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Abstract: An unusual chemical method has been applied for the preparation of 1-benzothiophene-3-carboxamide derivatives from esters by reaction with lithium amide in tetrahydrofurane.

Keywords: Amidation, 1-benzothiophene, carboxamide, lithium amide

INTRODUCTION

1-Benzothiophenes have been known to exhibit a wide range of pharmacological properties, namely antitumor, antiviral, antibacterial, and kinase inhibitory activities.[1–5] We have discovered a novel high-yielding method for the preparation of carboxamide derivatives from the corresponding esters in the process of building up a focused kinase inhibitor library.[6]

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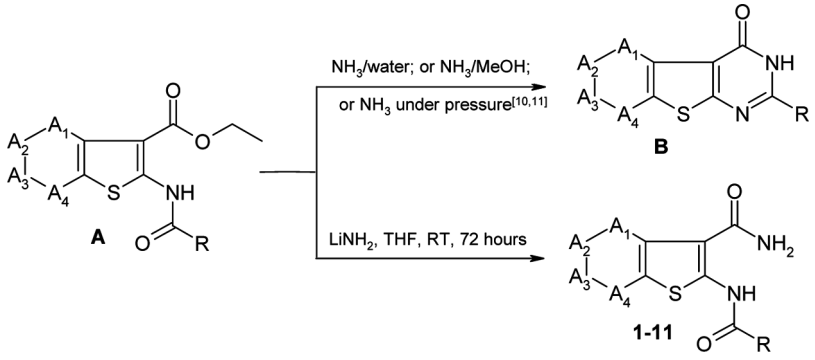

Scheme 1. Methods for the amidation of type **A** esters.

RESULTS AND DISCUSSION

The 2-acylamino-1-benzothiophene-3-carboxylic acid ethyl esters of type **A** could be synthesized by Gewald reaction[7] followed by acylation with adequate acyl chloride in pyridine.[6,8,9] These compounds could not be converted to amides by the application of widely used methods such as treatment with aqueous or alcoholic ammonia solution or ammonia gas.[10,11] Under mild reaction conditions, we have recovered the unconverted starting materials; higher temperature and pressure resulted in the formation of ring-closed products (**B**).[8,9] The successful amidation reaction was carried out with lithium amide in tetrahydrofurane, resulting in a series of 2-acylamino-1-benzothiophene-3-carboxamides in acceptable yields (67–84%), (Scheme 1, Table 1). Lithium amide, a strong Lewis

Table 1. Representative examples of the prepared derivatives (d: decomposition)

Compounds	A_1-A_2-A_3-A_4	R	Yield (%)	Mp (°C)
1	$-(CH_2)_4-$	Methyl	79	220
2	$-(CH_2)_4-$	Isopropyl	72	156
3	$-(CH_2)_4-$	Cyclopropyl	77	219
4	$-(CH_2)_4-$	2-Thienyl	84	224–225
5	$-(CH_2)_4-$	2-Furoyl	83	223
6	$-(CH_2)_2S(CH_2)-$	Cyclopropyl	69	232
7	$-(CH_2)_2O(CH_2)-$	Cyclopropyl	78	238–239 (d)
8	$-(CH_2)_2SO(CH_2)-$	Cyclopropyl	69	224
9	$-(CH_2)_2NCH_3(CH_2)-$	Cyclopropyl	67	189 (d)
10	$-(CH)_4-$	Cyclopropyl	68	205
11	$-(CH)_2CCH_3(CH)-$	Cyclopropyl	70	199

base, is used in C- and N-alkylation,[12–14] condensation,[15] and rearrangement[16] reactions but we have not found a publication about its application in the amidation reactions of deactivated esters. The products were characterized thoroughly by spectral data, elementally analyses, and melting points.

EXPERIMENTAL

Melting points were determined on a Büchi B-540 melting-point determination unit and are uncorrected. H^1 NMR analyses (300 MHz) were performed on a Bruker Avance 300 spectrometer at 25°C. DMSO-d_6 was generally used as solvent, the exceptions are noted. HPLC purity and mass spectra were determined on a Waters LC-MS Alliance 2795 HPLC equipped with Waters 996 DAD UV detector, Waters 2700 autosampler, and Waters 600 controller connected to a Micromass ZMD mass spectrometer. Elementary analyses were performed on a Elemtar-Vario EL III CHMS elemental analyser.

General Experimental Procedure for the Amidation of 2-Acylamino-1-benzothiophene-3-carboxylic Acid Ethyl Esters

Lithium amide (10 mmol) was added in one portion to the solution of 1 mmol of 2-acylamino-1-benzothiophene-3-carboxylic acid ethyl ester (**A**) in absolute tetrahydrofurane (THF) in a dry flask. The air-tight closed reaction mixture was stirred at room temperature for 72 h. The reaction was monitored by thin-layer chromatography (TLC). After the starting material disappeared, the reaction mixture was poured onto 100 g of crushed ice with continuous stirring in a fume hood. The pH of the solution was adjusted to between 4 and 5 with 1 M aqueous HCl. The precipitated product was filtered out, washed with 10 mL of water and 10 mL of n-hexane, and dried. The crude product was recrystallized from 80% ethanol.

Data

2-acetamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, **1**

NMR (300 MHz, DMSO-d6): 11.36 (s, 1H, NH), 7.2 (bd, 2H, NH_2), 2.62 (bd, 4H, 4,7-CH_2), 2.12 (s, 3H, -CH_3), 1.71 (bs, 4H, 5,6-CH_2). LCMS m/z 237 $(M-H)^-$, rt: 2.74 min. Anal. calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76; S, 13.45. Found: C, 55.63; H, 5.90; N, 11.60; S, 13.17.

2-(Isobutyrylamino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, **2**

NMR (300 MHz, DMSO-d6): 11.75 (s, 1H, NH), 7.2 (bd, 2H, NH_2), 2.64 (m, 5H, 4,7-CH_2,CH), 1.72 (bs, 4H, 5,6-CH_2), 1.13 (d, 6H, $J = 6.90$ Hz). LCMS m/z 265 $(M - H)^-$, rt: 3.01 min. Anal. calcd. for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S, 12.04. Found: C, 58.11; H, 6.88; N, 10.64; S, 12.27.

2-[(Cyclopropylcarbonyl)amino]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, **3**

NMR (300 MHz, DMSO-d6): 11.54 (s, 1H, NH), 7.2 (bd, 2H, NH_2), 2.66 (m, 2H, 4-CH_2), 2.59 (m, 2H, 7-CH_2, $J = 5.7$ Hz), 1.85 (m, 1H, CH), 1.72 (bs, 4H, 5,6-CH_2), 0.86 (m, 4H, 2′,3′-CH_2). LCMS m/z 263 $(M - H)^-$, rt: 2.96 min. Anal. calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.91; H, 6.11; N, 10.81; S, 12.19.

2-[(2-Thienylcarbonyl)amino]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide, **4**

NMR (300 MHz, DMSO-d6): 12.90 (s, 1H, NH), 7.96 (d, 1H, 3′-CH, $J = 4.11$ Hz), 7.69 (d, 1H, 5′-CH, $J = 2.85$ Hz), 7.27 (dd, 1H, 4′-CH), 7.20 (bs, 2H, NH_2, $J = 3.87$ Hz), 2.74 (s, 2H, 4-CH_2), 2.65 (m, 2H, 7-CH_2), 1.75 (s, 4H, 5,6-CH_2). LCMS m/z 305 $(M - H)^-$, rt: 3.21 min. Anal. calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.88; H, 4.61; N, 9.14; S, 20.93. Found: C, 56.24.; H, 4.63; N, 9.41; S, 20.88.

N-(3-Carbamoyl-4,5,6,7-tetrahydro-1-benzothien-2-yl)-2-furamide, **5**

NMR (300 MHz, DMSO-d6): 12.70 (s, 1H, NH), 8.00 (d, 1H, 3′-CH, $J = 1.02$ Hz), 7.29 (d, 1H, 5′-CH, $J = 3.51$ Hz), 6.75 (bd, 1H, 4′-CH), 2.74 (s, 2H, 4-CH_2), 2.65 (s, 2H, 7-CH_2), 1.75 (s, 4H, 5,6-CH_2). LCMS m/z 289 $(M - H)^-$, rt: 3.11 min. Anal. calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65; S, 11.04. Found: C, 58.03; H, 4.91; N, 9.31; S, 11.16.

2-[(Cyclopropylcarbonyl)amino]-4,7-dihydro-5*H*-thieno[2,3-*c*]thiopyran-3-carboxamide, **6**

NMR (300 MHz, DMSO-d6): 11.38 (s, 1H, NH), 7.40 (bs, 2H, NH_2), 3.73 (s, 2H, 7-CH_2), 2.91 (d, 2H, 5-CH_2, $J = 4.65$ Hz), 2.86 (d, 2H,

4-CH_2), 1.92 (m, 1H, 1′−CH), 0.85 (m, 4H, 2′,3′-CH_2). LCMS m/z 281 $(M-H)^-$, rt: 2.83 min. Anal. calcd. for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9.92; S, 22.71. Found: C, 51.37; H, 5.09; N, 9.87; S, 22.64.

2-[(Cyclopropylcarbonyl)amino]-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxamide, **7**

NMR (300 MHz, DMSO-d6): 11.72 (s, 1H, NH), 7.25 (bd, 2H, NH_2), 4.60 (s, 2H, 7-CH_2), 3.80 (t, 2H, 5-CH_2, $J=5.34$ Hz), 2.76 (t, 2H, 4-CH_2, $J=4.74$ Hz), 1.86 (m, 1H, 1′-CH), 0.85 (m, 4H, 2′,3′-CH_2). LCMS m/z 265 $(M-H)^-$, rt: 1.53 min. Anal. calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.43; H, 5.27; N, 10.38; S, 11.84.

2-[(Cyclopropylcarbonyl)amino]-4,7-dihydro-5*H*-thieno[2,3-*c*]-thiopyran-3-carboxamide 6-oxide, **8**

NMR (300 MHz, DMSO-d6): 11.44 (s, 1H, NH), 7.46 (bs, 2H, NH_2), 4.07 (d, 1H, 7-CH_2), 3.90 (d, 1H, 7-CH_2), 3.22 (m, 2H, 5-CH_2), 2.97 (m, 2H, 4-CH_2), 1.95 (m, 1H, 1′-CH), 0.87 (m, 4H, 2′,3′-CH_2). LCMS m/z 297 $(M-H)^-$, rt: 0.40 min. Anal. calcd. for $C_{12}H_{14}N_2O_3S_2$: C, 48.30; H, 4.73; N, 9.39; S, 21.49. Found: C, 48.71; H, 4.66; N, 9.27; S, 21.30.

2-[(Cyclopropylcarbonyl)amino]-6-methyl-4,5,6,7-tetrahydrothieno-[2,3-*c*]pyridine-3-carboxamide, **9**

NMR (300 MHz, DMSO-d6): 11.74 (s, 1H, NH), 7.20 (bd, 2H, NH_2), 3.38 (s, 2H, 7-CH_2), 2.75 (m, 2H, 5-CH_2), 2.56 (m, 2H, 4-CH_2), 2.31 (s, 3H, NCH_3), 1.85 (m, 1H, 1′H), 0.84 (m, 4H, 2′,3′-CH_2). LCMS m/z 280 $(M+H)^+$, rt: 0.39 min. Anal. calcd. for $C_{13}H_{17}N_3O_2S$: C, 55.89; H, 6.13; N, 15.04; S, 11.48. Found: C, 55.50; H, 6.09; N, 15.3; S, 11.70.

2-[(Cyclopropylcarbonyl)amino]-1-benzothiophene-3-carboxamide, **10**

NMR (300 MHz, DMSO-d6): 12.00 (s, 1H, NH), 7.93 (d, 1H, 7-CH, $J=2.82$ Hz), 7.77 (s, 2H, NH_2), 7.41 (t, 1H, 5-CH, $J=7.71$), 7.29 (t, 1H, 6-CH, $J=7.47$ Hz), 2.01 (m, 1H, 1′-CH), 0.94 (m, 4H, 2′,3′-CH_2). LCMS m/z 259 $(M-H)^-$, rt: 2.99 min. Anal. calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 60.37; H, 4.65; N, 10.44; S, 12.04.

2-[(Cyclopropylcarbonyl)amino]-6-methyl-1-benzothiophene-3-carboxamide, **11**

NMR (300 MHz, DMSO-d6): 12.02 (s, 1H, NH), 7.83 (d, 1H, 5-CH, $J = 8.3$ Hz), 7.70 (s, 2H, NH_2), 7.68 (s, 1H, 7-CH), 7.23 (d, 1H, 4-CH), 2.40 (s, 3H, -CH_3), 1.98 (m, 1H, 1′-CH), 0.94 (m, 4H, 2′,3′-CH_2). LCMS m/z 273 $(M - H)^-$, rt: 3.56 min. Anal. calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.27; H, 5.11; N, 10.42; S, 11.50.

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