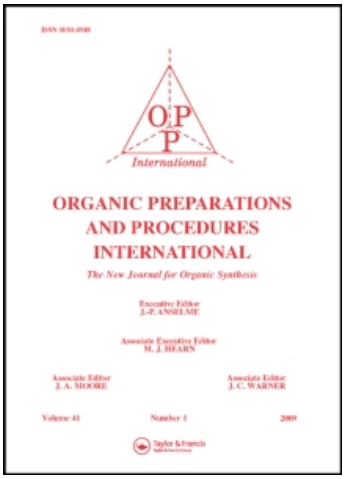

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AN IMPROVED METHOD FOR THE PREPARATION OF 2-(2'-AMINOARYL) OXAZOLINES FROM SUBSTITUTED ISATOIC ANHYDRIDES AND 2-CHLOROETHYLAMINE HYDROCHLORIDE

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AN IMPROVED METHOD FOR THE PREPARATION OF 2-(2'-AMINO-ARYL)OXAZOLINES FROM SUBSTITUTED ISATOIC ANHYDRIDES AND 2-CHLOROETHYLAMINE HYDROCHLORIDE

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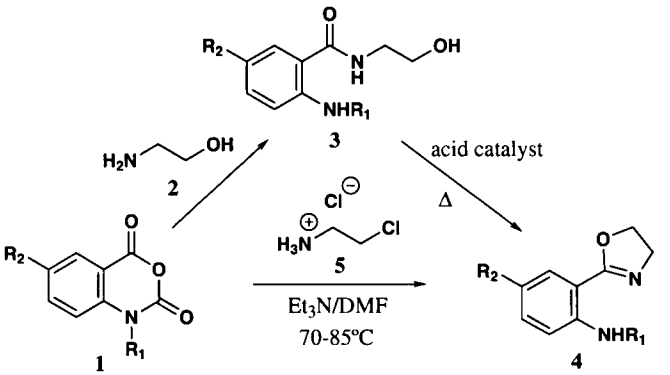
2-(2'-Aminoaryl)oxazolines (**4**) and their derivatives have been studied as ligands for a variety of metal chelates[1] and are known to possess biological activity in both free ligand[2,3c] and chelated[1b] forms. The standard methods for preparation of 2-(2'-aminoaryl)oxazolines employ a nucleophilic ring opening of 2H-3,1-aryloxazine-2,4(1H)-diones [*i. e.*, substituted isatoic anhydrides (**1**)] with an ethanolamine followed by cyclization of the intermediate β-hydroxyethylamide **3** with catalysts such as $ZnCl_2$,[1b] H_2SO_4,[3] AcOH/ NaOAc,[4] kaolinitic clay,[5] and $P(OEt)_3$[6] under reflux in a high boiling solvent. While the intermediate β-hydroxyethyl amide **3** is typically not isolated, it is clear that this preparative method may not be applicable to substrates which may be sensitive to these reaction conditions.

Herein is described a straightforward alternative one-pot procedure employing mild basic conditions which affords a variety of 2-(2'-aminoaryl)oxazolines in moderate to good yields. Conducting the reaction of a substituted isatoic anhydride as the starting material with 2-chloroethylamine hydrochloride and 2.5 equivalents of triethylamine as the HCl scavenger in anhydrous *N,N*-dimethylformamide at temperatures ranging from 70-85°C provides the desired

oxazolines in good yields with little side-product formation. Workup is straightforward and the crude reaction products are easily purified by flash chromatography on silica gel. As an example of the efficiency of the base-mediated method described herein, the preparation of the parent compound ($R_1 = R_2 = H$), problematic by the acid–catalyzed routes utilizing $ZnCl_2$/ethanolamine (yield = 2%)[1b] or AcOH/NaOAc/ethanolamine (yield = 40%),[4] proceeds in 77% yield.



This report demonstrates the applicability of this general method to prepare both *N*-substituted and aryl substituted derivatives. The availability of substituted isatoic anhydrides[7] and 2-chloroethylamine hydrochloride through commercial outlets or straightforward synthesis serves to extend the applicability of this simple method.

EXPERIMENTAL SECTION

N,N-Dimethylformamide was purchased as anhydrous (Aldrich) and was stored under a nitrogen blanket. ^1H nmr (300 MHz) and ^{13}C nmr (75 MHz) data were obtained from a Varian Gemini 300 300MHz nuclear magnetic resonance spectrometer referencing tetramethylsilane and utilized $CDCl_3$ lock. IR data were obtained from a Perkin-Elmer Model Spectrum 2000 FT-IR spectrometer. Microanalyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. All melting points were obtained from a Mel-Temp heating block apparatus and are uncorrected.

General Procedure.- A 50 mL round bottom flask equipped with a magnetic stirrer and oil bath was charged sequentially with the requisite 2H-3,1-aryloxazine-2,4(1H)-dione (10 mmol), 2-chloroethylamine hydrochloride (10 mmol), anhydrous DMF (30 mL), and triethylamine (25 mmol). The flask was fitted with a $CaCl_2$ drying tube, and the mixture was heated with stirring at 70-85°C for 2-2.5 h. The mixture was permitted to cool to room temperature and then poured into 125 mL H_2O. The mixture was then transferred to a separatory funnel and was extracted with 3 x 40 mL CH_2Cl_2. The combined organics were then washed with 5 x 50 mL H_2O. When emulsions resulted, a small amount of saturated brine solution was added. The organics were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel eluting with CH_2Cl_2.

2-(2'-Anilinyl)oxazoline (**4**: $R_1 = R_2 = H$: 1.24g, 76.5%) was isolated as an off-white microcrys-

talline solid, mp. 54.5-55.5°C, *lit.*[3] mp. 54-57°C; IR: 1627 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz): δ 3.97 (t, 2, oxazoline $C\underline{H}_2$), 4.19 (t, 2, oxazoline $C\underline{H}_2$), 5.94 (br s, 2, $N\underline{H}_2$), 6.54 (m, 2, Ar$\underline{H}$), 7.06 (m, 1, Ar$\underline{H}$), 7.57 (m, 1, Ar$\underline{H}$). ^{13}C nmr ($CDCl_3$, 75 MHz): δ 55.07, 65.86, 109.27, 115.77, 116.15, 129.74, 132.09, 148.58, 164.95.

2-(2'-N-Methylanilinyl)oxazoline (**4**: $R_1 = CH_3$; R_2 = H: 0.96g, 54.5%) was isolated as a pale yellow oil which crystallized on standing, mp. 61.5-63°C, *lit.*[3] mp. 62-62.5°C; IR: 1636 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz): δ 2.84 (s, 3, -$NC\underline{H}_3$), 3.97 (t, 2, oxazoline $C\underline{H}_2$), 4.16 (t, 2, oxazoline $C\underline{H}_2$), 6.49 (m, 2, Ar$\underline{H}$), 7.20 (m, 1, Ar$\underline{H}$), 7.61 (m, 1, Ar$\underline{H}$), 8.12 (br s, 1 –$N\underline{H}CH_3$). ^{13}C nmr ($CDCl_3$, 75 MHz) δ 29.62, 55.02, 65.65, 108.56, 109.90, 114.29, 129.94, 132.59, 150.01, 165.29.

2-(2'-N-Benzylanilinyl)oxazoline (**4**: $R_1 = CH_2Ph$; R_2 = H: 1.84g, 69%) was isolated as pale yellow rosettes, mp. 62-64°C; IR: 1631 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz): δ 3.98 (t, 2, oxazoline $C\underline{H}_2$), 4.20 (t, 2, oxazoline $C\underline{H}_2$), 4.39 (s, 2, -$NC\underline{H}_2Ph$), 6.49 (m, 2, Ar$\underline{H}$), 7.15 (m, 6, Ar$\underline{H}$), 7.64 (m, 1, Ar$\underline{H}$), 8.79 (br s, 1 –$N\underline{H}CH_3$). ^{13}C nmr ($CDCl_3$, 75 MHz) δ 47.03, 55.09, 65.69, 108.92, 110.93, 114.76, 126.96, 127.04, 128.64, 129.99, 132.48, 139.57, 149.01, 165.23.

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.11; H, 6.53; N, 10.87.

2-(4'-Bromo-2'-anilinyl)oxazoline (**4**: R_1 = H; R_2 = Br: 1.96g, 81.3%) was isolated as an off-white powder, mp. 97-98°C; IR: 1638 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz): δ 3.98 (t,2, oxazoline $C\underline{H}_2$), 4.17 (t, 2, oxazoline $C\underline{H}_2$), 5.97 (br s, 2 –$N\underline{H}_2$), 6.46 (d, 1, Ar$\underline{H}$), 7.13 (dd, 1, Ar$\underline{H}$), 7.68 (d, 1, Ar$\underline{H}$). ^{13}C nmr ($CDCl_3$, 75 MHz) δ 55.12, 66.05, 107.25, 110.72, 117.38, 132.01, 134.68, 147.48, 163.94.

Anal. Calcd for $C_9H_9BrN_2O$: C, 44.84; H, 3.76; Br, 33.14; N, 11.62. Found: C, 45.01; H, 3.62; Br, 33.15; N, 11.33.

2-(4'-Chloro-2'-anilinyl)oxazoline (**4**: R_1 = H; R_2 = Cl: 1.58g, 80.4%) was isolated as a white powder, mp. 78-79°C, *lit.*[3c] mp. 76-78°C; IR: 1642 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz): δ 3.98 (t, 2, oxazoline $C\underline{H}_2$), 4.21 (t, 2, oxazoline $C\underline{H}_2$), 5.97 (br s, 1 –$N\underline{H}_2$), 6.53 (d, 1, Ar$\underline{H}$), 7.01 (dd, 1, Ar$\underline{H}$), 7.55 (d, 1, Ar$\underline{H}$). ^{13}C nmr ($CDCl_3$, 75 MHz) δ 55.10, 66.07, 110.14, 117.02, 120.56, 129.11, 131.99, 147.10, 164.05.

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AN IMPROVED PREPARATION OF 2,2,4,4-TETRAMETHYL-6-AMINO-THIOCHROMAN, A KEY INTERMEDIATE TO UREA AND THIOUREA HETEROAROTINOIDS FOR ANTICANCER STUDIES

Submitted by (09/09/06)

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The synthesis of urea and thiourea analogs of the title aminothiochroman **6** is an area of current research for potential anticancer compounds of the heteroarotinoid class mimicking retinoids.[1,2] The recently reported preparation[1,3,4] of this late stage intermediate, however, suffers from a low overall yield of 5.3% from mesityl oxide that is limited by the nitration step and to a lesser degree upon the reduction employed in its preparation. Especially problematic was the 26% yield of the nitration step which introduced the nitrogen atom of the eventual amine moiety of the 6-aminothiochroman intermediate **6**. The 40% yield in the reduction of the nitro group with Fe/HOAc offered cost advantages and a greater ease of workup over the previously employed $TiCl_3$/HOAc method (50%)[4] which justified the lesser yield. These combined poor yields necessitated increasing the scale of the previous steps which limited both the throughput for the preparation of *in vivo* testing quantities of a single compound and the potential to prepare multiple other urea and thiourea analogs from **6**. The improved synthesis reported here is shorter and affords a higher overall yield of **6** that circumvents the nitration and the obligatory reduction by incorporating the nitrogen from the start of the synthesis.