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NEW METHODS FOR THE HOMOLOGATION OF THIAZOLES AND OXAZOLES BY REGIOSPECIFIC LITHIATIONS OF THIAZOLE- AND OXAZOLE-CARBOXYLIC ACID DERIVATIVES.

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Abstract:- Dianions [(5) and (7)] are obtained by regiospecific lithiations of the parent thiazole- and oxazole-carboxylic acids; when the 2-position is blocked by a phenyl group, 4-(or 5-) methyl groups can be lithiated in thiazole- or oxazole-5(or 4-)carboxylic acids [cf. (9) and (11)]. Lithiations of the 2,5-dimethyl isomers [(13) and (16)] are not regiospecific while those of the corresponding N,N-diethylamides give exclusively the monoanions (14) and (17); all of these new intermediates react efficiently with a range of electrophiles.

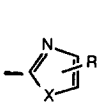
Examples which attest to the synthetic utility of metallated heteroaromatic species abound in the literature.[1] In general, direct lithiation (i.e. H/Li exchange) occurs at a position adjacent to a heteroatom; as such effects are additive, simple thiazoles and oxazoles usually undergo lithiation only at the 2-position to give the useful intermediates [(1); X=S or O]. Similarly, the 2-methyl homologues normally yield only the anions [(2); X=S or O]. We have recently shown[2] that carboxylate groups can be used to direct lithiations to only one of two similar sites: thus, furan-3-carboxylic acid yields only dianion (3) upon treatment with lithium diisopropylamide (LDA). Carboxylate residues can also direct lithiation to the less reactive 3-position of thiophen-2-carboxylic acid when n-butyl lithium (n-BuLi) is used as base[3] and to relatively unactivated methyl groups such as in the generation of dianion (4) directly from the parent acid and LDA.[4] The growing interest in thiazole and oxazole synthesis,[5] together with the reported failure[6] of vinyl anions derived from simple oxazole-4-carboxylic acids to couple with synthetically useful electrophiles prompted us to examine lithiations of various fully substituted thiazole and oxazole-carboxylic acids in the hope of finding some new and synthetically versatile intermediates. Especially useful would be species wherein the carboxylate group had directed lithiation to the usually less reactive 4- or 5-positions.

Our first series of experiments did not achieve this aim but nevertheless provided some valuable synthetic intermediates. Thus, lithiation of 2,4-dimethylthiazole-5-carboxylic acid [(6); R=H][7] under a variety of conditions [LDA at -78°C or -10°C; n-BuLi at -78°C; THF as solvent throughout] uniformly

gave only the dianion (5); thus the carboxylate group is not capable of overcoming the combined activating effect of the two heteroatoms in the thiazole ring. The regiospecificity was deduced from spectroscopic data and by the non-identity of the product [(6); R=CH_3] obtained from dianion (5) and iodomethane with a sample of the 4-ethyl-2-methyl isomer, prepared[7] from ethyl 2-chloro-3-oxopentanoate and thioacetamide. Dianion (5) proved to be a useful intermediate condensing efficiently with iodoethane (and hence other primary alkyl iodides[4]) and allyl bromide together with representative enolisable aldehydes and ketones [See isolated yields associated with formula (6)]. The corresponding oxazole [(8); R=H][8] displayed essentially the same chemistry giving rise to only dianion (7), which condensed efficiently with the same group of electrophiles. The regiospecificity was again proven by spectral data and the non-identity of product [(8); R=CH_3] with the 4-ethyl-2-methyl isomer obtained from ethyl 3-oxopentanoate.

When the 2-position is blocked with respect to lithiation then reaction at a 4- or 5-methyl group can be achieved in this type of heterocyclic carboxylic acid. Thus, 4-methyl-2-phenylthiazole-5-carboxylic acid was smoothly transformed into the dianion (9) using LDA at ca. -30°C. At lower temperatures, metallation of this relatively less activated methyl group was very slow using either LDA or n-BuLi while at temperatures above -50°C, n-BuLi began to attack the thiazole ring in a nucleophilic manner. A brief trial showed than dianion (9) is a useful intermediate, condensing efficiently with allyl bromide, acetophenone (an enolisable ketone) and 1,2-epoxybutane, the latter example indicating that the dianion is a powerful nucleophile, to give homologues (10) in the isolated yields shown. The isomeric dianion (11) was readily obtained from the parent acid [(12); R=H, prepared from ethyl 3-bromo-2-oxopentanoate and thiobenzamide[7]] using n-BuLi at -78°C, the lower temperature relative to dianion (9) reflecting the greater activation of the 5-methyl group by the heterocyclic ring. Despite this, the reactivities of dianions (9) and (11) appeared to be very similar, the latter giving comparable yields of products (12) with the same group of electrophiles. Much the same pattern of reactivity was found in the corresponding 2-phenyl-oxazolecarboxylic acids but, in our hands, the relative lack of availability of these compounds[10] (all of the foregoing carboxylic acids are easy to prepare in quantity) rather detracted from the utility of the dianionic species.

Finally, we examined lithiations of the readily-available 2,5-dimethyl-thiazole[7]- and -oxazole[11]-4-carboxylic acids [cf (13) and (16)]. In these cases we hoped that the combined effects of one heteroatom (S or O) and the carboxylate group would direct metallation to the 5-methyl function despite the dual activation by two heteroatoms of the usually more reactive 2-methyl substituent. These two combinations turned out to be approximately equivalent, resulting in lithiation at both methyl groups using either LDA or n-BuLi. The product ratio using iodomethane as electrophile varied slightly; for example,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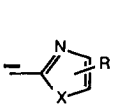
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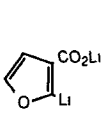
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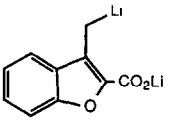
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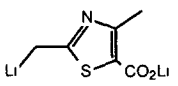
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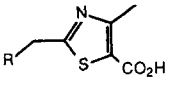
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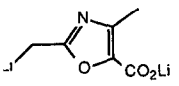
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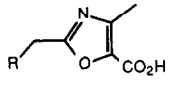
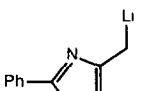

(8)

% (6)	R	% (8)
82	CH_3	87
77	CH_3CH_2	66
71	CH_2:$CHCH_2$	79
83	PhCH(OH)	87
80	n-C_6H_{13}CH(OH)	83
70	PhC(OH)Me	-
-	Ph_2C(OH)	78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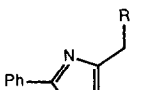
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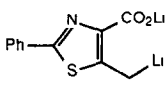
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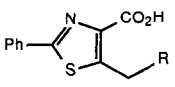
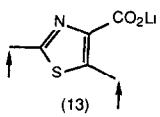

(12)

% (10)	R	% (12)
89	CH_3	86
84	CH_2:$CHCH_2$	75
60	PhC(OH)Me	51
66	CH_3CH_2CH(OH)CH_2	60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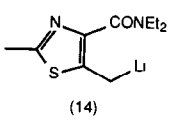
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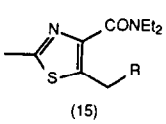
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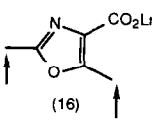
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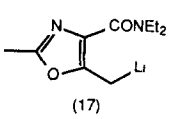
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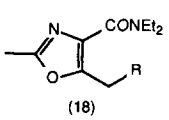
(18)

% (15)	R	% (18)
97	CH_3	98
98	CH_3CH_2	97
96	CH_2:$CHCH_2$	98
93	PhCH(OH)	98
92	PhC(OH)Me	-
-	n-C_3H_7CH(OH)	92

metallation of thiazole (13) using LDA -78°C gave a product ratio of 59:41 in favour of the 2-methyl isomer which increased to 67:33 at -15°C, while the most useful ratio obtained in the case of the oxazole (16) was 70:30 in favour of the 5-ethyl derivative using n-BuLi at -78°C. (The ratios were determined by ^{1}H n.m.r. comparisons with the authentic compounds). This last observation suggested that the balance could perhaps be tipped in favour of lithiation at the 5-methyl position by using n-BuLi and an alternative complexing group at the 4-position, for which suitable candidates were amide derivatives.[12] We were pleased to find that treatment of the corresponding N,N-diethylamides with one equivalent of n-BuLi at -78°C in THF gave only the monoanions (14) and (17) in quantitative yields as indicated by the isolated yields of the adducts [(15) and (18)] obtained by condensations with a range of electrophiles. The regiospecificity was determined by direct comparison with authentic amide [(15) and (18); R=CH_3] prepared from acyclic precursors.[7,11]

We anticipate that the novel lithiated species described herein will be of considerable use in the synthesis of a wide range of polysubstituted thiazoles and oxazoles especially as the initial products can be further elaborated by, for example, nucleophilic attack on the residual carboxylate or amide functions.

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