Cyanoacetamide MCR (III): Three-Component Gewald Reactions Revisited

Kan Wang, Dabin Kim, and Alexander Dömling*

University of Pittsburgh, Drug Discovery Institute, Pittsburgh 15261

Received October 4, 2009

Cyanoacetic acid derivatives are the starting materials for a plethora of multicomponent reaction (MCR) scaffolds. Here we describe valuable general protocols for the synthesis of arrays of 2-aminothiophene-3-carboxamides from cyanoacetamides, aldehydes or ketones, and sulfur via a Gewald-3CR variation. In many cases the reactions involve a very convenient work up by simple precipitation in water and filtration. More than 40 new products are described. We foresee our protocol and the resulting derivatives to become very valuable to greatly expanding the MCR scaffold space of cyanoacetamide derivatives.

In 1966 the German chemist Prof. Karl Gewald discovered that methylene-active carbonyl compounds reacted with methylene-active nitriles and sulfur at ambient temperature to yield 2-aminothiophenes.[1] This reaction constitutes a very versatile and useful multicomponent reaction (MCR).[2−4] As often found with MCRs, the reaction conditions are simple and do not foresee protection from atmosphere or moisture and are easily amenable to up-scaling (Figure 1).

In addition, this transformation is remarkable because it consists of one of the few organic reactions incorporating elemental sulfur at ambient temperature. Other examples are the Asinger-3CR and the Wilgeroth Kindler reaction.[5,6] The importance of the Gewald reaction steams from the formation of 2-aminothiophene which is abundantly used in the pharmaceutical industry to produce bioactive compounds.[3,4] The 2-amino-3-carbonyl thiophene is bioisostere to the anthranilic acid which per se is an important bioactive scaffold.[7] As opposed to anthranilic acid derivatives, however, which are difficult to access and only a few are commercially available, the Gewald-3CR allows virtually infinite access to substituted bioisostere 2-amino-3-carboxythiophenes. A prominent example of the thiophene-phenol bioisosterie is the atypical antipsychotic blockbuster drug olanzepine for the treatment of schizophrenia and bipolar disorder (Scheme 1).[8] The pharmacokinetic/dynamic properties of olanzapine are presumably even enhanced over the bioisosteric clozapine.

In addition, Gewald-3CR primary products are the starting materials for many other compound classes such as kinase inhibitor thienopyrimidines **1**,[9] thienoquinazolines **2**,[10] pyrimidines **3** and **4**,[11] diazocompounds **5**,[12] Schiff bases **6**,[13] tetracyclic thienopyrimidinones **7**,[14] and *N*-thieno-maleinicacid amides **9**[15] as shown in Scheme 2, just to name a few.

The scope of the Gewald-3CR, however, in the past was hampered by the almost exclusive use of structurally simple not variable activated nitrile components, for example, malonodinitrile, cyanoacetophenones,[16] cyanoacetic acid esters, and primary cyanoacetamides. Rarely, cyanoacetamides have been used as potentially versatile component in the Gewald-3CR. In cases where cyanoacetamides have been used they were based on aromatic amides or hydrazides.[17] In fact only very few references could be found using aliphatic amine derived cyanoacetamides in the Gewald-3CR.[18] Thus the Gewald-3CR can be described as a MCR with rather low dimensionality similar to the Hantzsch dihydropyrimidine and the Biginelli reaction, where the main variable component is the oxo component.[19] Examples of high dimensional MCRs are isocyanide-based MCRs, for example, Ugi, Passerini, and van Leusen reactions, where all of the components can be broadly varied.[20] To solve the problem of low dimensionality, we describe herein a major extension of current Gewald-3CR by introducing aliphatic cyanoacetamides as generally useful components and thus rendering the Gewald MCR with effectively only *one* diversity point in the past into a MCR comprising *two* highly variable inputs.

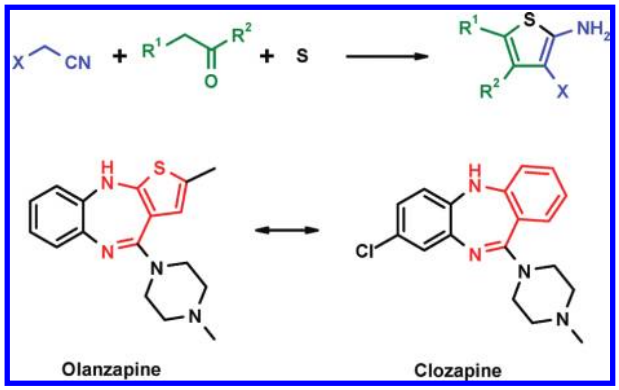
Recently, we communicated a versatile and experimentally very simple access to arrays of cyanoacetamides by the solventless mixing of methyl cyanoacetate and primary and secondary amines and filtration of the formed products.[21] Having easy access to such large arrays, we investigated the versatile MCR chemistry of this compound class.[22] We intended to investigate the Gewald-3CR of cyanoacetamides, and we herein report our results. First we reacted several cyanoacetamides with methylene active oxo components and sulfur in ethanol at 70 °C for several hours. Upon cooling to room temperature, no product precipitated, and TLC and HPLC MS analysis indicated several reaction products and even some left starting materials. We then experimented with addition of water and temperature, and indeed by pouring the reaction mixture into water and cooling to 0 °C, we noticed after some time the formation of significant precipitate. Filtration of the precipitate and NMR and HPLC analysis of it reveal Gewald products with purity of >95% and good yields. To elaborate a general procedure, we investigated several more reactions with different functional groups in the side chains (hydrophilic and hydrophobic, basic) and to our delight in all investigated cases we noticed

* To whom correspondence should be addressed. E-mail: asd30@pitt.edu.

10.1021/cc9001586
Published on Web 12/03/2009

Figure 1. Simple to perform large scale open vessel Gewald-3CR (courtesy of Prof. Ulrich Jordis, Vienna).

Scheme 1. Gewald-3CR and Phenol-Thiophene Based Biosisosterie between the Drugs Olanzapine and Clozapine



the formation of considerable product precipitation. Again after filtration and drying we noticed exceptional high purity in all cases. Next we synthesized an array of >40 Gewald compounds in parallel by the above procedure. Over a wide range of functional groups and substitutents, we isolated the products in moderate to good to high yields but always in excellent purity. We used 16 different ketones and aldehydes (**A1**-**A16**, Figure 2). To figure scope and limitations of the cyanoacetamide component we used 23 differentially substituted starting materials (**B1**-**B24**, Figure 2).

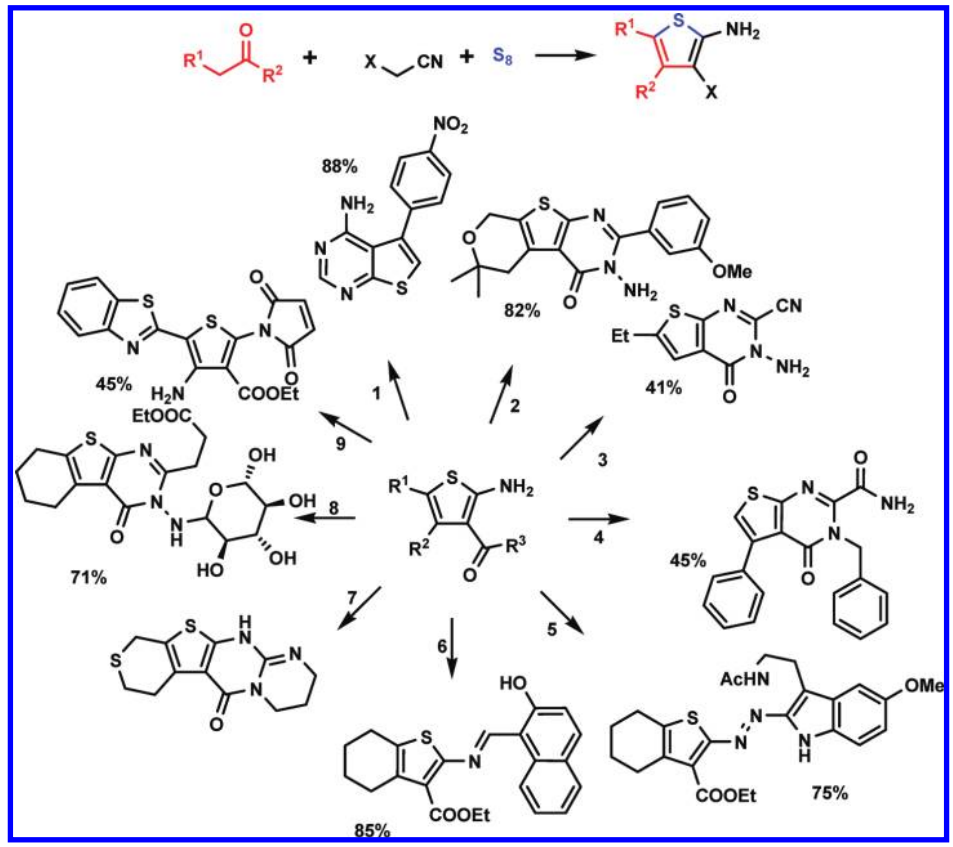
The purification of products differs depending on the solubility properties of the products. For some reactions, no solid could be filtered after water addition; for a few compounds, purities were less than 90% by HPLC-MS and NMR analysis, these crude products were purified by silica gel column chromatography. The products and their yield are shown in Table 1.

Some additional observations were made. For the phenolic starting material **B17** the Gewald reaction with 1 equiv of triethylamine base produced no target compound, but the condensation product (**D6,17**). Addition of two more equivalents of triethylamine, however, produced the product (**C6,17**) in 82% yield (Scheme 3). The basic condition is critical for the cyclization step.

Acetaldehyde (**A1**), which has a low boiling point, is not a good starting material for the Gewald 3-CR. However, the commercially available compound, 1,4-dithiane-2,5-diol (**A1′**), which is the dimer of the precondensation product 2-mercapto acetaldehyde (**A1″**) of acetaldehyde and sulfur, is a good substitute for acetaldehyde in the Gewald reaction.[23]

Other aldehyde with α-methylene moiety (**A2**-**A7**) also have good Gewald reactivity. The reaction performs well by simply mixing each 1 equiv of cyanoacetamides, sulfur, aldehyde, or ketones and triethylamine in the ratio of 1:1:1:1 in ethanol solvent, and generally good yields are obtained. A Boc protected chiral β-amino aldehyde (**A7**) was treated into this reaction with different cyanoacetamides to produce corresponding products (**C7**−**1,10,14,18,19,20,23**) with good yield (70−90%). It is interesting that two enantiomerically pure starting materials (**A7** and **B20**) produce the thiophene **C7,20** with not even traces of another diastereomer observed (Scheme 4). There is no significant racemization observed despite the fact that the reaction is base promoted. But in the reaction with another cyanoacetamide **B23**, which is derived from the methyl ester of valine amino acid, the corresponding product **C7,23** contains

Scheme 2. Diversity of Secondary Reactions Based on the Initial Gewald-MCR



two diastereomers in a 2:1 ratio; the result indicates that strong epimerization happens at the valine moiety under basic conditions. 2-Deoxy-D-ribose (**A8**), which contains three free hydroxyl groups, does not produce the target product under the conditions used here.

The Gewald reaction can be applied in the synthesis of thiophenediazepine.[24] For example the cyanoacetamides **B23** could be prepared simply from methyl ester of (*S*)-valine chloride salt with methyl cyanoacetate in the presence of 2 equiv of triethylamine without additional solvent. After Gewald reaction with aldehyde and sulfur, the desired thiophenes (**C2,23**, **C6,23** and **C7,23**) are generated in good yield. These intermediates would provide a different way to thiophenediazepine-2,5-diones (**E,** Scheme 5). The detailed cyclization conditions are in progress in our lab and will be reported in the future.

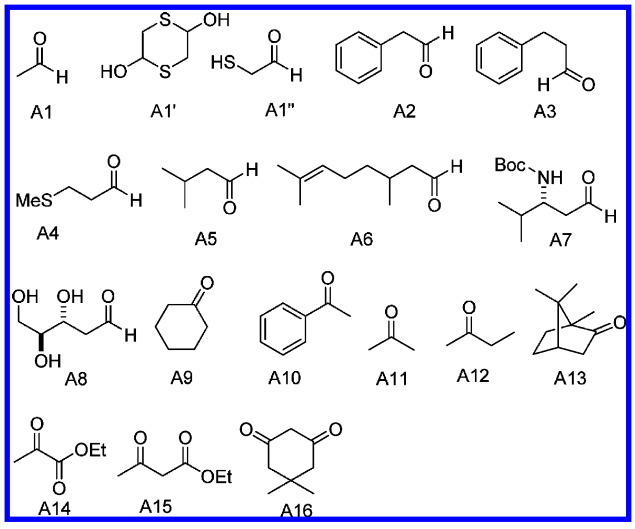


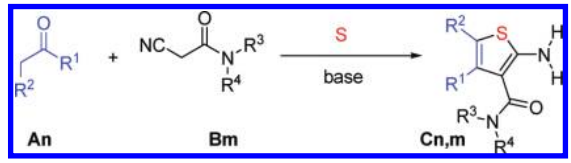
Figure 2. Aldehyde and ketone starting materials.

Ketone starting materials produced far poorer result compared to aldehyde staring materials. Cyclohexanone (**A9**) only produced less than 20% yield with 3 cyanoacetamides (**B1**, **B6** and **B11**) under the conditions used. The corresponding reaction with methyl cyanoacetate had obtained a much higher yield. Acetophenone (**A10**) produced target product **C10,3** in less than 10% yield, and it is difficult to purify the product. Other ketones, including acetone (**A11**), 2-butone (**A12**), (*R*)-camphor (**A13**), dimedone (**A16**), ethyl acyacetate (**A14**), and ethyl pyruvate (**A15**) do not yield the Gewald products at all under the herein described reaction conditions; despite starting materials were observed after the reactions were stopped. In many references therefore the use of precondensed Knoevenagel intermediates is described.[25]

Discussion

We herein describe a convenient way to synthesize arrays of Gewald thiophene-3-amides. The convenience of this procedure is based on two points: first, the reaction can be performed in many cases in a way that the Gewald products precipitate, and this leads to high quality products without the need to run time and cost intensive purifications. Second, the starting material class of cyanoacetamides was recently described by us to be accessible in a very convenient way by simply mixing methyl cyanoacetate with an appropriate primary or secondary amine, thus leading to potentially large arrays of starting materials for subsequent cyanoacetamide dependent MCRs. This extension of the Gewald-3CR is significant since

Table 1. Gewald Reaction to Prepare 2-Amino-thiophene-carboxamides (**Cn,m**)



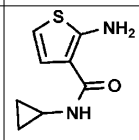
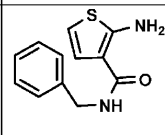
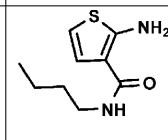
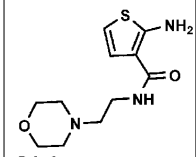
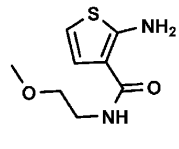
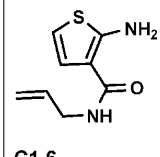
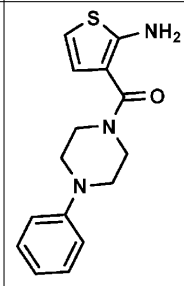
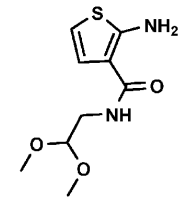
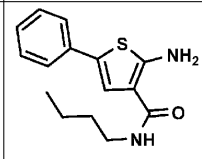
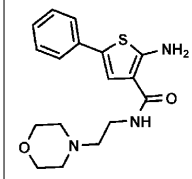
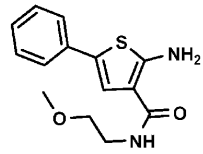
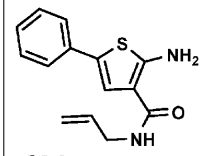
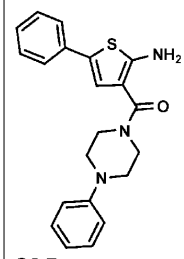
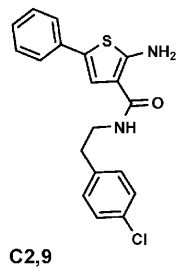
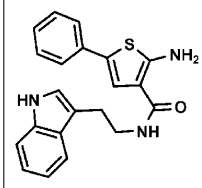
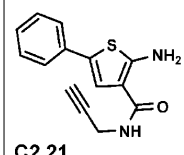
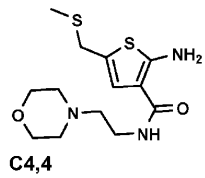
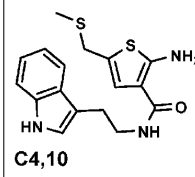
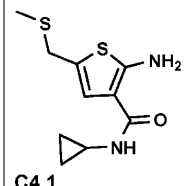
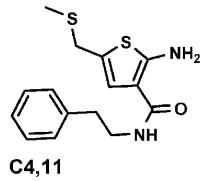
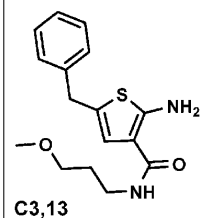
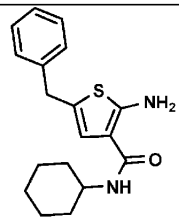
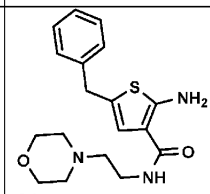
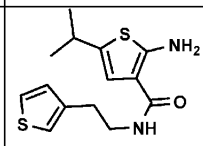
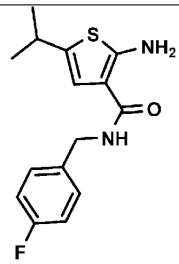
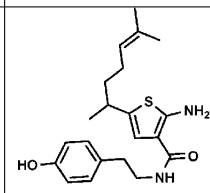
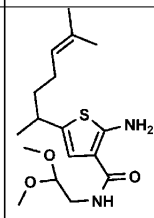
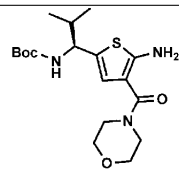
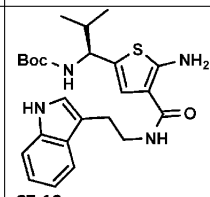
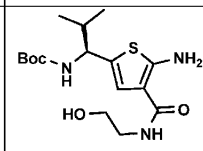
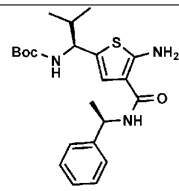
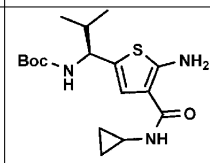
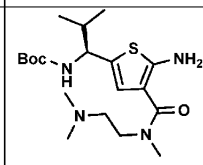
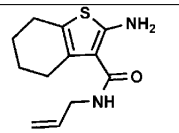
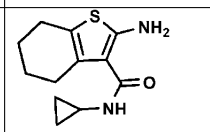
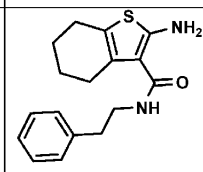
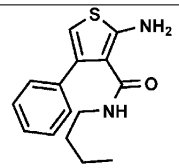
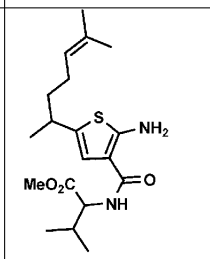
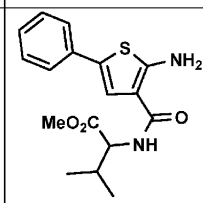
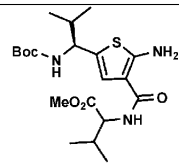
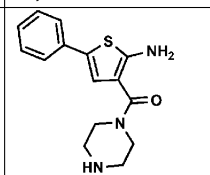
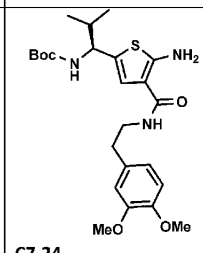
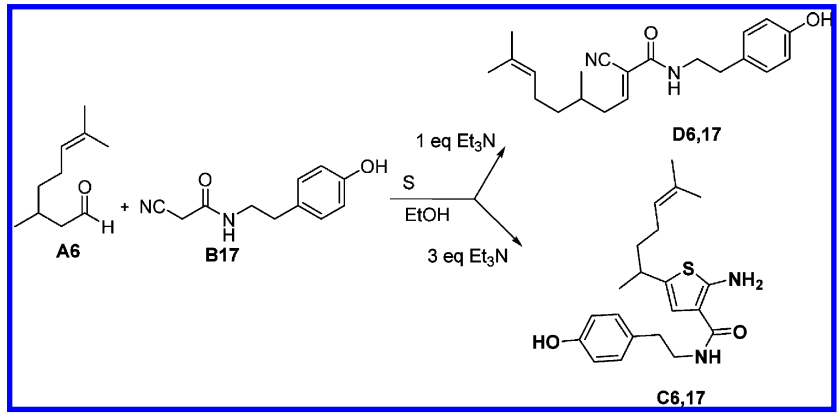
yield	Structure	yield	Structure	yield	Structure
45 %	 **C1,1**	56 %	 **C1,2**	60 %	 **C1,3**
62 %	 **C1,4**	41 %	 **C1,5**	38 %	 **C1,6**
70 %	 **C1,7**	65 %	 **C1,8**	70 %	 **C2,3**
78 %	 **C2,4**	75 %	 **C2,5**	82 %	 **C2,6**
90 %	 **C2,7**	72 %	 **C2,9**	85 %	 **C2,10**
77 %	 **C2,21**	52 %	 **C4,4**	60 %	 **C4,10**
64 %	 **C4,1**	75 %	 **C4,11**	70 %	 **C3,13**

Table 1. Continued

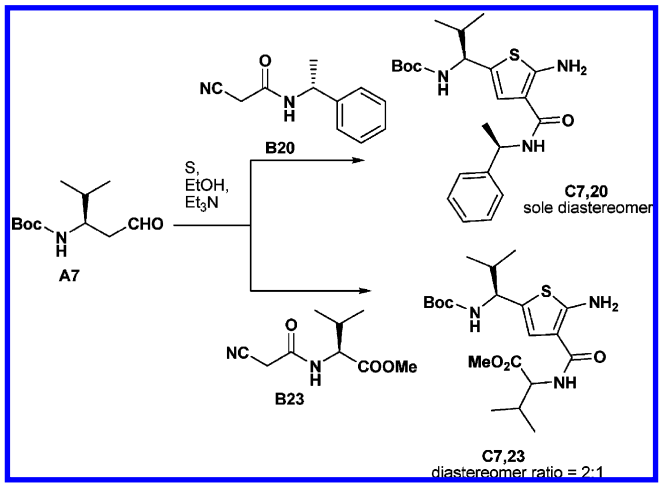
yield	Structure	yield	Structure	yield	Structure
95 %	 C3,12	75 %	 C3,4	74 %	 C5,16
67 %	 C5,15	90 %	 C6,17	50 %	 C6,8
75 %	 C7,18	84 %	 C7,10	86 %	 C7,14
90 %	 C7,20	90 %	 C7,1	71 %	 C7,19
17 %	 C9,6	19 %	 C9,1	20 %	 C9,11
9 %	 C10,3	65 %	 C6,23	78 %	 C2,23
84 %	 C7,23	24 %	 C2,22	93 %	 C7,24

in the past mostly simple and non variable malondinitrile, cyanoacetic acid, and their esters or hydrazides where used. Thus Gewald reaction variability in the past was mostly confined to the variation of the α-methylene oxo component

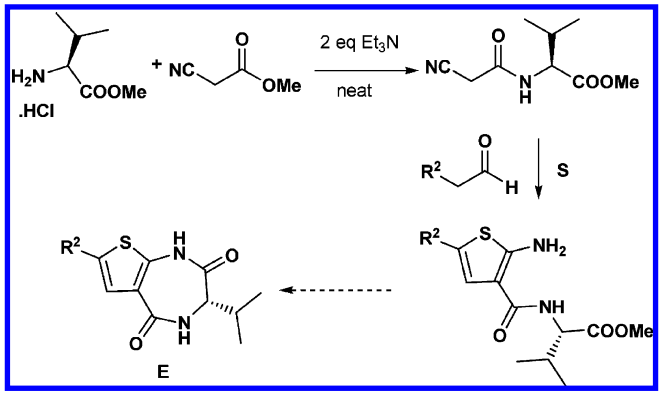
Scheme 3. Different Products Depending on Added Base Amounts



Scheme 4. Gewald-3CR of Chiral Starting Materials



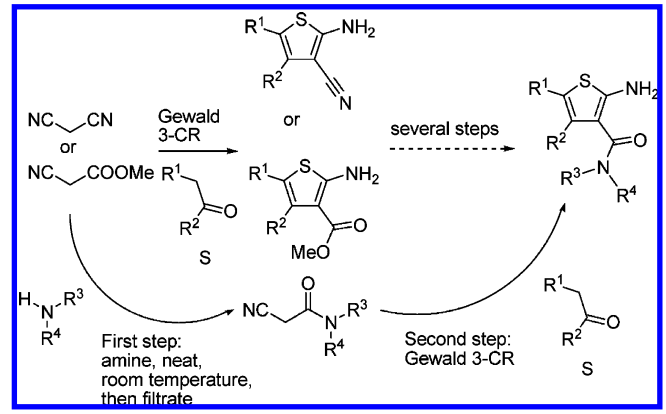
Scheme 5. Amidation-Gewald-Cyclization Sequence to Thiophenediazepine



and the secondary reactions of their primary Gewald products. The herein described and generally shown reaction of sulfur, and cyanoacetamides, however renders the Gewald-3CR a truly variable MCR with two points of diversity.

There are two routes to prepare 2-aminothiophene-3-carboxamides (Scheme 6). The first route uses the classical Gewald products 2-amino-3-cyanothiophene or 2-aminothiophene-3-carboxylic methyl esters resulting from malonodinitrile or methyl cyanoacetate, and further transformations after several additional steps lead to 2-aminothiophene-3-carboxamides. Thus, amide-substituted Gewald products have been described from the corresponding esters by the sequence saponification, activation and coupling or other methods, however in poor yields and lengthy sequences.[26]

Scheme 6. Different Route to 2-Aminothiophene-3-carboxamides



This route involves more steps and is less efficient, the yields, although potentially higher per step, at the end are always lower after several reaction steps. Additionally these reactions often involve harsh conditions.[26] The second herein described route starts from cyanoacetamides, which are easily and conveniently prepared from methyl cyanoacetate in a single step and on a gram scale if needed. In a one-step three-component Gewald reaction, 2-aminothiophene-3-carboxamides can be produced in high diversity. The advantage of the second route seems obvious.

The scope of this reaction is large (Table 1). Different cyanoacetamides work fine in the Gewald-3CR, and many function groups were tolerated (Figure 3), including alkenyl (**B6**), alkynyl (**B21**), acetal (**B8**), alcohol hydroxyl (**B14**), phenol (**B17**), indole (**B10**), ester (**B23**), secondary amino (**B22**), and tertiary amino (**B4**, **B7** and **B19**). Regarding the α-methylene oxo component we observed that aldehydes are superior substrates to ketones and generally react faster, more completely and give higher yields. The more hydrophobic the resulting Gewald product, the greater the isolated yield. This is a direct consequence of the workup procedure by aqueous precipitation. Amino acid side chains have been introduced at several positions of the Gewald scaffold thus rendering this chemistry potentially useful for the synthesis of peptidomimetics (**C4,m** methionine; **C3,m** and **Cn,2** phenylalanine; **C5,m** and **Cn,23** valine; **Cn,10** tryptophan). Compound **C7,23**, for example can be considered as a peptidomimetic containing the two valine amino acids encompassed on a stiff Gewald heterocycle. To show the potential to act as peptidomimetic we computationally

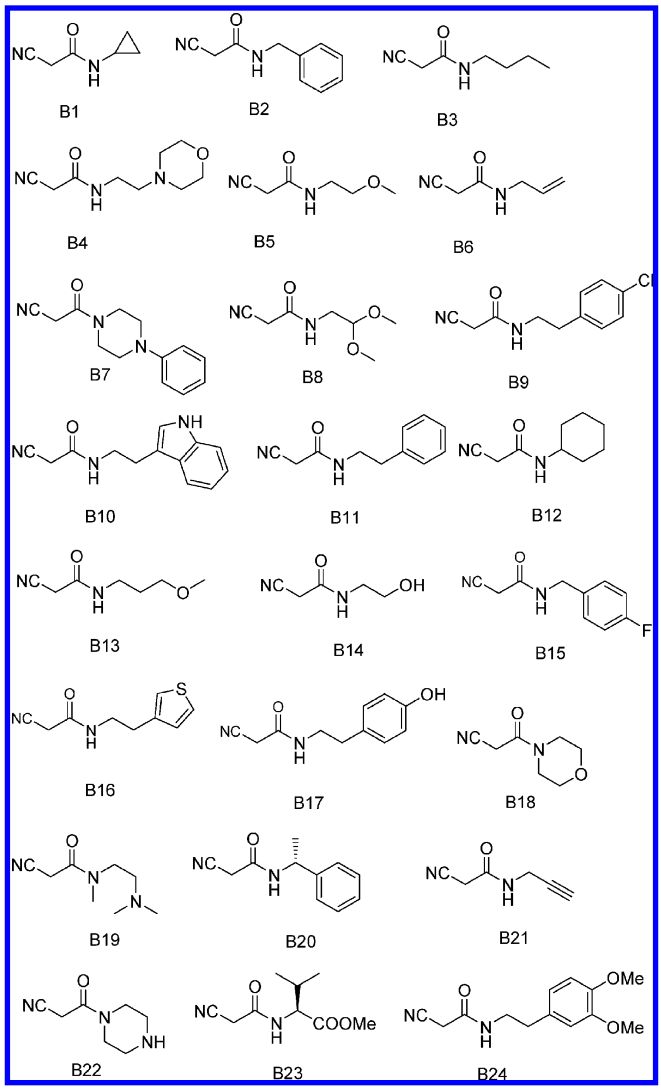


Figure 3. Cyanoacetoamide starting materials.

optimized the 3D-structure and overlapped it with an α-helix. As can be seen in Figure 4 there is a good overlap implying that such molecule might act as α-helix mimetic. The α-helix mimetics recently have become very important lead structures to (ant-)agonize protein protein interactions, for example, in p53/Hdm2, p53/Hdm4, or Bcl2 family members.[27]

Combinatorial chemistry is an important discipline in organic chemistry and highly useful to the pharmaceutical industry since the majority of drug discovery projects currently rely on high throughput screening of large compound collections. Gewald reactions have been described to be purification intensive in the past. Improvements to overcome this issue and to increase synthesis speed have been solid phase bound synthesis.[29] However, these methods have attached issues, such as low compound generation and the use of often special linker systems which compromise the chemistry. Other generally used methods include mass triggered automatic preparative HPLC or the faster and more efficient SC−CO_2−HPLC. The use of automatic HPLC purification systems, however, is expensive and needs special equipment. The best organic chemistry workup procedures can avoid chromatography and can purify the products by extraction and/or crystallization. These procedures are of particular value in the context of parallel synthesis since

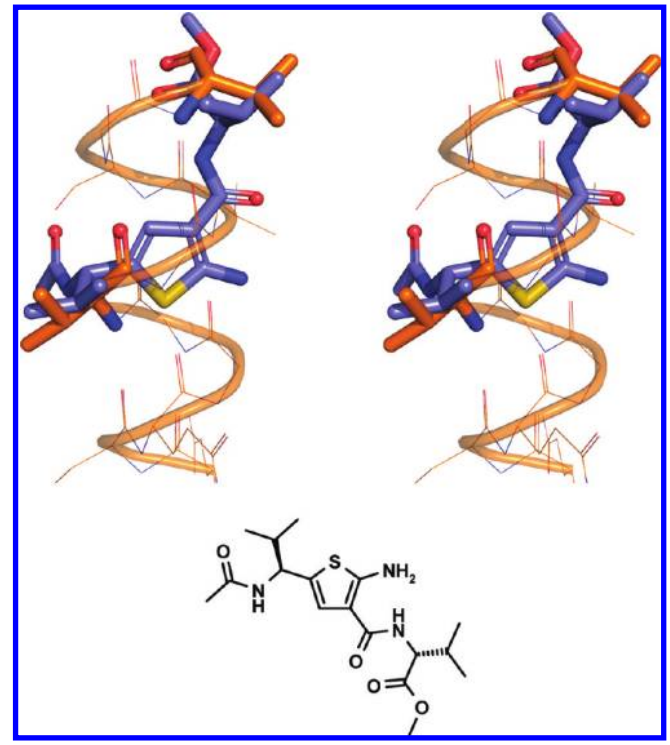


Figure 4. Stereoview of an overlap of an amphiphatic α-helix with two valine in *i* and *i*+*6* positions (orange sticks) with a Gewald thiophene-derived dipeptide mimetic (blue sticks). The small molecule derived from aldehyde **A7**, cyanoacetamide **B23**, sulfur was deprotected and *N*-acylated and then energy minimized using the MOLOC software.[28] An important feature of the Gewald-thiophene derivatives of cyanoacetamides is the intramolecular hydrogen bonding of the 2-amino group with the 3-amide carbonyl, reducing the conformational freedom of the amide group considerably. In support of the above hypothetical structure, the intramolecular hydrogen bridge can be seen in most of the published X-ray structure analysis.[4]

herein all efforts are multiplied. Therefore we believe that our described often chromatography free Gewald-3CR procedure based on simple precipitation and filtration is an advance in Gewald chemistry. Equally important is the general use of cyanoacetic acid amides as highly variable class of compounds in the Gewald-3CR which renders this reaction a true MCR with two highly variable inputs instead of mostly one in the past. Thus a skilled lab worker using very simple equipment can synthesize hundreds of Gewald products in a short time frame on a multi milligram scale with very high purity including the synthesis of the required cyanoacetamide building blocks.[20] In summary, the herein described modified Gewald-3CR procedure allows for the robust, fast, resource saving, and efficient construction of large arrays of highly substituted 3-amido-2-aminothiophenes.

Experimental Section

2-Amino-5-benzyl-*N*-cyclohexylthiophene-3-carboxamide (C3,12): General Condition of Gewald-3CR. A 20 mL vial with stir bar is charged with 3-phenylpropanal (**A3**, 670 mg, 5 mmol), 2-cyano-*N*-cyclohexylacetamide (**B12**, 830 mg, 5 mmol), sulfur (160 mg, 5 mmol), and triethylamine (505 mg, 5 mmol) in ethanol (5 mL, 1.0 M solution). The reaction is heated 60 °C in an oil bath for 10 h. Then, the reaction was cooled down to room temperature. A batch of 50 mL

ice water was poured into the mixture to yield a precipitate which was filtered and washed with cold ethanol to obtain 1.490 g (95%) of the title compound as brown powder. HR-MS ESL-TOF for $C_{18}H_{22}N_2OSNa$ ($M+Na^+$) found: *m/z*: 337.1362; Calc. Mass: 337.1351. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.31 (t, $J = 7.8$ Hz, 2H), 7.19−7.25 (m, 3H), 6.37 (s, 1H), 5.96 (s, 2H), 5.41 (d, $J = 7.2$ Hz, 1H), 3.92 (s, 2H), 3.80−3.90 (m, 1H), 1.97 (dd, $J = 12.6$, 3.0 Hz, 2H), 1.73 (dt, $J = 12.6$, 3.0 Hz, 2H), 1.38 (qt, $J = 13.2$, 3.0 Hz, 2H), 1.12−1.18 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.0, 159.8, 139.8, 128.6, 128.5, 126.7, 125.8, 119.8, 108.4, 47.9, 36.0, 33.6, 25.6, 25.1 ppm.

Acknowledgment. We thank Prof. Ulrich Jordis (Technical University Vienna, Austria) for Figure 1 of a large scale Gewald reaction (3.5 liter volume, 1 mol). This research has been partially supported by Grant GM087617 from the National Institutes of Health.

Supporting Information Available. Proton and carbon NMR, HR MS characterization and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Gewald, K.; Schinke, E.; Bottcher, H. *Chem. Ber.* **1966**, *99*, 94–100.
(2) Mayer, R.; Gewald, K. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 294–306.
(3) Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocyclic Chem.* **1999**, *36*, 333–345.
(4) Huang, Y., Dömling, A. *Mol. Diversity* **2009**, in press.
(5) (a) Asinger, F. *Angew. Chem.* **1956**, *68*, 413–413. (b) Asinger, F.; Thiel, M.; Pallas, E. *Liebigs Ann. Chem.* **1957**, *602*, 37–49. (c) Asinger, F.; Offermanns, H. *Angew. Chem.* **1967**, *79*, 953–956. (d) Asinger, F.; Leuchtenberg, W.; Offermanns, H. *Chem. Zeitung* **1974**, *98*, 610–615. (e) Asinger, F.; Gluzek, K. H. *Monats. Chem.* **1983**, *114*, 47–63.
(6) (a) Willgerodt, C. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2467–2469. (b) Willgerodt, C.; Merck, F. H. *J. Prakt. Chem.* **1909**, *80*, 192–195. (c) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431* (193), 222–224.
(7) Wiklund, P.; Bergman, J. *Curr. Org. Synth.* **2006**, *3*, 379–402.
(8) Meltzer, H. Y.; Fibiger, H. C. *Neuropsychopharmacology* **1996**, *14*, 83–85.
(9) Barnes, D. M.; Haight, A. R.; Hameury, T.; McLaughlin, M. A.; Mei, J. Z.; Tedrow, J. S.; Toma, J. D. R. *Tetrahedron* **2006**, *62*, 11311–11319.
(10) Mkrtchyan, A. P.; Noravyan, A. S.; Petrosyan, V. M. *Chem. Heterocycl. Compd.* **2002**, *38*, 238–241.
(11) Zavarzin, I. V.; Smirnova, N. G.; Chernoburova, E. I.; Yarovenko, V. N.; Krayushkin, M. M. *Russ. Chem. Bull.* **2004**, *53*, 1257–1260.
(12) Doss, S. H.; Mohareb, R. M.; Elmegeed, G. A.; Luoca, N. A. *Pharmazie* **2003**, *58*, 607–613.
(13) Roman, G.; Andrei, M. *Glasnikna Hemicaritei Tehnolozitena Makedonija* **2001**, *20*, 131–136.
(14) Frohlich, J.; Shaifullah Chowdhury, A. Z. M.; Hametner, C. *ARKIVOC* **2001**, 163–172.
(15) Elkholy, Y. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 115–122.
(16) See for example: Baraldi, P. G.; Zaid, A. N.; Lampronti, I.; Fruttarolo, F.; Pavani, M. G.; Tabrizi, M. A.; Shryock, J. C.; Leung, E.; Romagnoli, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1953–1957.
(17) (a) Bogolubsky, A. V.; Ryabukhin, S. V.; Plaskon, A. S.; Stetsenko, S. V.; Volochnyuk, D. M.; Tolmachev, A. A. *J. Comb. Chem.* **2008**, *10*, 858–862. (b) Hazra, K.; Saravanan, J.; Mohan, S. *Asian J. Chem.* **2007**, *19*, 3541–3544. (c) Hesse, S.; Perspicace, E.; Kirsch, G. *Tetrahedron Lett.* **2007**, *48*, 5261–5264. (d) Kovalenko, S. M.; Vlasov, S. V.; Chernykh, V. P. *Heteroatom Chem.* **2007**, *18*, 341–346. (e) Kovalenko, S. N.; Vlasov, S. V.; Chernykh, V. P. *Zhurnal Organichnoi ta Farmatsevtichnoi Khimii* **2006**, *4*, 43–46. (f) Nikolakopoulos, G.; Figler, H.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2006**, *14*, 2358–2365. (g) Huang, W.; Li, J.; Tang, J.; Liu, H.; Shen, J.; Jiang, H. *Synth. Commun.* **2005**, *35*, 1351–1357. (h) Treu, M.; Karner, T.; Kousek, R.; Berger, H.; Mayer, M.; McConnell, D. B.; Stadler, A. *J. Comb. Chem.* **2008**, *10*, 863–868.
(18) (a) Patra, B. R.; Mohan, S.; Saravanan, J. *Asian J. Chem.* **2007**, *19*, 4368–4372. (b) Al-Mousawi, S. M.; Abdelhamid, I. A.; Moustafa, M. S. *ARKIVOC* **2007**, 213–221. (c) Arhin, F.; Belanger, O.; Ciblat, S.; Dehbi, M.; Delorme, D.; Dietrich, E.; Dixit, D.; Lafontaine, Y.; Lehoux, D.; Liu, J.; McKay, G. A.; Moeck, G.; Reddy, R.; Rose, Y.; Srikumar, R.; Tanaka, K. S. E.; Williams, D. M.; Gros, P.; Pelletier, J.; Parr, T. R., Jr.; Far, A. R. *Bioorg. Med. Chem.* **2006**, *14*, 5812–5832. (d) Weber, K. H.; Daniel, H. *Liebigs Ann. Chem.* **1979**, 328–33.
(19) (a) Hantzsch, A. *Chem. Ber.* **1881**, *14*, 1637–1638. (b) Biginelli, P. *Chem. Ber* **1891**, *24*, 1317–1319, and 2962−2965.
(20) Dömling, A. *Chem. Rev.* **2006**, *126*, 17–89.
(21) Wang, K.; Nguyen, K.; Huang, Y.; Dömling, A. *J. Comb. Chem.* **2009**, *11*, 920–927.
(22) For example, for the 3-CR synthesis of 2-amino-1*H*-pyrrole-3-carboxamide, see: Wang, K.; Dömling, A. *Chem. Biol. Drug Des.* **2009**, submitted for publication.
(23) (a) See ref 18d;(b) Nagaoka, H.; Hara, H.; Mase, T. *Heterocycles* **1990**, *31*, 1241−1244; (c) Walser, A.; Flynn, T.; Mason, C.; Crowley, H.; Maresca, C.; Yaremko, B.; O'Donnell, M. *J. Med. Chem.* **1991**, *34*, 1209–1221.
(24) The Gewald-Ugi-Deprotection-Cyclization (GUDC) strategy for preparing thiophenediazepine, see: (a) HuangY. J.; Dömling, A. unpublished result;(b) Walser, A.; Flynn, T.; Mason, C. *J. Heterocycl. Chem.* **1991**, *28*, 1121–1125. (c) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Cruz-Lopez, O.; Iaconinoto, M. A.; Preti, D.; Shryock, J. C.; Moorman, A. R.; Vincenzi, F.; Varani, K.; Andrea Borea, P. *J. Med. Chem.* **2008**, *51*, 5875–5879.
(25) (a) Mohareb, R. M.; Ho, J. Z.; Alfarouk, F. O. *J. Chin. Chem. Soc.* **2007**, *54*, 1053–1066. (b) Kim, M.-H.; Park, C.-H.; Chun, K.-W.; Oh, B.-K.; Joe, B.-Y.; Choi, J.-H.; Kwon, H.-M.; Huh, S.-C.; Won, R.; Kim, K. H.; Kim, S.-M. PCT Int. Appl. 2007, WO 2007102679, *Chem. Abstr*. 147, 365516.
(26) (a) Brouillette, Y.; Sujol, G.; Martinez, J.; Lisowski, V. *Synthesis* **2009**, 389–394. (b) Pinkerton, A. B.; Lee, T. T.; Hoffman, T. Z.; Wang, Y.; Kahraman, M.; Cook, T. G.; Severance, D.; Gahman, T. C.; Noble, S. A.; Shiau, A. K.; Davis, R. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3562–3569. (c) Nikolakopoulos, G.; Figler, H.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2006**, *14*, 2358–2365.
(27) (a) Orner, B. P.; Ernst, J. T.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 5382–5383. (b) Antuch, W.; Menon, S.; Chen, Q.-Z.; Lu, Y.; Sakamuri, S.; Beck, B.; Schauer-Vukasinovic, V.; Agarwal, S.; Hess, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1740–1743. (c) Haridas, V. *Eur. J. Org. Chem.* **2009**, *30*, 5112–5128.
(28) Gerber, P. R.; Muller, K. *J. Comput. Aided Mol. Des.* **1995**, *9*, 251–268.
(29) (a) Castanedo, G. M.; Sutherlin, D. P. *Tetrahedron Lett.* **2001**, *42*, 7181–7184. (b) Hoener, A. P. F.; Henkel, B.; Gauvin, J.-C. *Synlett* **2003**, 63–66. (c) Zhang, H. Q.; Yang, G. C.; Chen, J. N.; Chen, Z. X. *Synthesis* **2004**, 3055–3059.

CC9001586