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Novel Synthesis of Fluorinated Cyanoketene *N,S*-Acetals and Their Conversions to Fluorinated Pyrazole Derivatives

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*Novel fluorinated ketene *N,S*-acetals **3** were readily prepared by the reaction of fluorosubstituted cyanoacetamide derivatives with arylisothiocyanate in the presence of potassium hydroxide, followed by the alkylation of the produced salts with methyl iodide. The reaction of compounds **3** with hydrazine afforded different fluorosubstituted pyrazoles **4**.*

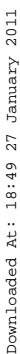
Keywords Arylisothiocyanate; activated nitriles; fluorinated cyanoketene *N,S*-acetals; fluorinated pyrazoles

INTRODUCTION

Fluorinated pyrazoles are the focus of much interest in modern medicinal chemistry.^{1–3} Moreover, in recent years, these derivatives have been extensively utilized as intermediates for the synthesis of fused pyrazoles of potential biological activity. During the course of our studies directed toward exploring the synthetic potential of ketene *S,S*- and *N,S*-acetals for synthesizing new classes of novel antimetabolites,^{4–6} we have recently reported different successful approaches for the synthesis of mercaptopurine and thioguanine analogues by the reaction of ketene dithioacetals with diazoles containing amino and active methylene functions.^{7,8} In an extension of this work, this article describes a novel synthesis of some novel fluorinated ketene *N,S*-acetals and their use in the synthesis of fluorinated aminopyrazole derivatives.

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catalytic amount of piperidine gave the corresponding fluorosubstituted pyrazole derivatives **4**. The structures of **4** were established on the basis of their elemental analysis and spectral data (MS, IR, ^1H NMR, and ^{13}C NMR). Structure **4a** was supported by its mass (m/z 311), which agrees with its molecular formula $\text{C}_{16}\text{H}_{14}\text{FN}_5\text{O}$. Its ^1H NMR spectrum displayed a broad signal at $\delta = 6.07$ ppm corresponding to the NH_2 group, a signal at $\delta = 6.77$ – 8.20 ppm related to the aromatic protons, and another three singlets at $\delta = 8.39$, 9.01 , and 11.50 ppm assignable to the three NH groups. The ^{13}C NMR spectra were characterized by a signal at $\delta = 123.51$ – 138.60 ppm assigned to aromatic carbons and a signal at 167.9 ppm corresponding to the carbonyl carbon atom.

CONCLUSION

In summary, we have achieved a novel synthesis of interesting fluorinated ketene *N,S*-acetals and their conversions to several fluorosubstituted pyrazole derivatives.

EXPERIMENTAL

^1H and ^{13}C spectra were recorded on a Bruker AMX-400 spectrometer with TMS as the internal standard. TLC was performed on Polygram[®] SIL G/UV₂₅₄ silica gel plates (0.2 mm layer thickness) and visualized with UV light.

2-Cyano-3-(methylthio)acrylamides (**3a–g**)

General Procedure

A mixture of *N*-substituted cyanoacetamide derivatives **1** (0.01 mol) and arylisothiocyanate (0.01 mol) was heated for 10–30 min in ethanol (25 mL) containing potassium hydroxide (0.01 mol). After cooling, methyl iodide (0.01 mol) was added and the mixture was stirred until the solid product precipitated. The precipitated solid product was collected by filtration and recrystallized from the appropriate ethanol.

3a: Yield 78%. The m.p. is 134°C . ^1H -NMR ($\text{DMSO}-d_6$): δ (ppm) = 2.23 (CH_3 , 3H, s), 7.07–7.59 (Ph, 9H, m), 9.29 (NH, 1H, s), 11.91 (NH, 1H, s). ^{13}C -NMR ($\text{DMSO}-d_6$): δ (ppm) = 16.8, 115.8, 116.0, 118.8, 124.3, 124.6, 126.6, 127.9, 129.6, 138.6, 154.6, 157.1, 165.0, 167.9. Analysis: $\text{C}_{17}\text{H}_{14}\text{FN}_3\text{OS}$ (MG 327.38); calcd.: C, 62.37; H, 4.31; N, 12.84; found: C, 62.37; H, 4.41; N, 12.68.

3b: Yield 79%. The m.p. is 136°C . ^1H -NMR ($\text{DMSO}-d_6$): δ (ppm) = 2.25 (CH_3 , 3H, s), 7.07–7.55 (Ph, 9H, m), 9.61 (NH, 1H, s), 11.68 (NH, 1H, s). ^{13}C -NMR ($\text{DMSO}-d_6$): δ (ppm) = 16.7, 79.7, 115.2, 115.4, 118.8, 123.5,

123.6, 124.0, 126.4, 134.8, 138.9, 157.6, 160.0, 164.7, 167.4. Analysis: $C_{17}H_{14}FN_3OS$ (MG 327.38); calcd.: C, 62.37; H, 4.31; N, 12.84; found: C, 62.35; H, 4.33; N, 12.75.

3c: Yield 83%. The m.p. is 124°C. 1H -NMR (DMSO- d_6): δ (ppm) = 2.25 (CH₃, 3H, s), 7.08–7.60 (Ph, 8H, m), 9.29 (NH, 1H, s), 11.82 (NH, 1H, s). ^{13}C -NMR (DMSO- d_6): δ (ppm) = 16.9, 115.8, 116.0, 116.2, 116.4, 118.8, 124.6, 124.9, 126.7, 126.8, 127.1, 135.1, 154.6, 157.0, 159.3, 161.7, 165.0, 168.3. Analysis: $C_{17}H_{13}F_2N_3OS$ (MG 345.37); calcd.: C, 59.12; H, 3.79; N, 12.17; found: C 59.08; H, 3.89; N, 12.29.

3d: Yield 81%. The m.p. is 138°C. 1H -NMR (DMSO- d_6): δ (ppm) = 2.35 (CH₃, 3H, s), 7.05–7.63 (Ph, 8H, m), 9.42 (NH, 1H, s), 11.78 (NH, 1H, s). ^{13}C -NMR (DMSO- d_6): δ (ppm) = 16.8, 115.3, 115.8, 116.2, 116.4, 118.7, 124.6, 124.9, 126.6, 126.8, 127.0, 134.8, 154.6, 157.6, 164.0, 165.0, 167.8. Analysis: $C_{17}H_{13}F_2N_3OS$ (MG 345.37); calcd.: C, 59.12; H, 3.79; N, 12.17; found: C 59.00; H, 3.91; N, 12.32.

3e: Yield 84%. The m.p. is 150°C. 1H -NMR (DMSO- d_6): δ (ppm) = 2.62 (CH₃, 3H, s), 7.08–7.18 (Ph, 2H, m), 7.19–7.29 (Ph, 2H, m), 7.34–7.46 (Ph, 2H, m), 7.48–7.61 (Ph, 2H, m) 9.63 (NH, 1H, s), 11.62 (NH, 1H, s). ^{13}C -NMR (DMSO- d_6): δ (ppm) = 16.9, 115.2, 115.4, 116.1, 116.4, 118.8, 123.5, 126.4, 134.8, 135.4, 157.6, 159.1, 160.0, 161.5, 164.6, 167.6. Analysis: $C_{17}H_{13}F_2N_3OS$ (MG 345.37); calcd.: C, 59.12; H, 3.79; N, 12.17; found: C, 59.32; H, 3.82; N, 12.06.

3f: Yield 80%. The m.p. is 132°C. 1H -NMR (DMSO- d_6): δ (ppm) = 2.29 (CH₃, 3H, s), 7.08–7.18 (Ph, 3H, m), 7.37–7.57 (Ph, 5H, m), 9.36 (NH, 1H, s), 11.71 (NH, 1H, s). ^{13}C -NMR (DMSO- d_6): δ (ppm) = 16.9, 115.8, 116.0, 118.7, 124.5, 124.6, 125.9, 126.6, 127.0, 127.1, 129.5, 130.6, 137.8, 164.6, 167.6. Analysis: $C_{17}H_{13}ClFN_3OS$ (MG 361.82); calcd.: C, 56.43; H, 3.62; N, 11.61; found: C, 56.27; H, 3.92; N, 11.51.

3g: Yield 82%. The m.p. is 157°C. 1H -NMR (DMSO- d_6): δ (ppm) = 2.31 (CH₃, 3H, s), 7.10–7.31 (Ph, 2H, t, J = 8.65 Hz), 7.37 (Ph, 2H, d, J = 8.65 Hz), 7.43 (Ph, 2H, d, J = 8.65 Hz), 7.46–7.47 (Ph, 2H, m), 9.68 (NH, 1H, s), 11.45 (NH, 1H, s). ^{13}C -NMR (DMSO- d_6): δ (ppm) = 16.8, 80.8, 115.2, 115.4, 118.7, 123.5, 123.4, 125.4, 129.4, 130.2, 134.8, 138.2, 157.6, 160.0, 164.0, 166.8. Analysis: $C_{17}H_{13}ClFN_3OS$ (MG 361.82); calcd.: C, 56.43; H, 3.62; N, 11.61; found: C, 56.38; H, 3.13; N, 11.93.

5-amino-3-(methylthio)-1H-pyrazole-4-carboxamides (4a–g)

General Procedure

A mixture of compounds **3** (0.01 mol) and hydrazine (0.015 mol) in ethanol (30 mL) containing a catalytic amount of piperidine were refluxed for 4 h. After removal of ethanol, the resulting formed solid product was filtered off and recrystallized from ethanol-ether.

4a: Yield 78%. The m.p. is 221°C. $^1\text{H-NMR}$ (DMSO-d_6): δ (ppm) = 6.07 (NH_2 , 2H, s), 6.77 (CH_3 , 3H, t, $J = 7.12$ Hz), 7.08–7.29 (Ph, 7H, m), 8.20 (NH, 1H, t, $J = 7.12$ Hz), 8.39 (NH, 1H, s), 9.01 (NH, 1H, s) 11.50 (NH, 1H, s). $^{13}\text{C-NMR}$ (DMSO-d_6): δ (ppm) = 115.8, 116.0, 118.8, 123.51, 124.6, 124.0, 126.6, 127.9, 129.6, 138.6, 154.6, 157.1, 165.0 167.9. Analysis: $\text{C}_{16}\text{H}_{14}\text{FN}_5\text{O}$ (MG 311.32); calcd.: C, 61.37; H, 4.53; N, 22.50; found: C 61.75; H, 4.69; N, 22.12.

4b: Yield 85%. The m.p. is 183°C. $^1\text{H-NMR}$ (DMSO-d_6): δ (ppm) = 6.03 (NH_2 , 2H, s), 6.78 (CH_3 , 3H, t, $J = 7.12$ Hz), 7.08–7.36 (Ph, 7H, m), 7.46–7.58 (Ph, 1H, m), 8.58 (NH, 1H, s), 8.76 (NH, 1H, s), 11.30 (NH, 1H, s). $^{13}\text{C-NMR}$ (DMSO-d_6): δ (ppm) = 115.2, 115.4, 119.2 121.9, 122.0, 129.0, 135.4, 143.5, 148.8, 150.1, 156.9, 159.3, 163.2. Analysis: $\text{C}_{16}\text{H}_{14}\text{FN}_5\text{O}$ (MG 311.32); calcd.: C, 61.37; H, 4.53; N, 22.50; found: C, 61.47; H, 4.84; N, 22.18.

4c: Yield 80%. The m.p. is 204°C. $^1\text{H-NMR}$ (DMSO-d_6): δ (ppm) = 5.85 (NH_2 , 2H, s), 6.77–7.01 (Ph, 7H, m), 7.95 (Ph, 1H, t, $J = 8.14$ Hz), 8.17 (NH, 1H, s), 8.83 (NH, 1H, s), 11.26 (NH, 1H, s). $^{13}\text{C-NMR}$ (DMSO-d_6): δ (ppm) = 115.3, 115.5, 115.7, 117.2, 117.3, 122.3, 124.0, 124.1, 124.7, 124.8, 127.2, 127.3, 140.9, 163.0. Analysis: $\text{C}_{16}\text{H}_{13}\text{F}_2\text{N}_5\text{O}$ (MG 329.31); calcd.: C, 58.36; H, 3.98; N, 21.27; found: C, 58.35; H, 4.02; N, 21.08.

4d: Yield 85%. The m.p. is 202°C. $^1\text{H-NMR}$ (DMSO-d_6): δ (ppm) = 6.05 (NH_2 , 2H, s), 6.93–7.28 (Ph, 7H, m), 8.19 (Ph, 1H, t), 8.40 (NH, 1H, s), 9.07 (NH, 1H, s), 11.51 (NH, 1H, s). $^{13}\text{C-NMR}$ (DMSO-d_6): δ (ppm) = 115.3, 115.5, 115.7, 117.3, 117.4, 122.3, 124.0, 124.1, 124.8, 127.2, 117.3, 140.9, 151.7, 154.1, 155.17, 157.5, 163.1. Analysis: $\text{C}_{16}\text{H}_{13}\text{F}_2\text{N}_5\text{O}$ (MG 329.31); calcd.: C, 58.36; H, 3.98; N, 21.27; found: C, 58.36; H, 4.02; N, 21.23.

4e: Yield 84%. The m.p. is 230°C. $^1\text{H-NMR}$ (DMSO-d_6): δ (ppm) = 6.03 (NH_2 , 2H, s), 6.98–7.08 (Ph, 2H, m), 7.10–7.19 (Ph, 2H, m), 7.30–7.41 (Ph, 2H, m), 7.52–7.61 (Ph, 2H, m), 8.59 (NH, 1H, s), 8.77 (NH, 1H, s), 11.28 (NH, 1H, s). $^{13}\text{C-NMR}$ (DMSO-d_6): δ (ppm) = 115.3, 115.4, 115.5, 115.6, 117.4, 117.5, 122.2, 122.3, 135.6, 140.1, 148.9, 150.6, 155.0, 157.1, 157.3, 159.5, 163.4. Analysis: $\text{C}_{16}\text{H}_{13}\text{F}_2\text{N}_5\text{O}$ (MG 329.31); calcd.: C 58.36; H, 3.98; N, 21.27; found: C, 58.35; H, 3.83; N, 21.45.

4f: Yield 79%. The m.p. is 202°C. $^1\text{H-NMR}$ (DMSO-d_6): δ (ppm) = 6.09 (NH_2 , 2H, s), 6.96–7.28 (Ph, 7H, m), 8.17 (Ph, 7H, t, $J = 7.88$ Hz) 8.56 (NH, 1H, s), 8.99 (NH, 1H, s), 11.53 (NH, 1H, s). $^{13}\text{C-NMR}$ (DMSO-d_6): δ (ppm) = 115.3, 115.5, 117.5, 122.4, 122.9, 124.1, 124.2, 124.8, 127.1, 127.2, 128.9, 143.4, 149.2, 149.9, 151.7, 154.2, 162.3. Analysis: $\text{C}_{16}\text{H}_{13}\text{ClFN}_5\text{O}$ (MG 345.76); calcd.: C, 55.58; H, 3.79; N, 20.25; found: C, 55.38; H, 3.71; N, 19.95.

4g: Yield 81%. The m.p. is 218°C. $^1\text{H-NMR}$ (DMSO-d_6): δ (ppm) = 6.04 (NH_2 , 2H, s), 7.06–7.16 (Ph, 1H, t), 7.23 (Ph, 2H, d, $J = 8.90$ Hz), 7.34

(Ph, 2H, d, $J = 8.65$ Hz), 7.48-7.64 (Ph, 1H, m), 8.72 (NH, 1H, s), 8.74 (NH, 1H, s), 11.31 (NH, 1H, s) ^{13}C -NMR (DMSO- d_6): δ (ppm) = 115.3, 115.5, 117.7, 122.3, 122.4, 128.8, 135.6, 142.5, 148.9, 150.2, 157.2, 159.5, 163.4. Analysis: $\text{C}_{16}\text{H}_{13}\text{ClFN}_5\text{O}$ (MG 345.76); calcd.: C, 55.58; H, 3.79; N, 20.25; found: C, 55.22; H, 3.40; N, 20.42.

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