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2-Oxazolines as activating groups towards metallation and stabilising groups against polymerization in N-substituted pyrroles

RAPHAEL I NGOCHINDO[+]

The Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, UK

[+] Present address: Department of Chemistry, Federal University of Technology, P.M.B. 1526, Owerri, Nigeria

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Abstract. Benzaldehyde is shown to be a more suitable electrophile than carbon dioxide in reactions involving the lithio derivatives of 2-(N-methylpyrrol-2-yl) oxazolines. The relative reactivities of the C3-Li and C5-Li bonds in ethereal solvents are examined. The 2-oxazolino group at a 2-position in N-substituted pyrrole is shown to possess an activating effect on the 5-position towards lithiation, and eliminates the propensity of the pyrrole nucleus towards polymerisation. The conditions for removal of the 2-protecting group are explored.

Keywords. 2-Oxazolines; N-substituted pyrroles; lithium derivatives; regioselective lithiation.

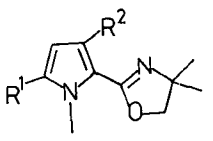
1. Introduction

The 2-oxazolino group is a synthetically versatile substituent which acts as a protecting group against reagents such as sodium tetrahydridoborate, alkylmagnesium halide, chromium(VI) oxide and mild acid and alkali (Hanson *et al* 1973; Meyers *et al* 1974). It also acts as a masked functionality for carboxylic acids, carboxylates and carbaldehydes (Nordin 1966; Meyers *et al* 1974; Vecchia and Vlattas 1977). Its use as an ortho-directing group in the metallation of pyrroles and conditions for regioselective lithiation have been reported (Chadwick *et al* 1982). Other effects of the 2-oxazolino group on pyrrole and conditions for deprotection are examined.

2. Results and discussion

Due to the only moderately isolable yields of 3- and 5-carboxylic acid derivatives of the 2-(N-methylpyrrol-2-yl)oxazoline (1) reported earlier (Chadwick *et al* 1982), benzaldehyde was used as electrophile in the present study instead of carbon dioxide. The resulting isomeric alcohols (2) and (3) were separated by preparative thin layer chromatography (PTLC) and found to be in the ratio 2·2:1. This ratio agrees well with that reported for deuterium oxide as electrophile (Chadwick *et al* 1982).

It is possible that the proximity of the 2-oxazolino moiety to the lithio-substituent at the 3-position could result in the differential reactivity of the C3–Li and C5–Li bonds due to, for example, differing degrees of ionic character and/or steric demand.



(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = CH(OH)Ph$
(3) $R^1 = CH(OH)Ph$, $R^2 = H$
(4) $R^1 = CH(OEt)Ph$, $R^2 = H$
(5) $R^1 = CH(OMe)Ph$, $R^2 = H$

Differential ionicity may be masked, however, by ethereal solvents which themselves encourage ionisation of the C–Li bond. The conditions established for 100% total lithiation with an α to β ratio of 2·1:1 were used in an experiment to examine the relative reactivities of the isomeric C–Li bonds in ethereal solvents. A mixture of the 3-lithio and 5-lithio derivatives of (1) in tetrahydrofuran (THF) was reacted with benzaldehyde (0·6 equiv.), followed by PTLC to give (2) (18%) and (3) (37%). With the lithio-intermediates competing for an insufficient amount of the electrophile the α to β ratio of 2·1:1 was maintained. This result suggests that the C3–Li and C5–Li bonds show similar reactivities in THF, as would be expected. Unfortunately, it is not possible to examine the relative reactivities of the isomeric C–Li bonds in hexane since N-substituted pyrroles only react poorly with organolithium reagents in the absence of tertiary amine chelating agents (Chadwick and Willbe 1977). N,N,N′,N′-tetramethylethylenediamine (TMEDA), for example, is required to increase the yield of the lithio-intermediate in hexane. However, TMEDA is likely to give results similar to those obtained for lithiation in THF.

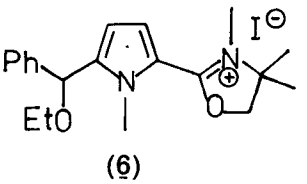
Another investigation that was conducted in THF as solvent was the effect of the 2-oxazolino group at an α-position on the second α-position. Metallation of (1) with *n*-butyl-lithium (1:1 ratio) in THF at 0°C in the absence of TMEDA, followed by reaction with deuterium oxide gives 60% of the α-deuterio derivative (Chadwick *et al* 1982). Under the same reaction conditions 1-methylpyrrole was found to give 13% of the α-deuterio product in the present study. This suggests that the 2-oxazolino group activates the second α-position towards lithiation. Thus, whereas β-metallation is directly a function of the ortho-directing ability of the 2-oxazolino group, α-metallation is a result of both the greater acidity of N-methylpyrrole H-5 (relative to H-3) and the activating ability of the ortho-directing group, and emphasises the nature of competition that exists between α- and β-lithiations. The apparently greater tendency towards α-lithiation can be overcome by a judicious choice of reaction conditions (Chadwick *et al* 1982). The observation of α-activation may also be important in any future study to assess the order of ortho-directing ability of substituents at the 2-position of N-substituted pyrroles, particularly with respect to electron-withdrawing groups. The α:β product ratio for these groups may depend on their ortho-directing ability relative to the activation of the α-position towards lithiation.

Although 2-oxazolines are reported to be easily solvolysed under alkaline or acidic conditions (Meyers *et al* 1974a, b; Vecchia and Vlattas 1977), the pyrrolyl derivative was found to be stable to both alkaline and acidic solvolyses. The 2-oxazolino substituent remained stable even after boiling under reflux for 15·5 h of a solution of compound (3) in ethanolic sulphuric acid (0·75 M). The ethoxy derivative (4) was isolated in high yields when the reaction was terminated after 4 h, and probably results from nucleophilic attack of ethanol on the carbenium ion formed at the benzylic cum

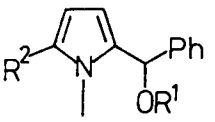
pyrrolic centre. The 2-oxazolino group was also stable to hydrolysis with refluxing 3 M aqueous hydrochloric acid, followed by a refluxing solution of 20% methanol in 40% aqueous sodium hydroxide. A mixture of starting material 3 (27%) and 5 (73%) [probably formed in a manner similar to the formation of 4] was isolated from the acidic solution. These results on ethanolysis and hydrolysis show a novel property of the 2-oxazolino substituent, probably unique to the pyrrolyl derivative, as a protecting group against strongly acidic and alkaline conditions.

N-alkylated oxazolines may be reduced with sodium tetrahydridoborate (Nordin 1966). The methiodide of 1 was reduced with ethereal lithium tetrahydridoaluminate to give, on acid work-up, a polymeric meterial. Since 1 is stable to acid (the hydrochloride is isolable), polymerization is associated with loss of stability to acid provided by the oxazolino group, and is consistent with the behaviour of α-unsubstituted pyrroles in the presence of an acid. The product of reduction in the present study is probably the N-methylaxazolidine derivative of 1.

Oxazoline derivatives with acid-sensitive groups may be converted to the corresponding carboxylic acid derivatives by alkaline hydrolysis of the methiodide of the oxazoline (Meyers *et al* 1974b). Application of this procedure to the ethoxy compound (4) afforded the 2-carboxylic acid (7). The 5-methoxy- and 5-hydroxy-derivatives (8) and (9) were also obtained, probably by a route similar to that which led to the formation of (4) from (3). The carboxylic acids (7)–(9) were converted quantitatively to their methyl carboxylates (10), (11) and (12) with ethereal diazomethane and were separated by PTLC to give yields of 69, 15 and 12%, respectively. The esters were observed to be volatile; purification by distillation was, therefore, not possible.



(6)



(7) $R^1 = Et$, $R^1 = CO_2H$
(8) $R^1 = Me$, $R^2 = CO_2H$
(9) $R^1 = H$, $R^2 = CO_2H$
(10) $R^1 = Et$, $R^2 = CO_2Me$
(11) $R^1 = Me$, $R^2 = CO_2Me$
(12) $R^1 = H$, $R^2 = CO_2Me$

Syntheses of quaternary methiodide salts of oxazoline derivatives such as (6) seem to require boiling of the substrate under reflux in iodomethane. Little, if any, conversion to the methiodide is observed at room temperature even after 20·5 h in iodomethane. The methiodide of (2) was obtained in only 3% yield, although the 3-alcohol was boiled under reflux with iodomethane for 21 h. This poor yield may be a consequence of steric crowding and intramolecular hydrogen bonding and may be of synthetical use in the separation of (1) from (2) as the latter is often contaminated with the former even after PTLC.

3. Experimental

General procedures for the preparation of heterocyclic lithio-derivatives, their reaction with electrophiles, spectroscopic characterisation of the products and solvent preparation, have been published previously (Chadwick *et al* 1982; Carpenter *et al* 1983; Ngochindo 1990).

3.1 *2-(3-Hydroxyphenylmethyl-1-methyl-2-pyrrolyl)-4,4-dimethyl-2-oxazoline (2) and 2-(5-hydroxyphenylmethyl-1-methyl-2-pyrrolyl)-4,4-dimethyl-2-oxazoline (3)*

BuLi in hexane (4·0 mmol) was added to a solution of the oxazoline (1) (0·36 g, 2·0 mmol) in dimethoxyethane (DME) (5 ml) at −78°C. The mixture was stirred at 0°C for 30 min and benzaldehyde (4·1 mmol) added. Stirring was continued at room temperature for 45 min and the mixture acidified with 0·1 M aqueous HCl. The organic layer was separated and extracted with 0·1 M aqueous HCl (4 × 3 ml), and the combined acidic solutions were basified with solid $NaHCO_3$. Extraction into $CHCl_3$, followed by PTLC on silica gel with CH_2Cl_2–EtOAc as eluant gave the less polar *3-carbinol* (2) (R_f 0·44) as a viscous oil (0·37 g, 65%) (Found: C, 71·5; H, 7·1; N, 9·6. $C_{17}H_{20}N_2O_2$ requires C, 71·80; H, 7·09; N, 9·85%); ν_{max} (CCl_4) 1640 and 3240 cm^{-1}; δ_H 1·16 (3 H, *s*, Me), 1·32 (3 H, *s*, Me), 3·76 (3 H, *s*, NMe), 4·02 (2 H, *s*, OCH_2), 5·70 (1 H, *d*, *J* 2·7 Hz, pyrrole 4-H), 5·83 (1 H, *s*, PhCH), 6·52 (1 H, *d*, *J* 2·7 Hz, pyrrole 5-H), and 7·18–7·48 (5 H, *m*, Ph); *m/z* 284 (M^+, 71%) and 77 (100).

The more polar component (R_f 0·16) was identified as the *5-carbinol* (3) (0·18 g, 30%), m.p. 108–109°C (from EtOAc–C_6H_{14}) (Found: C, 71·7; H, 7·3; N, 9·8, $C_{17}H_{20}N_2O_2$ requires C, 71·80; H, 7·09; N, 9·85%); ν_{max} ($CDCl_3$) 1655 and 3550 cm^{-1}; δ_H 1·27 (6 H, *s*, Me), 2·93 (1 H, *br s*, OH), 3·82 (3 H, *s*, NMe), 3·91 (2 H, *s*, OCH_2) 5·78 (1 H, *s*, PhCH), 5·86 (1 H, *d*, *J* 4·0 Hz, pyrrole 4-H), 6·62 (1 H, *d*, *J* 4·0 Hz, pyrrole 3-H), and 7·30 (5 H, *m*, Ph); *m/z* 284 (M^+, 64%) and 269 (100).

3.2 *2-(5-Ethoxyphenylmethyl-1-methyl-2-pyrrolyl)-4,4-dimethyl-2-oxazoline (4)*

A solution of the oxazoline derivative (3) (0·44 g, 1·6 mmol) in 0·75 M ethanolic H_2SO_4 (10 ml) was boiled under reflux for 4 h. The mixture was cooled, washed with saturated NaCl solution (3 × 6 ml) and extracted with $CHCl_3$ (8 × 12 ml). The extracts were combined, concentrated to about 5 ml and H_2O (5 ml) was added. The mixture was made basic with 45% aqueous NaOH and extracted into $CHCl_3$ to obtain compound (4) after PTLC (0·46 g, 94%) ν_{max} (CCl_4) 1655 cm^{-1}; δ_H 1·22 (3 H, *t*, *J* 7·3 Hz, $C\underline{H}_3CH_2$), 1·29 (6 H, *d*, *J* 1·7 Hz, Me), 3·52 (2 H, *dq*, *J* 1·1 and 7·3 Hz, $CH_3C\underline{H}_2$), 3·87 (3 H, *s*, NMe), 3·92 (2 H, *s*, oxazoline 5-H), 5·43 (1 H, *s*, PhCH), 5·84 (1 H, *d*, *J* 4·0 Hz, pyrrole 4-H), 6·65 (1 H, *d*, *J* 4·0 Hz, pyrrole 3-H), and 7·25–7·41 (5 H, *m*, Ph); *m/z* 312 (M^+, 62%) and 267 (100).

3.3 *2-(5-Ethoxyphenylmethyl-1-methyl-2-pyrrolyl)-4,4-dimethyl-2-oxazoline 3-methiodide (6)*

A solution of the ethoxy derivative (4) 0·22 g, 0·7 mmol) in iodomethane (192·8 mmol) was boiled under reflux for 23·5 h. The solution was cooled and excess of reagent removed by evaporation, followed by recrystallisation of the resulting solid, to obtain the methiodide (6) (0·22 g, 71%), m.p. 147–149°C (from $CHCl_3$–Et_2O); δ_H 1·05–1·35 (3 H, *m*, $C\underline{H}_3CH_2O$), 1·68 (6 H, *d*, *J* 3·5 Hz, Me), 3·30–3·75 (2 H, *m*, $CH_3C\underline{H}_2O$), 3·48 (3 H, *s*, oxazoline NMe), 3·96 (3 H, *s*, pyrrole NMe), 5·02 (2 H, *d*, *J* 1·7 Hz, oxazoline 5-H), 5·48 (1 H, *s*, PhCH), 6·12 (1 H, *d*, *J* 4·7 Hz, pyrrole 4-H), 7·17 (1 H, *d*, *J* 4·7 Hz, pyrrole 3-H), and 7·33–7·48 (5 H, *m*, Ph).

3.4 *Methyl 5-ethoxyphenylmethyl-1-methylpyrrole-2-carboxylate (10), methyl 5-methoxyphenylmethyl-1-methylpyrrole-2-carboxylate (11) and methyl 5-hydroxyphenylmethyl-1-methylpyrrole-2-carboxylate (12)*

A suspension of the methiodide (6) (118·4 mg, 0·26 mmol) in methanolic 2 M aqueous NaOH (75% 11 ml) was boiled under reflux for 6 h. The mixture was cooled and acidified to pH 1 with 2 M aqueous HCl. The aqueous material was decanted from the precipitate, extracted seven times with $CHCl_3$ (90 ml *in toto*) and the extracts were combined and dried ($MgSO_4$). Evaporation of solvent gave acid sample 'a' (41·2 mg) as a mixture of 5-ethoxyphenylmethyl-1-methylpyrrole-2-carboxylic acid (7) δ_H 1·27 (3 H, *t*, *J* 7·6 Hz, CH_3), 3·57 (2 H, *q*, *J* 7·6 Hz, CH_2), 3·87 (3 H, *s*, NCH_3), 5·48 (1 H, *s*, PhCH), 5·93 (1 H, *d*, *J* 4·0 Hz, pyrrole 4-H), 7·06 (1 H, *d*, *J* 4·0 Hz, pyrrole 3-H) and 7·38 (5 H, *m*, C_6H_5); 5-methoxyphenylmethyl-1-methylpyrrole-2-carboxylic acid (8) δ_H 3·43 (3 H, *s*, CH_3O), 3·86 (3 H, *s*, NCH_3) 5·39 (1 H, *s*, PhCH), 6·05 (1 H, *d*, *J* 4·0 Hz, pyrrole 4-H), 7·10 (1 H, *d*, *J* 4·0 Hz, pyrrole 3-H) and 7·43 (5 H, *m*, C_6H_5); and 5-hydroxyphenylmethyl-1-methylpyrrole-2-carboxylic acid (9). The precipitate that resulted from acidification (*vide supra*) was taken up into $CHCl_3$ (40 ml). The solution was dried ($MgSO_4$) and the solvent evaporated to give acid sample 'b' (29·1 mg) as a mixture of the ethoxy acid derivative (7) and the hydroxy acid derivative (9).

Acid sample 'a' in Et_2O (1 ml) was treated with ethereal diazomethane at 0°C for 1 h. Excess of diazomethane was evaporated by stirring the mixture at room temperature. The solvent was evaporated and the resulting mixture of products was partially separated by PTLC to give samples of the ethoxy ester (10) (24·6 mg) and methoxy ester (11) (10·7 mg) derivatives as a mixture R_f 0·69, and the hydroxy ester (12) (5·5 mg, R_f 0·40). Methylation with diazomethane of acid sample 'b', followed by PTLC afforded the ethoxy ester (10) (25·0 mg) and the hydroxy ester (12) (2·8 mg), bringing the total yield to 69% ethoxy ester (10) ν_{max} ($CHCl_3$) 1697 and 1708 cm^{-1}; δ_H 1·23 (3 H, *t*, *J* 6·9 Hz, CH_3CH_2), 3·52 (2 H, *q*, *J* 6·9 Hz, CH_3CH_2), 3·76 (3 H, *s*, Me), 3·84 (3 H, *s*, Me), 5·40 (1 H, *s*, PhCH), 5·80 (1 H, *d*, *J* 4·2 Hz, pyrrole 4-H), 6·84 (1 H, *d*, *J* 4·2 Hz, pyrrole 3-H), and 7·34 (5 H, *m*, Ph); *m/z* 273·1360 (M^+, 29%, $C_{16}H_{19}NO_3$ requires 273·1365) and 228 (100); 15% methoxy derivative (11) δ_H 3·39 (3 H, *s*, OMe), 3·82 (3 H, *s*) and 3·86 (3 H, *s*) (CO_2Me and NMe), 5·37 (1 H, *s*, PhCH), 5·94 (1 H, *d*, *J* 4·0 Hz, pyrrole 4-H), 6·94 (1 H, *d*, *J* 4·0 Hz, pyrrole 3-H), and 7·41 (5 H, *m*, Ph) and 12% hydroxy ester (12) ν_{max} ($CDCl_3$) 1695, 1704 and 3560 cm^{-1}; δ_H 3·76 (3 H, *s*) and 3·85 (3 H, *s*) (OMe and NMe), 5·87 (1 H, *s*, PhCH), 5·90 (1 H, *d*, *J* 4·1 Hz, pyrrole 4-H), 6·87 (1 H, *d*, *J* 4·1 Hz, pyrrole 3-H), and 7·35 (5 H, *m*, Ph); *m/z* 245·1042 (M^+, 31%, $C_{14}H_{15}NO_3$ requires 245·1052) and 57 (100).

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