Reactions of Some Substituted Isoxazoles with Organolithium Reagents

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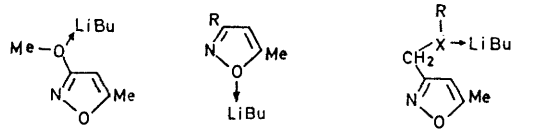
The selectivity of metallation in 3- and 3,4-substituted 5-methylisoxazoles by n-butyl-lithium is determined by the influence of exo- and endo-cyclic heteroatoms. In contrast, both series of isoxazoles are metallated specifically at the C-5 methyl group by lithium di-isopropylamide.

THE directing effect of heteroatomic functional groups on the site of lithiation by n-butyl-lithium is well established for the thiophen system.[1] Furthermore Bowden has

(1) R^1 = OMe, R^2 = Me
(2) R^1 = OMe, R^2 = CH_2Li
(3) R^1 = R^2 = Me
(4) R^1 = Me, R^2 = CH_2Li
(5) R^1 = CH_2·OMe, R^2 = CH_2Li
(6) R^1 = CH_2·OMe, R^2 = Et
(7) R^1 = CH_2·NMe_2, R^2 = Et
(8) R^1 = CH_2·OH, R^2 = Et

(9) R^1 = OMe, R^2 = Me, R^3 = Li
(10) R^1 = CH_2·OMe, R^2 = Me, R^3 = Li
(11) R^1 = CH_2·OMe, R^2 = R^3 = Me
(12) R^1 = CH_2·NMe_2, R^2 = R^3 = Me
(13) R^1 = Me, R^2 = Et, R^3 = CH_2·NH·CO_2Bu^t
(14) R^1 = Me, R^2 = Et, R^3 = CH_2·NEt·CO_2Bu^t
(15) R^1 = Me, R^2 = Et, R^3 = CH_2NMe_2
(16) R^1 = Me, R^2 = Et, R^3 = CH_2·OH



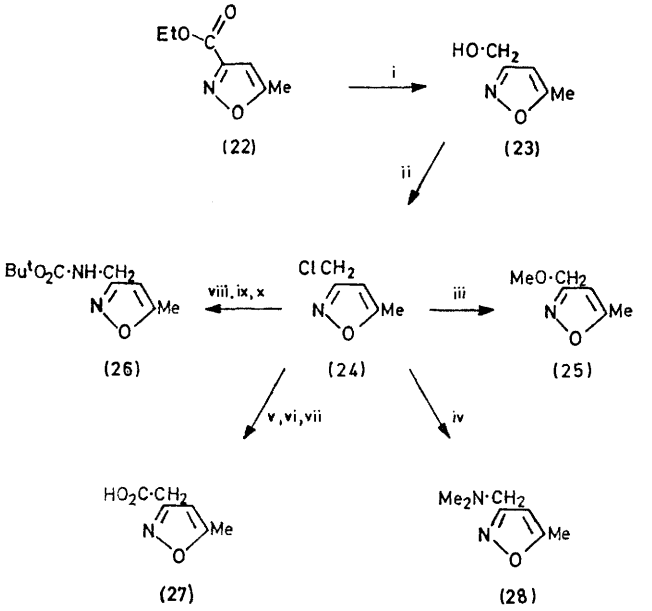
(17)
(18) R = OMe
(19) R = Me
(20) X = O, R = Me
(21) X = N, R = Me_2

shown recently that treatment of 3-methoxy-5-methylisoxazole (1) with n-butyl-lithium gives a mixture of the 4-lithio- (9) and the 5-lithiomethyl-isoxazole (2) in the ratio 17 : 83.[2] In the latter case the complexes (17) and (18) serve to hold the metallating agent close to the appropriate site leading to the ring- (9) and the side-chain-metallated product (2), respectively.

In contrast, similar treatment of 3,5-dimethylisoxazole (3) resulted in specific lithiation of the C-5 methyl group to give the lithiomethylisoxazole (4) exclusively.[3] In this case the complex (19) may play an intermediate directive role.

Using standard experimental procedures we have prepared the ether (25) [4] and the amine (28) from 3-ethoxycarbonyl-5-methylisoxazole (22) [5] by way of 3-hydroxymethyl- (23) [6] and 3-chloromethyl-5-methylisoxazole (24) [7] (Scheme 1). The ability of the methoxymethyl and dimethylaminomethyl side chains to complex n-butyl-lithium [(20), (21)] thus holding the reagent adjacent to the unsubstituted site on the aromatic ring was reflected in the metallation patterns.

n-Butyl-lithium reacted with the methoxymethylisoxazole (25) to give a mixture of side-chain-metallated (5) and ring-metallated (10) species; treatment of the crude product with methyl iodide gave 5-ethyl-3-methoxymethylisoxazole (6) and 3-methoxymethyl-4,5-dimethylisoxazole (11). The product after methylation was homogeneous to t.l.c. and g.l.c. analysis but a two-component mixture was clearly indicated by n.m.r. spectroscopy. Mass spectral and analytical data suggested that the two compounds were isomeric (M^+ 141), and from the combined spectroscopic data the two



SCHEME 1 Reagents: i, $LiAlH_4$; ii, $SOCl_2$; iii, NaOMe–MeOH; iv, Me_2NH–Me_2N·CHO; v, NaCN–H_2O–$PhCH_2$·$\overset{+}{N}Et_3Cl^-$–$(CH_2Cl)_2$; vi, HCl–EtOH; vii, NaOH; viii, potassiophthalimide; ix, N_2H_4,HCl; x, $Bu^tO_2CN_3$–NaOH

isomers were identified as (6) and (11), present in the ratio 4 : 1.

Similar treatment of 3-dimethylaminomethyl-5-methylisoxazole (28) with n-butyl-lithium followed by methyl

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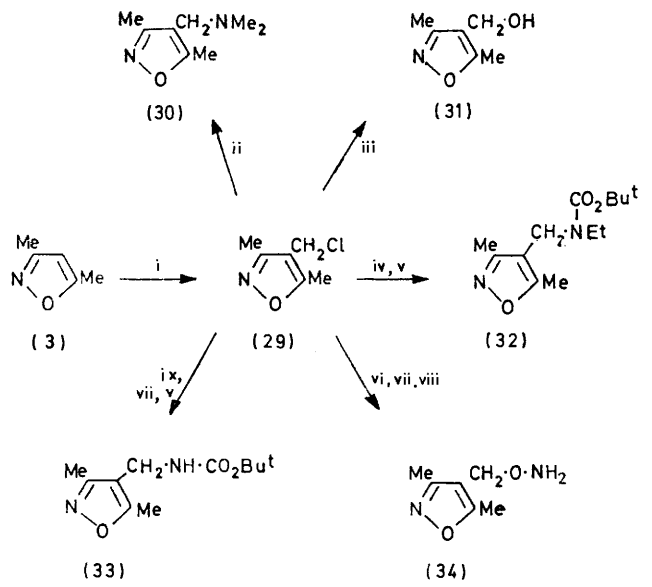
[2] K. Bowden, G. Crank, and W. J. Ross, *J. Chem. Soc.* (*C*), 1968, 172.
[3] R. G. Micetich, *Canad. J. Chem.*, 1970, **48**, 2006.
[4] C. Musante, *Gazzetta*, 1938, **68**, 240.
[5] Farbenfabriken Bayer A.G., Fr. Demande 2012604 (*Chem. Abs.*, 1971, **74**, 13134).
[6] A. Quilico, L. Panizzi, and C. Epifani, *Gazzetta*, 1939, **69**, 536.
[7] N. K. Kochetkov, E. D. Khomutova, and M. N. Bazilevskii, *Zhur. obshchei. Khim.*, 1958, **28**, 2736 (*Chem. Abs.*, 1959, **53**, 9187).

iodide gave an inseparable mixture of 3-dimethylaminomethyl-5-ethyl- (7) and 3-dimethylaminomethyl-4,5-dimethyl-isoxazole (12) in the ratio 1 : 1. The high proportion of product derived from ring metallation (12) may be due to favourable complexation of n-butyllithium to the tertiary amino-group.

In accord with the theory that ring metallation takes place through prior complex formation with side-chain



SCHEME 2 Reagents: i, $(ClCH_2)_2O$; ii, Me_2NH–Me_2N·CHO; iii, PbO; iv, $EtNH_2$–Me_2N·CHO; v, $But^tO_2CN_3$–NaOH; vi, *N*-hydroxyphthalimide–Me_2N·CHO; vii, N_2H_4,HCl; viii, NaOH; ix, potassiophthalimide–Me_2N·CHO

heteroatoms, 3-hydroxymethyl-5-methylisoxazole (23) was specifically metallated at the methyl group by using 2 mol. equiv. of n-butyl-lithium; 5-ethyl-3-hydroxymethylisoxazole (8) was the only product isolated after methylation with methyl iodide. The first formed alkoxide group obviously has no tendency to hold a second molecule of metallating reagent close to the aromatic ring.

Even more striking is the result of treatment of the isoxazoles (25) and (28) with lithium di-isopropylamide under the same experimental conditions. The lithium atom in the latter reagent does not co-ordinate with a heteroatom in the substrate so that the position of metallation is dictated by the 'acidity' of the available hydrogen atoms.[8] Specific high yield side-chain methylation of (25) and (28) was observed after successive treatment with lithium di-isopropylamide and methyl iodide, furnishing the 5-ethylisoxazoles (6) and (7), respectively. The synthetic utility of this specific metallation process will be described in a separate publication.

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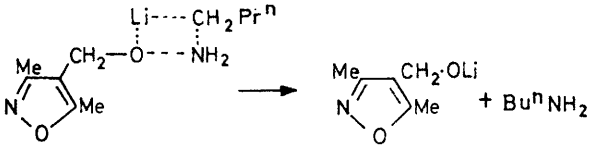
Surprisingly, metallation of the protected aminomethylisoxazole (26) (prepared as outlined in Scheme 1) did not occur; starting material was recovered after reaction under our standard conditions.

For further metallation studies we prepared various 3,4,5-trisubstituted isoxazoles (30)—(34) [9,10] from 4-chloromethyl-3,5-dimethylisoxazole (29) [7] as indicated in Scheme 2. Treatment of the aminomethylisoxazoles (33), (32), and (30) with n-butyl-lithium followed by methyl iodide gave the corresponding 5-ethylisoxazoles (13)—(15) exclusively in high yields. If co-ordination of the n-butyl-lithium to the exocyclic or the endocyclic heteroatom occurs at all, it serves only to guide the metallating reagent to the reactive C-5 methyl group.

Side-chain metallation of 4-hydroxymethyl-3,5-dimethylisoxazole (31) [7] by using 2 mol. equiv. of n-butyllithium proceeded relatively slowly owing to the influence of the neighbouring alkoxide group. The yield of the derived 5-ethylisoxazole (16) was low and starting material was recovered. The same isoxazole (16) was also obtained when 4-amino-oxymethyl-3,5-dimethylisoxazole (34) was treated with 3 mol. equiv. of n-butyllithium; the exocyclic N–O bond is obviously cleaved readily: brief treatment of (34) with 2 mol. equiv. of n-butyl-lithium yielded the pure hydroxymethylisoxazole (31) after addition of water. A four-centre mechanism leading to N–O bond rupture (Scheme 3) is likely.

Specific metallation of the C-5 methyl group in 3,5-dimethylisoxazoles was confirmed as follows. First, we synthesised 5-methylisoxazol-3-ylacetic acid (27) (Scheme 1) unambiguously and confirmed by n.m.r. spectroscopy the observation [3] that none of this compound is formed on treatment of 3,5-dimethylisoxazole (3) with n-butyllithium followed by carbon dioxide. Secondly the ^{13}C n.m.r. spectra of the 5-ethylisoxazole (13) and the



SCHEME 3

5-methylisoxazole (33) are similar except for the low field signal due to C-5.[11] The observed shift of the C-5 signal (4.66 p.p.m.) is indicative of methylation at the C-5 methyl group.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian T60 spectrometer for solutions in carbon tetrachloride unless otherwise stated. I.r. spectra were taken with a Perkin-Elmer SP 200 instrument. Microanalyses were performed by Dr. B. Boyle (Ciba-Geigy). Analytical t.l.c. was carried

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[11] M. Christl, J. P. Warren, B. L. Hawkins, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1973, **95**, 4392.

out with silica gel G (Merck) and column chromatography with B.D.H. silica gel. Mass spectra were obtained with an A.E.I. MS30 instrument operated at 24 eV.

The preparations of the isoxazoles (23)—(26), (28), (30), and (32)—(34) are described in Supplementary Publication No. SUP 21715 (8 pp.).*

(A) *Alkylation Reactions with n-Butyl-lithium.*—A solution of the isoxazole (0.04 mol) in dry tetrahydrofuran (80 ml) in a dry flask was cooled to the required reaction temperature (solid CO_2–acetone). A 9.1% (w/v) solution of n-butyl-lithium in hexane [(i) 0.04 mol, 28.8 ml, (ii) 0.08 mol, 57.6 ml, or (iii) 0.12 mol, 86.4 ml] was added slowly under dry nitrogen, with the temperature kept below −60 °C. The solution was then stirred (60 min unless otherwise stated) and treated with methyl iodide [(i) 0.06 mol, (ii) 0.12 mol, or (iii) 0.18 mol]. The mixture was stirred until it reached ambient temperature, then concentrated under reduced pressure, and the residue was dissolved in water. The solution was extracted with ethyl acetate (4 × 50 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to give the crude products.

(B) *Alkylation Reactions with Lithium Di-isopropylamide.*—A solution of di-isopropylamine (0.044 mol, 4.5 g) in dry tetrahydrofuran (80 ml) in a dry flask under nitrogen was cooled. n-Butyl-lithium in hexane (0.04 mol; 28.8 ml of a 9.1% w/v solution) was added slowly and the solution was stirred for 30 min. The mixture was then cooled to −70 °C, treated with a solution of the appropriate isoxazole [(i) 0.04 mol or (ii) 0.02 mol] in tetrahydrofuran (10 ml), and stirred for 1 h. Methyl iodide [(i) 0.06 mol, 8.5 g, or (ii) 0.03 mol, 4.25 g] was added, and after stirring for a further 1 h the crude products were isolated as described in method (A).

5-Ethyl-3-methyl-4-(t-butoxycarbonylaminomethyl)isoxazole (13). Alkylation of the dimethylisoxazole (33) with n-butyl-lithium under conditions A(ii) at −70 °C gave the *ethylisoxazole* (13) (85%), m.p. 46—48°, δ 5.57br (1 H, t, *J* 5.0 Hz), 3.91 (2 H, d, *J* 6.0 Hz), 2.71 (2 H, q, *J* 7.0 Hz), 2.13 (3 H, s), 1.38 (9 H, s), and 1.21 (3 H, t, *J* 7.0 Hz), $\nu_{max.}$ 3 390 and 1 665 cm^{-1} (Found: C, 59.85; H, 8.5; N, 11.5. $C_{12}H_{20}N_2O_3$ requires C, 60.0; H, 8.4; N, 11.65%).

5-Ethyl-4-(N-ethyl-t-butoxycarbonylaminomethyl)-3-methylisoxazole (14). Treatment of the isoxazole (32) with n-butyl-lithium under conditions A(i) at −70 °C gave the *ethylisoxazole* (14) (86%), b.p. 120—122° at 0.8 mmHg, δ 4.17 (2 H, s), 3.07 (2 H, q, *J* 7.0 Hz), 2.71 (2 H, q, *J* 7.0 Hz), 2.13 (3 H, s), 1.47 (9 H, s), 1.20 (3 H, t, *J* 7.0 Hz), and 1.00 (3 H, t, *J* 7.0 Hz), $\nu_{max.}$ 1 680 and 1 625 cm^{-1} (Found: C, 62.45; H, 8.85; N, 10.3. $C_{14}H_{24}N_2O_3$ requires C, 62.65; H, 9.0; N, 10.45%).

4-(Dimethylaminomethyl)-5-ethyl-3-methylisoxazole (15). Alkylation of the isoxazole (30) under conditions A(i) or B(i) at −30 °C gave the *ethylisoxazole* (15) (90%), b.p. 103—105° at 15 mmHg, δ 3.10 (2 H, s), 2.70 (2 H, q), 2.15 (3 H, s), 2.10 (6 H, s), and 1.23 (3 H, t), $\nu_{max.}$ 1 635 cm^{-1} (Found: C, 64.25; H, 9.85; N, 16.5. $C_9H_{16}N_2O$ requires C, 64.25; H, 9.6; N, 16.65%).

5-Ethyl-4-hydroxymethyl-3-methylisoxazole (16). Treatment of the isoxazole (31) under conditions A(ii) at −70 °C gave starting material (30%) and the *ethylisoxazole* (16) (65%), b.p. 100—102° at 0.4 mmHg, δ 4.55 (1 H, s), 4.23 (2 H, s), 2.67 (2 H, q), 2.10 (3 H, s), and 1.20 (3 H, t), $\nu_{max.}$ 3 390 and 1 635 cm^{-1} (Found: C, 59.9; H, 7.9; N, 10.3. $C_7H_{11}NO_2$ requires C, 59.55; H, 7.85; N, 9.9%).

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

Under conditions B(ii) at −70° the isoxazole (31) gave the ethylisoxazole (16) (70%).

The reaction of the amino-oxymethylisoxazole (34) under conditions A(iii) (10 min) gave the isoxazole (16) (68%). Under the same conditions with 2 mol. equiv. of n-butyl-lithium the isoxazole (34) gave the hydroxymethylisoxazole (31) on quenching the reaction with water.

3-(Dimethylaminomethyl)-5-ethylisoxazole (7) *and 3-dimethylaminomethyl-4,5-dimethylisoxazole* (12). 3-(Dimethylaminomethyl)-5-methylisoxazole (28) under conditions B(i) at −70 °C gave the *ethylisoxazole* (7) (84%), b.p. 92—94° at 12 mmHg, δ 5.90 (1 H, s), 3.37 (2 H, s), 2.71 (2 H, q), 2.21 (6 H, s), and 1.27 (3 H, t), $\nu_{max.}$ 1 605 cm^{-1} (Found: C, 62.4; H, 9.3; N, 18.05. $C_8H_{14}N_2O$ requires C, 62.3; H, 9.15; N, 18.15%).

Under conditions A(i) (40 and 60 min) at −70 °C the isoxazole (28) gave a mixture of the ethylisoxazole (7) and a second compound (Found: C, 62.0; H, 9.4; N, 17.85. Calc. for $C_8H_{14}N_2O$: C, 62.3; H, 9.15; N, 18.15%), identified from the n.m.r. spectrum of the mixture as the dimethylisoxazole (12), δ 3.30 (2 H, s), 2.21 (3 H, s), 2.15 (6 H, s), and 1.88 (3 H, s). N.m.r. integration indicated that the ratio of (7) to (12) was 1 : 1.

5-Ethyl-3-methoxymethylisoxazole (6) *and 3-methoxymethyl-4,5-dimethylisoxazole* (11). 3-Methoxymethyl-5-methylisoxazole (25) under conditions B(i) at −70 °C gave the *5-ethylisoxazole* (6) (90%), b.p. 82—84° at 12 mmHg, δ 5.90 (1 H, s), 4.33 (2 H, s), 3.27 (3 H, s), 2.71 (2 H, q), and 1.25 (3 H, t), $\nu_{max.}$ 1 600 cm^{-1} (Found C, 59.7; H, 8.15; N, 9.85. $C_7H_{11}NO_2$ requires C, 59.55; H, 7.85; N, 9.9%).

The reaction of 5-methylisoxazole (25) under conditions A(i) at −70 °C (40 min) gave a two-component mixture (90%), b.p. 60—62° at 2.5 mmHg, M^+ 141 (Found: C, 59.2; H, 7.8; N, 10.15. Calc. for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.9%). One component was the ethylisoxazole (6). The other was identified as the dimethylisoxazole (11) on the basis of n.m.r. evidence [δ 4.35 (2 H, s), 3.30 (3 H, s), 2.25 (3 H, s), and 1.50 (3 H, s)]. Integration indicated that the ratio of (6) to (11) was 4 : 1.

5-Ethyl-3-hydroxymethylisoxazole (8). 3-Hydroxymethyl-5-methylisoxazole (23) under conditions A(ii) or B(ii) at −70 °C gave the *ethylisoxazole* (8) (90%), b.p. 70° at 12 mmHg, δ 5.97 (1 H, s), 4.97 (1 H, s), 4.50 (2 H, s), 2.70 (2 H, q), and 1.25 (3 H, t), $\nu_{max.}$ 3 350 and 1 600 cm^{-1} (Found: C, 56.85; H, 7.4; N, 10.8. $C_6H_9NO_2$ requires C, 56.7; H, 7.15; N, 11.0%).

5-Methylisoxazol-3-ylacetic acid (27). A solution of sodium cyanide (5.0 g, 0.11 mol) and benzyltriethylammonium chloride (0.5 g, 0.002 mol) in water (20 ml) was added to a solution of 3-chloromethyl-5-methylisoxazole (24) (6.5 g, 0.01 mol) in methylene chloride (30 ml). The mixture was heated at reflux for 2 h, cooled, diluted with water (100 ml), and extracted with chloroform (3 × 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated. The residual oil was eluted from silica with toluene and ethyl acetate to give *5-methylisoxazol-3-ylacetonitrile* (47%), m.p. 36—39°, δ($CDCl_3$) 6.05 (1 H, s), 3.77 (2 H, s), and 2.41 (3 H, s), $\nu_{max.}$ 2 250 and 1 605 cm^{-1} (Found: C, 58.65; H, 5.05; N, 22.8. $C_6H_6N_2O$ requires C, 59.0; H, 4.95; N, 22.95%).

A solution of the nitrile (0.7 g, 0.005 mol) in dry ethanol (50 ml) was heated at reflux in a stream of dry hydrogen chloride for 2 h. The mixture was concentrated *in vacuo* and the residual suspension was diluted with water (100 ml). The aqueous solution was extracted with ethyl acetate

(4 × 20 ml) and the combined extracts were dried ($MgSO_4$). Evaporation gave *ethyl 5-methylisoxazol-3-ylacetate* (0.8 g, 94%) as a pale yellow oil, δ 5.91 (1 H, s), 4.08 (2 H, q, *J* 7.0 Hz), 3.53 (2 H, s), 2.33 (3 H, s), and 1.23 (3 H, t, *J* 7.0 Hz), $\nu_{max.}$ 1 730 and 1 605 cm^{-1}.

The ester (0.8 g, 0.0048 mol) in aqueous sodium hydroxide (20 ml) was kept at room temperature for 16 h. The cooled mixture was acidified with hydrochloric acid (6N) and extracted with ether (4 × 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give *5-methylisoxazol-3-ylacetic acid* (27) (0.6 g, 89%). Recrystallization from cyclohexane–ethyl acetate (3 : 1) gave prisms, m.p. 80—82°, δ($CDCl_3$) 11.70 (1 H, s, exchangeable), 6.05 (1 H, s), 3.75 (2 H, s), and 2.40 (3 H, s), $\nu_{max.}$ 1 715 and 1 605 cm^{-1} (Found: C, 50.75; H, 4.9; N, 9.8. $C_6H_7NO_3$ requires C, 51.05; H, 5.0; N, 9.9%).

[5/2153 *Received, 5th November,* 1975]