Nucleophilic Aromatic Substitution with the Anion of 3,5-Disubstituted Isoxazole-4-carboxylic Acids

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The preparation of the anion of a series of protected 3,5-disubstituted 4-isoxazolecarboxylic acids and the resulting addition of the anion to 9-chloroacridine is described. The addition-elimination reaction proceeds to give the expected acridinylmethylisoxazoles and has been justified based on calculated molecular mechanics energies and solvent effects.

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Lateral metalation of 3,5-dimethylisoxazole was first attempted by Micetich in 1970 [1]. Since then, the scope of this procedure has been elucidated to include metalations in the presence of groups substituted at the isoxazole C(4) position. For instance, it has been shown that the electrophilic quenching of the dianion of a 3,5-disubstituted-4-isoxazolylcarboxylic acid with methyl iodide or a benzyl halide can be accomplished [2]. Yet, when the carboxylic acid is suitably protected as the oxazoline or as the diisopropylamide, the reaction is more general in nature providing higher yields of the expected product [3,4,5,6]. In fact, lateral metalation of 3,5-dimethyl-4-isoxazolyloxazoline has been shown to provide the expected products in excellent yields.

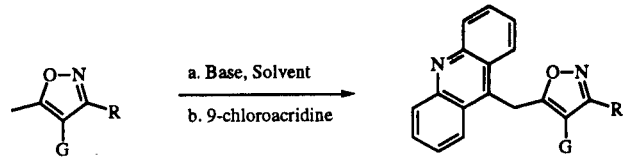
Application of this methodology to the preparation of DNA intercalators has forced our laboratory to examine acridines as potential electrophiles. While the use of simple alkyl and benzylic halides as electrophiles has been shown to provide exceptional yields of the desired products, nucleophilic aromatic substitution of the isoxazole anion to 9-chloroacridine has been difficult.

Generation of the C(5) carbanion of a series of protected 4-isoxazolecarboxylic acids **1** with a strong base and addition of 9-chloroacridine to the resulting mixture provided the data shown in the accompanying Table. Of particular interest is the fact that the carboxamide **1a** provides the greatest yield of the expected product **2a** when compared to the oxazolines **1b, 1g-1k**. This stands in contradiction to the predicted outcome [3], and has compelled us to determine the most likely solution-state structure of the isoxazolyloxazoline anion.

Molecular mechanics calculations of the possible localized anionic structures of the isoxazolyloxazoline are shown in the accompanying Scheme. The relative MM2-level energies of the individual structures indicate that the anion most likely resides on the C(4) position of isoxazole (structure **3b**). Those structures involving lithioamides reside at relatively higher energies. When one considers that MM2-level calculations can accurately reveal steric repulsions and do not correctly represent electronic effects, this structure seems logical as the sterically most favorable.

Table

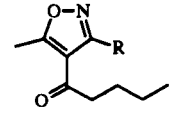
Protected Isoxazolyl-4-carboxylic Acid Anions with 9-Chloroacridine



1 **2**

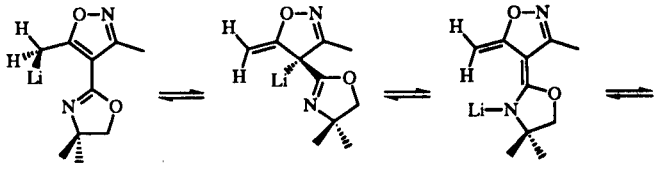
	R	G	Base	Solvent	Yield
a	$-CH_3$	$CON(iPr)_2$	*n*-BuLi,40°	THF	53%
b	$-CH_3$	oxazoline	*n*-BuLi -78°	THF	5.5%
c	$-CH_3$	-COOH	2*n*-BuLi, -78°	THF	–
e	$-CH_3$	-COOEt	*t*-BuLi -78°	THF	–
f	$-CH_3$	-COOEt	*n*-BuLi -78°	THF	see A below
g	-Ph	oxazoline	*n*-BuLi, -78°	THF	12%
h	-Ph	oxazoline	*n*-BuLi, -78°	THF:HMPA 6:1	20%
i	-Ph	oxazoline	*n*-BuLi, -78°	THF:HMPA 3:1	22%
j	-Ph	oxazoline	*n*-BuLi, -78°	TMEDA	–
k	-Ph	oxazoline	*n*-BuLi, -24°	DME	5%

A - the major product (70%) of this reaction was:

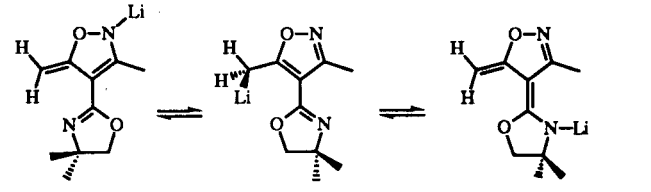


Scheme

Relative MM2 Energies in kcal/mol



3a E = 17.8286 **3b** E = 16.0769 **3c** E = 20.9647



3d E = 19.6718 **3e** E = 18.2306 **3f** E = 19.7978

These calculations are in agreement with the data obtained during a preliminary solvent effect study. Addition of anhydrous hexamethylphosphoramide (HMPA) to the reaction mixture does increase the yield of the reaction, presumably by solvating the metal cation and forming a more reactive free anion [7]. Increasing the amount of hexamethylphosphoramide as co-solvent does not increase the overall yield above 22%. It is postulated that the anion is solvated sufficiently to increase the amount of delocalization of the anion, making it softer and less likely to undergo nucleophilic aromatic substitution. The structure of this anion is predicted to exist as a hybrid of the **3a, 3b**, and **3e** resonance forms which are similar in steric energies.

Addition of dimethoxyethane (DME) or tetramethylethylenediamine (TMEDA) decreased the yield of the expected product, presumably by solvating the metal-anion pair and decreasing the energy of the lithioamide resonance forms (structures **3c, 3d**, and **3f**).

A series of PM3 calculations [8] is currently being performed to examine the molecular orbitals of the various isoxazolyl anion geometries and will be used to assist in determining the possible sites of electrophilicity. This study will allow for a better understanding of the structure and reactivity of the isoxazole anion.

EXPERIMENTAL

Mass spectra were obtained on a VG 7070 GC/MS with model 11/250 data system. The ^{1}H and ^{13}C nmr were obtained on a Brüker AF200 200 MHz multinuclear FT-NMR. Combustion analyses were performed by Desert Analytics Laboratory, PO Box 41838, Tucson, Arizona. All reactions were performed under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl immediately before use. Flash chromatography was performed on silica gel (70-230 mesh) with freshly distilled solvents by the method of Still [9]. Organolithium reagents were titrated using the procedure of Ronald [10]. 9-Chloroacridine was prepared in 77% overall yield from aniline and *o*-chlorobenzoic acid [11] and recrystallized immediately before use due to its ability to undergo autocatalyzed hydrolysis to 9-acridinone [12].

Standard Procedure.

To a solution of the isoxazole (0.7713 g, 3.01 mmoles) in dry THF (20 ml) at -78° was added a hexane solution of *n*-butyllithium (2.30 ml, 3.16 mmoles). After 2 hours at -78°, the resulting yellow-red solution was quenched by the addition of 9-chloroacridine (0.690 g, 3.22 mmoles) in tetrahydrofuran (15 ml) *via* syringe. The solution instantly became deep blue-purple (presumably indicating a charge-transfer complex) and was maintained at -78° for 1 hour, before warming slowly to room temperature overnight during which time the blue color was replaced by an orange fluorescence. The reaction was then partitioned between a saturated solution of sodium bicarbonate (30 ml) and ether (30 ml). The organic phase was washed with water (30 ml), dried over magnesium sulfate, filtered, and evaporated to give a crude oil.

5-(9'-Acridinylmethyl)-4-(*N*",*N*"-diisopropylcarboxamidyl)-3-methylisoxazole (**2a**).

Chromatography on silica gel (flash, hexane to 7:3 hexane:ethyl acetate gradient) gave 0.6405 g (53%) of the desired compound as yellowish white crystals. Recrystallization of the solid from ethyl acetate/hexane gave analytically pure material; ^{1}H nmr (deuterochloroform): δ 8.22 (d, J = 6.6 Hz, 2H), 8.12 (d, J = 6.6 Hz, 2H), 7.67 (ddd, J = 1.2, 6.6, 6.6 Hz, 2H), 7.49 (ddd, J = 1.2, 6.6, 6.6 Hz, 2H), 4.96 (s, 2H), 3.21 (bs, 2H), 2.09 (s, 3H), 1.21 (bs, 6H); ^{13}C nmr (deuterochloroform): δ 166.8, 161.5, 157.3, 148.4, 137.9, 129.9, 126.5, 125.2, 124.3, 115.0, 24.7, 20.5. 10.4.

Anal. Calcd. for $C_{25}H_{27}O_2N_3$: C, 74.79; H, 6.78; N, 10.45. Found: C, 75.03; H, 6.65; N, 10.28.

5-(9'-Acridinylmethyl)-4-(4",4"-dimethyl-Δ^2-oxazolin-2"-yl)-3-methylisoxazole (**2b**).

Chromatography on silica gel (flash, 7:3 hexane:ethyl acetate) gave 0.0615 g (5.5%) of the desired compound as off-white crystals. Recrystallization of the solid from ethylacetate/hexane gave analytically pure material; ms: m/z 371 M+, 194, 179, 97; ^{1}H nmr (deuterochloroform): δ 8.56 (d, J = 6.2 Hz, 2H), 8.36 (d, J = 6.2 Hz, 2H), 7.69 (ddd, J = 1.2, 6.2, 6.2 Hz, 2H), 7.47 (ddd, J = 1.2, 6.2, 6.2 Hz, 2H), 5.37 (s, 2H), 4.04 (s, 2H), 2.33 (s, 3H), 1.41 (s, 6H); ^{13}C nmr (deuterochloroform): δ 171.4, 159.3, 155.8, 148.7, 130.2, 130.0, 129.8, 129.7, 129.6, 126.2, 124.9, 78.5, 67.6, 28.6, 25.3, 11.9.

Anal. Calcd. for $C_{23}H_{21}O_2N_3 \cdot H_2O$: C, 70.93; H, 5.95; N, 10.71. Found: C, 70.70; H, 5.72; N, 10.31.

5-(9'-Acridinylmethyl)-4-(4",4"-dimethyl-Δ^2-oxazolin-2"-yl)-3-phenylisoxazole (**2i**).

The best yield was obtained when the reaction solvent was 20 ml of a 3:1 mixture of hexamethylphosphorus triamide and tetrahydrofuran. The crude oil obtained from this mixture was subjected to flash chromatography (silica, 8:2 hexane:ethyl acetate) to provide 0.287 g (22%) of the desired product as a tan solid; mp, 237.5° with sintering 223-235°; ms: m/z 433 M+, 361, 294, 241, 192, 169, 143, 105, 77; ^{1}H nmr (deuterochloroform): δ 8.46 (d, J = 7 Hz, 2H), 8.27 (d, J = 7 Hz, 2H), 7.80 (dd, J = 7, 7 Hz, 2H), 7.61 (m, 4H), 7.42 (m, 3H), 5.51 (s, 2H), 3.96 (s, 2H), 1.42 (s, 6H); ^{13}C nmr (deuterochloroform): δ 172.1, 161.7, 155.7, 148.8, 138.4, 130.3, 129.9, 129.8, 129.0, 128.3, 128.1, 127.7, 126.4, 125.7, 124.6, 78.7, 67.7, 28.3, 25.3.

Anal. Calcd. for $C_{28}H_{23}O_2N_3$: C, 77.58; H, 5.35; N, 9.69. Found: C, 77.92; H, 5.01; N, 9.94.

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