Gewald Synthesis of Aminothiophene Carboxylic Acids Providing New Dipeptide Analogues

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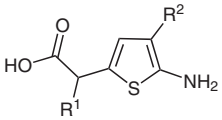
Abstract: A new multicomponent synthesis of 2-aminothiophene carbocyclic acids **4** by reaction of methyl 2-siloxycyclopropanecarboxylates **1**, alkyl cyanoacetates, and elemental sulfur is reported. This version of the Gewald thiophene synthesis rapidly provides a new type of δ-amino acids, which can be considered as dipeptide analogues. Smooth protective-group manipulations allowed regio- and chemoselective couplings with L-phenylalanine derivatives furnishing new tripeptide analogues such as **5** and **8** or products of type **10**.

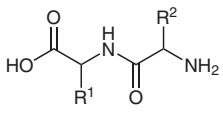
Key words: multicomponent reaction, thiophenes, cyclopropanes, amino acids, peptide analogues

The synthesis of substituted 2-aminothiophenes via condensation of carbonyl compounds with methylene active nitriles and elemental sulfur in the presence of organic bases was reported in the 1960s by Gewald and co-workers.[1] This novel multicomponent reaction turned out to become the most versatile and important method for the preparation of 2-aminothiophenes.[2] The thiophene scaffold is required for a broad range of products including dyes,[3] pharmaceuticals,[4] and agrochemicals.[2a] In addition, this heterocyclic core is present in several natural products.[5]

We explored the Gewald reaction as key step for the synthesis of unnatural amino acids **A** containing a thiophene backbone. Compounds **A** are δ-amino acids[6] and can be considered as isosters to a natural dipeptide **B** (Figure 1). We planned to use the conformationally restricted aminothiophene acids **A** as building blocks in the synthesis of linear and cyclic peptides and were therefore interested in their efficient and flexible preparation.



A



B

Figure 1 2-Aminothiophene carboxylic acids **A** as isosters of dipeptides **B**

In the original Gewald protocol ketones, aldehydes, or 1,3-dicarbonyl compounds were used to synthesize substituted thiophenes. We planned to employ vicinally donor-acceptor-substituted cyclopropanes such as **1**[7] serving as equivalents of carbonyl compounds **2**. The smooth in situ ring opening of **1** in protic solvents or in the presence of mild acids or fluoride reagent generates carbonyl compounds **2** (Figure 2). Our group already developed other multicomponent reactions employing cyclopropanes **1** as masked carbonyl compounds, which led to various functionalized heterocycles.[8]

1 **2**

Figure 2 Vicinally donor-acceptor-substituted cyclopropane derivatives **1** as equivalents of carbonyl compounds **2**

The aminothiophene derivatives **4a–d** were synthesized employing two different protocols. We applied the classical one-pot/one-stage Gewald procedure and an alternative one-pot/two-stage procedure. In the first method the methyl siloxycyclopropanecarboxylate **1a** reacts with the methylene active nitrile **3** in the presence of elemental sulfur and methanol to furnish thiophenes **4a–d**. In the alternative one-pot/two-stage process the siloxycyclopropanecarboxylates **1** were cleaved with a fluoride source to intermediate aldehydes **2** prior to addition of nitrile **3** and elemental sulfur (Scheme 1).

In general, thiophene derivatives **4a–d** were obtained in moderate to good yields (see Scheme 2). Method A provided aminothiophene **4a** (R^1 = H, R^2 = *t*-Bu) in 66% yield[9] whereas the alternative method B furnishes **4a** in a yield of only 44%.[10] The corresponding methyl ester **4b** (R^1 = H, R^2 = Me) was isolated in 43% using method A, whereas the use of the two-stage protocol afforded this compound in 54%. With benzyl cyanoacetate **3c** as precursor the 3-methoxycarbonyl-substituted thiophene **4b** (R^1 = H, R^2 = Me) was formed as a result of transesterification of the benzyl ester intermediate. However, using the two-stage protocol with DMF as solvent, the 3-benzyloxycarbonyl group was retained and thiophene derivative **4c** (R^1 = H, R^2 = Bn) was isolated in 44% yield.

Trisubstituted cyclopropane derivative **1b** bearing an additional benzyl substituent at C-1[11] was also used as starting material. The multicomponent reaction with **3a** (method A) furnished aminothiophene **4d** in moderate

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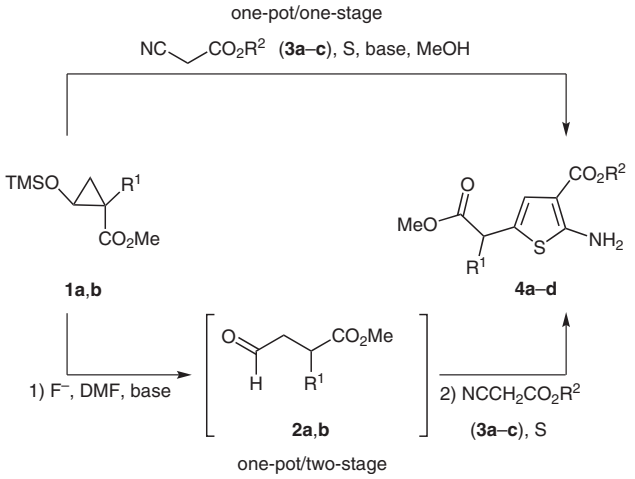
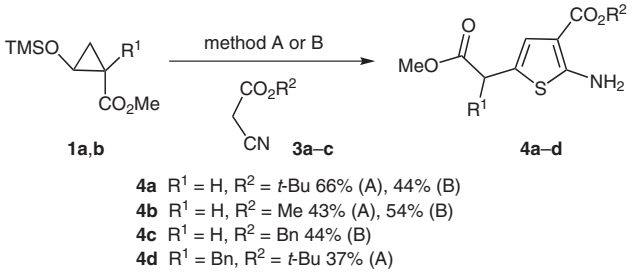


Scheme 1 Synthesis of 2-aminothiophene carboxylic acids **4a–d** via one-pot/one-stage Gewald reaction (method A) and the alternative one-pot/two-stage procedure (method B; for substituents R^1 and R^2 see Scheme 2)

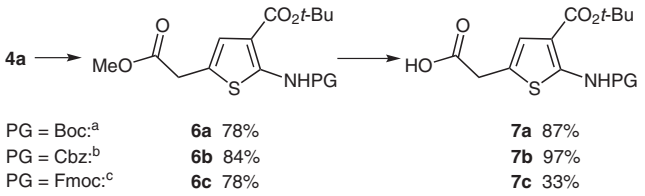


Scheme 2 Synthesis of thiophene derivatives **4a–d**. *Reagents and conditions*: method A: one-pot/one-stage procedure: **1a**,**b** (1.05 equiv), **3a–c** (1.0 equiv), S (1.0 equiv), Et_2NH (1.0 equiv), MeOH, reflux, 7 h, r.t., overnight; method B: one-pot/two-stage procedure: a) **1a** (1.05 equiv), DMF, Et_3N (2.9 equiv), $Et_3N{\cdot}HF$ (37%, 1.2 equiv), r.t., 1 h; b) **3a–c** (1.0 equiv), S (1.0 equiv.), 60–75 °C, 7 h, r.t., overnight.

37% yield. This product can be regarded as dipeptide isoster with a phenylalanine substructure. Other substituents at C-1 of the precursor cyclopropane **1** should allow the preparation of different aminothiophene carboxylic acids of type **4** mimicking other dipeptides.

We investigated the applicability of the aminothiophene carboxylic acids **4a–d** in the synthesis of small peptide analogues. Coupling of **4a** with N-Cbz-protected L-phenylalanine (Cbz–Phe–OH) using PyBOP as reagent[12] and DMAP in CH_2Cl_2 gave tripeptide analogue **5** in very good yield (Scheme 3).

The use of amino-protected thiophene carboxylic acids in peptide coupling reactions was also examined. Typical amino protective groups such as Boc, Cbz, and Fmoc[13] were effectively introduced transforming **4a** into **6a–c** (Scheme 4). Saponification of **6a** (PG = Boc) and **6b** (PG = Cbz) with LiOH at room temperature smoothly gave the corresponding carboxylic acids **7a** and **7b** in very good yields (87–97%). Hydrolysis of the Fmoc-protected derivative **6c** using 3 equivalents of LiOH at 0 °C furnished **7c** in only 33% yield. Not unexpectedly, the N-deprotected thiophene derivative was isolated in 29% as side product.[14]

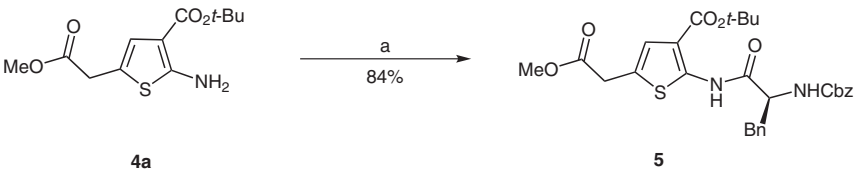


Scheme 4 Synthesis of amino-protected thiophene derivatives **6a–c** and amino-protected thiophene carboxylic acids **7a–c**. *Reagents and conditions*: protection: a) 1) Boc_2O (1.6 equiv), DMAP (1.0 equiv), MeCN, r.t., 10 min. 2) *t*-BuOH (1.6 equiv), MeCN, reflux, 62 h.[15] b) CbzCl (1.6 equiv), EtOAc, reflux, 1 d.[16] 3) FmocCl (1.2 equiv), Et_2O, 0 °C, 20 min, then r.t., 89 h.[17] Hydrolysis: a) LiOH (3.0 equiv), THF–H_2O (3:2), r.t., 24 h; b) LiOH (3.0 equiv), THF–H_2O (3:2), r.t., 2 h; c) 0.2 N LiOH (3.0 equiv), THF, 0 °C, 1 h.[18]

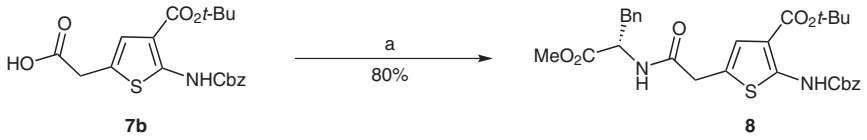
The PyBROP-mediated coupling[12] of carboxylic acid **7b** with L-phenylalanine methyl ester hydrochloride (H–Phe–OMe·HCl) in the presence of Hünig base provided the desired tripeptide analogue **8** in 80% yield (Scheme 5).

The presence of the methoxycarbonyl and the *tert*-butylcarbonyl groups allows clear differentiation of the two functional groups of compounds such as **6b**. The high yielding cleavage of the *tert*-butyl ester of **6b** was accomplished using trifluoroacetic acid in the presence of triethylsilane without touching the methyl ester (Scheme 6).[19] Components such as **9** may also serve as amino acid isosters, here with the potential to induce a β-turn.[20] Peptide coupling of thiophene carboxylic acid **9** with L-phenylalanine methyl ester hydrochloride (H–Phe–OMe·HCl) using BOP as reagent[12] and DMAP in CH_2Cl_2 yielded **10** in almost quantitative yield (Scheme 6).

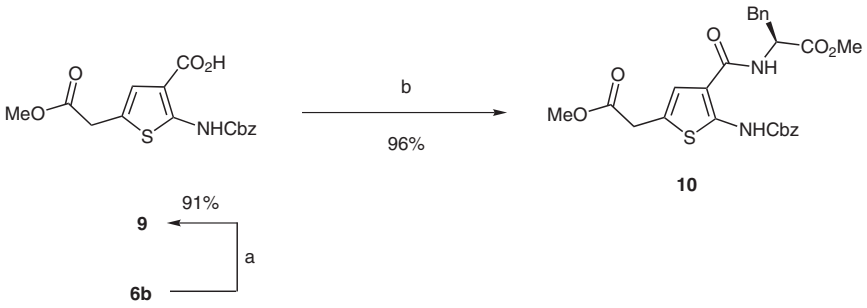
In conclusion, several 2-aminothiophene carboxylic acids are smoothly available by the multicomponent reaction employing siloxycyclopropanes in the Gewald reaction. We could demonstrate that selective protections and



Scheme 3 Synthesis of tripeptide analogue **5**. *Reagents and conditions*: a) Cbz–Phe–OH (1.2 equiv), PyBOP (1.5 equiv), DMAP (3.0 equiv), CH_2Cl_2, r.t., 24 h.



Scheme 5 Synthesis of tripeptide anlogue **8**. *Reagents and conditions*: a) H–Phe–OMe·HCl (1.0 equiv), PyBrOP (1.5 equiv), DIPEA (3.0 equiv), CH_2Cl_2, r.t., 24 h.



Scheme 6 Cleavage of the *tert*-butyl ester of N- and C-protected thiophene **6b** and synthesis of peptide analogue **10**. *Reagents and conditions*: a) TFA (13 equiv), Et_3SiH (2.5 equiv), CH_2Cl_2 (32 equiv), r.t., 12 h; b) Phe–OMe·HCl (1.0 equiv), BOP (1.5 equiv), DMAP (3.0 equiv), CH_2Cl_2, r.t., 24 h.

deprotections are possible affording precursors for peptide couplings in three different positions leading to new peptide analogues.[21] The synthesis of extended acyclic and of macrocyclic peptides incorporating the new 2-aminothiophenes will be reported in due course.

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References and Notes

(1) Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94.

(2) For a review on the synthesis of 2-aminothiophenes by Gewald reaction, see: (a) Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocycl. Chem.* **1999**, *36*, 333. For a review on multicomponent reactions of carbonyl compounds and derivatives of cyanoacetic acid, see: (b) Shestopalov, A. M.; Shestopalov, A. A.; Rodinovskaya, L. A. *Synthesis* **2008**, 1.

(3) Maradiya, H. R. *Turk. J. Chem.* **2001**, *25*, 441.

(4) (a) LaPorte, M. G.; Lessen, T. A.; Leister, L.; Cebzanov, D.; Amparo, E.; Faust, C.; Ortlip, D.; Bailey, T. R.; Nitz, T. J.; Chunduru, S. K.; Young, D. C.; Burns, C. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 100. (b) Gütschow, M.; Kuerschner, L.; Neumann, U.; Pietsch, M.; Löser, R.; Koglin, N.; Eger, K. *J. Med. Chem.* **1999**, *42*, 5437.

(5) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197.

(6) (a) Bonauer, C.; Zabel, M.; König, B. *Org. Lett.* **2004**, *6*, 1349. (b) Gervay, J.; Ramamoorthy, P. S.; Mamuya, N. N. *Tetrahedron* **1997**, *53*, 11039. (c) Gervay, J.; Flaherty, T. M.; Nguyen, C. *Tetrahedron Lett.* **1997**, *38*, 1493. (d) Baldauf, C.; Günther, R.; Hofmann, H.-J. *J. Org. Chem.* **2004**, *69*, 6214. (e) Sünnemann, H. W.; Hofmeister, A.; Magull, J.; de Meijere, A. *Chem. Eur. J.* **2006**, *12*, 8336.

(7) (a) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 512. For reviews of donor-acceptor-substituted cyclopropanes, see: (b) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

(8) (a) Reichelt, I.; Reissig, H.-U. *Synthesis* **1984**, 786. (b) Grimm, E. L.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 242. (c) Grimm, E. L.; Zschiesche, R.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 5543. (d) Ullmann, A.; Schnaubelt, J.; Reissig, H.-U. *Synthesis* **1998**, 1052. (e) Zimmer, R.; Ziemer, A.; Gruner, M.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Synthesis* **2001**, 1649. (f) Patra, P. K.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 4195. (g) Veljkovic, I.; Zimmer, R.; Reissig, H.-U.; Brüdgam, I.; Hartl, H. *Synthesis* **2006**, 2677.

(9) **Typical Procedure for the Synthesis of 2-Aminothiophene 4a Using the One-Pot/One-Stage Procedure**
Siloxycyclopropanecarboxylate **1a** (0.209 g, 1.06 mmol), *tert*-butyl cyanoacetate (0.143 g, 1.01 mmol) and sulfur (0.032 g, 1.01 mmol) were suspended in MeOH (2 mL), then Et_2NH (0.11 mL, 1.01 mmol) was added. The mixture was refluxed for 7 h, and then stirred overnight at r.t. After addition of water and EtOAc the layers were separated and the aqueous layer was extracted two times with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (SiO_2, hexane–EtOAc = 8:1 to 7:1 to 6:1) provided 0.180 g (66%) **4a** as a brownish oil.
Analytical Data for *tert*-Butyl 2-Amino-5-(2-methoxy-2-oxoethyl)thiophene-3-carboxylate (4a)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 3.56 (s, 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 5.90 (br s, 2 H, NH_2), 6.70 (s, 1 H, CH). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 28.3 [q, $C(CH_3)_3$], 35.0 (t, CH_2), 52.1 (q, OCH_3), 79.9 [s, $C(CH_3)_3$], 107.6 (s, C-2), 115.4 (s, C-5), 125.4 (d, C-4), 162.0 (s, C-3), 164.7, 170.9 (2 s, CO). IR (film): 3445–3255 (NH), 3070–2845 (CH), 1740, 1670 (C=O), 1590, 1500, 1455 (NH, CSNH) cm^{-1}. MS (EI, 80 eV, 60 °C): *m/z* (%) = 271 (14) $[M]^+$, 215 (59) $[M - C_4H_9]^+$, 197 (33) $[M - C_5H_{12}]^+$, 156 (100) $[M - C_5H_{12}O_2]^+$, 138 (61), 57 (37) $[C_4H_9]^+$. HRMS (EI, 80 eV, 60 °C): *m/z* calcd for $C_{12}H_{17}NO_4S$: 271.0878; found: 271.0880. Anal. calcd for $C_{12}H_{17}NO_4S$ (271.3): C, 53.12; H,

6.32; N, 5.16; S, 11.82. Found: C, 53.37; H, 6.43; N, 5.16; S, 11.95.

(10) We also prepared thiophene **4a** in 61% yield starting from commercially available aldehyde **2a** using a one-pot/one-stage Gewald procedure (method A). Although the result is comparable with the yield we achieved with cyclopropane **1a** the very high cost of aldehyde **2a** (100 mg, 77 €) is almost prohibitive for large-scale preparations of **4a**.

(11) Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 531.

(12) (a) For a review on recent development of peptide coupling reagents in organic synthesis, see: Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447. (b) For a review on chemical synthesis of natural product peptides, see: Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.

(13) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 4th ed.; Wiley: New York, **2006**.

(14) Alternatively, **7c** was synthesized in 59% overall yield by a reversed reaction sequence.

(15) Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1996**, *37*, 5861.

(16) Kruse, C. H.; Holden, K. G. *J. Org. Chem.* **1985**, *50*, 2792.

(17) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404.

(18) Burke, T. R.; Ye, B. Jr.; Akamatsu, M.; Ford, H.; Yan, X. Jr.; Kole, H. K.; Wolf, G.; Shoelson, S. E.; Roller, P. P. *J. Med. Chem.* **1996**, *39*, 1021.

(19) Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett.* **1992**, *33*, 5441.

(20) For reviews, see: (a) Hirschmann, R. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1278; *Angew. Chem.* **1991**, *103*, 1305. (b) Giannis, A.; Kolter, T. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244; *Angew. Chem.* **1993**, *105*, 1303.

(21) During peptide couplings presented here we did not observe racemization of the amino acid moiety since subsequent couplings with a second amino acid provided only one diastereomer.