Valuable Synthetic Building Blocks: Useful 2-Substituted 5-Aminopyrimidines from a Stable Precursor

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Received 9 February 2005

Abstract: An efficient large-scale synthesis of 5-aminopyrimidine derivatives is described. The dihexafluorophosphate salt of a vinamidinium cation important in 5-aminopyrimidine synthesis has been prepared as a stable, easily purified intermediate. It has been used to prepare several 2-functionalized aminopyrimidines, valuable as synthetic building blocks.

Key words: heterocycles, pyrimidines, condensation, amidine, vinamidinium

2,5-Disubstituted pyrimidines with have been widely synthesized. However, very few methods are available for the preparation of otherwise unsubstituted 2-functionalized 5-aminopyrimidines **1** or related[2] compounds. Nevertheless, such compounds are valuable synthetic building blocks. Present syntheses are unsuitable for large-scale chemistry, as they use hazardous precursors such as potentially explosive nitromalonaldehyde[3] or vinamidinium salts. Key compounds derived from the latter include **2**, accessed by Arnold et al.[4] via the vinamidinium diperchlorate **3a**[5] (Figure 1).

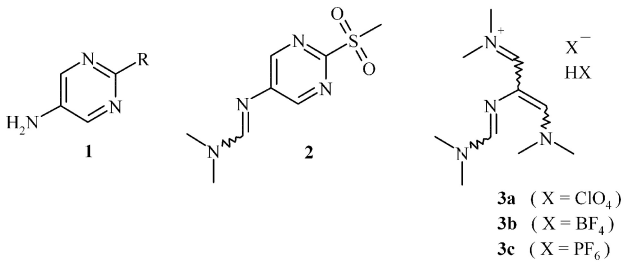
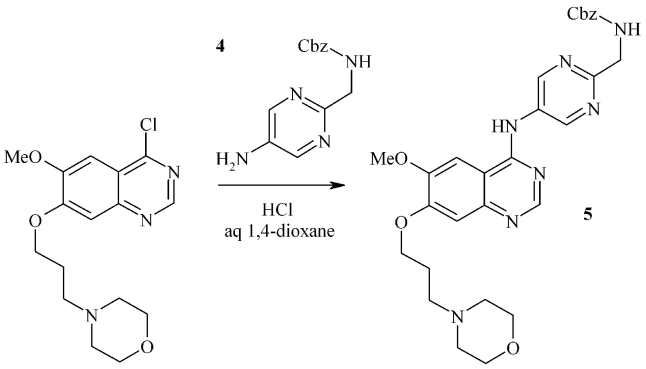


Figure 1

Recently, we required access to a wide variety of 2-functionalized 5-aminopyrimidines. Some of these were used in the preparation of potential anti-cancer compounds or their precursors, by reaction with 4-chloroquinazolines as described in our recent patent application[6] and as exemplified in the conversion of **4** to **5** (Scheme 1).

The likely thermal- and proven shock-sensitivity of vinamidinium perchlorate salts[7] made the salt **3a** unsuitable for use by us as a large scale intermediate. It has also to be isolated by crystallization from a viscous solution in aqueous DMF at –10 to –35 °C. Other salts of related vinamidinium cations previously described and used by Arnold and others include tetrafluoroborates,[7–9] and hexafluorophosphates.[9]



Scheme 1

We were unable to isolate the ditetrafluoroborate salt **3b** usefully owing to its high solubility, and therefore turned our attention to the dihexafluorophosphate.[10]

Hexafluorophosphate salts of amines and similar compounds are more easily isolated and less water-soluble than most other salts, for instance as diazonium salts in the Balz–Schiemann reaction;[11] also, widely used reagents such as HATU are commonly supplied as stable non-hygroscopic hexafluorophosphate salts.

We have prepared the vinamidinium species as its dihexafluorophosphate salt **3c** and have shown it to be an easily isolated, stable salt. The vinamidinium species was prepared, using a modification of Arnold's conditions,[5] from glycine hydrochloride in DMF and phosphorus oxychloride (see safety note[12]). Research into improved preparations of similar salts from other less volatile formamides is ongoing.

In our hands Arnold's original reaction conditions of 125 °C for two hours gave, in addition to the product **3c**, significant amounts of a by-product (Scheme 2) that formed a hexafluorophosphate salt inseparable from **3c**; data from NMR and mass spectroscopy suggested this impurity was the previously undescribed salt **6**. This presumably forms by attack on the product by dimethylamine generated from the decomposition of DMF. At 80 °C the proportion of this by-product became almost negligible.

SYNTHESIS 2005, No. 11, pp 1817–1821
Advanced online publication: 25.04.2005
DOI: 10.1055/s-2005-865338; Art ID: P01805SS
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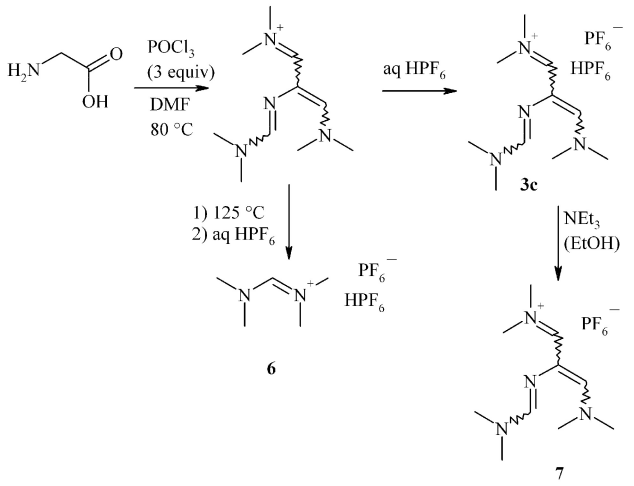
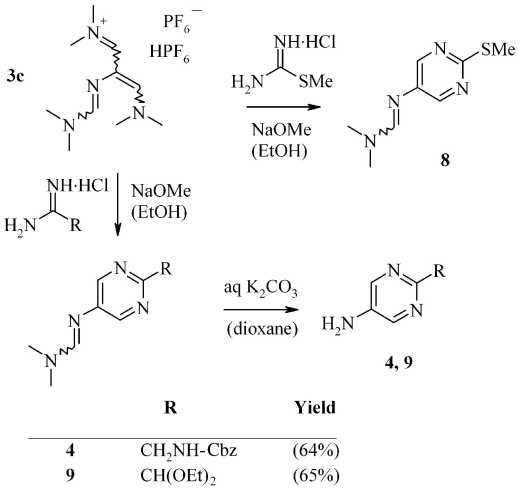


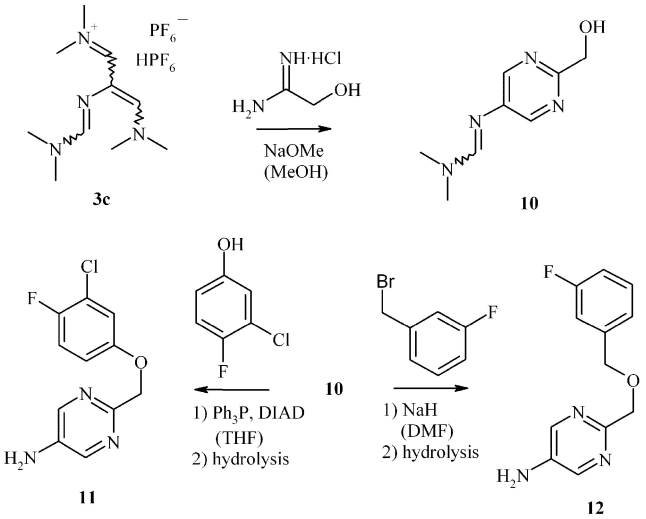
Scheme 2



Scheme 3

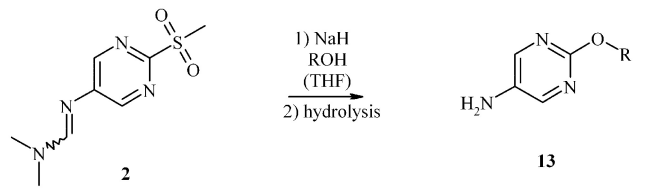
Preparation of the useful salt **3c** was achieved in a straightforward manner by addition to the quenched reaction mixture at 5 °C of two equivalents of hexafluorophosphoric acid, from which the dihexafluorophosphate precipitates immediately in good yield. After washing with ethanol the crude salt (containing a little free acid) can be air-dried and is sufficiently pure for further chemistry. We have stored it for over a year at room temperature without change, and have shown it by DSC calorimetry to be thermally stable for chemistry up to at least 150 °C. The stoichiometric mono-salt **7** was also prepared with triethylamine analogously to the method used by Arnold for the mono-perchlorate.[4]

The facile condensation of **3c** with 2-methyl-2-thiopseudourea sulfate (Scheme 3) in the presence of sodium methoxide, as described for the diperchlorate salt,[4] gave **8** in comparable yield with that reported; **2** was successfully prepared from it on large scale. Similarly, the reaction of other functionalized amidines, via the dimethylaminomethylene protected 5-aminopyrimidines, followed by base hydrolysis with either potassium carbonate or hydroxide in water or aqueous dioxane, gave novel versatile building blocks such as **4** and **9**, with only slight hydrolysis of the Cbz protecting group in **4**. These were not further deprotected before conversion to aminoquinazolines as described. The amidines used were commercially available or (in the case of **4**[13] and **9**[6]) readily prepared from commercially available nitriles by reported Pinner chemistry. Glycolamidine hydrochloride[14] was used to prepare the protected 2-pyrimidinemethanol **10**. This could readily be converted either to the aryl ether **11** or to the benzyl ether **12** (Scheme 4).



Scheme 4

A selection of 5-aminopyrimidine ethers **13** were also made by alkoxide displacement from the known sulfone **2** (Scheme 5; Table 1).



Scheme 5

The vinamidinium dihexafluorophosphate **3c** is a stable, easily isolated salt. It provides an efficient method for large-scale synthesis of 5-aminopyrimidine derivatives, giving access to a range of 2-functionalized aminopyrimidines useful as synthetic building blocks.

NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz, on a Bruker DPX-300 MHz NMR spectrometer. Mass spectra were determined on a Waters 996 spectrometer. Melting points were measured using a Büchi B545 melting point apparatus and are uncorrected. Microanalyses were done by NRM Ltd. DSC Calorimetry was done on a Mettler Toledo DSC821 instrument. All sol-

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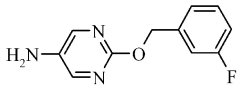
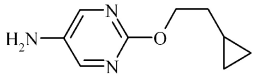
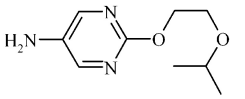
Table 1 Some 2-Alkoxy-5-pyridinamines Prepared from Sulfone **2**

Entry	ROH	Product	Yield (%)	Structure
1	(*m*-FC_6H_4)CH_2OH	**13a**	82	
2	(*c*-Pr)CH_2CH_2OH	**13b**	73	
3	(*i*-Pr)OCH_2CH_2OH	**13c**	86	

vents (anhydrous where appropriate) and reagents were used as received.

N-(3-(Dimethylamino)-2-{[(dimethylamino)methylene]amino}prop-2-en-1-ylidene)-*N*-methylmethanaminium Hydrogen Dihexafluorophosphate (3c)

$POCl_3$ (70 mL, 0.75 mol) was added dropwise to DMF (150 mL) at 10 °C, and the mixture was then stirred for 20 min at 20 °C. This solution was cooled to 5 °C and powdered glycine hydrochloride (27.9 g, 0.25 mol) was added in portions; the temperature of the reaction mixture was maintained at 20 °C. The mixture was then heated to 80 ± 2 °C (internal temperature). The solid rapidly disappeared and there was a slight effervescence. After 4 h, the still hot, dark brown solution was poured directly in a fine stream into H_2O (400 mL), pre-cooled to 5 °C, the temperature of the solution was kept below 20 °C with a dry ice/*i*-PrOH bath. After stirring the solution for 5 min, it was cooled to –5 °C and treated from a plastic vessel with 60% aq HPF_6 (74 mL, 0.5 mol). A thick precipitate formed immediately and was filtered off, washed with EtOH (500 mL), and air-dried to constant weight over 2 h. In subsequent runs the product contained up to 0.2 extra equiv of HPF_6.

Yield: 73.1 g (60%); off-white solid; mp 165–185 °C (dec.).

^{1}H NMR (DMSO-d_6): δ = 10.15 (d, *J* = 12 Hz, 1 H), 8.05 (d, *J* = 12 Hz, 1 H), 7.67 (s, 2 H), 3.27 (m, 9 H), 3.15 (m, 9 H).

^{13}C NMR (DMSO-d_6): δ = 161.11, 158.53, 100.85, 49.17, 43.96, ca. 40 (under DMSO), 36.97.

MS: *m*/*z* = 197 (M^+).

Anal. Calcd for $C_{10}H_{22}N_4PF_6 \cdot 1.2HPF_6$: C, 23.2; H, 4.29; N, 10.82. Found: C, 23.46; H, 4.26; N, 10.60.

Benzyl [(5-Aminopyrimidin-2-yl)methyl]carbamate (4)

A slurry of **3c** (23.0 g, 44 mmol) and benzyl (2-amino-2-iminoethyl)carbamate hydrochloride[13] (11.88 g, 49 mmol) in MeOH (70 mL) was stirred under nitrogen while NaOMe in MeOH (31.7 mL, 146 mmol, 25% w/w) was added dropwise at r.t. The mixture was heated slowly to 60 °C over 40 min and was then maintained at that temperature for 10 min. The mixture was cooled, diluted with CH_2Cl_2 (100 mL), washed with H_2O (150 mL), and the aqueous phase washed with CH_2Cl_2 (2 × 50 mL). The combined organic solutions were dried and evaporated to an oil. This was dissolved in CH_2Cl_2–MeOH (100:10), filtered through silica gel (40 g) and evaporated once more to an oil, which contained a little benzyl alcohol. The oil was taken up in dioxane (100 mL) and 5% aq K_2CO_3 (200 mL) and the mixture refluxed for 6 h, cooled, treated with brine (50 mL), and extracted with EtOAc–MeOH (4:1, 1 × 100 mL) and EtOAc (2 × 100 mL); the combined organic solutions were dried and evaporated. After purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 100:3→100:10), the product was recrystallized from EtOAc–isohexane (1:1).

Yield: 7.27 g (64%); off-white crystals.

^{1}H NMR (DMSO-d_6): δ = 8.06 (s, 2 H), 7.50 (m, 1 H), 7.32 (m, 5 H), 5.36 (s, 2 H), 5.00 (s, 2 H), 4.19 (d, *J* = 7 Hz, 2 H).

MS: *m*/*z* = 258 (M^+).

Anal. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.46; H, 5.46; N, 21.69. Found: C, 60.42; H, 5.52; N, 21.72.

Benzyl [(5-{[6-Methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}pyrimidin-2-yl)methyl]carbamate (5)

A stirred slurry of 4-chloro-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazoline[6] (8.61 g, 25.5 mmol) in H_2O (34 mL) was maintained at 20 °C while a solution of 4 M HCl in 1,4-dioxane (10.5 mL, 42 mmol) was added over 3–4 min, giving a clear orange solution. This was treated in one portion with a solution of **4** (3.87 g, 15 mmol) in a mixture of 1,4-dioxane (40 mL) and H_2O (20 mL). The mixture was heated to 60 °C for 40 min. The reaction mixture was cooled, basified with aq $NaHCO_3$, and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were extracted with 20% aq NaCl (5 × 50 mL) and then evaporated. The residue was taken up in CH_2Cl_2–MeOH (5:1, 50 mL), dried ($MgSO_4$), and evaporated. After purification by chromatography on silica gel (CH_2Cl_2–MeOH, 100:8→100:15), the product was crystallized from CH_2Cl_2–MeOH–EtOAc (3:1:1).

Yield 5.96 g (71%); off-white powder.

^{1}H NMR (DMSO-d_6): δ = 9.71 (br s, 1 H), 9.14 (s, 2 H), 8.47 (s, 1 H), 7.80 (s, 1 H), 7.74 (t, *J* = 6 Hz, 1 H), 7.26–7.40 (m, 5 H), 7.21 (s, 1 H), 5.05 (s, 2 H), 4.40 (d, *J* = 6 Hz, 2 H), 4.18 (t, *J* = 6.4 Hz, 2 H), 3.96 (s, 3 H), 3.57 (m, 4 H), 2.44 (t, *J* = 7.1 Hz, 2 H), 2.37 (m, 4 H), 1.95 (m, 2 H).

MS: *m*/*z* = 560 (M^+).

Anal. Calcd for $C_{29}H_{33}N_7O_5$: C, 62.24; H, 5.94; N, 17.52. Found: C, 61.9; H, 5.94; N, 17.2.

N-[3-(Dimethylamino)-2-{[(dimethylamino)methylene]amino}prop-2-en-1-ylidene]-*N*-methylmethanaminium Hydrogen Monohexafluorophosphate (7)

A suspension of the crude dihexafluorophosphate **3c** (10 g, 19.3 mmol) in EtOH (80 mL) was treated with Et_3N (8 mL, 58 mmol) and heated to 70 °C giving a clear solution which was cooled immediately. The solution was cooled to –20 °C and the heavy, cream-colored solid was filtered off, washed with very cold EtOH (50 mL) and Et_2O (50 mL), and air-dried under a nitrogen blanket.

Yield: 6.6 g (94%).

^{1}H NMR (DMSO-d_6): δ = 7.33 (s, 1 H), 7.13 (s, 2 H), 3.16 (s, 12 H), 2.95 (s, 3 H), 2.89 (s, 3 H).

MS: *m*/*z* = 197 (M^+).

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Anal. Calcd for $C_{10}H_{21}N_4PF_6$: C, 35.09; H, 6.18; N, 16.37. Found: C, 35.1; H, 6.17; N, 16.1.

2-(Diethoxymethyl)pyrimidin-5-amine (9)

A slurry of **3c** (125.8 g, 242 mmol) and 2,2-diethoxyethanimidamide hydrochloride[6] (51.6 g, 283 mmol) in EtOH (500 mL) was stirred under nitrogen while NaOMe in MeOH (186.6 g, 864 mmol, 25% w/v) was added dropwise, the mixture was heated to reflux halfway through the addition. After refluxing for 135 min, the mixture was cooled to 0 °C, the inorganic precipitate was filtered off, washed with EtOH (2 × 50 mL), and the filtrate evaporated. The residue was taken up in CH_2Cl_2 (700 mL), extracted with H_2O (3 × 150 mL), dried ($MgSO_4$), and evaporated to an oil. This in turn was taken up in CH_2Cl_2–MeOH (10:1, 170 mL), filtered through silica gel (30g) and evaporated to an orange oil.

A 37 g sample of this oil was taken up in dioxane (230 mL), treated with 5% aq K_2CO_3 (385 mL), and refluxed for 6 h. The solution was evaporated to dryness, co-evaporated with toluene (300 mL), taken up in CH_2Cl_2–MeOH (10:1, 330 mL), filtered through silica gel (30g) evaporated to dryness and the solid washed with Et_2O.

Yield: 20.27 g (65%); off-white solid.

^{1}H NMR (DMSO-d_6): δ = 8.08 (s, 2 H), 5.58 (s, 2 H), 5.28 (s, 1 H), 3.53 (m, 4 H), 1.09 (t, J = 7 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 142.94, 154.37, 141.99, 102.86, 62.02, 15.99.

MS: m/z = 197 (M^+).

Anal. Calcd for $C_9H_{15}N_3O_2$: C, 54.59; H, 7.67; N, 21.22. Found: C, 54.42; H, 7.62; N, 20.98.

***N′*-[2-(Hydroxymethyl)pyrimidin-5-yl]-*N*,*N*-dimethylimidoformamide (10)**

A slurry of **3c** (21.3 g, 41 mmol) and glycolamidine hydrochloride[14] (5.0 g, 45 mmol) in EtOH (80 mL) was heated to reflux and NaOMe in MeOH (34.1 mL, 158 mmol, 25% w/w) was added dropwise. After refluxing for 2 h, the mixture was cooled to 0 °C, the inorganic precipitate was filtered off, washed with EtOH (2 × 50 mL), the filtrate evaporated, and the residue purified by chromatography on silica gel, (EtOAc–MeOH, 100:10→100:25) to give the product as an oil, 5.32 g (72%). From a solution in *tert*-butyl methyl ether was obtained a sample of analytically pure white crystals.

Yield: 5.32 g (72%); mp 62–63 °C.

^{1}H NMR (DMSO-d_6): δ = 8.36 (s, 2 H), 7.93 (s, 1 H), 5.06 (t, J = 6.2 Hz, 1 H), 4.49 (d, J = 6.2 Hz, 2 H), 3.05 (s, 3 H), 2.96 (s, 3 H).

MS: m/z = 180 (M^+).

Anal. Calcd for $C_8H_{12}N_4O$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.0; H, 6.74; N, 30.8.

2-[(3-Chloro-4-fluorophenoxy)methyl]pyrimidin-5-amine (11)

A solution containing **10** (1.8 g, 10 mmol), 3-chloro-4-fluorophenol (1.54 g, 10.5 mmol) and PPh_3 (3.93 g, 15 mmol) in THF (50 mL) was treated, with stirring at –15 °C over 20 min, with a solution of DIAD (3.13 g, 15.5 mmol) in THF (10 mL). The mixture was allowed to warm to r.t. and stirred for 2 h. The solution was evaporated to dryness, the product was chromatographed on silica gel (EtOAc–MeOH, 100:5→100:7.5). This gave 1.73 g of an off-white solid, which was hydrolyzed in dioxane and aq K_2CO_3 as described for **6a**, giving after recrystallization from THF–isohexane an off-white solid.

Yield: 1.13 g (45%).

^{1}H NMR (DMSO-d_6): δ = 8.09 (s, 2 H), 7.26 (m, 1 H), 7.19 (m, 1 H), 6.95 (m, 1 H), 5.60 (s, 2 H), 5.00 (s, 2 H).

MS: m/z = 255, 253 (M^+).

Anal. Calcd for $C_{11}H_9ClFN_3O$: C, 52.09; H, 3.58; N, 16.57. Found: C, 51.90; H, 3.53; N, 16.43.

2-{[(3-Fluorobenzyl)oxy]methyl}pyrimidin-5-amine (12)

A solution of **10** (0.9 g, 5 mmol) in DMF (3 mL) was treated with NaH (60% dispersion in oil; 220 mg, 5.5 mmol) with stirring under nitrogen. 3-Fluorobenzyl bromide 1.04 g, 5.5 mmol) was added dropwise and the mixture stirred for 1 h. The reaction was quenched with H_2O (10 mL) and evaporated to dryness. The residue was taken up in dioxane (5 mL), H_2O (1 mL) and EtOH (10 mL), treated with 2 M aq NaOH (9 mL, 18 mmol), and refluxed for 18 h. The mixture was cooled, extracted with EtOAc (3 × 10 mL), the organic solutions dried ($MgSO_4$), evaporated, and the product purified by chromatography on silica gel (CH_2Cl_2→CH_2Cl_2–MeOH, 100:10). The product was recrystallized from CH_2Cl_2–isohexane (1:5).

Yield: 0.37 g (32%); off-white crystals.

^{1}H NMR (DMSO-d_6): δ = 8.10 (s, 2 H), 7.37 (m, 1 H), 7.15 (m, 1 H), 6.95 (m, 1 H), 5.52 (s, 2 H), 4.56 (s, 2 H), 4.48 (s, 2 H).

MS: m/z = 233 (M^+).

Anal. Calcd. for $C_{12}H_{12}FN_3O$: C, 61.79; H, 5.19; N, 18.02. Found: C, 61.49; H, 5.23; N, 17.67.

2-Alkoxy-5-aminopyrimidines 13a–c; General Procedure

To a solution of the required commercially available alcohol (24 mmol) in THF (30 mL) was added NaH (60% dispersion in oil; 22 mmol) portionwise. After stirring for 5 min, the milky solution was treated over 2 min with a solution of the sulfone **2** (20 mmol) in DMF (30 mL). After 10 min, the mixture was poured into 5% aq $NaHCO_3$ (200 mL). A solid which formed was filtered off and washed with H_2O. The solid was dissolved in dioxane (50 mL) and treated with 2 M aq KOH (40 mL), followed by addition of 50% aq dioxane until the mixture was almost homogeneous. The mixture was refluxed for 4 h, cooled, extracted with EtOAc (3 × 100 mL), the organic layer dried ($MgSO_4$), and evaporated to an oil which was purified by column chromatography on silica gel (50g; CH_2Cl_2–MeOH, 100:10). The product was recrystallized from CH_2Cl_2–isohexane.

13a

^{1}H NMR (DMSO-d_6): δ = 7.96 (s, 2 H), 7.39 (m, 1 H), 7.20 (m, 1 H), 7.10 (m, 1 H), 5.24 (s, 2 H), 4.99 (s, 2 H).

MS: m/z = 219 (M^+).

Anal. Calcd for $C_{11}H_{10}FN_3O$: C, 60.27; H, 4.60; N, 19.17. Found: C, 60.29; H, 4.64; N, 19.19.

13b

^{1}H NMR (DMSO-d_6): δ = 7.95 (s, 2 H), 4.92 (s, 2 H), 4.18 (t, J = 0.7 Hz, 2 H), 1.58 (m, 2 H), 0.68 (m, 1 H), 0.44 (m, 2 H), 0.09 (m, 2 H).

MS: m/z = 179 (M^+).

Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.23; H, 7.30; N, 23.57.

13c

^{1}H NMR (DMSO-d_6): δ = 7.96 (s, 2 H), 4.94 (s, 2 H), 4.23 (m, 2 H), 3.62 (m, 3 H), 1.09 (d, J = 8 Hz, 6 H).

MS: m/z = 197 (M^+).

Anal. Calcd for $C_9H_{15}N_3O_2$: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.77; H, 7.58; N, 21.26.

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Acknowledgment

We wish to thank Phil Walker for DSC calorimetry, Madeleine Vickers for mass spectra and Chris de Savi for useful comments during the preparation of the manuscript.

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(12) Safety Note: It should be noted that the combination of $POCl_3$ and DMF is now presumed to generate small quantities of the potent carcinogen *N*,*N*-dimethylcarbamoyl chloride (DMCC). See: Levin, D. *Org. Process Res. Dev.* **1997**, *1*, 182; and references therein.
(13) Mengelberg, M. *Chem. Ber.* **1956**, *89*, 1185.
(14) McCasland, G. E.; Tarbell, D. S. *J. Am. Chem. Soc.* **1946**, *68*, 2393.

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