ELSEVIER

Journal of Fluorine Chemistry 90 (1998) 5–8

JOURNAL OF FLUORINE CHEMISTRY

Synthesis of some fluorinated *N*-alkenyl amides

G. Aguirre, R. Somanathan *, L.H. Hellberg

Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Apdo Postal 1166, 22000 Tijuana, B.C., México

Received 4 June 1997; accepted 27 January 1998

Abstract

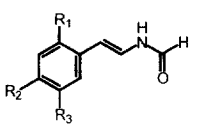
Commercially available difluorinated cinnamic acids were converted to the *N*-alkenyl amides via the Curtius rearrangement.

Keywords: *N*-alkenyl amides (enamides); Curtius rearrangement; Difluorocinnamoyl azides; Difluorostyryl isocyanates

1. Introduction

N-Alkenyl amides are a rapidly emerging class of naturally occurring substances, widely distributed in higher plants, marine and microorganisms, and they exhibit very interesting biological properties [1–7]. Two simple *N*-alkenyl amides that have received much attention in recent years are Tuberine (**1a**) and Erbastatin (**1b**).

Tuberine (**1a**) was isolated from *Streptomyces amakusaensis* [3]. and is known to exhibit antibiotic properties. Erbastatin (**1b**), was isolated from the broth of *Streptomyces* sp (MH435-hF3) and is known to inhibit Tyrosine-specific protein kinase (TPK) [2]. Here we describe the synthesis of a number of difluorinated *N*-alkenyl amides as possible mimics of (**1a**) and (**1b**) with the goal of attaining maximum biological activity.



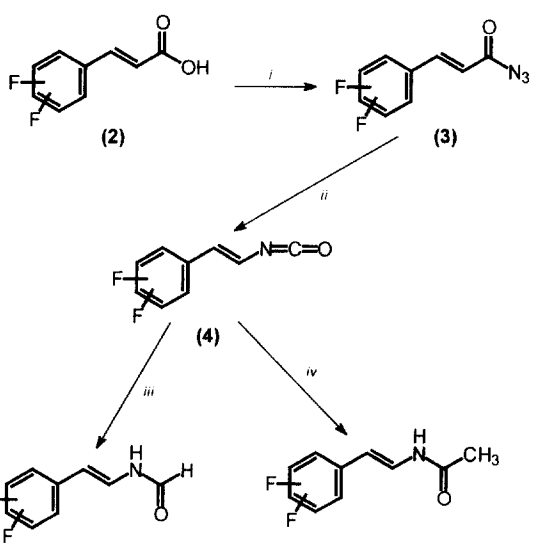
(1)

(a) $R_1 = R_3 = H$, $R_2 = OCH_3$
(b) $R_1 = R_2 = OH$, $R_2 = H$

Earlier, we synthesised several *N*-alkenyl amides via syn-elimination of sulfoxides [8,9], and we concluded that this method was superior to an earlier method for generating such compounds via the Curtius rearrangement. However, for the desired difluorinated *N*-alkenyl amides, the ready availability of many difluorocinnamic acids made the Curtius rearrangement a potentially more attractive route [10].

Commercially available difluorocinnamic acids (**2**) were converted to their azides (**3**), then subjected to the Curtius rearrangement to give the isocyanates (**4**) in reasonably good yields [10]. Reduction of the isocyanates with lithium tri-*tert*-butoxy-aluminohydride gave the *N*-styryl-formamides (**5**) in 40–70% yields, after purification by radial thin layer chromatography. Finally, addition of methyl magnesium chloride to the isocyanates (**4**) led to the corresponding *N*-styryl-acetamides (**6**) in 50–70% yields (Scheme 1).

Hence, this method is complementary to the route employed by Massey and Harrison [10] in their synthesis of



Scheme 1. (a)2,6-difluoro; (b)3,4-difluoro; (c)3,5-difluoro; (d)2,4-difluoro; (e)2,5-difluoro. (i) $ClCO_2C_2H_5/NaN_3$; (ii) Δ, $C_6H_5CH_3$; (iii) $LiAl(O\text{-}t\text{-}Bu)_3H$; (iv) CH_3MgCl/THF.

* Corresponding author. Department of Chemistry, College of Sciences, San Diego State University, 5500 Campanile Drive, San Diego CA 92182-1030, USA. Fax: +1-619-5944634.

0022-1139/98/$19.00
PII S0022-1139(98)00143-2

Tuberine. These fluorinated N-alkenyl amides were all characterized by ^{1}H, ^{13}C, ^{19}F-NMR and MS, and are currently being examined for biological activity.

2. Experimental

Melting points were obtained on an Electrothermal 88629 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer (^{13}C, 50 MHz; ^{19}F, 188 MHz), using $CDCl_3$ as solvent. Chemical shifts for ^{1}H NMR spectra are relative to internal Me_4Si. The ^{13}C NMR spectra were run with ^{1}H decoupling and the chemical shifts are reported in ppm vs. Me_4Si. ^{19}F NMR chemical shifts were referenced relative to external α,α,α-trifluorotoluene standard (δ 63.73), which in turn was referenced to $CFCl_3$ [11]. High resolution MS were determined at 70 eV with a VG 7070 spectrometer, UCR Mass Spectrometry Facility, Riverside, CA.

2.1. General preparation of difluorinated cinnamoyl azides

To a stirred mixture of *trans*-2,6-difluorocinnamic acid (0.404 g, 2.19 mmol) (**2a**) and triethylamine (0.250 g, 2.47 mmol) in acetone (7 ml) was added ethyl chloroformate (0.263 g, 2.42 mmol) in acetone (0.5 ml) at −5 to 0°C during 1 min. After the mixture was stirred for 15 min, sodium azide (0.284 g, 4.37 mmol) in water (3 ml) was added at −5 to 0°C during 1 min, the 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 crystals (**3a**).

2,6-Difluorocinnamoyl azide (**3a**): Yield 94%. IR (KBr) (cm^{-1}): 3058, 2158, 1690, 1625. ^{1}H NMR ($CDCl_3$) δ: 7.70 (d, 1H, J=16 Hz, CH=); 7.22 (m, 1H, Ar–H); 6.82 (t, 2H, J=8.7 Hz, Ar–H); 6.60 (d, 1H, J=16 Hz, CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 171.54; 161.45 (d, J_{CF}=254 Hz); 161.33 (d, J_{CF}=254 Hz); 132.00; 131.63 (t, J_{CF}=11 Hz); 124.33 (t, J_{CF}=9.1 Hz); 111.57 (d, J_{CF}=23 Hz); 111.55 (d, J_{CF}=23 Hz); 111.55 (t, J_{CF}=23 Hz) ppm. MS (*m/e*): 209 (M^+).

3,4-Difluorocinnamoyl azide (**3b**): Yield 87%. IR (KBr) (cm^{-1}): 3063, 2134, 1678, 1609. ^{1}H NMR ($CDCl_3$) δ: 7.60 (d, 1H, J=16 Hz, CH=); 7.22 (m, 3H, Ar–H); 6.31 (d, 1H, J=16 Hz, CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 172.00; 151.50 (dd, J_{CF}=250, J_{CF}=7 Hz); 150.50 (dd, J_{CF}=250, J_{CF}=7 Hz); 143.74; 131.00; 125.21 (dd, J_{CF}=7, J_{CF}=4 Hz); 119.81; 117.70 (d, J_{CF}=17 Hz); 116.44 (d, J_{CF}=17 Hz) ppm. MS (*m/e*): 209 (M^+).

3,5-Difluorocinnamoyl azide (**3c**): Yield 94%. IR (KBr) (cm^{-1}): 3092, 2142, 1689, 1629. ^{1}H NMR ($CDCl_3$) δ: 7.70 (d, 1H, J=16 Hz, CH=); 7.13 (m, 2H, Ar–H); 6.94 (m, 1H, Ar–H); 6.49 (d, 1H, J=16 Hz, CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 172.00; 162.97 (d, J_{CF}=250 Hz); 162.72 (d, J_{CF}=250 Hz); 143.30; 136.11 (t, J_{CF}=11 Hz); 121.34; 110.76 (d, J_{CF}=25 Hz); 110.50 (d, J_{CF}=25 Hz); 105.24 (t, J_{CF}=25 Hz) ppm. MS (*m/e*): 209 (M^+).

2,4-Difluorocinnamoyl azide (**3d**): Yield 93%. IR (KBr) (cm^{-1}): 3070, 2147, 1677, 1618. ^{1}H NMR ($CDCl_3$) δ: 7.73 (d, 1H, J=16 Hz, CH=); 7.47 (m, 1H, Ar–H); 6.84 (m, 2H, Ar–H); 6.40 (d, 1H, J=16 Hz, CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 172.00; 164.19 (dd, J_{CF}=250, J_{CF}=12 Hz); 161.50 (dd, J_{CF}=250, J_{CF}=7 Hz) 137.76; 130.38 (dd, J_{CF}=10 J_{CF}=4 Hz); 120.81 (d, J_{CF}=7 Hz); 118 (d, J_{CF}=25 Hz); 112.07 (dd, J_{CF}=22, J_{CF}=4 Hz); 104.54 (t, J_{CF}=25 Hz) ppm. MS (*m/e*): 209 (M^+).

2,5-Difluorocinnamoyl azide (**3e**): Yield 92%. IR (KBr) (cm^{-1}): 3066, 2149, 1679, 1626. ^{1}H NMR ($CDCl_3$) δ: 7.75 (d, 1H, J=16 Hz, CH=); 7.12 (m, 3H, Ar–H); 6.44 (d, 1H, J=16 Hz, CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 172.00; 158.25 (d, J_{CF}=250, Hz); 157.18 (d, J_{CF}=250 Hz); 137.37; 122.80 (dd, J_{CF}=25 J_{CF}=9 Hz); 122.23 (d, J_{CF}=6 Hz); 118.72 (dd, J_{CF}=25, J_{CF}=8 Hz); 117.21 (dd, J_{CF}=25, J_{CF}=8 Hz); 114.54 (dd, J_{CF}=25, J_{CF}=3 Hz) ppm. MS (*m/e*): 209 (M^+).

2.2. General preparation of difluorinated isocyanates

The reaction was carried out under a N_2 atmosphere. The thermally-induced rearrangement of 2-6-difluorocinnamoyl azide (0.400 g, 1.91 mmol) (**3a**) in toluene (5 ml) generated the isocyanate (**4a**), and it was isolated by concentration in vacuo. The reaction was monitored by appearance of the isocyanate band in the IR at 2259 cm^{-1}, and disappearance of the azide band at 2158 cm^{-1}.

The other azides were similarly transformed to their isocyanates. The yields appeared quantitative; they were used without further purification.

2.3. General preparation of the N-(β-difluorostyryl) formamides

A solution of 2,6-difluorostyryl isocyanate (0.345 g crude, 1.91 mmol) (**4a**) in tetrahydrofuran (7 ml) was added dropwise to a stirred and cooled (ice bath) solution of lithium tri-*tert*-butoxyaluminohydride (0.585 g, 2.30 mmol) in tetrahydrofuran (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 filtrate was dried over anhydrous sodium sulphate. Removal of the solvent gave the crude product which was purified by radial thin layer chromatography using mixtures of petroleum ether and methylene chloride as eluant. Yields cited below are overall from the purified azides.

For the *N*-(β-difluorostyryl) formamides, the ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra exhibit a doubling of signals due to restricted rotation about the amide (N–CO) bond, leading to two rotational conformations (approximately 2:1 to 3:1 mixtures). The more abundant *trans* (*Z*) rotamer

(*trans*: non-hydrogen substituents [12]; *Z*: Cahn–Ingold–Prelog priority [13]; as applied to the amide's zwitterion resonance structure) is stabilized by approximately 0.5–1.0 kcal/mol with respect to the (*E*) rotamer.[1] In contrast, the *N*-(β-difluorostyryl) acetamides exist exclusively as the (*Z*) rotamer.

N-(β-2,6-Difluorostyryl) formamide (**5a**): mp 91°C, Yield 70%. IR (KBr) (cm^{-1}): 3209, 1716, 1655 1582. ^1H NMR ($CDCl_3$) δ: 9.60 (br. d, 1H, J = 11 Hz, NH); 8.42 (d, 0.33H, J = 11 Hz, CHO); 8.19 (s, 0.67H, CHO); 7.80 (dd, 0.67H, J = 15, J = 11 Hz, NCH=C); 7.40 (dd, 0.33H, J = 15, J = 11 Hz, NCH=C); 7.08 (m, 1H, Ar–H); 6.85 (m, 2H, Ar–H); 6.28 (d, 0.67H, J = 15 Hz, Ar–CH=); 6.17 (d, 0.33H, J = 15 Hz, Ar–CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 162.95; 158.55; 160.45 (d, J_{CF} = 250 Hz); 259.50 (d, J_{CF} = 250 Hz); 129.50 (t, J_{CF} = 9.3 Hz); 126.41 (t, J_{CF} = 10.5 Hz); 110.97 (d, J_{CF} = 25 Hz); 110.91 (d, J_{CF} = 25 Hz); 110.91 (t, J_{CF} = 25 Hz); 110.31; 98.91 ppm. ^{19}F NMR ($CDCl_3$) δ: −113.457 (t, 0.67 F, J = 6 Hz); −113.968 (t, 0.33F, J = 6 Hz) ppm. HRMS (EI) *m/e*: Calcd. for $C_9H_7F_2NO$ 183.049570; Obsd. 183.048800.

N-(β-3,4-Difluorostyryl) formamide (**5b**): mp 103°C, yield 42%. IR (KBr) (cm^{-1}): 3189, 1705, 1659. ^1H NMR ($CDCl_3$) δ: 9.00 (br. s, 1H, NH); 8.27 (d, 0.33H, J = 11 Hz, CHO); 8.04 (s, 0.67H, CHO); 7.28 (dd, 1H, J = 15, J = 11 Hz, NCH=C); 6.90 (m, 3H, Ar–H); 6.02 (d, 0.77H, J = 15 Hz, Ar–CH=); 5.93 (d, 0.33H, J = 15 Hz, Ar–CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 162.97; 158.69; 149.50 (dd, J_{CF} = 250, J_{CF} = 7 Hz); 148.50 (dd, J_{CF} = 250, J_{CF} = 7 Hz); 130.00; 124.89; 122.06; 121.75 (m); 117.00 (d, J_{CF} = 17 Hz); 114.10 (d, J_{CF} = 17 Hz); 113.75 (d, J_{CF} = 17 Hz); 112.36; 111.06 ppm. ^{19}F NMR ($CDCl_3$) δ: −137.99 (m, 1F); −140.06 (m, 1F) ppm. HRMS (EI) *m/e*: Calcd. for $C_9H_7F_2NO$ 183.049570; Obsd. 183.050300.

N-(δ-3,5-Difluorostyryl) formamide (**5c**): mp 121°C, yield 55%. IR (KBr) (cm^{-1}): 3189, 1705, 1660. ^1H NMR ($CDCl_3$) δ: 8.43 (d, 0.30H, J = 11 Hz, CHO); 8.24 (s, 0.70H, CHO); 7.54 (dd, 0.70H, J = 15, J = 11 Hz, NCH=C); 7.58 (br. s, 1H, NH); 7.04 (dd, 0.30H, J = 14 Hz, J = 11 Hz, NCH=C); 6.81 (m, 2H, Ar–H); 6.64 (m, 1H, Ar–H); 6.13 (6, 0.70H, J = 14 Hz, Ar–CH=); 6.04 (d, 0.30H, J = 14 Hz, Ar–CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 162.67; 157.98; 162.07 (d, J_{CF} = 250 Hz); 161.80 (d, J_{CF} = 250 Hz); 139.17 (t, J_{CF} = 10 Hz); 126.99; 122.73; 110.32; 108.29; 106.79 (d, J_{CF} = 25 Hz); 106.50 (d, J_{CF} = 25 Hz); 100.15 (t, J_{CF} = 25 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −111.14 (t, 0.30F, J = 9 Hz); −111.29 (t, 0.70F, J = 9 Hz) ppm. HRMS (EI) *m/e*: Calcd. for $C_9H_7F_2NO$ 183.049570; Obsd. 183.049200.

N-(β-2,4-Difluorostyryl) formamide (**5d**): mp 101°C, Yield 70%. IR (KBr) (cm^{-1}): 3210, 1720, 1655 1582, ^1H NMR ($CDCl_3$) δ: 8.44 (d, 0.35H, J = 11 Hz, CHO); 8.22 (s, 0.65H, CHO); 7.90 (br. s, 1H, NH); 7.53 (dd, 0.65H, J = 15, J = 11 Hz, NCH=C); 7.35 (m, 1.35H, Ar–H); 6.80 (m, 2H, Ar–H); 6.27 (d, 0.65H, Ar–CH=); 6.11 (d, 0.35H, J = 15 Hz, Ar–CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 163.13; 161.60 (dd, J_{CF} = 250, J_{CF} = 15 Hz); 159.75 (dd, J_{CF} = 250, J_{CF} = 12 Hz): 163.23; 128.06 (dd, J_{CF} = 10, J_{CF} = 5 Hz); 127.35 (dd, J_{CF} = 10, J_{CF} = 5 Hz); 125.35 (d, J_{CF} = 5 Hz); 122.07 (d, J_{CF} = 5 Hz); 119.62 (dd, J_{CF} = 15, J_{CF} = 9 Hz); 119.80 (dd, J_{CF} = 15, J_{CF} = 9 Hz); 111.62 (dd, J_{CF} = 21, J_{CF} = 4 Hz); 111.59 (dd, J_{CF} = 21, J_{CF} = 4 Hz); 106.42 (d, J_{CF} = 4 Hz); 106.17 (d, J_{CF} = 4 Hz); 104.06 (t, J_{CF} = 25 Hz); 104.28 (t, J_{CF} = 25 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 112.099 (m, 0.65F); −112.382 (m, 0.35F); −112.982 (m, 0.35F); −114.175 (m, 0.65F) ppm. HRMS (EI) *m/e*: Calcd. for $C_9H_7F_2NO$ 183:049570; Obsd. 183.048800.

N-(β-2,5-difluorostyryl) formamide (**5e**): mp 106°C, Yield 42%. IR (KBr) (cm^{-1}): 3188, 1749, 1646, 1477, ^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, NCH=C); 7.08 (m, 3H, Ar–H); 6.33 (d, 0.75H, J = 15 Hz, Ar–CH=); 6.15 (d, 0.25H, J = 15 Hz, Ar–CH=) ppm. ^{13}C NMR ($CDCl_3$) δ: 163.00; 158.67; 158.50 (d, J_{CF} = 250 Hz); 154.50 (d, J_{CF} = 250 Hz); 127.50 (d, J_{CF} = 5 Hz); 123.86 (d, J_{CF} = 5 Hz); 116.24 (dd, J_{CF} = 25, J_{CF} = 9 Hz); 113.63 (dd, J_{CF} = 25, J_{CF} = 9 Hz); 112.02 (dd, J_{CF} = 25, J_{CF} = 4.3 Hz); 105.48; 105.00 ppm. ^{19}F NMR ($CDCl_3$) δ: −120.21 (m, 1F); −124.18 (m, 0.25F); −125.22 (m, 0.75F) ppm. HRMS (EI) *m/e*: Calcd. for $C_9H_7F_2NO$ 183:049570; Obsd. 183.0506.

2.4. General preparation of N-(β-difluorostyryl) acetamides

A solution of 2,6-difluorostyryl isocyanate (0.345 g crude, 1.91 mmol) (**4a**) in tetrahydrofuran (7 ml) was added dropwise to a stirred, cooled (−25°C) solution of 3.0 M methylmagnesium chloride (0.7 ml, 0.157 g, 2.10 mmol) in tetrahydrofuran (5 ml) under an atmosphere of N_2. After stirring for a further 30 min at −25°C, then another 30 min at RT, the resultant product was hydrolyzed with aqueous ammonium chloride solution (10%), and then extracted with methylene chloride. The extract was dried over anhydrous sodium sulphate. Removal of the solvent gave the crude product, *N*-(β-2,6-difluorostyryl) acetamide (**6a**), which was purified by radial thin layer chromatography using mixtures of petroleum ether and methylene chloride as eluant. Yields cited below are overall from the purified azides.

N-(β-2,6-difluorostyryl) acetamide (**6a**): mp 130°C, Yield 65%. IR (KBr) (cm^{-1}): 3261, 1647, 1582, 1541. ^1H NMR ($CDCl_3$) δ: 9.25 (br. d, 1H, J = 11 Hz, NH); 7.70 (dd, 1H, J = 16, J = 11 Hz, NCH=C); 6.90 (m, 1H, Ar–H); 6.70 (m, 2H, Ar–H); 6.10 (d, 1H, J = 16 Hz, Ar–CH=); 2.01 (s, 3H, COMe) ppm. ^{13}C NMR ($CDCl_3$) δ: 167.92; 160.00 (d, J_{CF} = 250 Hz); 159.50 (d, J_{CF} = 250 Hz); 128.61 (t, J_{CF} = 9.3 Hz); 125.94 (t, J_{CF} = 10.5 Hz); 110.97 (d, J_{CF} = 25 Hz); 110.97 (d, J_{CF} = 25 Hz); 110.91 (t, J_{CF} = 25 Hz); 98.44; 22.87 ppm. ^{19}F NMR ($CDCl_3$) δ: −113.72 (t, 1F, J = 6.2 Hz) ppm. HRMS (EI) *m/e*: Calcd. for $C_{10}H_9F_2NO$ 197.065221; Obsd. 197.065500.

[1] The rotamers of the formamides will be discussed in a future paper.

N-(β-3,4-Difluorostyryl) acetamide (**6b**): mp 107°C, yield 60%. IR (KBr) (cm^{-1}): 3303, 1644, 1508. ^1H NMR ($CDCl_3$) δ: 8.87 (br. d, 1H, $J=11$ Hz, NH); 7.42 (dd, 1H, $J=15$, $J=11$ Hz, NCH=C); 6.97 (m, 3H, Ar–H); 6.06 (d, 1H, $J=15$ Hz, Ar–CH=); 1.98 (s, 3H, COMe) ppm. ^{13}C NMR ($CDCl_3$) δ: 168.00; 149.50 (dd, $J_{CF}=250$, $J_{CF}=7$ Hz); 148.50 (dd, $J_{CF}=250$, $J_{CF}=7$ Hz); 134.00; 123.95; 121.04 (dd, $J_{CF}=6$, $J_{CF}=4$ Hz); 116.91 (d, $J_{CF}=17$ Hz); 113.33 (d, $J_{CF}=17$ Hz) 109.88; 22.81 ppm. ^{19}F NMR ($CDCl_3$) δ: −138.30 (m, 1F); −140.80 (m, 1F) ppm. HRMS (El) *m/e*: Calcd. for $C_{10}H_9F_2NO$ 197.065221; Obsd. 197.064700.

N-(β-3,5-Difluorostyryl) acetamide (**6c**): mp 146°C, yield 51%. IR (KBr) (cm^{-1}): 3302, 1640, 1508. ^1H NMR ($CDCl_3$) δ: 7.50 (dd, 1H, $J=14$, $J=11$ Hz, NCH=C); 7.47 (br. s, 1H, NH); 6.80 (dd, 2H, $J=8$, $J=2$ Hz, Ar–H); 6.61 (tt, 1H, $J=8$, $J=2$ Hz, Ar–H); 5.97 (d, 1H, $J=14$ Hz, Ar–CH=); 2.13 (s, 3H, COMe) ppm. ^{13}C NMR ($CDCl_3$) δ: 167.69; 160.93 (d, $J_{CF}=250$ Hz); 160.67 (d, $J_{CF}=250$, Hz); 139.59 (t, $J_{CF}=10$ Hz); 124.80; 110.48; 108.09 (d, $J_{CF}=25$ Hz); 101.79 (t, $J_{CF}=25$ Hz) 23.29 ppm. ^{19}F NMR ($CDCl_3$) δ: −111.91 (t, 1F, $J=7.7$ Hz) ppm. HRMS (El) *m/e*: Calcd. for $C_{10}H_9F_2NO$ 197.065221; Obsd. 197.064300.

N-(β-2,4-Difluorostyryl) acetamide (**6d**): mp 135°C, Yield 73%. IR (KBr) (cm^{-1}): 3276, 1651, 1502 ^1H NMR ($CDCl_3$) δ: 7.84 (br. d, 1H, $J=10$ Hz, NH); 7.50 (dd, 1H, $J=15$, $J=10$ Hz, NCH=C); 7.33 (m, 1H, Ar–H); 6.80 (m, 2H, Ar–H); 6.16 (d, 1H, $J=15$ Hz, Ar–CH=); 2.13 (s, 3H, MeO) ppm. ^{13}C NMR ($CDCl_3$) δ: 167.83; 161.53 (dd, $J_{CF}=250$, $J_{CF}=12$ Hz); 159.42 (dd, $J_{CF}=250$, $J_{CF}=12$ Hz); 126.73 (dd, $J_{CF}=10$, $J_{CF}=5$ Hz); 124.21 (d, $J_{CF}=5$ Hz); 120.10 (dd, $J_{CF}=15$, $J_{CF}=5$ Hz); 111.53 (dd, $J_{CF}=21$, $J_{CF}=4$ Hz); 104.21 (d, $J_{CF}=4$ Hz); 103.96 (t, $J_{CF}=25$ Hz); 23.21 ppm. ^{19}F NMR ($CDCl_3$) δ: −112.84 (m, 1F) −114.73 (m, 1F) ppm. HRMS (El) *m/e*: Calcd. for $C_{10}H_9F_2NO$ 197.065221; Obsd. 197.0645.

N-(β-2,5-difluorostyryl) acetamide (**6e**): mp 142°C Yield 52%. IR (KBr) (cm^{-1}): 3261, 1647, 1582, 1541. ^1H NMR ($CDCl_3$) δ: 7.84 (br. d, 1H, $J=10$ Hz, NH); 7.57 (dd, 1H, $J=15$, $J=10$ Hz, NCH=C); 6.95 (m, 3H, Ar–H); 6.17 (d, 1H, $J=15$ Hz, Ar–CH=); 2.14 (s, 3H, COMe) ppm. ^{13}C NMR ($CDCl_3$) δ: 167.87; 159.50 (d, $J_{CF}=250$ Hz); 155.55 (d, $J_{CF}=250$ Hz); 125.51 (d, $J_{CF}=5$ Hz); 116.53 (dd, $J_{CF}=25$, $J_{CF}=9$ Hz); 113.92 (dd, $J_{CF}=25$, $J_{CF}=8$ Hz); 112.20 (dd, $J_{CF}=25$, $J_{CF}=5$ Hz); 104.18; 23.22 ppm. ^{19}F NMR ($CDCl_3$) δ: −119.57 (m, 1F); −124.92 (m, 1F) ppm. HRMS (El) *m/e*: Calcd. for $C_{10}H_9F_2NO$ 197.065221; Obsd. 197.065300.

Acknowledgements

We gratefully acknowledge support of this project No. 640.96-P by COSNET.

References

[1] R. Brettle, A.J. Mosedale, J. Chem. Soc., Perkin Trans. 1 (1988) 2185.
[2] H. Umezawa, M. Imoto, T. Sawa, K. Isshiki, N. Matsuda, T. Uchida, H. Linuma, M. Hamada, T. Takeuchi, J. Antibiot. 39 (1986) 170.
[3] K. Okuma, K. Anzai, S. Suzuki, J. Antibiot. 15 (1962) 115.
[4] R.C. Bruening, E.M. Oltz, J. Furukawa, K. Nakanishi, J. Am. Chem. Soc. 107 (1985) 5298.
[5] M.P. Kirkup, R.E. Moore, Tetrahedron Lett. 24 (1983) 2087.
[6] R.J. Stonard, R.J. Andersen, J. Org. Chem. 45 (1987) 3687.
[7] R.J. Stonard, R.J. Andersen, Can. J. Chem. 58 (1980) 2121.
[8] J. Obrecht, L. Hellberg, R. Somanathan, J. Chem. Soc. Chem. Commun. (1987) 1219.
[9] R. Somnathan, I.A. Rivero, G. Aguirre, M. Ramirez, L.H. Hellberg, F. Bakir, Synth. Commun. 26 (1996) 1023.
[10] I.J. Massey, I.T. Harrison, Chem. Ind. (London) (1977) 920.
[11] A.J. Gordon, R.A. Ford, The Chemist's Companion, Wiley, New York, 1972, pp. 288–293.
[12] V.P. Manea, K.J. Wilson, J.R. Cable, J. Am. Chem. Soc. 119 (1997) 2033.
[13] E.L. Eliel, S.H. Wilen, Stereochemistry of Organic Compounds, Wiley-Interscience, New York, 1994, pp. 541–543, pp. 615–627.