

Synthesis and Detailed Spectroscopic Characterization of Two Novel *N*-(3-Acetyl-2-thienyl)acetamides

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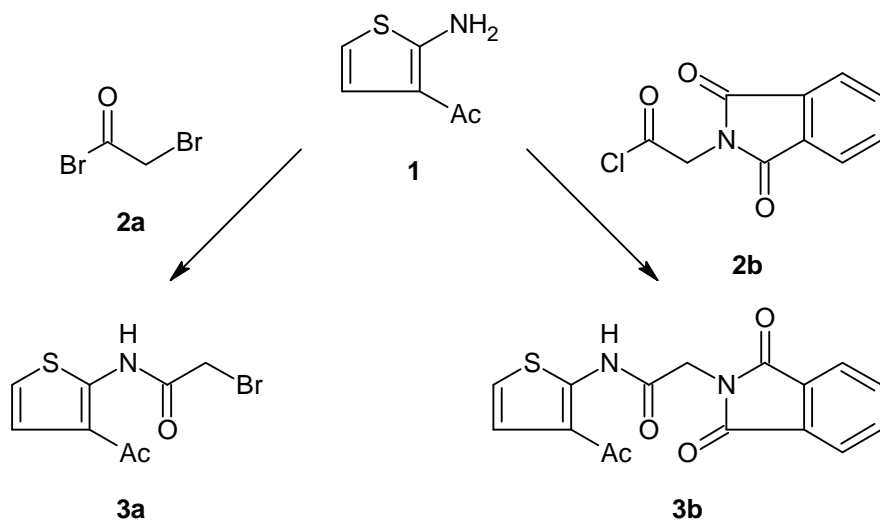
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Abstract:

The title compounds – *N*-(3-acetyl-2-thienyl)-2-bromoacetamide and *N*-(3-acetyl-2-thienyl)-2-phthalimidoacetamide – were synthesized in one step from 3-acetylthiophen-2-amine and the corresponding acetyl halogenides. Detailed spectroscopic data (^1H NMR, ^{13}C NMR, ^{15}N NMR, MS, IR) for these compounds are presented.

Recently, we have investigated a modified Gewald reaction [1] for the preparation of 3-acetyl-2-aminothiophenes [2]. We here report the synthesis of two acetamides derived from 3-acetylthiophen-2-amine (**1**) (Scheme 1). These molecules are expected to be versatile intermediates for advanced investigations regarding the chemistry of 3-acetylthiophenes of type **1**.



Scheme 1. Preparation of the title compounds **3a** and **3b**

***N*-(3-Acetyl-2-thienyl)-2-bromoacetamide (3a):**

Under stirring at room temperature, to 4.23 g (30 mmol) thiophenamine **1** [2] in 70 mL of dry 1,4-dioxane were added dropwise 6.06 g (30 mmol) of bromoacetyl bromide (**2a**) in 20 mL of 1,4-dioxane. After 3 h the reaction mixture was poured into ice-cold H₂O (ca. 300 mL), the resulting precipitate was filtered off, washed with H₂O, and dried under reduced pressure to afford pure **3a** (4.72 g, 60%) as a beige powder. The compound slowly decomposes in DMSO- or MeOH-solution.

Melting point: 96–97°C.

IR (KBr) [3]: 1660, 1640 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆) [4]: δ (ppm) 12.18 (s, 1H, NH), 7.43 (d, ³*J*(H4,H5) = 5.8 Hz, 1H, H4), 7.06 (d, ³*J*(H4,H5) = 5.8 Hz, 1H, H5), 4.43 (s, 2H, CH₂), 2.52 (s, 3H, CH₃).

¹H NMR (500 MHz, CDCl₃) [5]: δ (ppm) 12.66 (s, 1H, NH), 7.23 (d, ³*J*(H4,H5) = 5.8 Hz, 1H, H4), 6.81 (d, ³*J*(H4,H5) = 5.8 Hz, 1H, H5), 4.09 (s, 2H, CH₂), 2.55 (s, 3H, CH₃).

¹³C NMR (75 MHz, DMSO-*d*₆) [4]: δ (ppm) 195.8 (COCH₃), 164.6 (NCO, ²*J*(NCO,CH₂) = 4.3 Hz, ²*J*(NCO,NH) = 4.3 Hz), 147.0 (C2), 125.2 (C4, ¹*J* = 170.2 Hz, ²*J*(C4,H5) = 4.2 Hz), 121.8 (C3), 117.1 (C5, ¹*J* = 189.3 Hz, ²*J*(C5,H4) = 6.0 Hz), 29.0 (CH₂, ¹*J* = 155.6 Hz), 28.8 (CH₃, ¹*J* = 127.7 Hz).

¹³C NMR (125 MHz, CDCl₃) [5]: δ (ppm) 196.0 (COCH₃, ²*J*(COCH₃,CH₃) = 5.9 Hz, ³*J*(CO,H4) = 0.9 Hz), 164.1 (NCO, ²*J*(NCO,CH₂) = 4.5 Hz), 148.3 (C2, ²*J*(C2,NH) = 2.1 Hz, ³*J*(C2,H4) = 10.0 Hz, ³*J*(C2,H5) = 7.6 Hz), 124.4 (C4, ¹*J* = 168.8 Hz, ²*J*(C4,H5) = 3.6 Hz), 122.0 (C3, ²*J*(C3,H4) = 5.8 Hz, ³*J*(C3,H5) = 9.1 Hz), ³*J*(C3,CH₃) = 1.3 Hz), 116.9 (C5, ¹*J* = 187.7 Hz, ²*J*(C5,H4) = 5.0 Hz), 28.7 (CH₃, ¹*J* = 127.9 Hz), 27.9 (CH₂, ¹*J* = 153.9 Hz).

¹⁵N NMR (50 MHz, CDCl₃) [6]: δ (ppm) –248.9 (NH).

MS (m/z, %) [7]: 263 (M⁺, 27), 261 (M⁺, 25), 141 (100), 126 (75), 43 (59).

Elemental Analysis: Calculated for C₈H₈BrNO₂S (262.12) · 0.1 H₂O: C, 36.41%; H, 3.13%; N, 5.31%. Found: C, 36.15%; H, 2.92%; N, 5.03%.

***N*-(3-Acetyl-2-thienyl)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetamide (3b):**

At room temperature, to 2.12 g (15 mmol) of thiophenamine **1** [2] in 20 mL of dry 1,4-dioxane were added dropwise 3.35 g (15 mmol) of phthalimidoacetyl chloride (**2b**) [8] in 20 mL of 1,4-dioxane. The reaction mixture was stirred overnight and then poured into H₂O (ca. 100 mL). Upon neutralization with solid NaHCO₃ a yellowish precipitate was formed which was filtered off, washed with H₂O, and dried under reduced pressure to afford pure **3b** (4.33 g, 88%) as a yellowish powder.

Melting point: 208–212 °C.

IR (KBr) [3]: 1773, 1719, 1693, 1635 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) [5]: δ (ppm) 12.25 (s, 1H, NH), 7.91 (m, 2H, Phth-H3,6), 7.76 (m, 2H, Phth-H4,5), 7.17 (d, $^3J(\text{Th-H4},\text{Th-H5}) = 5.8$ Hz, 1H, Th-H4), 6.75 (d, $^3J(\text{Th-H5},\text{Th-H4}) = 5.8$ Hz, 1H, Th-H5), 4.65 (s, 2H, CH_2), 2.49 (s, 3H, CH_3).

^{13}C NMR (125 MHz, CDCl_3) [5]: δ (ppm) 196.1 (COCH_3), 167.4 (Phth-CO), 164.1 (HNCO), 148.5 (Th-C2), 134.4 (Phth-C4,5), 131.9 (Phth-C1,2), 124.2 (Th-C4), 123.8 (Phth-C3,6), 121.5 (Th-C3), 116.6 (Th-C5), 40.7 (CH_2), 28.6 (CH_3).

^{15}N NMR (50 MHz, CDCl_3) [6]: δ (ppm) -228.8 (NCH_2), -252.7 (NH).

MS (m/z, %) [7]: 328 (M^+ , 17), 168 (17), 160 (100), 141 (27).

Elemental Analysis: Calculated for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$ (328.34) \cdot 0.1 H_2O : C, 58.21%; H, 3.72%; N, 8.49%. Found: C, 57.86%; H, 3.87%; N, 8.40%.

References and Notes

1. Gewald, K. *Chem. Ber.* **1965**, 98, 3571–3577.
2. Eller, G. A.; Holzer, W. *Molecules* **2006**, 11, 371–376.
3. The spectrum was obtained on a Perkin-Elmer FTIR 1605 spectrophotometer.
4. The spectrum was obtained on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^1H , 75.43 MHz for ^{13}C) at 28 °C. The center of the solvent signal was used as an internal standard which was related to TMS with δ 2.49 ppm (^1H NMR) and δ 39.5 ppm (^{13}C NMR).
5. The spectrum was obtained on a Bruker Avance 500 spectrometer (500.13 MHz for ^1H , 125.77 MHz for ^{13}C) at 294 K. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^1H NMR) and δ 77.0 ppm (^{13}C NMR).
6. The spectrum was obtained on a Bruker Avance 500 spectrometer (50.68 MHz for ^{15}N) and was referenced against neat, external nitromethane (coaxial capillary).
7. The spectrum was obtained on a Shimadzu QP 1000 instrument (EI, 70eV).
8. Usifoh, C. O.; Lambert, D. M.; Wouters, J.; Scriba, G. K. E. *Arch. Pharm. (Weinheim, Ger.)* **2001**, 334, 323–331.