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DOUBLE ACTIVATION PREPARATION OF AN ACRIDINYL-ISOXAZOLYL-LEXITROPSIN

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Abstract: The coupling of a sterically hindered acridinyl isoxazole ester directly to the amine group of a lexitropsin is significantly improved by double activation, using trimethylaluminum to activate the amine portion and samarium (III) chloride to enhance the carboxylate reactivity. © 1997 Elsevier Science Ltd.

Lexitropsins have recently been found by Dervan to enter cells and bind selectively to B-DNA,[1] thus raising the expectation that this class of compounds will ultimately lead to useful medicines. We have been interested in developing the use of isoxazolyl substituted lexitropsins to improve drug delivery[2] and to act as a tether to B-DNA binding groups. Lown has recently observed that the nature of the tether of a lexitropsin to another functional moiety critically effects its antitumor activity.[3] We had previously reported the synthesis of acridinyl isoxazoles,[4] and noted that the intercalating group is presented in perpendicular fashion in three dimensions to the isoxazole group.[5] Together with our previous observation that the isoxazole is approximately co-planar with coupled pyrroles[2] would allow the hybrid intercalator minor-groove binder to present both functional groups in the correct attitude with respect to B-DNA binding with minimal conformational flexibility, which could be expected to dramatically enhance binding affinity. The preparation of the molecule designed to test our hypothesis, however, presented formidable steric problems.

In the course of related studies on the effect of lanthanide catalysis of 2-oxazoline and amide synthesis, we noted that the addition of an oxophilic lanthanide (III) salt often improved yields of acyl substitution reactions in the presence of other interfering nitrogen heterocycles.[6] While direct lexitropsin coupling to esters with trimethyl aluminum[7] proceeds in reasonable efficiency for the less hindered isoxazolyl esters (Table, Entries 1 and 2), the coupling was disappointing with the sterically bulky anthrancenyl isoxazole ester (Entry 3). The yield after isolation and purification is significantly higher with the lanthanide catalyst than without (compare Entries 3 and 4), and was 94% based on recovered acridinyl ester (Entry 5).

This synthetic method allows facile entry into a new class of intercalating lexitropsins with minimal conformational flexibility, and we will report on our progress in this arena in due course.

Scheme 1. **a**: R = Me, n = 1; **b**: R = Me, n = 2; **c**: R = 5-Anthracenyl, n = 2; **d**: R = 9 Acridinyl, n = 2.

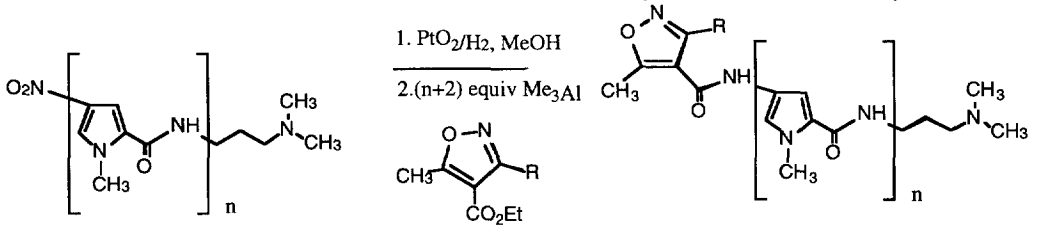

Table 1. Coupling of hindered esters with 4-amino-N-methyl-pyrrole-2-carboxylates.

Entry	n	R	$SmCl_3$(equiv)	Conditions	Product	Yield(%)
1	1	Me	No	RT, 24 h	a	71
2	2	Me	No	RT, 24 h	b	70
3	2	5-Anthracenyl	No	Reflux, 24 h	c	27
4	2	5-Anthracenyl	0.5	Reflux, 24 h	c	63
5	2	9-Acridinyl	0.5	Reflux, 24 h	d	52

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7. The general experimental procedure is mild and convenient, as illustrated for Entry 5. The nitro pyrrole dimer[8] (308.3 mg, 0.819 mmol)) was stirred over PtO_2 (20 mg) in methanol (25 mL), under an atmosphere of hydrogen, until TLC indicated that the nitro pyrrole dimer had been consumed. The mixture was filtered, the PtO_2 washed with dry THF, and the combined solution concentrated and dried in vacuo for 1 h. The residue was dissolved in dry THF (25 mL), cooled to 0 °C, and trimethylaluminum was added dropwise (1.6 mL of a 2 M solution in hexane). The resulting solution was transferred via cannula to a suspension of samarium trichloride (52.6 mg, 0.205 mmol) and acridinyl ester [4](ethyl 3-[9′acridinyl]-5-methyl isoxazole-4-carboxylate, 136 mg, 0.41 mmol) in dry THF (25 mL), and the reaction was warmed to reflux for 24 h. After cooling to room temperature, saturated aqueous ammonium chloride (25 mL) was then added, and the suspension was filtered through Celite, and the solution extracted with ethyl acetate (2 × 20 mL) and the combined organic layers washed with water (2 × 20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to an amber oil. Radial chromatography (SiO_2, 10% $CHCl_3$/MeOH) provided the faster moving unreacted acridinyl ester (61 mg), followed by the coupling product **d** as a solid, mp 146–8 °C (dec.) 134 mg, 52%. The yield is 94% based on recovered starting material.

   Characterization data: Compound **c** (5-Anthracenyl): tan solid; mp 140–2 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 8.14–8.17 (m, 2H), 7.72–7.75 (m, 3H), 7.54–7.72 (m, 3H), 7.16 (s, 1H), 7.10 (d, J = 1.5 Hz, 2H), 6.44 (s, 1H), 6.36 (s, 1H), 6.26 (s, 1H), 5.75 (s, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 3.47 (q, J = 6 Hz, 2H), 3.02 (s, 3H), 2.57 (t, J = 6 Hz, 2H), 2.39 (s, 6H), 1.80 (t, J = 6 Hz, 2H); ^{13}C NMR($CDCl_3$) δ 176.2, 161.6, 158.5, 158.1, 157.5, 131.1, 130.9, 130.5, 128.9, 127.9, 126.1,124.8, 123.3, 121.1, 120.0, 118.5, 118.4, 112.3, 103.2, 102.7, 58.9, 46.1, 45.4, 39.3, 36.6, 36.5, 25.8, 13.7, 10.3. MS: 632 (M+).

   Compound **d** (9-Acridinyl): yellow solid; mp 146–8 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.32 (s, 1H), 7.76–7.91 (m ,4H), 7.55–7.76 (m, 3H), 7.28 (s, 1H), 7.06 (d, J = 1.5 Hz, 1H),6.42 (d, J = 1.8 Hz, 1H), 6.38 (s, 1H), 6.34 (d, J = 2.1 Hz, 1H), 5.76 (d, J =1.8 Hz, 1H), 3.86 (s, 3H), 3.68 (s, 3H), 3.43 (q, J = 6.9 Hz, 2H), 3.0 (s, 3H), 2.50 (t, J = 5.9, 5.4 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 176.2, 161.6,158.3, 157.5, 155.3, 148.7, 130.9, 130.2, 128.0, 125.0, 123.8, 119.8, 118.6, 118.5, 102.7, 58.6, 45.2, 39.0, 36.6, 36.4, 25.7, 13.5. MS: 633 (M+), 287 (M - amide dimer).

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