REGIOSELECTIVITY IN THE 3,5-DIALKYLATION OF 3,5-DIMETHYL-4-(4-METHYLCYCLOHEXEN-1-YL)ISOXAZOLE

Cecilia Polo, Vicente Ramos, and Tomás Torroba*
Departamento de Química Orgánica, Facultad de Veterinaria, Universidad de Extremadura, 10071 Cáceres, Spain
Ricardo Bossio, Stefano Marcaccini, and Roberto Pepino
Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, Via Gino Capponi 9, 50121 Firenze, Italy

Abstract- 3,5-Dimethyl-4-(4-methylcyclohexen-1-yl)isoxazole reacts with β-methallyl chloride and either lithium isopropylcyclohexylamide or n-buthyllithium in THF to afford the three alkylation products II, III, IV, in yields controled by the ratio of isoxazole:base:halide.

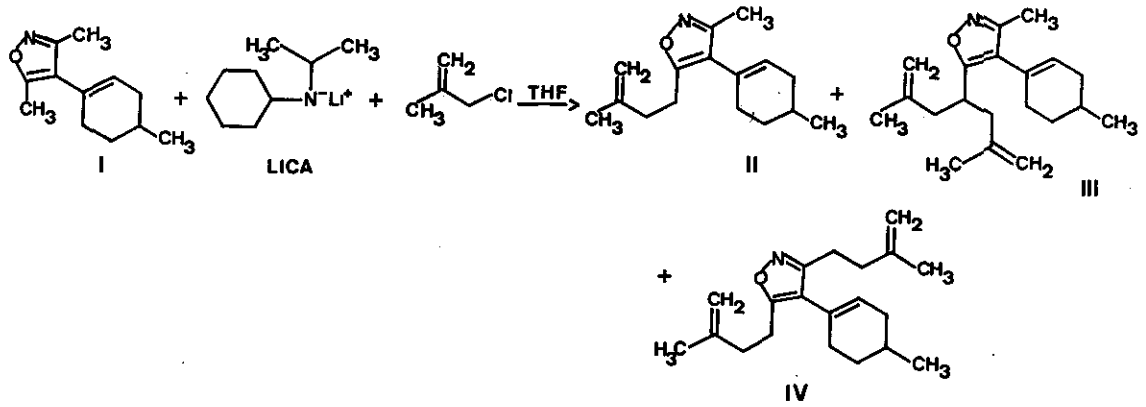
INTRODUCTION

The isoxazole ring is an important tool for organic synthesis of natural products,[1] and the syntheses are based on well-established isoxazole chemistry.[2] Most information regarding extension of the side chain in the isoxazole ring reports a preferential reactivity of the 5-methyl or 5-methylene groups in 3,5-dimethyl-4-substituted or 3-methyl-5-alkyl-4-substituted isoxazoles[3] when these are reacted with n-butyllithium or lithium dialkylamide and an excess of electrophilic reactant. Such a differential reactivity of 5-alkyl groups is maintained even if the 4-substituent is a sterically large group.[4] Until now there has been only a single report of kinetic metalation to produce C-3 alkylation.[5] This paper reports that certain 3-methyl-5-alkyl-4-substituted isoxazoles can show preferential alkylation on the 3-methyl group.

RESULTS AND DISCUSSION

When 3,5-dimethyl-4-(4-methylcyclohexen-1-yl)isoxazole I is treated with β-methallyl chloride and n-butyllithium or lithium isopropylcyclohexylamide (LICA) three products are obtained (Scheme 1, Table 1). The 5-alkylation compounds

II and III are always found as major or minor products. However, we have found that, under such conditions, the 3,5-dialkylation compound IV is also obtained in significant amounts (7 to 45%) even if the electrophile is in deficit in the reaction medium. Compound IV is the main product when isoxazole I is treated with methallyl chloride and 2 equivalents of the base.



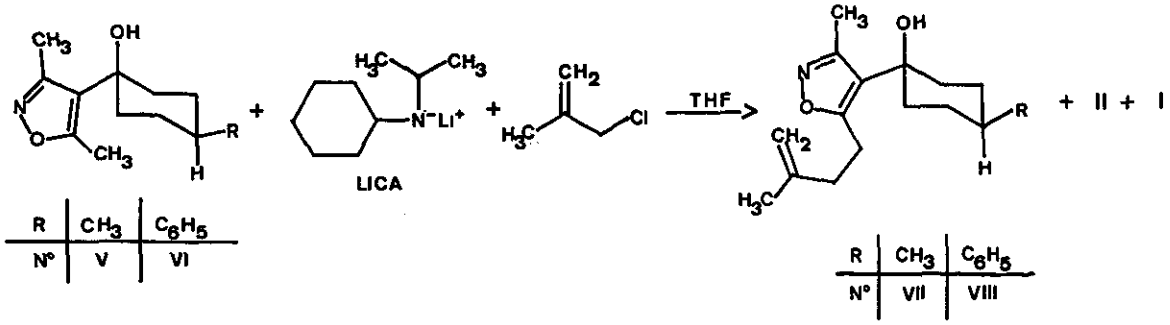
Scheme 1

Table 1

Molar Proportion of Reactants				Percentages of the Products		
I	LICA	n-C_4H_9Li	Halide	II	III	IV
1	1		2	65	7	7
1	2		2	21	18	45
1		1	2	65	7	7
1		2	2	21	18	45
1	2		1	3	11	17

When the molar proportion of isoxazole:LICA:halide is 1:2:1, 34 per cent of I is recovered in addition to the products. Compound IV is also obtained as a by-product when equimolecular amounts of isoxazole I and base are added to methallyl chloride. The presence of compound IV in all the reactions indicates that the 3-methyl group of I adds a second alkyl group about as fast as the 5-methylene group, independent of the base employed.

In order to see if the 3,5-dialkylation reactions can be extended to a wider range of isoxazoles, we have conducted the alkylation reaction on 3,5-dimethyl-4-(1-hydroxycyclohexyl)isoxazoles. Compound I is obtained by thermal dehydration of the corresponding alcohol V, which is not isolated under the previously published conditions of reaction and purification.[6] However, it is possible to obtain pure 3,5-dimethyl-4-(4-methyl-1-hydroxycyclohexyl)isoxazole V from the addition of the 4-lithio-isoxazole to 4-methylcyclohexanone after careful hydrolysis and column chromatography purification of the reaction residue. Only the trans-isomer was employed in this work. By an analogous reaction[6] it was possible to obtain 3,5-dimethyl-4-(4-phenyl-1-hydroxycyclohexyl)isoxazole VI. Compound VI was obtained as a single trans-isomer by spontaneous crystallization , after hydrolysis and solvent removal. To compare reactivity of C-3 and C-5 methyl groups in I with those in V and VI, latter were reacted with LICA and the same halide. Scheme 2 and Table 2 show the molar proportion of reactants and percentages of products. Compound V adds a single methallyl group to the 5-methyl group when it reacts in a 1:3:3 molar proportion of isoxazole:LICA:halide. Some dehydration by-products (compounds I and II) are also obtained (Scheme 2 and Table 2). When the molar proportion of isoxazole:LICA:halide is 1:2:2, only dehydration by-products are obtained. Compound VI affords the 5-methyl monoalkylation product when it reacts under a 1:2:2 molar proportion of isoxazole:LICA:halide. None of the 3,5- or 5,5-dialkylation products are isolated. In addition, compound VI is recovered from the medium when LICA is substituted by n-BuLi. The fact that compounds V and VI fail to reproduce the 3,5-dialkylation confirms previously reported information regarding similar 4-hydroxymethylisoxazolic compounds.[7] It also suggests that the unexpected behaviour shown by compound I is related to the existence of a double bond in the C-1 position of the cyclohexane moiety. Thus, the 3,5-dialkylation of I may represent an efficient way for the synthesis of 4-substituted 3,5-dialkylisoxazoles, which in turn may be regarded as useful intermediates.



Scheme 2

Table 2

Molar Proportion of Reactants					Percentages of the Products			
V	VI	LICA	$n\text{-}C_4H_9Li$	Halide	VII	VIII	II	I
1		3		3	33		10	13
1		2		2	--		--	40
	1	2		2		85		
	1		2	2		--		

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 deuteriochloroform with tetramethylsilane as internal standard. Ir spectra were registered on a Shimadzu IR-408 spectrophotometer in liquid film. Mass spectral data were taken with a Hewlett-Packard 5970A capillary GLC/mass spectrometer at 75 eV. Elemental analysis, carried out on a Perkin Elmer 240-B apparatus, were in agreement with the expected structures. Separations of products were obtained by using column chromatography (120 cm length, 5 cm diameter) filled with silica gel G type 60 (Merck) and benzene as eluent.

Synthesis of I, V and VI:

Compound I was synthesized as in the bibliography.[6] The same procedure affords the compound **V** when the reaction is hydrolyzed with cold aqueous solution of ammonium chloride and the reaction residue is purified on column chromatography. Compound **VI** was synthesized in the same conditions following the standard procedure.[6,8] After working up, the reaction residue is crystallized from benzene-hexane.

Preparation of lithium salt of I, and dilithium salt of V and VI:

First Method:

A vigorously stirred solution of lithium isopropylcyclohexylamide (LICA) in tetrahydrofuran (30 ml), prepared[9] at -60 °C from isopropylcyclohexylamine (0.015 mol) and an hexane solution of n-butyllithium (1.6 M, 9.4 ml, 0.015 mol), is

treated dropwise with the appropriate isoxazolic compound (0.015 mol of I or 0.0075 mol of V or VI), dissolved in tetrahydrofuran (15 ml). The mixture is stirred at -60 °C for 2 h.

Second Method:

A vigorously stirred solution of the appropriate isoxazolic compound (0.03 mol of I or 0.015 mol of V or VI) in tetrahydrofuran (30 ml) at -60 °C is treated dropwise with an hexane solution of n-butyllithium (1.6 M, 18.8 ml, 0.03 mol). The mixture is stirred at -60 °C for 2 h.

Reaction of lithium salt of I, and dilithium salt of V and VI with β-methallyl chloride:

The solution of the lithium salt of I (0.015 mol), or the dilithium salt of V or VI (0.015 mol), is treated dropwise with β-methallyl chloride (0.03 mol) dissolved in tetrahydrofuran (15 ml). The mixture is stirred at -60 °C for 2 h, warmed to room temperature, and stirred for 2 h. Removal of the solvent under reduced pressure leaves a residue which is hydrolyzed for 20 min with an aqueous solution of 20% hydrochloric acid (50 ml) and extracted with ether (5x100 ml). The combined ethereal extracts are dried over magnesium sulfate and evaporated. The crude product mixture is then purified by column chromatography.

The physical and spectral data of compounds II-VIII are summarized as follows:

3-Methyl-4-(4-methylcyclohexen-1-yl)-5-(3-methylbuten-3-yl)isoxazole (II):

Oil; ir ν (cm^{-1}): 1650(isox), 1620(C=C); ^{1}H-nmr δ (ppm): 1.00(d,3H,J=4.0,C$\underline{H}_3$CH), 1.75(s,3H,C$\underline{H}_3$C=C), 1.80(m,3H,$CH_2C\underline{H}_2C\underline{H}CH_2$), 2.20(s,3H,3-C$\underline{H}_3$), 2.20(m,4H,$C\underline{H}_2C$=CHC$\underline{H}_2$), 2.40(m,2H,$H_2C$=C($CH_3$)C$\underline{H}_2$), 2.80(m,2H,C$\underline{H}_2$-isox), 4.70(m,2H,$\underline{H}_2C$=C($CH_3$)), 5.60(m,1H, $\underline{H}$C=C); EM m/z (%): 246($(M+1)^+$,2), 245(M^+,10), 217($(M-C_2H_5)^+$,54), 190($(M-C_4H_7)^+$,10), 189($(M-C_4H_8)^+$,12), 176($(M-C_5H_9)^+$,23), 160(42), 148($(M-C_6H_9O)^+$,24), 91($C_7H_7^+$,51), 77($C_6H_5^+$,44), 43($C_3H_7^+$,26), 42($C_3H_6^+$,33), 41($C_3H_5^+$,100). Anal. Calcd for $C_{16}H_{23}ON$: C,78.37; H,9.39; N,5.71. Found: C,78.29; H,9.28; N,5.89.

3-Methyl-4-(4-methylcyclohexen-1-yl)-5-(1-(2-methylallyl)-3-methylbuten-3-yl)isoxazole (III):

Oil; ir ν (cm^{-1}): 1650(isox), 1615(C=C); ^{1}H-nmr δ (ppm): 1.00(d,3H,J=4.0,C$\underline{H}_3$CH),

1.70(d,6H,J=6.0,2x$C\underline{H}_3C$=C), 1.80(m,3H,$CH_2C\underline{H}_2C\underline{H}CH_2$), 2.20(s,3H,3-$C\underline{H}_3$), 2.20(m,4H, $C\underline{H}_2C$=CH$C\underline{H}_2$), 2.40(m,4H,2x$\underline{H}_2C$=C(CH_3)$C\underline{H}_2$), 2.80(m,1H,$C\underline{H}$-isox), 4.70(m,4H,2x$\underline{H}_2C$=C (CH_3)), 5.60(m,1H,C=C$\underline{H}$); EM m/z (%): 299(M^+,2), 217((M-2xC_3H_5)$^+$,100), 202((M-C_6H_9O)$^+$,14), 188((M-2xC_4H_7,H)$^+$,72), 91($C_7H_7^+$,24), 77($C_6H_5^+$,16), 43($C_3H_7^+$,9), 42 ($C_3H_6^+$,10), 41($C_3H_5^+$,40). Anal. Calcd for $C_{20}H_{29}ON$: C,80.27; H,9.70; N,4.68. Found: C,80.20; H,9.83; N,4.65.

4-(4-Methylcyclohexen-1-yl)-3,5-di(3-methylbuten-3-yl)isoxazole (IV):

Oil; ir ν (cm^{-1}): 1650(isox), 1615(C=C); ^{1}H-nmr δ (ppm): 1.00(d,3H,J=4.0,$C\underline{H}_3$CH), 1.75(s,6H,2x$C\underline{H}_3$C=C), 1.80(m,3H,$CH_2C\underline{H}_2C\underline{H}CH_2$), 2.20(m,4H,$C\underline{H}_2C$=CH$C\underline{H}_2$), 2.40(m,4H,2x $\underline{H}_2C$=C(CH_3)$C\underline{H}_2$), 2.60-2.90(m,4H,2x$C\underline{H}_2$-isox), 4.70(m,4H,2x$\underline{H}_2C$=C(CH_3)), 5.60(m,1H, C=C$\underline{H}$); EM m/z (%): 299(M^+,3), 244((M-C_4H_7)$^+$,14), 202((M-C_6H_9O)$^+$,34), 188(27), 91 ($C_7H_7^+$,14), 77($C_6H_5^+$,12), 43($C_3H_7^+$,8), 42($C_3H_6^+$,8), 41($C_3H_5^+$,100). Anal. Calcd for $C_{20}H_{29}ON$: C,80.27; H,9.70; N,4.68. Found: C,80.18; H,9.86; N,4.60.

3,5-Dimethyl-4-(4-methyl-1-hydroxycyclohexyl)isoxazole (V):

mp: 69-70 °C (benzene-hexane); ir ν (cm^{-1}): 3400(OH), 1610(isox); ^{1}H-nmr δ (ppm): 0.90(s,3H,$C\underline{H}_3$CH), 1.48-1.87(m,9H,4x$C\underline{H}_2C\underline{H}$), 2.24(s,3H,3-$C\underline{H}_3$), 2.37(s,3H,5-$C\underline{H}_3$), 3.71 (s,1H,O$\underline{H}$). Anal. Calcd for $C_{12}H_{19}O_2N$: C,68.90; H,9.09; N,6.70. Found: C,68.75; H,8.99; N,6.79.

3,5-Dimethyl-4-(4-phenyl-1-hydroxycyclohexyl)isoxazole (VI):

mp: 140-141 °C (benzene-hexane); ir ν (cm^{-1}): 3400(OH), 1600(isox), 1580, 1500, 700, 750(phenyl); ^{1}H-nmr δ (ppm): 1.80(s,1H,O$\underline{H}$), 1.85-1.95(m,9H,4x$C\underline{H}_2$ and C$\underline{H}$), 2.35 (s,3H,3-$C\underline{H}_3$), 2.45(s,3H,5-$C\underline{H}_3$), 7.25(s,5$\underline{H}$arom); EM m/z (%): 271(M^+,1), 152 ((M-$C_6H_5CH_2CH_2CH_2$)$^+$,100), 124($C_6H_6NO^+$,22), 91($C_7H_7^+$,20), 82($C_4H_4NO^+$,13), 79($C_6H_7^+$, 4), 77($C_6H_5^+$,7), 43(CH_3CO^+,43), 42(CH_3CNH^+,7). Anal. Calcd for $C_{17}H_{21}O_2N$: C,75.28; H,7.75; N,5.17. Found: C,75.43; H,7.68; N,5.09.

4-(4-Methyl-1-hydroxycyclohexyl)-3-methyl-5-(3-methylbuten-3-yl)isoxazole (VII):

Oil; ir ν (cm^{-1}): 3450(OH), 1650(isox), 1620(C=C); ^{1}H-nmr δ (ppm): 0.94(d,3H,J=4.0, $C\underline{H}_3$CH), 1.41-1.82(m,9H,$C\underline{H}_2C\underline{H}_2C\underline{H}C\underline{H}_2C\underline{H}_2$), 1.80(s,1H,O$\underline{H}$), 1.75(s,3H,$C\underline{H}_3$C=C), 2.31 (s,3H,3-$C\underline{H}_3$), 2.40(m,2H,C=C($CH_3$)$C\underline{H}_2$), 3.00(m,2H,$C\underline{H}_2$-isox), 4.71(m,2H,$\underline{H}_2C$=C($CH_3$)). Anal. Calcd for $C_{16}H_{25}O_2N$: C,73.00; H,9.50; N,5.32. Found: C,73.45; H,9.46; N,5.39.

4-(4-Phenyl-1-hydroxycyclohexyl)-3-methyl-5-(3-methylbuten-3-yl)isoxazole (VIII): mp: 124-125 °C (benzene-hexane); ir ν (cm^{-1}): 3450(OH), 1650(isox), 1600(C=C), 1500, 745, 700(phenyl); ^{1}H-nmr δ (ppm): 1.80(s,3H,C$\underline{H}_3$C=C), 2.00(s,9H,C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$C$\underline{H}_2$C$\underline{H}_2$), 2.05(s,1H,O$\underline{H}$), 2.25-2.60(m,2H,C=C(CH$_3$)C$\underline{H}_2$), 2.40(s,3H,3-C$\underline{H}_3$), 3.10(m,2H,C$\underline{H}_2$-isox), 4.75(m,2H,$\underline{H}_2$C=C(CH$_3$)), 7.25(s,5Harom); EM m/z (%): 326($(M+1)^+$,0.2), 206 ($(M-C_6H_5C_3H_7)^+$,60), 151($(M-R_4O)^+$,100), 91($C_7H_7^+$,47), 77($C_6H_5^+$,12), 43($C_3H_7^+$,25), 42 ($C_3H_6^+$,18), 41($C_3H_5^+$,36). Anal. Calcd for $C_{21}H_{27}O_2N$: C,77.54; H,8.31; N,3.31. Found: C,77.73; H,8.21; N,4.18.

ACKNOWLEDGEMENTS

The authors thank to C.A.I.C.Y.T. for the financial support of this research (Grant No. PB86-0255).

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Received, 24th July, 1989