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Synthesis of Z-*N*-Alkenylformamides

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Abstract: Commercially available difluorinated benzaldehyde was converted to the Z-*N*-alkenylformamides via Horner–Emmons olefination and Curtius rearrangement, followed by reduction with tri-*tert*-butoxy-aluminohydride.

Keywords: Z-*N*-alkenylformamides (enamides), Curtius rearrangement, Horner–Emmons olefination, isocyante

INTRODUCTION

N-Alkenylamides include natural products isolated from a variety of sources, ranging from micro- and marine organisms to higher plants. These compounds display a wide variety of physiological properties.[1–9] This prompted us to synthesize a number of naturally occurring *N*-alkenylformamides and study their biological and physical properties.[10–13] Using 2D EXSY NMR, we found the E-*N*-alkenylformamides had a rotational barrier of 17–19 kcal/mol. This subsequently led us to study the barriers to rotation in the Z-*N*-alkenylformamides isomer, which showed similar energy values[14,15] in spite of the fact that the double bond is orthogonal to the benzene ring (Fig. 1). Because the E-*N*-alkenylformamides have been exhaustively studied, it was interesting us to investigate the potential biological properties of the Z-*N*-alkenylformamide isomers. In particular, the orthogonality of the Z

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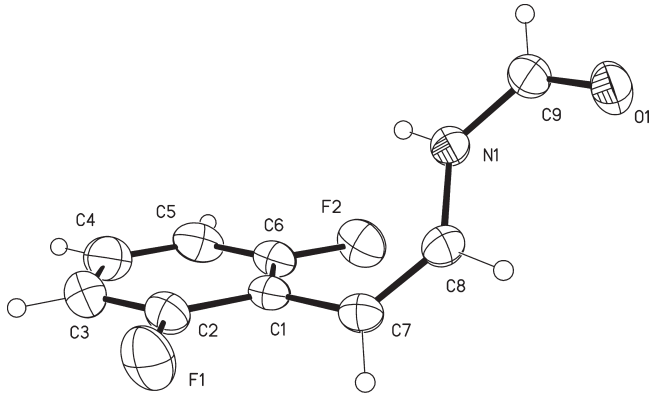


Figure 1. X-ray structure of the Z-*N*-alkenylformamide **12*Z***.

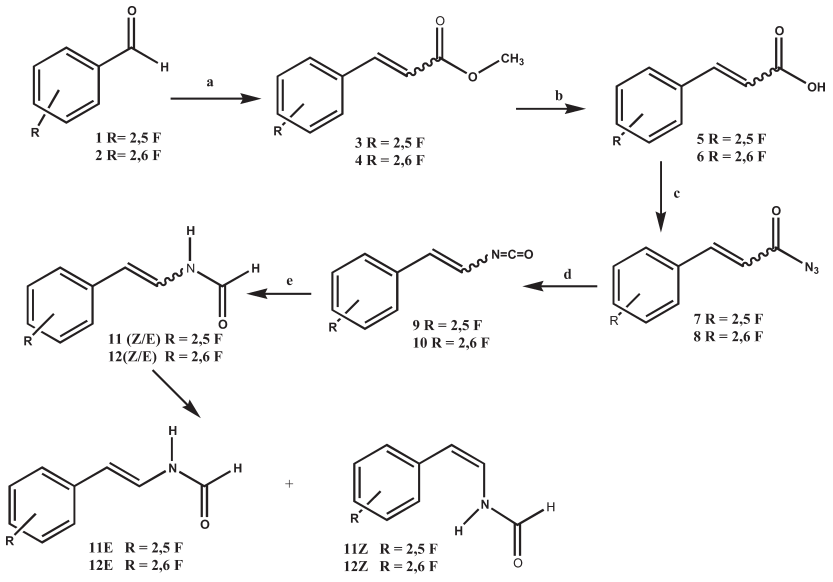
double bond to the benzene ring, a unique structural feature, may lead to interesting biological properties.

We report here a general synthetic route to Z-*N*-alkenylformamides (**11, 12**), which can be made in adequate amounts to be subjected to biological testing.

RESULTS AND DISCUSSION

Most of the syntheses reported for *N*-alkenylformamides have shown the Z-*N*-alkenylformamide to be a minor component obtained in yields ranging from 5 to 25% (by NMR).[1,16–22] Most of the detailed synthetic studies have been on erbstatin and tuberine, both isolated from microorganisms and exhibiting interesting physiological properties. Erbstatin was shown to inhibit tyrosine specific kinases,[2] and the latter was shown to exhibit mild antibiotic properties.[3] In most of the reported cases, the Z-isomer was never isolated, characterized, or biologically tested. Recently Furstner, Taylor, and Hartenstein have independently reported excellent synthetic routes to Z-*N*-alkenylamides.[22]

As a model for our synthesis on N-alkenylformamides, we selected 2,5- and 2,6-difuorobezaldehydes (**1**, **2**), which were subjected to Horner–Emmons olefination reaction using the ylid derived from bis(trifluoroethyl) phosphonoester to give the olefins (**3**, **4**) in 78–80% yield, with Z/E ratios of 75:25 for **3** and 78:22 for **4** (by NMR).[23,24] The mixture was then carried through various steps without separation until the final step (Scheme 1). Hydrolysis of the olefinic ester to the acid (**5**, **6**) in 90–97% yield followed by mixed anhydride formation and azide addition gave the acylazides (**7**, **8**) in 80–81% yield. Subsequent thermal Curtius rearrangement to give the isocyanates (**9**, **10**), followed by reduction with lithium tri-*tert*-butoxy-aluminohydride, gave the mixture of *N*-alkenylformamides (**11**, **12**) in 77% yield. Purification by preparative thin-layer chromatography (TLC) coated with $AgNO_3$ 10%



Scheme 1. Synthesis of Z-*N*-alkenylformamide (**11*Z***, **12*Z***).

(wt/vol.) in methanol and then activated for 1 h at 100–110°C afforded Z-*N*-alkenylformamides (**11*Z***, **12*Z***) and E-*N*-alkenylformamide (**11*E***, **12*E***).

The crystal structure of **11*Z*** (Data collected at 294 K using highly oriented graphite crystal monochromated MoK α radiation. The stucture was solved by direct methods and non-hydrogen atoms were refined anisotropically. In the final least-squares refinement cycle on F, R = 8.885% *w*R2 = 15.26%. The crystal data are a = 14.213(4) Å, b = 8.325(3) Å, c = 7.352(2) Å, $\alpha = 90^\circ$ $\beta = 95.05^\circ$ $\gamma = 90^\circ$, V = 856.5(5) Å3, space group Pc, Z = 4. CCDC number 225592 for compound **11*Z***) and **12*Z*** (Data collected at 294 K using highly oriented graphite crystal monochromated MoK α radiation. The stucture was solved by direct methods and non-hydrogen atoms were refined anisotropically. In the final least-squares refinement cycle on F, R = 4.7%, *w*R2 = 9.95%. The crystal data are a = 8.954(2) Å, b = 8.216(2) Å, c = 11.664(3) Å, $\alpha = 90^\circ$, $\beta = 94.80^\circ$, $\gamma = 90^\circ$, V = 855.1(3) Å3, space group P21/c. CCDC number 225593 for compound **12*Z***) show the π plane of the CH═CHN group to be turned 49° by steric repulsion from the π plane of the benzene ring.[15]

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer FT-IR 1605 spectrometer. NMR spectra were recorded on a Varian Gemini (200-MHz) spectrometer

using $CDCl_3$ as solvent. Chemical shifts for ^1H NMR spectra are relative to internal Me_4Si. MS were determined with a GC HP-5971 spectrometer. Elementary analyses for carbon and hydrogen were conducted by Galbraith Laboratories, Inc. (Knoxville, TN). The products were isolated by TLC/$AgNO_3$ 10% (wt/vol.).

General Preparation of Methyl 3-(difluorophenyl)acrylate

A solution of bis-(2,2,2-trifluoroethyl)(methoxycarbonyl) phosphonate (0.320 g, 1.0 mmol) and 18-crown-6 (0.320 g, 5.0 mmol) in anhydrous THF (5 mL) was cooled to $-78^\circ C$ and treated with $KN(TMS)_2$ (0.19 g, 0.95 mmol) under an N_2 atmosphere. The resulting mixture was stirred for 20 min, and 2,5-difluorobenzaldehyde **1** (0.130 g, 0.93 mmol) was then added. After stirring for 1 h at $-78^\circ C$, saturated NH_4Cl was added, and the product was extracted with diethyl ether (3×30 mL). The combined ethereal extracts were washed with saturated aqueous sodium chloride, dried, and evaporated, and the crude product was purified by flash chromatography using hexane–ethyl acetate (98:2) to afford a yellow liquid.

(Z/E) Methyl 3-(2,5-Difluorophenyl)acrylate (**3**)

(Z/E) 75:25 Yield (0.143 g, 78%). IR ν_{max} (neat): 2953, 1731, 1643, 1487 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.60$ (m, 2H, Ar-H); 7.34 (m, 1H, Ar-H); 7.08 (d, 0.25H, $J = 15.0$, CH=); 6.85 (d, 0.75H, $J = 11.2$ Hz, CH=); 6.50 (d, 0.25H, $J = 15.0$ Hz, CH=); 5.85 (d, 0.75H, $J = 11.2$ Hz, CH=); 3.81 (s, 3H, O-Me). Anal. calcd. for $C_{10}H_8F_2O_2$: C, 60.61; H, 4.07. Found: C, 60.81; H, 3.97.

(Z/E) Methyl 3-(2,6-Difluorophenyl)acrylate (**4**)

(Z/E) 78:22 Yield (0.147 g, 80%). IR ν_{max} IR (neat): 2953, 1726, 1621, 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.78 (d, 0.22H, $J = 16.4$ Hz, CH=); 7.30 (m, 1H, Ar-H); 6.89 (t, 2H, $J = 8.0$ Hz, Ar-H); 6.82 (d, 0.78H, $J = 12.6$ Hz, CH=); 6.75 (d, 0.22H, $J = 16.0$ Hz, CH=); 6.22 (d, 0.78H, $J = 12.2$ Hz, CH=); 3.80 (s, 3H, O-Me). Anal. calcd. for $C_{10}H_8F_2O_2$: C, 60.61; H, 4.07. Found: C, 60.52; H, 4.05.

General Preparation of 3-(Difluorophenyl)acrylic Acid

(Z/E) Methyl 3-(2,5-difluorophenyl)acrylate **3** (0.060 g, 0.31 mmol) was dissolved in MeOH (2 mL)/THF (3 mL), and lithium hydroxide (1 N, 1 mL) was added to the resulting solution. The reaction mixture was heated at $70^\circ C$ for 3 h and cooled to rt, and the solvent was removed in vacuo. The residue was taken up in ethyl acetate (50 mL), and the organic phase was

washed with 2 N HCl (50 mL), filtered, and dried ($MgSO_4$). The solvent was removed in vacuo. The product was chromatographed on silica gel, eluting with CH_2Cl_2–MeOH (90:10) to afford a yellow solid.

(Z/E) 3-(2,5-Difluorophenyl)acrylic Acid (**5**)

(Z/E) 75:25 Yield (0.051 g, 90%). IR ν_{max} IR (neat): 3300, 3061, 2976, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.97 (br. s, 1H, OH); 7.69 (d, 0.25H, $J = 16.0$ Hz, CH═); 7.60 (m, 2H, Ar-H); 7.36 (m, 1H, Ar-H); 6.96 (d, 0.75H, $J = 12.7$ Hz, CH═); 6.50 (d, 0.25H, $J = 16.0$ Hz, CH═); 6.00 (d, 0.75H, $J = 12.7$ Hz, CH═). Anal. calcd. for $C_9H_6F_2O_2$: C, 58.70; H, 3.28. Found: C, 58.60; H, 3.23.

(Z/E) 3-(2,6-Difluorophenyl)acrylic Acid (**6**)

(Z/E) 78:22 Yield (0.055 g, 97%). IR ν_{max} IR (neat): 3330, 3057, 2915, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.25 (br. s, 1H, OH); 7.86 (d, 0.22H, $J =$ 16.6 Hz, CH═); 7.3 (m, 1H, Ar-H); 6.92 (m, 2H, Ar-H); 6.91 (d, 0.78H, $J = 12.6$ Hz, CH═); 6.74 (d, 0.22H, $J = 16.4$ Hz, CH═); 6.23 (d, 0.78H, $J = 12.0$ Hz, CH═). Anal. calcd. for $C_9H_6F_2NO_2$: C, 58.70; H, 3.28. Found: C, 58.98; H, 3.26.

General Preparation of 3-(Difluorophenyl)acryloyl Azide

To a stirred mixture of (Z/E) 3-(2,5-difluorophenyl)acrylic acid (0.410 g, 2.19 mmol), **5**, and triethylamine (0.25 g, 2.47 mmol) in acetone (10 mL), ethyl chloroformate (0.26 g, 2.42 mmol) in acetone (1 mL) was added at −5 to 0°C over 5 min. After the mixture was stirred for 15 min, sodium azide (0.28 g, 4.37 mmol) in water (5 mL) was added at −5 to 0°C over 1 min. This mixture was stirred for 45 min at rt, poured into ice water (50 mL), and extracted with diethyl ether (3 × 30 mL). The combined ethereal extracts were washed with saturated aqueous sodium chloride, dried, and concentrated, leaving yellow liquid.

(Z/E) 3-(2,5-Difluorophenyl)acryloyl Azide (**7**)

(Z/E) 60:40 Yield (0.366 g, 80%). IR ν_{max} IR (neat): 3070, 2149, 1679, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.78 (d, 0.40H, $J = 16.0$ Hz, CH═); 7.70 (m, 1H, Ar-H); 7.41 (m, 2H, Ar-H); 7.21 (d, 0.60H, $J = 12.7$ Hz, CH═); 6.46 (d, 0.40H, $J = 16.0$ Hz, CH═); 6.11 (d, 0.60H, $J = 12.7$ Hz, CH═); MS (EI, 70 eV): m/z (%) = 167 (100), 209 (32) [M^+]. Anal. calcd. for $C_9H_5F_2N_3O$: C, 51.68; H, 2.41. Found: C, 51.78, H; 2.33.

(Z/E) 3-(2,6-Difluorophenyl)acryloyl Azide (**8**)

(Z/E) 60:40 Yield (0.371 g, 81%). IR ν_{max} IR (neat): 3069, 2143, 1691, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.85 (d, 0.40H, $J = 15.6$ Hz, CH═); 7.32 (m, 1H, Ar-H); 6.91 (t, 2H, $J = 8.0$ Hz, Ar-H); 6.90 (d, 0.60H, $J = 11.6$ Hz, CH═); 6.68 (d, 0.40H, $J = 16.2$ Hz, CH═); 6.16 (d, 0.60H, $J = 11.8$ Hz, CH═); MS (EI, 70 eV): m/z (%) = 167 (100), 209 (32) [M^+]. Anal. calcd. for $C_9H_5F_2N_3O$: C, 51.68; H, 2.41. Found: C, 51.68; H, 2.44.

General Preparation of Difluoro-2-(2-isocyanatovinyl)benzene

The reaction was carried out under an N_2 atmosphere. The thermally induced rearrangement of (Z/E) 3-(2,5-difluorophenyl)acryloyl azide (0.400 g, 1.91 mmol) and **7** in toluene (10 mL) generated the isocyanate **9**, which was isolated by concentration in vacuo. The reaction was monitored by IR appearance of the isocyanate band at 2341 cm^{-1} and disappearance of the azide band at 2143 cm^{-1}. The azides **8** were similarly transformed to their isocyanates **10**. The yields appeared quantitative; they were used without further purification.

General Preparation of the N-(Difluorostyryl)formamides

A solution of (Z/E) 1,4-difluoro-2-(2-isocyanatovinyl)benzene (0.350 g crude, 1.91 mmol) and **9** in THF (10 mL) was added dropwise to a stirred and cooled (ice bath) solution of lithium tri-*tert*-butoxyaluminohydride (0.570 g, 2.30 mL) in THF (5 mL) under an atmosphere of N_2. After stirring for a further 15 min, aqueous ammonium chloride solution (10%) was added, and the resultant precipitate was filtered and washed with ethyl acetate. The combined extracts was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was passed through a short pad of silica gel using dichloromethane to afford a yellow liquid. The yields cited (0.269 g, 77%) are overall from the purified azides, and isomers were separated by preparative thin-layer chromatography (TLC) coated with $AgNO_3$ 10% (wt/vol.) and elution with dichloromethane–methanol (95:5) to afford a yellow solid.

This ^1H NMR spectrum exhibits a doubling of signals due to restricted rotation about the amide (N-CO) bond, leading to two rotational conformers (*anti* and *syn*).[14,15] The more abundant rotamer is the s*yn* for both E and Z-*N*-alkenylformamides (**11**, **12**).

(Z)-N-(2,5-Difluorostyryl)formamides (**11Z**)

Mp 108–109°C, yield (0.112 g, 32%). IR ν_{max} IR (neat): 3301, 2926, 1716, 1653, 1503 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.80 (d, 0.30H, $J = 11.8$ Hz, CHO);

7.40 (dd, 1H, $J = 11.2$, $J = 10.4$ Hz, NCH═C); 7.26 (s, 0.70H, CHO); 7.14 (br. s, 1H, NH); 7.04 (m, 2H, Ar-H); 7.01 (d, 0.70H, $J = 10.0$ Hz, CH═); 6.98 (m, 1H, Ar-H); 6.10 (d, 0.30H, $J = 10.8$ Hz, CH═); MS (EI, 70 eV): m/z (%) = 127 (60), 183 (100) [M^+]. Anal. calcd. for $C_9H_7F_2NO$: C, 59.02; H, 3.85. Found: C, 58.98; H, 3.82. Single crystals suitable for X-ray structure analysis were obtained by slow evaporation from a concentrated solution in chloroform at 23°C. [Data collected at 294 K using highly oriented graphite crystal monochromated MoK α radiation. The structure was solved by direct methods, and nonhydrogen atoms were refined anisotropically. In the final least-squares refinement cycle on F, R = 8.885%, *w*R2 = 15.26%. The crystal data are a = 14.213(4) Å, b = 8.325(3) Å, c = 7.352(2) Å, $\alpha = 90°$ $\beta = 95.05°$, $\gamma = 90°$, V = 856.5(5) $Å^3$, space group Pc, Z = 4. CCDC number 225592 for compound **11Z**.]

(E)-N-(2,5-Difluorostyryl)formamides (**11*E***)

Mp 106–107°C, yield (0.157 g, 45%). IR ν_{max} IR (neat): 3188, 1749, 1646, 1477 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.50 (br. d, 1H, $J = 11$ Hz, NH); 8.44 (d, 0.25H, $J = 11$ Hz, CHO); 8.22 (s, 0.75H, CHO); 7.60 (dd, 0.75H, $J = 15$, $J = 11$ Hz, NCH═C); 7.20 (dd, 0.25H, $J = 15$, $J = 11$ Hz, NCH═C); 7.08 (m, 3H, Ar-H); 6.33 (d, 0.75H, $J = 15$ Hz, Ar-CH═); 6.15 (d, 0.25 H, $J = 15$ Hz, Ar-CH═); m/z (%) = 127 (57), 183 (100) [M^+]. Anal. calcd. for $C_9H_7F_2NO$: C, 59.02; H, 3.85. Found: C, 58.96; H, 3.94.

(Z)-N-(2,6-Difluorostyryl)formamides (**12*Z***)

Mp 95–96°C, yield (0.192 g, 55%). IR ν_{max} IR (neat): 3245, 3187, 1705, 1653, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.37 (d, 0.35H, $J = 11.2$ Hz, CHO); 8.23 (s, 0.65H, CHO); 7.36 (br. s, 1H, NH); 7.23 (m, 1H, Ar-H); 6.95 (m, 2H, Ar-H); 6.69 (dd, 1H, $J = 11.2$, $J = 9.4$ Hz, NCH═C); 5.64 (d, 0.65H, $J = 9.8$ Hz, Ar-CH═); 5.55 (d, 0.35H, $J = 9.8$ Hz, Ar-CH═); m/z (%) = 127 (60), 183 (100) [M^+]. Anal. calcd. for $C_9H_7F_2NO$: C, 59.02; H, 3.85. Found: C, 59.08; H, 3.78. Single crystals suitable for X-ray structure analysis were obtained by slow evaporation from a concentrated solution in chloroform at 23°C. [Data collected at 294 K using highly oriented graphite crystal monochromated MoK α radiation. The structure was solved by direct methods, and nonhydrogen atoms were refined anisotropically. In the final least-squares refinement cycle on F, R = 4.7%, *w*R2 = 9.95%. The crystal data are a = 8.954(2) Å, b = 8.216(2) Å, c = 11.664(3) Å, $\alpha = 90°$, $\beta = 94.80°$, $\gamma = 90°$, V = 855.1(3) $Å^3$, space group $P2_1/c$. CCDC number 225593 for compound **12Z**.]

(E)-N-(2,6-Difluorostyryl)formamides (**12*E***)

Mp 91–92°C, yield (0.077 g, 22%). IR ν_{max} IR (neat): 3206, 3126, 1714, 1656, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.60 (br. d, 1H, $J = 11$ Hz, NH); 8.40 (d,.33H, $J = 11.2$ Hz, CHO); 8.23 (s, .67H, CHO); 7.82 (dd, .67H, $J = 15$, $J = 11.2$ Hz, NCH═C); 7.40 (dd, .33H, $J = 15$, $J = 11.2$ Hz, NCH═C); 7.06 (m, 1H, Ar-H); 6.91 (m, 2H, Ar-H); 6.21 (d, .67H, $J = 15$ Hz, Ar-CH═); 6.06 (d, .33H, $J = 15$ Hz, Ar-CH═); m/z (%) = 127 (55), 183 (100) [M^+]. Anal. calcd. for $C_9H_7F_2NO$: C, 59.02; H, 3.85. Found: C, 59.09; H, 3.78.

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