Heterocyclic Letters
Vol. 9| No.3|235-238|May-July|2019
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

THE PREPARATIONOF ω-CHLOROALKYLANTHRANILAMIDES FROM SUBSTITUTED ISATOIC ANHYDRIDES

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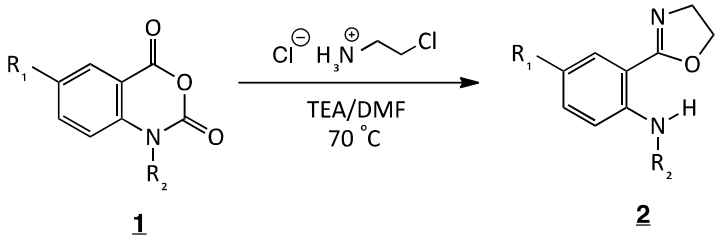
Abstract: Reaction of substituted isatoic anhydrides with ω-chloropropyl- and butylamines provides ω-chloropropyl- and ω-chlorobutylanthranilamides in low-moderate yields with no discernable cyclization by-product.

Keywords: Isatoic anhydrides, ω-chloroalkylanthranilamides

Introduction

The reaction of isatoic anhydrides (**1**) with nitrogen nucleophiles to afford anthranilamides is well known and has been well documented[I]. Anthranilamides are of interest due to their analgesic, antipyretic, and anti-inflammatory, fungicidal, and CNS depressant activities[II]. Use of this reactionmethodology with chloroethylamine hydrochloride to provide an efficient entry into the 2-(4,5-dihydrooxazol-2-yl)aniline system (**2**)has been described (Scheme 1)[III].

Scheme 1



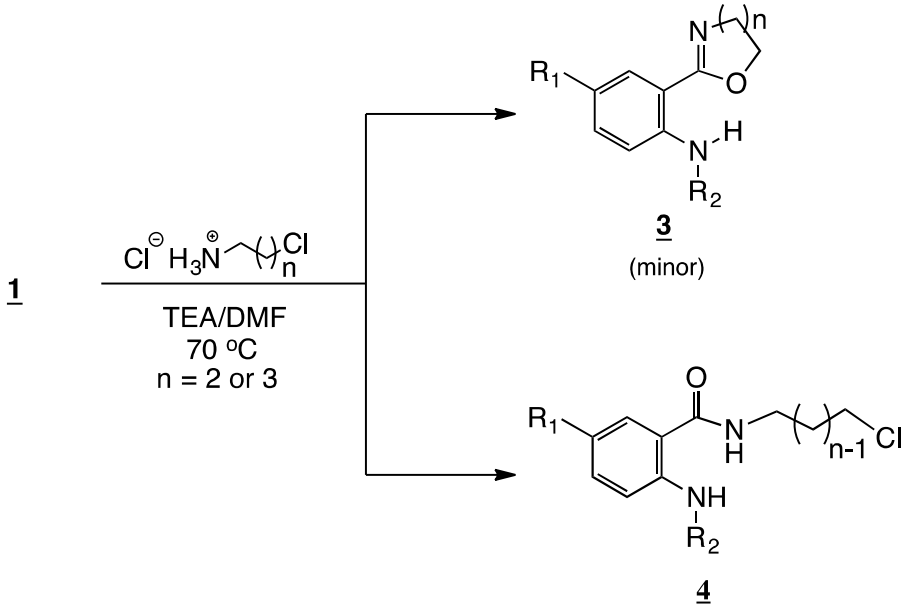
1 **2**

In an effort to determine whether this methodology could be extended to prepare larger ring sizes (**3**), we undertook a study of the reaction of isatoic anhydrides with higher order ω-chloroalkylamines (as the corresponding hydrochloride salt) (Scheme 2).

Currently, routes to the 2-(4,5-dihydrooxazino-2-yl)aniline system have utilized reaction of the corresponding ω-aminopropanol with o-aminobenzonitrile with sulfur at 100 ^{o}C[IV] or

using a sulfur/$Co(NO_3)_2$ catalyst system, both of which afford product in excellent yield [V]. Other reported methods include the reaction of the alkanolamine with isatoic anhydride in the presence of $ZnCl_2$ and chlorobenzene, followed by an 18h reflux to provide the product in low yield[VI].

Scheme 2



Compound	R_1	R_2	n	%yield
4a	H	CH_3	2	32
4b	Cl	H	2	20
4c	Br	H	2	33
4d	H	Bz	2	24
4e	H	H	2	24
4f	H	H	3	24
4g	Cl	H	3	32

When the reactions as shown in Scheme 2were carried out with 2.0-2.5 equivalents of triethylamine, the only products isolated were the ω-chloro derivatives **4**. While we were able to detect cyclized products of the type **3** by GC/MS in most cases, they were not present in enough quantity to permit isolation.The products were characterized by $^1H/^{13}C$ NMR, IR, and GC/MS. The reaction appears to be quite robust, regardless of either ring substitution or N-substitution.

While very little is known regarding these compounds, one such compound has been reported in the literature to serve as an intermediate in drug design[VII]. Future work will focus on developing robust methods for the preparation of the cyclic derivatives **3**.

Experimental

General

^{1}H NMR data were obtained from a Varian Gemini 300 300MHz nuclear magnetic resonance spectrometer referencing tetramethylsilane. ^{13}C NMR data were obtained at 75 MHzreferencing tetramethylsilane.IR data were obtained from a Perkin-Elmer Model Spectrum 2000 FT-IR spectrometer; mass spectra were obtained from a Varian Model CP-3800 gas chromatograph interfaced to a Varian Saturn 2000 GC/MS/MS.

General procedure for the preparation of ω-chloroalkylanthranilamides 4. Preparation of 2-amino-*N*-(3-chloropropyl)benzamide (**4a**).Isatoic anhydride (10 mmol), ω-chloropropyl ammonium chloride (10 mmol),DMF (30 mL), and triethylamine (20-25 mmol) are sequentially charged to a 100 mL round-bottom flask equipped with a reflux condenser and $CaCl_2$ drying tube. The mixture is heated and stirred for 2h after reaching 70 C°, then quenched by addition to water. The crude product is isolated after CH_2Cl_2extraction, followed by recrystallization or purification by flash chromatography on silica gel.

4a:
Off-white solid, mp 69-69.5 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.98 (pentet, *J*=6.6 Hz, 2H, -CH_2), 2.74 (d, *J*=4.8 Hz, 3H, -$NHCH_3$), 3.45 (q, *J*=6.0 Hz, 2H, -$NHCH_2$), 3.53 (t,*J*=6.0 Hz, 2H,-CH_2Cl), 5.40 (br s, 2H, NH_2), 6.11 (br s, 1H, -NH), 6.45 (m, 2H,-ArH), 7.18 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$)δ 29.76, 32.21, 37.30, 42.79, 111.30, 114.58, 127.16, 133.09, 150.72, 170.21; IR 3385, 3292, 1623 cm^{-1}; massspectrum(70eV)m/z226, 228 (M^+)

4b:
Tan solid, mp 116.5-119 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.99 (pentet, *J*=6.0 Hz, 2H, -CH_2), 3.46 (q, *J*=6.0 Hz, 2H, -$NHCH_2$), 3.53 (t,*J*=6.0 Hz, 2H,-CH_2Cl), 5.40 (br s, 2H, NH_2), 6.10 (br s, 1H, -NH), 6.50 (d, *J*=8.7 Hz, 1H,-ArH), 7.16 (dd, *J*=8.7, 2.4 Hz, 1H, ArH), 7.28 (d, *J*=2.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$)δ32.14, 37.47, 42.67, 116.13, 118.26, 118.53, 127.81, 131.84, 149.08, 168.18;IR 3428, 3288, 1630 cm^{-1}; massspectrum(70eV)m/z246, 248 (M^+)

4c:
Tan solid, mp 119-121 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.98 (pentet, *J*=6.0 Hz, 2H, -CH_2), 3.47 (q, *J*=6.0 Hz, 2H, -$NHCH_2$), 3.53 (t,*J*=6.0 Hz, 2H,-CH_2Cl), 5.40 (br s, 2H, NH_2), 6.10 (br s, 1H, -NH), 6.45 (d, *J*=8.4 Hz, 1H,-ArH), 7.16 (dd, *J*=8.4, 2.2 Hz, 1H, ArH), 7.28 (d, *J*=2.2 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$)δ 32.14, 37.47, 42.67, 107.78, 117.39, 119.06, 129.63, 135.15, 147.80, 168.41;IR 3427, 3356, 3305, 1621 cm^{-1}; massspectrum(70eV)m/z289, 291, 293 (M^+)

4d:
Off-white solid, mp 74-77 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.99 (pentet, *J*=6.0 Hz, 2H, -CH_2), 3.46 (q, *J*=6.0 Hz, 2H, -$NHCH_2$), 3.55 (t,*J*=6.0 Hz, 2H, -CH_2Cl), 4.30 (d, *J*=6Hz, 2H, -CH_2Ph), 6.14 (br s, 1H, NH), 6.48 (m, 1H,-ArH), 7.20 (m, 3H, ArH), 7.94 (br s, 1H, -NH); ^{13}C NMR ($CDCl_3$)δ 32.18, 37.36, 42.82, 47.23, 112.343, 115.10,127.14, 127.20, 127.28, 128.73, 133.04, 139.23, 149.67, 170.10;IR 3391, 3242, 1630 cm^{-1}; massspectrum(70eV)m/z302, 304 (M^+)

4e:
Off-white solid, mp74.5-77.5 ^{o}C; ^{1}H NMR ($CDCl_3$) δ1.99 (pentet, *J*=6.6 Hz, 2H,-CH_2), 3.46 (q, *J*=6.0 Hz, 2H, -$NHCH_2$), 3.53 (t,*J*=6.0 Hz, 2H,-CH_2Cl), 5.40 (br s, 2H, NH_2), 6.14 (br s, 1H, -NH), 6.54 (m, 2H, ArH), 7.09 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$)δ 32.19, 37.32, 42.82, 116.76, 117.49, 127.14, 132.53, 148.87, 169.67; IR 3425, 3321, 1634 cm^{-1}; massspectrum(70eV)m/z212, 214 (M^+)

4f:
Off-white solid, mp 110-111 ^{o}C; ^{1}H NMR (d_6-DMSO) δ1.99 (m, 4H, -CH_2CH_2), 3.06 (q, *J*=6.0 Hz, 2H, -$NHCH_2$), 3.84 (m, 2H, -CH_2Cl), 6.36 (br s, 2H, NH_2), 6.54 (m, 2H, ArH), 7.09 (m, 2H, ArH), (br t, *J*=4.8 Hz, 1H, -NH); ^{13}C NMR (d_6-DMSO)δ 26.06, 27.14, 38.71, 62.48, 115.10,115.53, 116.86, 128.55, 132.07, 150.11, 169.43; IR 3465, 3364, 3305, 1618 cm^{-1}; massspectrum(70eV)m/z226, 228 (M^+)

4g:
Tan solid, mp 158-159 ^{o}C; ^{1}H NMR (d_6-DMSO) δ1.99 (m, 4H, -CH_2CH_2), 3.06 (q, *J*=6.0 Hz, 2H, -$NHCH_2$), 3.84 (m, 2H, -CH_2Cl), 6.36 (br s, 2H, NH_2), 6.55 (d, *J*=8.4 Hz, 1H, ArH), 7.09 (dd, *J*=8.4, 2.4 Hz, 1H, ArH), 7.37 (d, *J*=2.4 Hz, 1H, ArH), 8.21 (br t, *J*=4.8 Hz, 1H, -NH); ^{13}C NMR ($CDCl_3$)δ25.89, 27.07, 38.78, 62.38, 116.14, 118.24, 118.51, 127.83, 131.85, 149.07, 168.18; IR 3480, 3378, 3305, 1625 cm^{-1}; massspectrum(70eV)m/z260, 262 (M^+)

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Received on August 2, 2019.