole, 9 (R = CH_3) and its methyl iodide, 10.

n-Butyllithium in hexane (3 ml of a 2.1 molar solution, 6.3 mmole) was added dropwise to a stirred, cold (-70°C) solution of 3-(2,6-dichlorophenyl)-4-(dimethylaminomethyl)isoxazole (1.63 g, 6 mmole) in dry THF (20 ml), under a nitrogen atmosphere. The reaction mixture was stirred an additional 30 min at -70°C, and methyl iodide (1 ml, about 15 mmole) added all at once, when the temperature rose to -30°C. The reaction mixture was allowed to warm to room temperature, and stirred an additional1h at this temperature, when a white solid separated. The reaction mixture was concentrated to dryness and then stirred well with ether (150 ml) and water (100 ml). The ether layer was back extracted with water (2 x 25 ml), dried ($MgSO_4$), filtered and concentrated to give 1 g of a dark coloured oil. Distillation gave 0.85 g of 9 (R = CH_3) as a pale yellow oil, bp130°C/0.2 mm; pmr ($CDCl_3$) spectrum: δ 1.87(s,3H,C_4-CH_3), 2.30(s,6H,$N(CH_3)_2$), 3.65(s,2H,CH_2N), and 7.40(s,3H,$C_6H_3Cl_2$). The initial aqueous extract was extracted with chloroform (3 x 50 ml), and the combined extracts dried ($MgSO_4$), filtered and concentrated. The residue was triturated with ether, and the resulting white solid filtered and dried to give 1.2 g of a white solid, 10, mp 198°C (sinters) and melts at 206°C; pmr (CH_3OHd_4) spectrum: δ 2.13(s,3H,C_4-CH_3), 3.38(s,9H,$N(CH_3)_3$), 5.08(s,2H,CH_2N), 7.60(s,3H,$C_6H_3Cl_2$).

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