PREPARATION OF 6-(3,5-DIMETHYLISOXAZOL-4-YL)-6-OXOHEXANOIC ACIDS VIA 3,5-DIMETHYLISOXAZOL-4-YLMAGNESIUM IODIDE OR 3,5-DIMETHYLISOXAZOL-4-YLLITHIUM

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Abstract——— 3,5-Dimethylisoxazol-4-ylmagnesium iodide 1 or 3,5-dimethylisoxazol-4-yllithium 3 react with cyclohexanones 2a-c to give 4-(methylcyclohexen-1-yl)-3,5-dimethylisoxazoles 4a-c which in turn gave the title acids by oxidation.

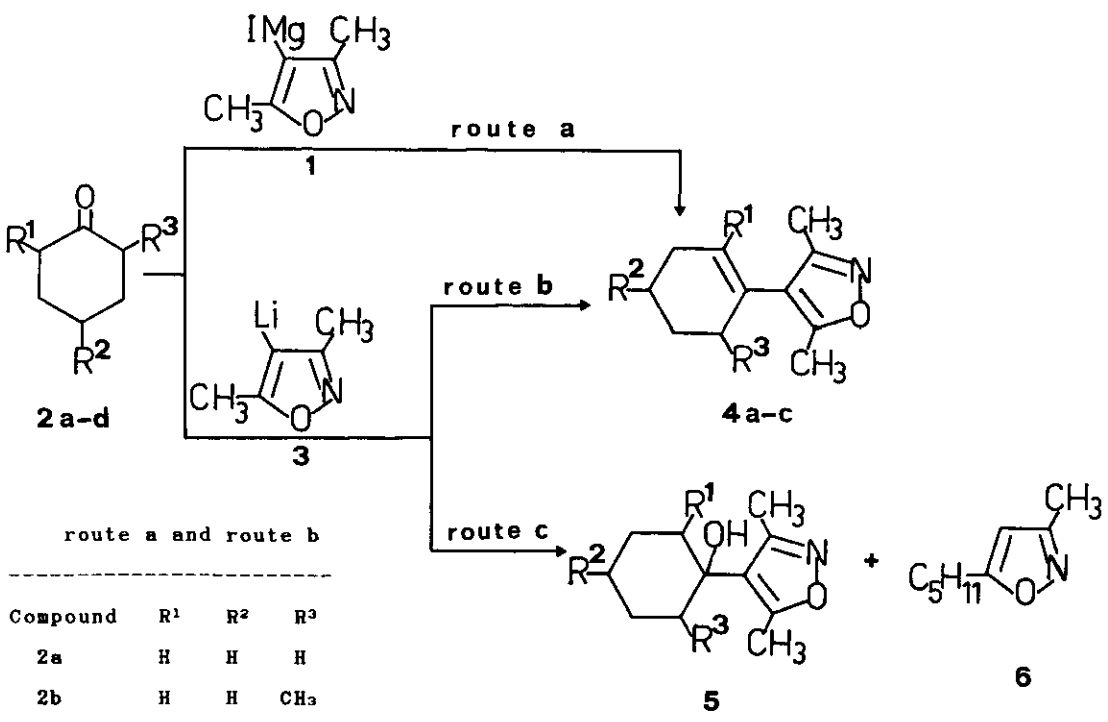
INTRODUCTION

Even though isoxazol-4(3)-ylmagnesium halides are known,[1-5] only a few of them have been used, and in a limited way at that, for synthetic purposes.[4,5] These Grignard reagents can be easily obtained from 4-iodo-3,5-dialkyl(diphenyl)-isoxazoles,[1,2] in halogen-metal exchange conditions. In addition isoxazolyllithium and isoxazolylmethyllithium derivatives, prepared by using n-butyl (or s-butyl)lithium, were considered to be useful intermediates[6-12] for the synthesis of a large variety of compounds. In particular 3,5-dimethylisoxazole[7] and 5-methoxymethyl-3-alkylisoxazoles[8,9] gave the corresponding isoxazol-5-ylmethyllithium compounds when reacted with n-butyllithium. Alternatively 5-alkylisoxazol-3-ylmethyllithium derivatives were produced by reaction of 3-methyl-5-alkylisoxazoles with s-butyllithium.[10] The lithiation in the C-4 position of the 3,5-dimethylisoxazole through halogen-metal exchange in 4-iodo-3,5-dimethylisoxazole[11,12] may be considered as a good entry to the corresponding 3,5-dimethylisoxazol-4-yllithium 3, which in turn could also be useful as an intermediate.

In this paper we report a study on the reactivity of 3,5-dimethylisoxazol-4-ylmagnesium iodide 1 and 3,5-dimethylisoxazol-4-yllithium 3 towards cyclohexanones 2a-c with the aim of preparing 4-(methylcyclohexen-1-yl)-3,5-dimethylisoxazoles 4a-c which were in turn used for the preparation of the title acids upon oxidation.

RESULTS AND DISCUSSION

The intermediate 1, prepared following the literature[1], when refluxed with cyclohexanones 2a-d gave after dehydration 4-(cyclohexen-1-yl)-3,5-dimethyl-isoxazoles 4a-c following route a in the Scheme 1. The above condensation reactions appeared to be dramatically impeded by steric effects. In fact 1 does not react with 2d and therefore the expected compound 4d is not formed, probably owing to steric hindrance between the methyl groups present in the 2,6-positions of the cyclohexanone and the Grignard portion of 1. During the preparation of 4b the isomeric compound 4-(2-methylcyclohexen-1-yl)-3,5-dimethylisoxazole 4b' was obtained as the major product. In fact the ^1H nmr spectrum of the reaction mixture showed, among others, a weak signal at δ= 5.50 (Table 2) due to a vinyl proton of 4b(minor). This attribution was confirmed by taking the ^1H nmr of compound 4b, which was later prepared according to route b in the Scheme 1.



route a and route b

Compound	R^1	R^2	R^3
2a	H	H	H
2b	H	H	CH_3
2c	H	CH_3	H
2d	CH_3	H	CH_3

(route c only for 2d)

Scheme 1

The reaction conditions together with the yields of these products are given in Table 1. Spectroscopic data for the above products reported in table 2 are in

agreement for the proposed structures. Alternatively compounds 4a-c were obtained by reaction of 3,5-dimethylisoxazol-4-yllithium[11] with 2a-c as shown in the route b Scheme 1. This method besides giving compounds 4a-c with good yields, allowed us to obtain from 2b only compound 4b (route b) probably because the dehydration leading to 4b occurs under kinetic control during the reaction, whereas in the previous procedure a dehydration reaction is required to obtain the polysubstituted cyclohexenyl group. Another interesting feature of this method is the reactivity of 3 with the sterically hindered 2d to give the corresponding alcohol 5 (mixture of stereoisomers) along with 3-methyl-5-n-pentylisoxazole 6 (20 % yield) as reported in Scheme 1 (route c) whereas the same reaction does not occur when 1 is used. This different behaviour may be ascribed to a lesser steric effect of 3 as compared with that of 1. Compound 6 is also obtained (50 % yield) when n-butyllithium and 4-iodo-3,5-dimethylisoxazole are left to react for 6 h. This result accounts for the presence of 6 together with 5 when 3 reacts with 2d; the relative yields of 5 and 6 would depend on the reaction rate of 3 with 2d. However additional data are requested to explain the formation of 3-methylisoxazol-5-ylmethyllithium, which we invoke for the synthesis of 6. In fact it is known[10] that the above lithium compound reacts with n-butyl iodide, formed in our case during the preparation of 3.

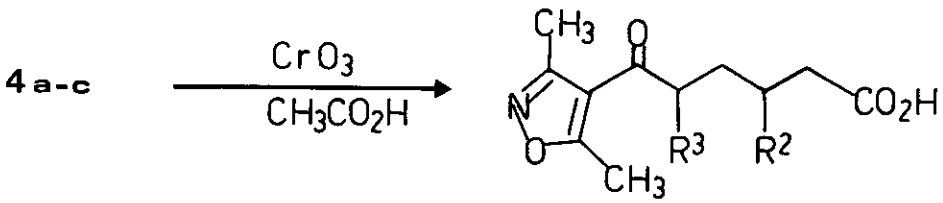
TABLE 1. Products from reactions of cyclohexanones 2a-d with compounds 1 and 3.

	Yield %		
Compound	route a	route b	route c
4a	75	75	--
4b*	10	70	--
4c	75	75	--
4d	0	0	--
5	--	--	35
6	--	--	20

* Compound 4b' (R^1=CH_3; R^2=H; R^3=H; yield 60%) was obtained together with 4b (route a)

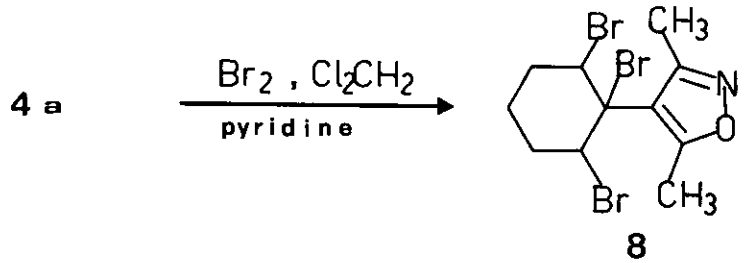
Chromic oxidation under Fieser and Szmuszkovicz's conditions,[13] of compounds 4a-c gives the corresponding 6-(3,5-dimethylisoxazol-4-yl)-6-oxohexanoic acids 7a-c (7b-c mixture of stereoisomers) as shown in scheme 2 whereas 5 is not affected by the above oxidation method. Even in the mass spectra for 5 there is no evidence of dehydration or loss of the hydroxyl group in the fragments with

higher m/z reported in Table 2. Because the oxidation with potassium permanganate of **4a** afforded adipic acid, one may expect that also in this case compound **7a** is the first oxidation product which in turn is then oxidized to the dicarboxylic acid.



Compound	R^2	R^3
7a	H	H
7b	H	CH_3
7c	CH_3	H

7 a-c



8

Scheme 2

When we tested the reactivity of **4a** with bromine in presence of pyridine we found that the tribromo derivative **8** was formed as shown in Scheme 2. This finding is explained by considering that hydrogen bromide may be lost after the first addition of bromine to **4a** leading to an intermediate with a double bond which then adds bromine to give **8**. The mass spectrum of **8** shows the peak $(M - Br)^+$ whereas the molecular ion was not detectable. In addition we noticed the decomposition of **8** at the reported melting point (Table 2). These findings may be related to the lability of bromine on the carbon atom adjacent to the isoxazole ring.

We wish to emphasize that route b is more versatile with respect to route a for the preparation of compounds **4a-c** and therefore for achieving the 6-(3,5-dimethylisoxazol-4-yl)-6-oxohexanoic acids **7a-c**. In addition the possibility of preparing long chain functionalized acids by the above methods seems to be promising for the preparation of more complex molecules. Thus for example com-

pound 7c could be conveniently modified in the 5- position of the isoxazole ring for the synthesis of the carbon skeleton of the Juvenile hormone.

EXPERIMENTAL

Melting points were determined using a Gallenkamp MFB-595 capillary melting point apparatus and are uncorrected. ^{1}H nmr spectra were recorded on a Perkin Elmer R-32 spectrometer, in Cl_3CD with tetramethylsilane as internal standard. Ir spectra were registered on a Beckman IR-4240 spectrophotometer, in nujol mulls. Mass spectral data were taken with a Hitachi Perkin Elmer RMU-6M6 mass spectrometer, by using a direct inlet system heated to 180 °C. The ionizing energy was 75 eV. Elemental analysis for new compounds carried out on Perkin Elmer 240-B apparatus gave satisfactory results. Melting points, boiling points and spectroscopic data for new compounds are reported in table 2. Cyclohexanones 2a-d, supplied by Fluka were used without further purification. Compound 2d was a mixture of stereoisomers.

General Procedure for the Reaction of Cyclohexanones 2a-d with 3,5-Dimethylisoxazol-4-ylmagnesium Iodide 1:

A vigorously stirred solution containing 3,5-dimethylisoxazol-4-ylmagnesium iodide 1, prepared[1] from ether (150 ml), magnesium (5 g 0.205 mol), ethyl bromide (15 g, 0.14 mol) and 4-iodo-3,5-dimethylisoxazole (14 g, 0.605 mol), was evaporated under reduced pressure in a nitrogen atmosphere, at room temperature, until ether stopped distilling. After addition of dry benzene (150 ml), the solution was treated dropwise with the requisite cyclohexanone (0.205 mol) dissolved in dry benzene (25 ml) and refluxed for 8 h (12 h in the attempted preparation of 4d). Hydrolysis carried out with an aqueous saturated solution of ammonium chloride (200 ml) was followed by extraction with ether (500 ml). The combined ethereal fractions were worked up and evaporated to give a residue to which was added sulphuric acid (10 N, 30 ml) and heated at 100 °C for 5 min under stirring. The resulting mixture was extracted with ether, and the combined fractions were washed with an aqueous saturated solution of sodium hydrogen carbonate, dried ($MgSO_4$), filtered and evaporated with a rotavapor to give a liquid which was then distilled under reduced pressure. The fraction corresponding to the isoxazole derivative was purified by chromatography through a

silica gel column (benzene as eluent). Evaporation of the solvent left compounds **4a-c**. When the above reaction was carried out in ether as solvent the yield of the **4a** was 60 %.

General Procedure of the Reaction of Cyclohexanones **2a-d** with 3,5-Dimethylisoxazol-4-yllithium **3**:

A vigorously stirred solution of 3,5-dimethylisoxazol-4-yllithium **3**, prepared[11] from 4-iodo-3,5-dimethylisoxazole (15 g, 0.067 mol) in ether (225 ml), and n-butyllithium (1.6 M in hexane, 42 ml, 0.067 mol) was treated dropwise with the requisite cyclohexanone (0.054 mol) dissolved in THF (36 ml) at -55 °C for 3 h (4.5 h for compound **5**). The resulting mixture is then hydrolyzed with water (250 ml), extracted with ether (500 ml) and the ethereal combined portions dried ($MgSO_4$) and worked up to give a residue (**4a-c,5**) which was distilled under reduced pressure. Further purification of the products was carried out by column chromatography (benzene as eluent). Solid **5** was crystallized from benzene-hexane.

Alternative Preparation of Compound **6**:

To 4-iodo-3,5-dimethylisoxazole (15 g, 0.067 mol) in ether (225 ml), kept at -55 °C, was added n-butyllithium (1.6 M in hexane, 42 ml, 0.067 mol) and the solution stirred for 6 h. The mixture was allowed to warm to room temperature and then hydrolyzed and treated as reported in the general procedure to give 3-methyl-5-pentylisoxazole (yield 50 %) which was distilled under reduced pressure.

Chromic Oxidation of 4-(1-Cycloalkenyl)-3,5-dimethylisoxazoles **4a-c**:

A vigorously stirred solution of the isoxazole derivative (0.209 mol) dissolved in glacial acetic acid (150 ml) was heated at 30 °C for 1 h with chromium trioxide (12 g, 0.12 mol) following the standard procedure.[13] The acid residue was crystallized from benzene-hexane up to constant melting point. Compound **7c** was a viscous liquid. The yields (%) were the following: (65),**7a**; (60),**7b**; (70),**7c**.

Bromination of **4a**:

A vigorously stirred solution of compound **4a** (3 g, 0.017 mol) in methylene chloride (30 ml) and pyridine (3 ml) was treated dropwise with bromine in the usual manner. The residue was worked up (yield 60 % and purified by succesive crystallizations from benzene-hexane to give **8**.

TABLE 2. Physical and spectroscopic characteristics of the new products.

No	m p °C or b p °C/mm	Ir cm^{-1}	^{1}H nmr, ppm(δ), J(Hz)	Mass spectra m/z (%)
4a	95-100/2	1640 (C=C-ISOX)	1.65(m,4H,2x$\underline{CH_2}$) 2.00-2.20(m,4H,2x$\underline{CH_2}$C=) 2.10(s,3H,3-$\underline{CH_3}$) 2.25(s,3H,5-$\underline{CH_3}$) 5.50(m,1H,$\underline{H}$C=)	177,M$^+$(17);162,M-15(9) 134,M-43(9);43,CH_3CO(100) 42,CH_3CNH(9);91,C_7H_7(15) 79,C_6H_7(12);77,C_6H_5(17)
4b'	92-95/1	1630 (C=C-ISOX)	1.45(s,3H,R^1-$\underline{CH_3}$) 1.65,(m,4H,2x$\underline{CH_2}$) 2.00-2.20(m,4H,2x$\underline{CH_2}$C=) 2.00(s,3H,3-$\underline{CH_3}$) 2.15(s,3H,5-$\underline{CH_3}$)	191,M$^+$(10);176,M-15(5) 148,M-43(7);91,C_7H_7(17) 79,C_6H_7(19);77,C_6H_5(14) 43,MeCO(100);42,MeCNH(16) 41,CH_3CN(27)
4b	100-105/2	1620 (C=C-ISOX)	0.85(d,3H,R^3-$\underline{CH_3}$,J=6.0) 1.65(m,4H,2x$\underline{CH_2}$) 2.00-2.20(m,3H,$\underline{CH_2}$C=C$\underline{CH}$) 2.10(s,3H,3-$\underline{CH_3}$) 2.25(s,3H,5-$\underline{CH_3}$) 5.50(m,1H,$\underline{H}$C=)	191,M$^+$(11);176,M-15(6) 148,M-43(6);91,C_7H_7(16) 79,C_6H_7(13);77,C_6H_5(15) 43,MeCO(100);42,MeCNH(15) 41,CH_3CN(25)
4c	92-94/0.5	1620 (C=C-ISOX)	1.00(d,3H,R^2-$\underline{CH_3}$,J=4.0) 1.80(m,3H,$\underline{CH_2}\underline{CH}$) 2.10(s,3H,3-$\underline{CH_3}$) 2.20(m,4H,2x$\underline{CH_2}$C=) 2.25(s,3H,5-$\underline{CH_3}$)	191,M$^+$(48);176,M-15(14) 149,M-42(20);148,M-43(19) 134,$C_9H_{12}N$(30);107,C_7H_7N (21);91,C_7H_7(16);79,C_6H_7 (17);77,C_6H_5(12);43,CH_3CO (100);42,MeCNH(19);41,MeCN (19)
5	93	3400 (O-H) 1610 (ISOX)	0.65(d,6H,R1;R3-2xCH_3, J=6.0);1.50(m,6H,3x$\underline{CH_2}$) 1.75(m,4H,2x$\underline{CH_2}$COH) 1.95(s,1H,exch.,O$\underline{H}$) 2.25(s,3H,3-$\underline{CH_3}$) 2.45(s,3H,5-$\underline{CH_3}$)	224,M+H(40);223,M$^+$(18) 166,M-CH_3CNO(51);124, $C_8H_8NO_2$(40);82,C_4H_4NO(22) 43,MeCO(100);42,MeCNH(24) 41,MeCN(54)

TABLE 2 (continued)

No	m p °C or b p °C/mm	Ir cm^{-1}	^1H nmr, ppm(δ), J(Hz)	Mass spectra m/z (%)
7a	81	3500-3000 br. (O-H) 1750-1700 br. (C=O) 1600 (ISOX)	1.90(m,4H,2x$\underline{CH_2}$) 2.40-2.80(m,4H,2x$\underline{CH_2}CO$) 2.40(s,3H,3-$\underline{CH_3}$) 2.70(s,3H,5-$\underline{CH_3}$) 8.40(s,1H,exch.,br., $CO_2\underline{H}$)	225,M^+(1);139,$C_7H_9NO_2$(43) 124,$C_6H_6NO_2$(81);82,C_4H_4NO (56);43,CH_3CO(100)
7b	109	3300-2800 br. (O-H) 1730-1650 br. (C=O) 1580 (ISOX)	1.35(d,3H,R^3-$\underline{CH_3}$,J=6.0) 1.70(m,4H,2x$\underline{CH_2}$) 2.35(t,2H,$\underline{CH_2}CO_2H$,J=6.0) 2.45(s,6H,3;5-2x$\underline{CH_3}$) 3.55(m,1H,$\underline{CH}CO$) 7.25(s,1H,exch.,br.,$CO_2\underline{H}$)	239,M^+(3);124,$C_6H_5NO_2$(90) 82,C_4H_4NO(60);43,MeCO(100)
7c	oil	3600-2500 br. (O-H) 1720 (CO_2H) 1680 (C=O) 1580 (ISOX)	1.05(d,3H,R^2-$\underline{CH_3}$,J=4.0) 1.75(m,3H,$\underline{CH_2}\underline{CH}$) 2.35(m,2H,$\underline{CH_2}CO_2H$) 2.50(s,3H,3-$\underline{CH_3}$) 2.70(s,3H,5-$\underline{CH_3}$) 2.80(t,2H,$\underline{CH_2}CO$,J=4.0) 8.75(s,1H,exch.,br., $CO_2\underline{H}$)	239,M^+(1);139,$C_7H_9NO_2$(20) 124,$C_6H_6NO_2$(80);82,C_4H_4NO (50);43,CH_3CO(100)
8*	133(dec)	1600 (ISOX)	1.90-2.40(m,6H,3x$\underline{CH_2}$) 2.60(s,3H,br.,3-$\underline{CH_3}$) 2.80(s,3H,5-$\underline{CH_3}$) 4.80(m,1H,$\underline{HC}Br$) 5.00(m,1H,$\underline{HC}Br$)	M^+not observed;338,336,334 M-Br(13)(25)(13);257,255, M-2xBr(4)(4); 256,254, M-2xBrH(4)(4);176,M-3xBr (45);91,C_7H_7(30);43,CH_3CO (100)

* Mol. weight (osmometric): calculated: 415.86; found: 415.41

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