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

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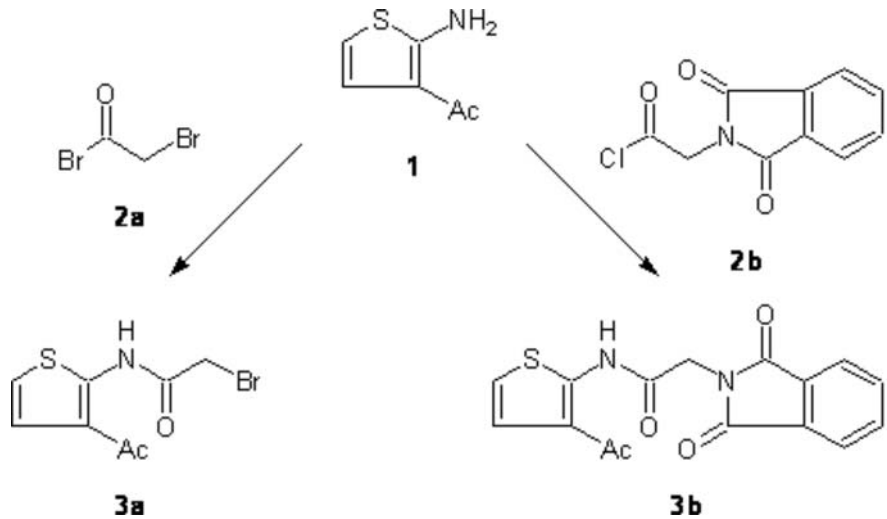
Abstract:
The title compounds – *N*-(3-acetyl-2-thienyl)-2-bromoacetamide and *N*-(3-acetyl-2-thienyl)-2-phthalimidoacetamide – were synthesized in one step from 3-acetylthiophen-2-amine and the corresponding acetyl halogenides. Detailed spectroscopic data (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, MS, IR) 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 H_2O (ca. 300 mL), the resulting precipitate was filtered off, washed with H_2O, 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, ^3J(H4,H5) = 5.8 Hz, 1H, H4), 7.06 (d, ^3J(H4,H5) = 5.8 Hz, 1H, H5), 4.43 (s, 2H, CH_2), 2.52 (s, 3H, CH_3).

^1H NMR (500 MHz, $CDCl_3$) [5]: δ (ppm) 12.66 (s, 1H, NH), 7.23 (d, ^3J(H4,H5) = 5.8 Hz, 1H, H4), 6.81 (d, ^3J(H4,H5) = 5.8 Hz, 1H, H5), 4.09 (s, 2H, CH_2), 2.55 (s, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6) [4]: δ (ppm) 195.8 ($COCH_3$), 164.6 (NCO, ^2J(NCO,CH_2) = 4.3 Hz, ^2J(NCO,NH) = 4.3 Hz), 147.0 (C2), 125.2 (C4, ^1J = 170.2 Hz, ^2J(C4,H5) = 4.2 Hz), 121.8 (C3), 117.1 (C5, ^1J = 189.3 Hz, ^2J(C5,H4) = 6.0 Hz), 29.0 (CH_2, ^1J = 155.6 Hz), 28.8 (CH_3, ^1J = 127.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) [5]: δ (ppm) 196.0 ($COCH_3$, ^2J($COCH_3$,CH_3) = 5.9 Hz, ^3J(CO,H4) = 0.9 Hz), 164.1 (NCO, ^2J(NCO,CH_2) = 4.5 Hz), 148.3 (C2, ^2J(C2,NH) = 2.1 Hz, ^3J(C2,H4) = 10.0 Hz, ^3J(C2,H5) = 7.6 Hz), 124.4 (C4, ^1J = 168.8 Hz, ^2J(C4,H5) = 3.6 Hz), 122.0 (C3, ^2J(C3,H4) = 5.8 Hz, ^3J(C3,H5) = 9.1 Hz), ^3J(C3,CH_3) = 1.3 Hz), 116.9 (C5, ^1J = 187.7 Hz, ^2J(C5,H4) = 5.0 Hz), 28.7 (CH_3, ^1J = 127.9 Hz), 27.9 (CH_2, ^1J = 153.9 Hz).

^{15}N NMR (50 MHz, $CDCl_3$) [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 $C_8H_8BrNO_2S$ (262.12) · 0.1 H_2O: 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 H_2O (ca. 100 mL). Upon neutralization with solid $NaHCO_3$ a yellowish precipitate was formed which was filtered off, washed with H_2O, 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(Th-H4,Th-H5) = 5.8 Hz, 1H, Th-H4), 6.75 (d, ^3J(Th-H5,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 $C_{16}H_{12}N_2O_4S$ (328.34) · 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 ^{1}H, 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 (^{1}H NMR) and δ 39.5 ppm (^{13}C NMR).
5. The spectrum was obtained on a Bruker Avance 500 spectrometer (500.13 MHz for ^{1}H, 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 (^{1}H 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.