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Syntheses of 2-(bromodifluoromethyl)benzoxazole and 5-(bromodifluoromethyl)-1,2,4-oxadiazoles

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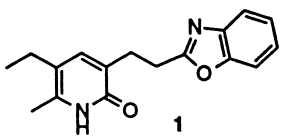
Abstract

Facile syntheses of CF_2Br-substituted heterocycles are reported. Preparation of 2-(bromodifluoromethyl)benzoxazole (**2**) was achieved in two steps by reaction of 2-aminophenol (**3**) with CF_2BrCO_2Et to give amide (**4**), followed by cyclization of **4** with PPA to give **2**. The 5-(bromodifluoromethyl)-1,2,4-oxadiazoles (**6a–c**) were prepared by one step reaction of amidoximes (**5a–c**) with CF_2BrCO_2Et. These CF_2Br-substituted heterocycles are intermediates in an ongoing investigation of the synthesis of inhibitors of HIV reverse transcriptase having a CF_2 substitution.

1. Introduction

The AIDS epidemic has become a global problem with millions of people currently infected by HIV. Recent efforts to find a cure have centered on the development of non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as **1** [1]. Although they are very active against HIV-1 in clinical trials, NNRTIs are not clinically useful for treating AIDS due to the rapid emergence of resistant HIV strains.



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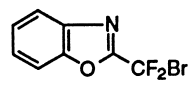

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Dramatic enhancements of activity have been reported in many cases for partially fluorinated analogs of biologically active compounds [2]. As part of an ongoing project investigating the synthesis of fluorine-containing heterocycles, a decision was taken to develop a synthetic method by which various analogs of **1** could be prepared where one CH_2 is replaced with CF_2. It is hoped that activity against resistant strains of HIV might be induced upon fluorine substitution. A retrosynthetic analysis revealed that 2-(bromodifluoromethyl)benzoxazole (**2**) would be a useful synthetic intermediate. Since there is very little precedent in the literature for the synthesis of CF_2Br-substituted heterocycles, to find a facile synthesis of **2** as well as other CF_2Br-heterocycles became the immediate goal.

2. Results and discussion

Initial attempts at brominating the CF_2H group of 5-(difluoromethyl)-2-nitrofuran by photolysis with NBS (*N*-bromosuccinimide) showed that despite working fine for benzene CF_2H groups [3], this synthetic route is not viable for preparing CF_2Br-heterocycles. The reaction gave a multitude of products having an unreacted CF_2H group and no product with the desired CF_2Br. For this reason, attention was turned to utilizing commercially available CF_2BrCO_2Et as the source of the CF_2Br group. It is now reported that **2** can be prepared in two easy steps from 2-aminophenol (**3**).

Heating a solution of **3** in ethyl acetate with equimolar amounts of CF_2BrCO_2Et and NEt_3 gave a good yield of amide **4**. Three aspects of this reaction are worth mentioning. Firstly, the fluorine atoms of CF_2BrCO_2Et facilitate immensely the reactivity of the ester by their strong electron withdrawing effect [4], and it is worth noting that the EtOAc solvent does not react at all with **3**. Secondly, since no reaction occurs without NEt_3, it must serve as a catalyst for the reaction. Thirdly, the OH group of **3** is necessary for the success of the reaction since 2-aminobiphenyl (where the OH of **3** has been replaced by a phenyl) does not give a clean

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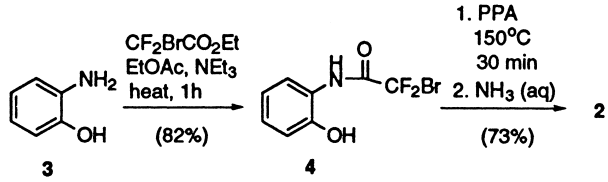
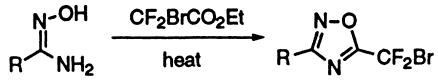
reaction with CF_2BrCO_2Et.



Amide **4** undergoes facile cyclization upon heating with PPA (polyphosphoric acid) to give a good yield of **2**. For this cyclization, only PPA was effective, and other acids did not give any of the desired **2**. An important feature of this procedure is the work-up with ice and aqueous NH_3, which prevents the conversion of **2** back to **4** by acid-catalyzed hydrolysis.

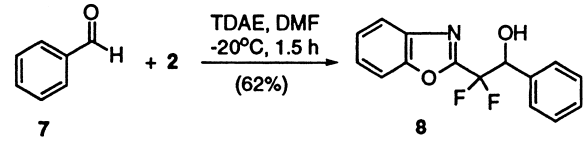
Syntheses of CF_2Br-oxadiazoles (**6a–c**) were achieved in one step by condensation of CF_2BrCO_2Et with amidoximes (**5a–c**). The amidoximes are readily available by reaction of the appropriate nitriles with hydroxylamine [5–7]. Although the isolated yields of **6a–c** are low, the one-step procedures are extremely convenient and can be carried out easily on a large scale. In the case of **6a**, the low yield was due to the formation of PhCN as a side-product as well as a substantial amount of non-volatile, polymeric material. Analysis by ^{19}F NMR of the reaction mixture before work-up, using internal standard bearing fluorine, revealed that all of CF_2BrCO_2Et took part in the reaction and that the yield of **6a** varied from 34% to 40%, thus demonstrating that the low yield was not due to a loss of **6a** during the work-up procedure. Further attempts to increase the yield using a two-fold excess of CF_2BrCO_2Et resulted in no improvement.



5a: R = Ph **6a: R = Ph, 35%**
5b: R = Me **6b: R = Me, 24%**
5c: R = *n*-Pr **6c: R = *n*-Pr, 41%**

The CF_2Br groups of compounds **2** and **6a** display useful reactivity. In recent published results from this laboratory [8], it has been reported that **2** and **6a** react with aldehydes when treated with tetrakis(dimethylamino)ethylene (TDAE) to give β,β-difluoroalcohols such as **8**. Addition to aldehyde proceeds by generation of the anion of **2** or **6a** by a two-electron reduction.

Benzene derivatives with a CF_2Br group have also been reported by Haas and coworkers [3] to react with nucleophiles such as phenolate, thiolate, and azide anions. Since the fluorine atoms of the CF_2Br group prevent attack of nucleophiles by an S_N2 mechanism, only nucleophiles that can react by an $S_{RN}1$ mechanism [9] will displace bromide. Work is currently in progress to determine the scope and synthetic utility of the reactions of **2** (as well as **6a–c**) with selected nucleophiles, and to prepare some novel CF_2-substituted structures as potential NNRTIs for structure-activity studies.



3. Experimental section

3.1. General comments

Melting points were uncorrected. The ^1H NMR spectra were measured at 300 MHz, and chemical shifts reported in ppm downfield of internal $SiMe_4$. The ^{19}F NMR spectra were measured at 282 MHz, and chemical shifts reported in ppm upfield of internal $CFCl_3$. The ^{13}C NMR spectra were measured at 75 MHz with all the protons decoupled, and the chemical shifts reported in ppm downfield of $SiMe_4$. The mass spectra were recorded at 70 eV. The IR spectra were recorded using a Fourier transform spectrometer.

All of the solvents and reagents were used as received from the supplier without purification.

3.2. 2-Bromo-2,2-difluoro-N-(2-hydroxyphenyl)acetamide (4)

A solution of 30.00 g (0.275 mol) of 2-aminophenol (**3**), 60.00 g (0.296 mol) of ethyl bromodifluoroacetate, and 30.00 g (0.296 mol) of triethylamine in 300 ml of ethyl acetate was heated at reflux for 1 h. After cooling to room temperature, 300 ml of ethyl acetate was added and the solution was washed once with 1200 ml of dilute HCl (one part concentrated HCl to nine parts water). The aqueous layer was extracted three times with 300 ml portions of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure to give 74.77 g of a crude tan solid which was recrystallized from 635 ml of $CHCl_3$ (ice bath cooling for 1.5 h) to give 60.0 g (82%) of straw-colored crystals (mp 138.5–140.2°C), which was **4**: ^1H NMR (DMSO-d_6): δ 10.20 (br s, 1H), 9.92 (br s, 1H), 7.32 (dd, 1H, $J = 1.5$ and 7.8 Hz), 7.13 (dt, 1H, $J_d = 1.7$ and $J_t = 7.8$ Hz), 6.93 (dd, $J = 1.2$ and 8.1 Hz), 6.83 (dt, $J_d = 1.2$ and $J_t = 7.6$ Hz); ^{19}F NMR (DMSO-d_6): ϕ −59.4 (s); ^{13}C NMR (DMSO-d_6): δ 158.0 (t, $J_{CF} = 27.2$ Hz), 151.0 (s), 127.6 (s), 125.7 (s), 122.6 (s), 118.9 (s), 116.0 (s), 111.8 (t, $J_{CF} = 315.2$ Hz); IR (KBr) 1686 (C=O) cm^{-1}; HRMS (70 eV) calcd. for $C_8H_6BrF_2NO_2$, 264.9550; found, 264.9583. Anal. Calcd. for $C_8H_6BrF_2NO_2$: C, 36.12; H, 2.27; N, 5.26. Found: C, 35.93; H, 1.93; N, 5.03.

3.3. 2-(Bromodifluoromethyl)benzoxazole (2)

To a 1000 ml, single-necked, round-bottom flask equipped with a drying tube and an egg-shaped stir bar was added 89 g of polyphosphoric acid and 30.00 g (0.113 mol) of **4**. The flask was submerged in an oil bath

which was heated rapidly to 150°C. After 30 min at 150°C, all of the solid amide was dissolved, and the solution was allowed to cool to room temperature. To the flask was added 1120 ml of crushed ice, followed by 207.5 ml of concentrated ammonia (30% NH_3), and the mixture was triturated using a spatula until all of the polyphosphoric acid was dissolved. The dissolving of polyphosphoric acid can be facilitated by not stirring the mixture thoroughly so that the bottom of the flask becomes slightly warm. The aqueous solution was extracted five times with 200 ml portions of $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure to give an amber liquid which was purified by simple vacuum distillation to give 20.6 g (73%) of a clear, colorless liquid which was pure **2** (bp 62°C at 1.5 mm): ^{1}H NMR ($CDCl_3$): δ 7.87 (m, 1H), 7.66 (m, 1H), 7.50 (m, 2H); ^{19}F NMR ($CDCl_3$): ϕ −51.9 (s); ^{13}C NMR ($CDCl_3$): δ 155.7 (t, $J_{CF} = 32.7$ Hz), 150.6 (s), 139.6 (s), 127.7 (s), 125.9 (s), 121.9 (s), 111.6 (s), 108.9 (t, $J_{CF} = 301.9$ Hz); HRMS (70 eV) calcd. for $C_8H_4BrF_2NO$, 246.9444; found, 246.9455. Anal. Calcd. for $C_8H_4BrF_2NO$: C, 38.74; H, 1.63; N, 5.65. Found: C, 38.66; H, 1.36; N, 5.76.

3.4. Benzamidoxime (**5a**)

A solution of 20.00 g (0.194 mol) of benzonitrile, 14.47 g (0.210 mol) of hydroxylamine hydrochloride and 8.69 g (0.217 mol) of NaOH in 290 ml of 95% ethanol and 72 ml of water was heated a reflux for 25 h. Concentration by rotary evaporation at reduced pressure (water aspirator, heating at 70°C) gave a mixture of a colorless oil and a white solid which was dissolved in 200 ml of $CHCl_3$ and filtered to remove the insoluble NaCl. The $CHCl_3$ filtrate was dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure to give a clear, colorless oil which was subjected to full vacuum (0.3 mm) for 1 h. Cooling and scratching produced very slow crystallization. After standing overnight, 22.20 g of a crude, white solid was obtained, which was recrystallized from 124 ml of $CHCl_3$ and 111 ml of hexanes (scratching done to prevent oil formation; cooling in an ice bath for 40 min) to give 16.80 g (64%) of **5a** as short white needles, mp 63.5–76.0°C ([5–7] mp 76–78°C): ^{1}H NMR ($CDCl_3$): δ 9.0 (br s, 1H), 7.63 (m, 2H), 7.40 (m, 3H), 4.9 (br s, 2H).

3.5. Acetamidoxime (**5b**)

A solution of 30.3 ml (23.82 g, 0.580 mol) of CH_3CN, 26.07 g (0.652 mol) of NaOH, and 43.41 g (0.625 mol) of hydroxylamine hydrochloride in 870 ml of 95% ethanol and 216 ml of water was heated at reflux for 24 h. Concentration by rotary evaporation at reduced pressure (water aspirator, 75°C) gave a white solid which was dissolved in 900 ml of absolute ethanol and filtered to remove the insoluble NaCl. Concentration of the filtrate by rotary evaporation gave 37.85 g of a crude white solid. Recrystallization of the solid from 100 ml of 2-propanol (ice cooling for 1 h) gave 34.06 g (79%) of a white solid, mp 130–134.5°C ([5–7] mp 134–136°C), which was **5b**: ^{1}H NMR (DMSO-d_6): δ 8.7 (br s, 1H), 5.3 (br s, 2H), 1.6 (s, 3H).

3.6. Butyramidoxime (**5c**)

A solution of 50.5 ml (40.1 g, 0.580 mol) of butyronitrile, 26.07 g (0.652 mol) of NaOH, and 43.41 g (0.625 mol) of hydroxylamine hydrochloride in 870 ml of 95% ethanol and 216 ml of water was heated at reflux for 24 h. Concentration by rotary evaporation at reduced pressure (water aspirator, 80°C) gave a mixture of an oil and a white solid. The oil was dissolved in 600 ml of $CHCl_3$ and filtered to remove the insoluble NaCl. The filtrate was concentrated by rotary evaporation to give a clear, colorless oil. Purification by fractional distillation at reduced pressure using a 15 cm Vigreux column gave 38.31 g (64%) of a clear, colorless oil, bp 90°C at 0.3 mm ([5–7] bp 88–90°C at 0.5 mm), which was **5c**: ^{1}H NMR ($CDCl_3$): δ 9.1 (br s, 1H), 4.6 (br s, 2H), 2.12 (t, 2H, $J = 7.7$ Hz), 1.58 (hextet, 2H, $J = 7.6$ Hz), 0.95 (t, 3H, $J = 7.3$ Hz).

3.7. 5-(Bromodifluoromethyl)-3-phenyl-1,2,4-oxadiazole (**6a**)

A solution of 61.8 g (0.454 mol) of benzamidoxime (**5a**), 63 ml (99.7 g, 0.491 mol) of CF_2BrCO_2Et and 70 ml (50.8 g, 0.502 mol) of NEt_3 in 250 ml of toluene was heated at reflux for 3 h. After cooling in an ice bath for 1.5 h, suction filtration gave 34.53 g of an insoluble solid which was discarded. The toluene filtrate was washed once with 500 ml of dilute aqueous HCl (nine parts water to one part concentrated HCl) and the aqueous layer was extracted three times with 250 ml portions of $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure (water aspirator, heating at 65°C) to give a crude, brown liquid. Purification by fractional vacuum distillation using a 36 cm Vigreux column wrapped with glass wool and aluminum foil gave about 10 ml of a fore-run consisting of benzonitrile and NEt_3 (bp 28–30°C at 0.6 mm) followed by distillation of 44.25 g (35%) of **6a** as a clear, colorless liquid (bp 70°C at 1 mm): ^{1}H NMR ($CDCl_3$): δ 8.12 (m, 2H), 7.5–7.58 (m, 3H); ^{19}F NMR ($CDCl_3$): ϕ −52.4 (s); ^{13}C NMR ($CDCl_3$): δ 169.6 (t, $J_{CF} = 33.5$ Hz), 169.0 (s), 132.1 (s), 129.0 (s), 127.6 (s), 125.1 (s), 107.2 (t, $J_{CF} = 303.9$ Hz); HRMS (70 eV) calcd. for $C_9H_5BrF_2N_2O$, 273.9553; found, 273.9532. Anal. Calcd. for $C_9H_5BrF_2N_2O$: C, 39.30; H, 1.83; N, 10.18. Found: C, 39.39; H, 1.93; N, 10.15.

3.8. 5-(Bromodifluoromethyl)-3-methyl-1,2,4-oxadiazole (**6b**)

A mixture of 20.00 g (0.270 mol) of acetamidoxime (**5b**), 60.3 g (0.297 mol) of CF_2BrCO_2Et, and 30.00 g

(0.297 mol) of NEt_3 was heated at reflux for 3 h. After cooling to ambient temperature, 150 ml of water was added and the layers were separated. The aqueous layer was extracted five times with 50 ml portions of ether. The combined organic layers were dried over Na_2SO_4 and then concentrated by fractional distillation at ambient pressure using a 23 cm Vigreux column. The distillate (bp 35–77.5°C) was discarded. A total of 29 g of a crude, amber liquid remained undistilled. The crude product was subjected to vacuum fractional distillation using a 15 cm Vigreux column. After the first fraction (bp 50–75°C at 214 mm, 3.19 g) was collected, the product distilled as an azeotrope with water (bp 89–93°C at 214 mm). The aqueous layer was separated and the cloudy liquid product was dried over activated molecular sieves to give 13.68 g (24%) of a clear, colorless liquid, which was **6b**: ^{1}H NMR ($CDCl_3$): δ 2.51 (s); ^{19}F NMR ($CDCl_3$): ϕ −52.43 (s); ^{13}C NMR ($CDCl_3$): δ 169.3 (t, $J_{CF} = 33.5$ Hz), 168.0 (s), 107.1 (t, $J_{CF} = 303.4$ Hz), 11.3 (s); HRMS (70 eV) calcd. for $C_4H_3BrF_2N_2O$, 211.9397; found, 211.9377. Anal. Calcd. for $C_4H_3BrF_2N_2O$: C, 22.56; H, 1.42; N, 13.15. Found: C, 23.71; H, 1.64; N, 13.10.

Analysis by GC indicated that the product had a purity of 91.5%. A second fractional distillation did not improve the purity significantly. The impurities present in **6b** did not interfere with subsequent $S_{RN}1$ reactions.

3.9. 5-(Bromodifluoromethyl)-3-propyl-1,2,4-oxadiazole (**6c**)

A mixture of 20.00 g (0.196 mol) of butyramidoxime (**5c**), 43.7 g (0.215 mol) of CF_2BrCO_2Et, and 21.7 g (0.214 mol) of NEt_3 was heated at reflux for 3 h. After cooling to ambient temperature, 110 ml of water was added and the layers were separated. The aqueous layer was extracted five times with 35 ml portions of ether. The combined organic layers were dried over Na_2SO_4 and ether was removed by fractional distillation at ambient pressure using a 23 cm Vigreux column (bp 35–82°C). The residue was purified by fractional distillation at reduced pressure using a 15 cm Vigreux column. After a small fore-run, the product distilled as a clear, colorless liquid (bp 68–70°C at 20 mm). A total of 19.39 g (41%) of **6c** was obtained: ^{1}H NMR ($CDCl_3$): δ 2.81 (t, 2H, $J = 7.5$ Hz), 1.83 (hextet, 2H, $J = 7.5$ Hz), 1.01 (t, 3H, $J = 7.4$ Hz); ^{19}F NMR ($CDCl_3$): ϕ −52.3 (s); ^{13}C NMR ($CDCl_3$): δ 171.3 (s), 169.3 (t, $J_{CF} = 33.0$ Hz), 107.2 (t, $J_{CF} = 303.7$ Hz), 27.7 (s), 20.0 (s), 13.4 (s); HRMS (POS CI/methane) calcd. for $C_6H_8BrF_2N_2O$, 240.9788; found, 240.9735.

Analysis by GC indicated that the purity of **6c** was 72%. A second fractional distillation gave 14.93 g of distillate with a GC purity of 79%. The impurities present in **6c** did not interfere with subsequent $S_{RN}1$ reactions.

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