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SYNTHESIS OF 4-CARBOSUBSTITUTED ISOXAZOLE DERIVATIVES

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Abstract- 3,5-Disubstituted 4-lithioisoxazoles were synthesized selectively and in good yields by *exchange* between 4-bromoisoxazoles and n-BuLi as it is proved carboxylation. Reactions of 3,5-disubstituted 4-lithioisoxazoles with *saturated or* α,β-unsaturated carbonyl compounds, esters, nitriles and amides allow the introduction of carbon-chains with different functionality at C-4.

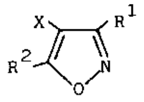
INTRODUCTION

Several applications of isoxazole derivatives as equivalent synthons of β-diketones, β-aminoenones, etc.[1-4], require the presence of alkyl, alkenyl, acyl or another group referable to them at C-4 position of heterocyclic system. As 4-alkyl- and 4-acylisoxazoles cannot be obtained by direct alkylation or acylation of the ring according to F&C[5], the development of methods to make possible the heterocycle 4-carbosubstitution has a great synthetic interest. As a more immediate way, it has been studied 4-halo-[6-8] and 4-hydroxyalkylation[9] of isoxazole compounds and the use of 4-lithio derivatives[10-12] or Grignard compounds as intermediates[13].

In this paper, the synthesis of 3,5-disubstituted 4-lithioisoxazoles and their behaviour with several types of electrophile compounds is studied. The extent of the direct lithiation of the isoxazole ring at C-4 position depends on the nature of substituents at the C-3 and C-5 positions[14]. The methyl groups at C-5 are particulary acid toward n-butyllithium and their metalation is always the predominant reaction[15,16]. Although the alkoxy and thioalkoxy groups at C-3 position facilitate the lithiation at C-4[16], this lithiation only happens exclusively when the substrate is a 5-arylsubstituted isoxazole[10]. Although the presence of an atom of chlorine at C-5 facilitates the metalation at C-4[17], the preparation of 3,5-dimethyl-4-lithioisoxazole (7) by exchange between 3,5-dimethyl-4-iodoisoxazole and n-butyllithium[11], opens an alternative pathway of 4-lithiation with interesting prospects. The intermediate (7) has been used in the synthesis of 1,4-benzodiazepines[11] and benzylpiperazines of potential pharmacological interest[12] and in several processes of 4-silylation and 4-stannylation of isoxazole derivatives[18].

RESULTS AND DISCUSSION

The impossibility to apply direct metalation at C-4 position has been proved in several preliminary experiences carried out with 3-methyl-5-phenyl- (2) and 3,5-diphenylisoxazole (3): their reactions with n-butyllithium followed by carbon dioxide, propionaldehyde or benzaldehyde lead to the results summarised in Table I.



1; $R^1=R^2=Me$, X=H

2; $R^1=Me$, $R^2=Ph$, X=H

3; $R^1=R^2=Ph$, X=H

4; $R^1=R^2=Me$, X=Br

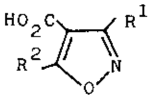
5; $R^1=Me$, $R^2=Ph$, X=Br

6; $R^1=R^2=Ph$, X=Br

7; $R^1=R^2=Me$, X=Li

8; $R^1=Me$, $R^2=Ph$, X=Li

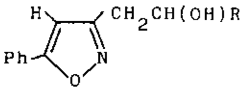
9; $R^1=R^2=Ph$, X=Li



10; $R^1=R^2=Me$

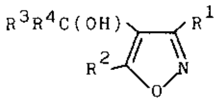
11; $R^1=Me$, $R^2=Ph$

12; $R^1=R^2=Ph$



13; R=Et

14; R=Ph



15; $R^1=R^2=R^3=Me$, $R^4=H$

16; $R^1=R^2=Me$, $R^3=Et$, $R^4=H$

17; $R^1=R^2=Me$, $R^3=Ph$, $R^4=H$

18; $R^1=R^2=Me$, R^3=PhCH=CH, $R^4=H$

19; $R^1=R^2=Me$, $R^3=CH_2=CH$, $R^4=H$

20; $R^1=R^2=R^4=Me$, R =PhCH=CH

21; $R^1=R^2=Me$, R^3=PhCH=CH, $R^4=Ph$

22; $R^1=R^2=R^4=Me$, $R^3=Me_2C=CH$

23; $R^1=R^2=R^4=Me$, $R^3=Et$

24; $R^1=R^2=R^4=Me$, $R^3=Ph$

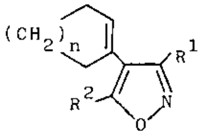
25; $R^1=Me$, $R^2=Ph$, $R^3=Et$, $R^4=H$

26; $R^1=Me$, $R^2=R^3=Ph$, $R^4=H$

27; $R^1=Me$, $R^2=R^3=Ph$, $R^4=Me$

28; $R^1=R^2=Ph$, $R^3=Et$, $R^4=H$

29; $R^1=R^2=R^3=Ph$, $R^4=H$



30; $R^1=R^2Me$, n=1

31; $R^1=R^2=Me$, n=2

Scheme 1

Table I

Reactions of 3-methyl-5-phenyl- (2) and 3,5-diphenylisoxazole (3) with n-butyllithium

Isoxazole	Time (h)	4-Li-deriv.	Electroph.	Time (h)	Products (%) [a]
2	2	8	EtCHO	6	13(11), 25(22), 2(40)
2	3	8	PhCHO	6	14(3), 26(29), 2(38)
3	1,5	9	CO_2	-b	12(10), 3(76)
3	2	9	EtCHO	2	28(9), 3(73)

[a] Yields refer to pure products, isolated usually by column chromatography, except 13 and 14, obtained as a mixture with 25 and 26 compounds, respectively, and identified from the NMR spectra of the mixture.

[b] CO_2 is made bubbled to saturation.

On the contrary, formation of 4-lithio derivatives (7, 8, 9) takes place satisfactorily when 4-bromo-3,5-dimethyl- (4), 4-bromo-3-methyl-5-phenyl- (5) and 4-bromo-3,5-diphenylisoxazole (6) react with n-butyllithium. Although the position of exchange equilibrium depends on the nature of the groups attached to the halogen and to the metal[19-21], 7, 8 and 9 are obtained *selectively and* in good or acceptable yields, as it is proved by carboxylation (Table II).

Table II

Reactions of 4-bromo-3,5-dimethyl- (4), 4-bromo-3-methyl-5-phenyl- (5) and 4-bromo-3,5-diphenylisoxazole (6) with n-butyllithium followed by CO_2[a]

Isoxazole	Time(min)	4-Li-deriv.	Products (%)[b]
4	75	7	10 (96)
5	15	8	11 (60), 2 (32)
5	75	8	11 (70)
6	15	9	12 (78), 3 (19)
6	75	9	12 (80)

[a] CO_2 is made bubbled to saturation.

[b] Yields are referred to purified products.

Reactions of 7, 8 and 9 with saturated or α,β-unsaturated carbonyl compounds, allow the union to C-4 position of very different carbon-chains to give the respective alcohols (with cyclic ketones they give the respective olefins) with yields dependent on the nature of groups attached to C-3 and C-5 (Table III), which steric hindrance upon C-4 increases with their size [13,22,23].

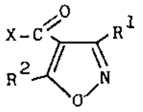
Table III

Reactions of 4-lithio-3,5-dimethyl- (7), 4-lithio-3-methyl-5-phenyl- (8) and 4-lithio-3,5-diphenylisoxazole (9) with oxocompounds

4-Lithioisoxazole	Oxo compound	Time(h)	Products (%)[a]
7	MeCHO	6	15 (60), 1 (19)
7	EtCHO	6	16 (59), 1 (6)
7	PhCHO	6	17 (80), 1 (10)
7	PhCH=CHCHO	6	18 (90)
7	CH_2=CHCHO	7	19 (50), 1 (45)
7	EtCOMe	3	23 (70)
7	PhCOMe	6,5	24 (64), 1 (3)
7	PhCH=CHCOPh	6,5	21 (95)
7	Me_2C=CHCOMe	6	22 (95)
7	PhCH=CHCOMe	6	Polymer
7	cycloC_5H_8O	6	30 (72), 1 (17)
7	cyclo$C_6H_{10}O$	6	31 (69)
8	EtCHO	6	25 (20), 2 (40)
8	PhCHO	6	26 (25), 2 (27)
9	EtCHO	6	28 (48), 3 (35)
9	PhCHO	3,5	29 (15), 3 (73)

[a] Yields are referred to pure isolated products.

Reactions of 4-lithioisoxazoles with N,N-dialkylamides take place also as usual and give 4-acylderivatives in acceptable or high yields; nitriles without acid hydrogens in α position lead likewise to 4-acylisoxazoles after acid hydrolysis of respective imines. Finally, the resultant products of the reactions of 7 with esters are tertiary alcohols (conventional esters) or 3,5-dimethylisoxazol-4-carboxylic acid derivatives (ethyl chloroformate and ethyl carbonate). The results of these reactions are summarised in Table IV.



32; $R^1=R^2=Me$, X=H

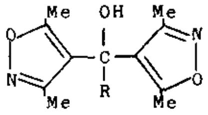
33; $R^1=R^2=Me$, X=Me

34; $R^1=R^2=Me$, X=Ph

35; $R^1=Me$, $R^2=Ph$, X=H

36; $R^1=R^2=Ph$, X=H

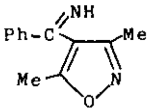
37; $R^1=R^2=Me$, X=OEt



38; R=Me

39; R=nPr

40;



Scheme 2

Table IV

Reactions of 4-lithioisoxazoles with amides, nitriles and esters

4-Li-deriv.	Substrate	Exptal. Cond.[a]	Products (%)
7	$HCONMe_2$	-78°, 6^h; 25°, 2^h	32 (75), 1 (3)
7	$MeCONMe_2$	-78°, 6^h; 25°, 2^h	33 (64), 1 (11)
7	$PhCONMe_2$	-78°, 6^h; 25°, 2^h	34 (41), 1 (40)
8	$HCONMe_2$	-78°, 6^h; 25°, 2^h	35 (45), 2 (53)
9	$HCONMe_2$	-78°, 6^h; 25°, 2^h	36 (30), 3 (62)
7	PhCN	-78°, 6^h; 25°, 2^h	40 (85) → 34 (90)
7	MeCN	-78°, 6^h; 25°, 2^h	Polymer
7	PhCH=CHCN	-78°, 6^h; 25°, 2^h	Polymer
7	$MeCO_2Et$	-78°, 6^h; 25°, 1^h	38 (16), 1 (25)
7	$nPrCO_2Et$	-78°, 5^h; 25°, 1^h	39 (44), 1 (29)
7	$ClCO_2Et$	-78°, 4^h; 25°, 1^h	37 (73), 1 (4)
7	$CO(OEt)_2$	-78°, 4^h; 25°, 1^h	37 (80), 2 (2)

[a] It has been used in all these cases n-BuLi in molar ratio substrate:organometallic=1:1,1 in dry Et_2O or THF (the result are the same) and under dry nitrogen atmosphere.

[b] Yields are referred to pure products, isolated by column chromatography on silica gel with dichloromethane as eluent.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were recorded for potassium bromide pellets in the case of solids or film in the case of liquids, using a Perkin-Elmer Model 577 spectrophotometer. Nuclear magnetic resonance spectra were determined at 60 MHz on a Hitachi-Perkin-Elmer R-24 B and a Varian T-60 A spectrometers using $CDCl_3$ and CCl_4 solutions and TMS as standard reference; chemical shifts were measured in the δ scale. Electron ionization mass spectra were obtained on a Hitachi PMW-6L. Elemental analysis were measured on a Perkin-Elmer 240 B analyzer. Merck silicagel 60 was used for column chromatography, solvents and reagents were purified by conventional methods.

Isoxazole synthesis

3,5-Dimethylisoxazole [24](1), 3-methyl-5-phenylisoxazole [25](2), 3,5-diphenylisoxazole[26] (3) were prepared by established procedures; 4-bromo-3,5-dimethylisoxazole[27] (4), 4-bromo-3-methyl-5-phenylisoxazole (5) and 4-bromo-3,5-diphenylisoxazole (6) were prepared by treating the respective 3,5-disubstituted isoxazoles with bromine and nitric acid according to the literature methods[28].

Metalation of 3,5-disubstituted isoxazoles and subsequent reactions

A solution of the isoxazole (0.018 moles) in dry tetrahydrofuran (50 ml) in a dry flask was cooled to -75°C (solid CO_2-acetone). n-Butyllithium (12.5 ml of 1,6M solution in hexane, 0.02 moles) was added slowly under dry nitrogen. The solution was stirred and the temperature kept at -75°C for the suitable time (Table I). The mixture was treated with solution of the appropriate carbonyl substrate (0.018 moles) in 25-30 ml of dry tetrahydrofuran. The reaction mixture was then stirred at -75°C for 2 to 6 h. After addition of water, the solution was stirred until it reached ambient temperature, then the layers were separated and the aqueous layer extracted with ether. The combined extracts were dried (Na_2SO_4) and evaporated to give the crude products. The products were separated and purified by distillation, crystallitation or column chromatography.

3-(2-Hydroxybutyl)-5-phenylisoxazole (13) and 4-(1-hydroxypropyl)-3-methyl-5-phenylisoxazole (25)

Metalation of isoxazole (2) with n-BuLi followed by treatment with propionaldehyde gave a mixture of (13) and (25). The 3-(2-hydroxybutyl)-5-phenylisoxazole (13) was identified from the ^1H-nmr spectrum of the mixture (CCl_4): 7.65-7.15 (m, 5H), 6.25 (s, 1H), 4.00-3.70 (m, 1H), 2.80 (d, 2H), 1.90-1.20 (m, 2H), 1.00-0.60 (t, 3H).

4-(1-Hydroxypropyl)-3-methyl-5-phenylisoxazole (25), white solid from methanol-water, mp 68-71°C. The ir (KBr): 3450, 3120, 1620 cm^{-1}; ^1H-nmr (CCl_4): 7.50-7.00 (m, 5H), 4.50 (t, 1H), 3.40 (br s, 1H), 2.10 (s, 3H), 1.60 (m, 2H), 0.85 (t, 3H). Nmr integration indicated that the ratio of (25) to (13) was 2:1.

3-(2-Phenyl-2-hydroxyethyl)-5-phenylisoxazole (14) and 4-(hydroxybenzyl)-3-methyl-5-phenylisoxazole (26)

Metalation of isoxazole (2) with n-BuLi followed by treatment with benzaldehyde gave a mixture of (14) and (26). The 3-(2-phenyl-2-hydroxyethyl)-5-phenylisoxazole (14) was identified from the ^{1}H-nmr spectrum of the mixture (CCl$_4$): 7.50-6.90 (m, 10H), 6.10 (s, 1H), 4.80 (t, 1H), 4.30-4.10 (br s, 1H), 2.95 (d, 2H).

4-(Hydroxybenzyl)-3-methyl-5-phenylisoxazole (26), white solid from methanol-water, mp 88-90°C. The ir (KBr): 3400-3100, 1620 cm^{-1} ; ^{1}H-nmr (CCl$_4$): 7.40-6.80 (m, 10H), 4.65 (t, 1H), 3.50 (br s, 1H), 1.80-1.30 (m, 2H), 0.70 (t, 3H).

4-(1-Hydroxypropyl)-3,5-diphenylisoxazole (28), white solid from methanol-water, mp 135-137°C. The ir (KBr): 3360, 1630, 1380 cm^{-1}; ^{1}H-nmr (CDCl$_3$): 7.80 - 7.10 (m, 10H), 4.65 (t, 1H), 3.50 (br s, 1H), 1.80-1.30 (m, 2H), 0.70 (t, 3H).

3,5-Diphenylisoxazole-4-carboxylic acid (12)

The 4-lithio-3,5-diphenylisoxazole was made in the same way as described before and the mixture was stirred for 1 h, poured into excess dry ice and allowed to warm to room temperature. The product was extracted with 2N sodium hydroxide solution. The basic solution was acidified with dilute hydrochloric acid and the resultant solid was filtered and recrystallised from ethanol-water to yield 3,5-diphenylisoxazole-4-carboxilic acid (12) as a white solid, mp 234-236°C. Anal. Calc for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.15; N, 5.28. Found: C, 72.53; H, 4.24; N, 5.21. The ir (KBr): 3300-2700, 1725, 1605 cm^{-1}; ^{1}H-nmr (DMSO-d$_6$):8.00-7.10 (m, 11H).

Metalation of 3,5-disubstituted 4-bromoisoxazoles and subsequent reactions

The general procedure used in these reactions is similar to method for 3,5-disubstitued isoxazoles.

In the reactions with 4-bromo-3,5-dimethylisoxazole (4), dry diethyl ether was used as solvent and the organic substrates (oxo compounds, esters, nitriles and amides) were added to reaction mixture just after formation of organolithium compound. The reaction products were separated and purified by distillation under reduced pressure and crystallization.

In the case of 4-bromo-3-methyl-5-phenylisoxazole (5) and 4-bromo-3,5-diphenylisoxazole (6), the solvent was dry THF and the metalation reaction time was 20 min. The products were separated by column chromatography on silica gel with dichloromethane as eluent.

4-(1-Hydroxyethyl)-3,5-dimethylisoxazole (15), colourless liquid, bp 93-94°C at 1 mm. The ir (film): 3350, 1630, 1370 cm^{-1} ; ^{1}H-nmr (CCl$_4$): 4.60 (q, 1H), 3.80 (br s, 1H), 2.30 (s, 3H), 2.10 (s, 3H), 1.35 (d, 3H); ms: m/z (relative intensity) 141 M$^+$ (13), 123 (6), 126 (75), 84 (59), 66 (14), 43 (100).

4-(1-Hydroxypropyl)-3,5-dimethylisoxazole (16), colourless liquid, bp 102-103°C at 1.4 mm. The ir (film): 3400, 1635, 1380 cm^{-1} ; ^{1}H-nmr (CCl$_4$): 4.30 (t, 1H), 3.60 (br s, 1H), 2.35 (s, 3H), 2.15 (s, 3H), 1.95-1.25 (m, 2H), 0.85 (t, 3H); ms: m/z (relative intensity) 155 M$^+$ (10), 137 (4), 126 (100), 84 (81), 66 (13), 43 (100).

4-(1-Hydroxybenzyl)-3,5-dimethylisoxazole (17), colourless liquid, bp 140°C at 0.2-0.3 mm. The ir (film): 3350, 1630, 750, 700 cm^{-1} ; ^{1}H-nmr (CCl_4): 7.20 (s, 5H), 5.60 (s, 1H), 4.05 (br s, 1H), 2.25 (s, 3H), 2.00 (s, 3H); ms: m/$_z$ (relative intensity) 203 M^{+} (62), 182 (21), 126 (68), 107 (100), 84 (59), 66 (13), 43 (86).

4-(1-Hydroxy-3-phenyl-2-propenyl)-3,5-dimethylisoxazole (18), white solid from ethanol-water, mp 72°C. Anal. Calc for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55;N, 6.11. Found: C, 73,25 ; H, 6,51; N, 6,17. The ir (KBr): 3300, 1630, 980, 750, 690 cm^{-1}; ^{1}H-nmr (CCl_4): 7.20 (s, 5H), 6.45 (d, J=16 Hz, 1H), 6.20-5.90 (m, 1H), 5.00 (d, J=4 Hz, 1H), 3.80 (br s, 1H), 2.30 (s, 3H), 2.10 (s, 3H).

4-(1-Hydroxyallyl)-3,5-dimethylisoxazole (19), colourless liquid, bp 102-103°C at 1.3 mm. Anal. Calc for $C_8H_{11}O_2N$: C, 62.74; H, 7.19; N, 9.15. Found: C, 62.65; H, 7.15; N, 9.31. The ir (film): 3460, 1630, 985, 920 cm^{-1} ; ^{1}H-nmr (CCl_4): 6.25-5.70 (m, 1H), 5.25 (m, 2H), 3.90 (br s, 1H), 2.30 (s, 3H), 2.10 (s, 3H).

4-(1-Hydroxy-1-methyl-3-phenyl-2-propenyl)-3,5-dimethylisoxazole (20), by distillation gave polimeric compound. The ir (CCl_4): 3380, 1665, 1605, 965, 680 cm^{-1}; ^{1}H-nmr: 7.00 (m, 5H), 6.35 (d, J=15 Hz, 1H), 6.20 (d, J=15 Hz, 1H), 3.60 (br s, 1H), 2.30 (2, 3H), 2.10 (s, 3H), 1.60 (s, 3H).

4-(1-Hydroxy-1,3-diphenyl-2-propenyl)-3,5-dimethylisoxazole (21), white solid from ethanol-water, mp 101-103°C. The ir (CCl_4): 3600, 3360, 1615, 980, 700 cm^{-1}; ^{1}H-nmr (CCl_3D): 7.50-7.00 (m, 10H), 6.50 (s, 2H), 3.40 (br s, 1H), 2.10 (s, 3H), 1.90 (s, 3H); ms: m/z (relative intensity) 305 M^{+} (9), 260 (12), 209 (24), 131 (27), 105 (100), 43 (42).

4-(1-Hydroxy-1,3-dimethyl-2-butenyl)-3,5-dimethylisoxazole (22), colourless liquid, bp 137-139°C at 1.5 mm. Anal. Calc for $C_{11}H_{18}O_2N$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.21; H, 9.44; N, 7.13. The ir (CCl_4): 3620, 3400, 1670, 1625, 1375, 1370 cm^{-1}; ^{1}H-nmr (CCl_4): 5.50 (br s, 1H), 2.80 (br s, 1H), 2.40 (s, 3H), 2.10 (s, 3H), 1.70-1.50 (3s, 9H).

4-(1-Hydroxy-1-methylpropyl)-3,5-dimethylisoxazole (23), white solid from ethanol-water, mp 65-66°C. Anal. Calc for $C_9H_{15}O_2N$: C, 63.90; H, 8.87; N, 8.28. Found: C, 64.02; H, 8.84; N, 8.23. The ir (film): 3400, 1620 cm^{-1}; ^{1}H-nmr (CCl_4): 2.95 (br s, 1H), 2.40 (s, 3H), 2.15 (s, 3H), 1.90-1.30 (m, 2H), 1.45 (s, 3H), 0.80 (t, 3H).

4-(1-Hydroxy-1-methylbenzyl)-3,5-dimethylisoxazole (24), white solid from ethanol-water mp 99-100°C. Anal. Calc for $C_{13}H_{15}O_2N$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.79; H, 7.01; N, 6.48. The ir (KBr): 3360, 1625, 750, 695 cm^{-1};^{1}H-nmr (CCl_3D): 7.30 (s, 5H), 2.35 (s, 3H), 2.10 (br s, 1H), 2.00 (s, 3H), 1.90 (s, 3H).

4-(1-Hydroxy-1-methylbenzyl)-3-methyl-5-phenylisoxazole (27), white solid from methanol-water, mp 85-87°C. Anal. Calc for $C_{18}H_{17}O_2N$: C, 77.41; H, 6.09; N, 5.01. Found: C, 77.39; H, 6.12; N, 5.06. The ir (KBr): 3400, 3100, 1620, 765, 695 cm^{-1}; ^{1}H-nmr (CCl_4): 7.30-6.90 (m, 10H), 3.65 (br s, 1H), 1.95 (s, 3H), 1.60 (s, 3H).

4-(1-Hydroxybenzyl)-3,5-diphenylisoxazole (29), white solid from methanol, mp 140-142°C. Anal. *Calc for* $C_{22}H_{17}O_2N$: *C,* 80.81; *H,* 5.23; *N,* 4.28. *Found:* C, 80.63; H, 5.25; N, 4.33. The ir (KBr): 3550, 3300, 1600, 720, 680 cm^{-11}; ^{1}H-nmr ($CDCl_3$): 7.70-7.10 (m, 15H), 6.10 (d, 1H), 3.00 (d, 1H).

4-(1-Cyclopentenyl)-3,5-dimethylisoxazole (30), colourless liquid, bp 98-100°C at 4 mm. The ir (film): 1640, 1610 cm^{-1} ; ^{1}H-nmr (CCl_4): 5.65 (m, 1H), 2.70-1.70 (m, 6H), 2.35 (s, 3H), 2.20 (s, 3H); ms: m/z (relative intensity) 163 M^+ (24), 148 (23), 120 (28), 43 (100).

4-(1-Cyclohexenyl)-3,5-dimethylisoxazole (31), colourless liquid, bp 95-100°C at 2 mm. The ir (film): 1660, 1615 cm^{-1} ; ^{1}H-nmr (CCl_4): 5.40 (m, 1H), 2.20-1.90 (m, 4H), 2.20 (s, 3H), 2.00 (s, 3H), 1.60 (m, 4H); ms: m/z (relative intensity) 177 M^+ (49), 162 (16), 134 (27), 43 (100).

3,5-Dimethylisoxazole-4-carbaldehyde (32), white solid, mp 34-36°C[29].

4-Acetyl-3,5-dimethylisoxazole (33), white solid, mp 46°C[30].

4-Benzoyl-3,5-dimethylisoxazole (34), yellow solid, mp 67°C[8].

3-Methl-5-phenylisoxazole-4-carbaldehyde (35), white solid, mp 85-87°C[31].

3,4-Diphenylisoxazole-4-carbaldehyde (36), white solid, mp 113-114°C[31].

3,5-Dimethyl-4-ethoxycarbonylisoxazole (37), colourless liquid, bp 82°C at 4 mm[32].

1,1-Di(3,5-dimethyl-4-isoxazolyl)-1-hydroxyethane (38), white solid, mp 111-113°C from ethanol-water. The ir *(KBr): 3400, 1620, 1370* cm^{-1}; ^{1}*H-nmr* (CCl_4): 3.00 (br s, 1H), 2.40 (s, 6H), 2.05 (s, 6H), 1.90 (s, 3H); ms: m/z (relative intensity) 236 M^+ (14), 221 (100), 124 (3), 82 (56), 43 (78).

1,1-Di(3,5-dimethyl-4-isoxazolyl)-1-hydroxybutane (39), white solid, mp 148-149°C from ethanol-water. The ir (KBr): 3560, 3350, 1620, 1365 cm^{-1} ; ^{1}H-nmr ($CDCl_3$): 2.55 (br s, 1H), 2.50 (s, 6H), 2.30-1.90 (m, 2H), 2.10 (s, 6H), 1.90-1.20 (m, 2H), 1.20-0.90 (t, 3H); ms: m/z (relative intensity) 221 M-43 (100), 124 (33), 82 (17), 43 (78).

(3,5-Dimethyl-4-isoxazolyl)phenyl ketimine (40), yellow solid, mp 75-77°C. The ir (CCl_4): 3260, 1660, 1615 cm^{-1} ; ^{1}H-nmr (CCl_4): 9.00 (br s, 1H), 3.20 (s, 5H), 2.15 (s, 3H), 2.00 (s, 3H); ms: m/z (relative intensity) 201 $M^{+\cdot}$+1 (27), 200 M^+ (56), 199 M^+-1 (100), 185 (11), 104 (38), 43 (76).

3,5-Disubstituted isoxazole 4-carboxylic acids

The 4-lithio compounds (7, 8, 9) were obtained in the same way as described before. The reaction time is *shown in the table II. The mixture was poured* into excess dry ice and stirred until it reached ambient temperature. The product was extracted with 2N sodium hydroxide solution. The basic solution was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was dried (Na_2SO_4) and the solvent removed in vacuo to yield the respective acids.

3,5-Dimethylisoxazole-4-carboxylic acid (10), white solid, mp 141°C[33].

3-Methyl-5-phenylisoxazole-4-carboxylic acid (11), yellow solid, mp 190-192°C[34].

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