Cyanoacetamide Multicomponent Reaction (I): Parallel Synthesis Of Cyanoacetamides

Kan Wang, Katrina Nguyen, Yijun Huang, and Alexander Dömling*

University of Pittsburgh, Drug Discovery Institute, Pittsburgh 15261, Pennsylvania

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Cyanoacetic acid derivatives are the starting materials for a plethora of multicomponent reaction (MCR) scaffolds. However the diversity of these scaffolds is hampered by the low variability of the cyanoacetic acid derivatives in the past. Here we describe valuable protocols for the parallel synthesis of arrays of cyanoacetamides on a multigram scale and involving very convenient work up by simple filtration and washing. Fifty-two products are described, and several applications are indicated. We foresee our protocol and the resulting derivatives to become very valuable to greatly expanding the large MCR scaffold space of cyanoacetic acid derivatives.

Multicomponent reactions (MCRs) are among the most proliferative reaction classes of use in combinatorial and medicinal chemistry.[1] This can be attributed to the facts of simple and convergent one-pot reactions and workups, a multitude of accessible heterocyclic and acyclic scaffolds, and the commercial availability of many different starting materials thus leading to a potentially very large chemical space; MCRs can be classified according to their starting materials, e.g. isocyanide-based MCRs (IMCRs). Another important class of starting materials useful in MCRs are cyanoaceticacid derivatives. Several resulting compounds are marketed drugs or in (pre)clinical evaluation, e.g. olanzepine and others (Figure 1).

Cyanoaceticacid derivatives are key starting materials in the classical Gewald reaction (G-3CR) together with sulfur and methylene active ketones or aldehydes, leading to highly substituted 2-aminothiophenes **16**.[5] However, they are also starting materials leading to a plethora of additional interesting scaffolds[6] (Scheme 1) including cyclopropanes **5**,[7] substituted pyrrole **6**,[8] tetrahydroaminonaphthalenes **7**,[9] 3-aminobenzoisothiazoles **8**,[10] pyridines **9**,[11] 2-amino-6-methyl-5-ethoxycarbonyl-3-cyano-4*H*-pyrans **10**,[12] pyrans **11**,[13] bicyclopentadienes **12**,[14] 2-amino-5,6,7,8-tetrahydrobenzo[*b*]pyrans **13**,[15] spiro indolinone **14**,[16] 2-amino-4*H*-cromenes **15**,[17] 2-aminothiophenes **16**,[18] 6-amino-2*H*,4*H*-pyrano[2,3-*c*]pyrazoles **17**,[19] dihydrothiophenes **18**,[20] 7-aminopyrano[2,3-*d*]pyrimidines **19**,[21] bis furans **20**,[22] isothiazoles **21**,[23] 1,2-dithiolone **22**,[24] and thiazole **23**, just to name a few.[25]

These MCRs are based on the α-acidity of the cyanoaceticacid derivatives, frequently involving a Knoevenagel-type condensation with oxo components, e.g. aldehydes and ketones, subsequent Michael-type additions by another component, thus *in situ* formation of nucleophiles which finally react intramolecularly with the nitrile to form an often heterocyclic scaffold comprising an exocyclic NH_2 moiety. Thus, the hallmark of this class of MCRs is the bireactive cyanoaceticacid derivative allowing for condensation and nucleophilic addition reactions.

From a structural point of view, these MCRs also have in common the use of unique nucleophiles which determine the physicochemical properties of the scaffolds, e.g. their H-bond donor and acceptor propensity. For example, the C-nucleophiles dimethyl acetonedicarboxylate, cyclohexane-1,3-diones, and phenol yield the unique scaffolds pyran **11**, 2-amino-5,6,7,8-tetrahydrobenzo[*b*]pyran **13**, and 2-amino-4*H*-chromene **15**, respectively; all comprising different hydrogen donor−acceptor pharmacophore points. Additionally, from a combinatorial chemistry point of view, a potential drawback of these MCRs has been the use of only a handful of cyanoaceticacid derivatives, including cyanoaceticacid and esters, malondinitrile, and cyanomethylketones.[5−23] Consequently, in these MCRs, often only the oxocomponent can be varied and can contribute to the overall number of achievable compounds in one scaffold. Cyanoacetic acid amides, in contrast and despite their much greater variability, have been rarely used in these MCRs.[26] In general the value of an MCR can be determined by the broad availability of all classes of starting materials besides other factors. For example, more than 1000 isocyanides are commercially available, e.g., from their primary amine precursor, and thus, Ugi, Passerini, and van Leusen reactions are very versatile and useful to produce directed or general libraries and to discover biologically active leads.

To overcome the limitations of cyanoaceticacid-based MCRs, we would like to report an experimentally simple, cheap, mild, scalable, and diverse parallel approach to cyanoacetamides which we believe will transport the class of cyanoaceticacid-based MCR on a hitherto unprecedented expansion of total accessible compounds. Additionally, current processes to prepare cyanoacetamides often involve drastic conditions, e.g. strongly basic and high temperatures which are not always compatible with a wide functional group tolerance.[27]

* Corresponding author: E-mail: asd30@pitt.edu.

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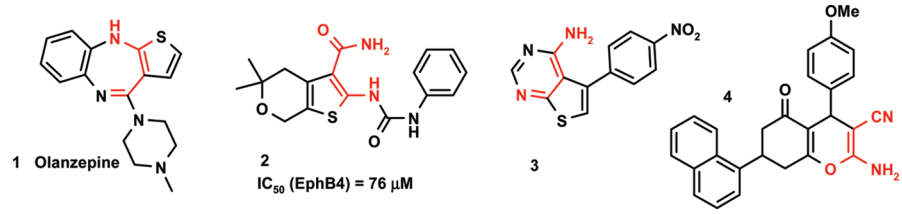
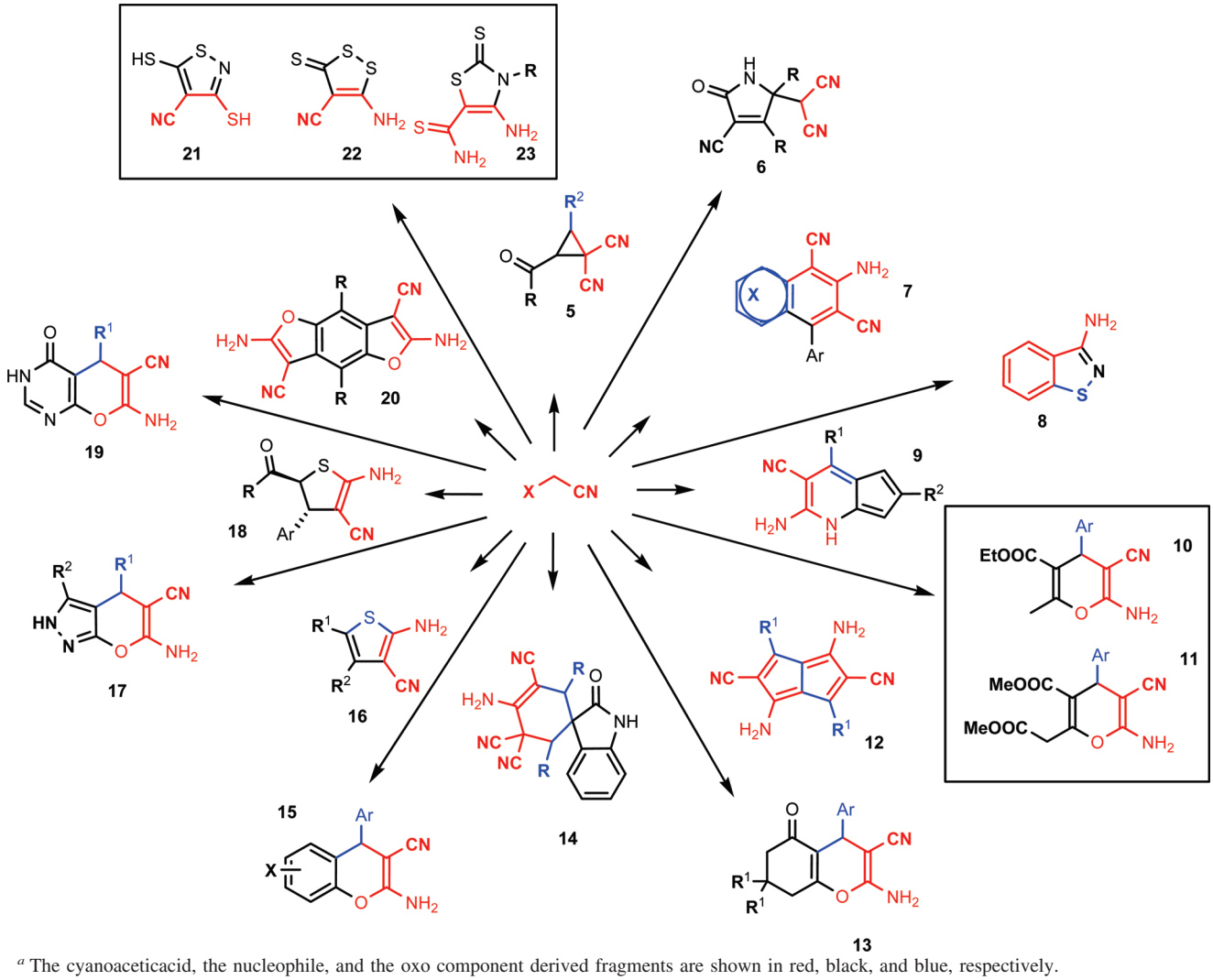


Figure 1. Examples of cyanoacetic acid derivatives on the market or in development: the schizophrenia and bipolar disorder drug olanzepine **1**, EphB4 inhibitor **2**,[2] kinase inhibitor **3**,[3] and human excitatory amino acid transporter subtype 1 (EAAT1) inhibitor **4**.[4] The cyanoaceticacid derived moiety is marked in red.

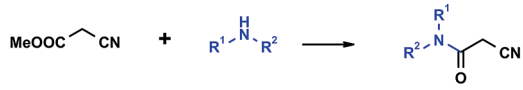
Scheme 1. Selection of MCR-Derived and Other Scaffolds Based on Cyanoaceticacid Derivatives[a]

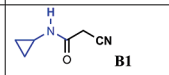
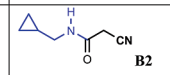
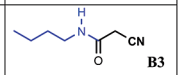
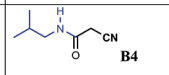
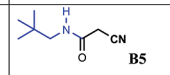
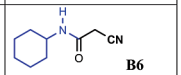
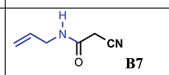
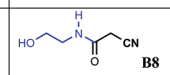
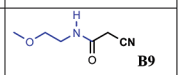
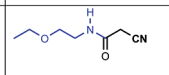
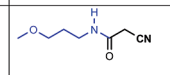
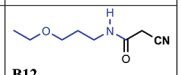
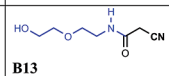
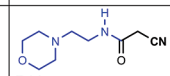
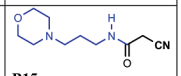
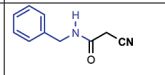
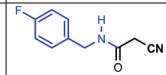
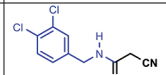
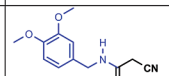
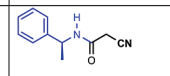
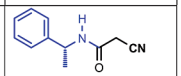
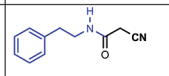
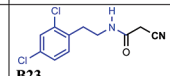
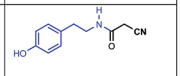
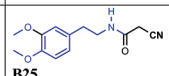
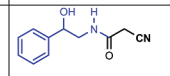
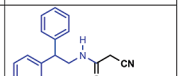
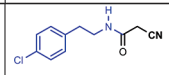
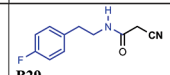
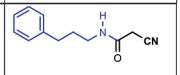


[a] The cyanoaceticacid, the nucleophile, and the oxo component derived fragments are shown in red, black, and blue, respectively.

In continuation of our search for reactions compatible with parallel chemistry leading to high diversity of given scaffolds/useful building blocks, we investigated conditions for the one-pot amidation of the bulk and cheap material cyanoaceticacid methylester.[28] For example, we recently described a one pot amidation of aminoacid derived isocyanoaceticacid methylesters under solventless conditions and ambient temperature.[29] Additionally, we recently reported on the combinatorial and direct one-pot amidation of different MCR scaffolds using the organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) together with primary and secondary amines under solvent-free conditions.[30] In analogy to our recently found reaction between α-acidic isocyanoaceticacid methylester and primary and secondary amines, we reasoned if a similar reaction would be possible between cyanoaceticacid methylester and primary and secondary amines under equally mild and effective conditions. We found that cyanoaceticacid methylester reacted with a broad range of primary and secondary amines in good to very good yields under solventless conditions (Table 1). Thus, by simply mixing each 1 equivalent of primary or secondary amine and cyanoaceticacid methylester yielded the amide product after some reaction time (Table 1). In a pilot experiment in order to spearhead the scope and limitations of this reaction, we have reacted 67 primary and secondary amines and "aminoides" spanning very broad physicochemical properties, including different bulkiness, electronic features, and functional groups (Figure 2).

Table 1. Structures of Produced Cyanoaceticacid Amides and Isolated Yields



yield	Structure (number)	yield	Structure (number)	yield	Structure (number)
82	 **B1**	49	 **B2**	39	 **B3**
95	 **B4**	11	 **B5**	91	 **B6**
74	 **B7**	90	 **B8**	91	 **B9**
89	 **B10**	88	 **B11**	90	 **B12**
91	 **B13**	80	 **B14**	78	 **B15**
87	 **B16**	98	 **B17**	78	 **B18**
97	 **B19**	71	 **B20**	73	 **B21**
45	 **B22**	91	 **B23**	90	 **B24**
90	 **B25**	89	 **B26**	97	 **B27**
90	 **B28**	96	 **B29**	94	 **B30**

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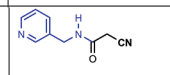
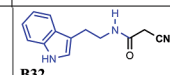
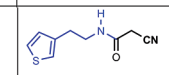
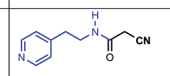
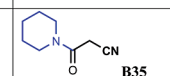
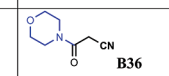
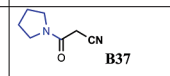
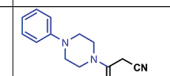
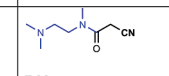
62	 **B31**	97	 **B32**	62	 **B33**
91	 **B34**	71	 **B35**	95	 **B36**
76	 **B37**	90	 **B38**	76	 **B39**
22	**B40**	25	**B41**	99	**B42**
97	**B43**	99	**B44**	99	**B45**
66	**B46**	97	**B47**	82	**B48**
83	**B49**	50	**B50**	99	**B51**
67	**B52**				

The reactions were performed in readily available 25 mL screw glasses by placing 1.0 equiv (50 mmol) of amine and a stirring bar, adding 1.0 equiv of cyanoacetic acid methyl ester (50 mmol) to it, and stirring on a multiplex plate (Figure 3). In analogy to our previous report in the isocyano series, the amides in most cases typically precipitate after some seconds to hours. The workup consists of a simple filtration and washing procedure with a suitable solvent to result in gram quantities of sufficiently NMR-pure cyanoacetic acid amides (>93% purity). In some cases (**A2**, **A7**, **A10**, and **A11**), no precipitate was observed first, however, removing the formed methanol or/and putting it in the freezer helped the crystallization process. In other cases (**A29**, **A31**, **A38**, and **A45**), the amides are liquid and simply removing the formed methanol generates amides. In rare cases (**A39** and **A63**), salt formation is observed and products could be purified by acid and base washing.

We found, that 52 out of 67 reactions worked (78%) and lead to multigram isolation of the products (Table 1). The yield distribution of the performed reactions is shown in Figure 4. A broad range of primary and secondary amines reacted nicely, including starting materials with additional functional groups (e.g., acetal B51), various degrees of bulkiness, and heterocycles. Including all reactions, 25 out of 52 reactions (48%) and 41 out of 52 reactions (79%) obtained yields >90% and >70%, respectively. Only 15 reactions did not yield target compounds or in very small amount (Figure 4).

Detailed inspection of the results reveals that phenolic and aliphatic hydroxyl groups react smoothly, and there is no need for protecting groups (**A17**, **A30**, **A31**, **A32**, and **A62**). Tertiary amines are tolerated as functional groups (**A12**, **A13**, **A43**, and **A45**). Heterocycles can react well (**A26**, **A27**, **A28**, and **A29**). Primary diamines yielded the expected difunc-

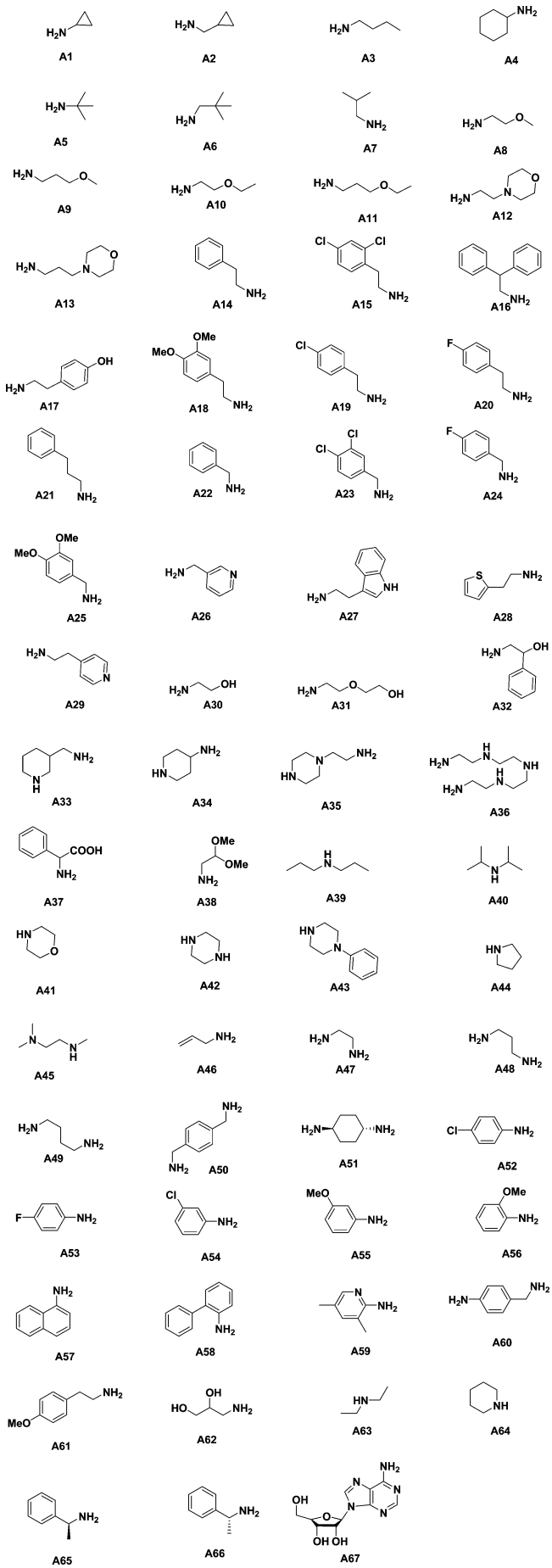


Figure 2. Investigated amine components for the one-pot amidation reaction.

Figure 3. Parallel experimental setup of the amidation reaction.

tionilized products (**A47**, **A48**, **A49**, **A50**, and **A51**) with 2 equivalent of methyl cyanoacetate reagent. The reaction was performed under complete stereoretention with chiral phenylethylamine as shown by chiral HPLC (**A65** and **A66**). Also of note is the very good water solubility of several compounds (e.g., **B13**, which shows much more water solubility than in ethyl acetate or dichloromethane), which is of high importance for the synthesis of compound libraries with sufficient water solubility. Water solubility is a key factor in drug discovery to ensure transportation of the compound to yield high concentration of compound in target tissue to trigger biological response. Amines that are not reacting under the described conditions are anilines, 2-aminopyridine, and 4-aminopyrimidine derivatives (**A52** to **A59** and **A67**). This is not surprising since they have reduced basicity and nucleophilicity due to the delocalization of the basic electron pair of the nitrogen into the extended π-system of the aromatic ring and the latter two (A59 and A67) rather behave like amidines. Therefore, the 4-(aminomethyl)aniline (**A60**) chemoselectively generates only the benzyl amide. All new compounds are fully characterized by NMR and HPLC-MS and HR-MS (SI).

Steric factors affect this amidation reaction. Bulky amines, e.g. *tert*-butyl amine (**A5**) and diisopropyl amine (**A40**), do not give the target amides. However, the amine salts of cyanoacetic acids are formed probably due to concomitant hydrolysis of the methylester (Scheme 2). For slightly less bulky amines, such as diethyl amine (**A63**) and di-*n*-propyl amine (**A39**), the amidation reaction produces no precipitate. However, crude proton NMR indicates that the reaction is a mixture of amide and ammonium salt. Conveniently, the salts can be removed with acidic and basic extraction. It is interesting that no salt was observed in the amidation of cyclic secondary amine (**A41** to **A44**). For some cases (**A33**, **A34**, and **A35**), in which a diamine containing both primary amino and secondary amino groups were used, are formed. In these cases, the NMR indicates the presence of several

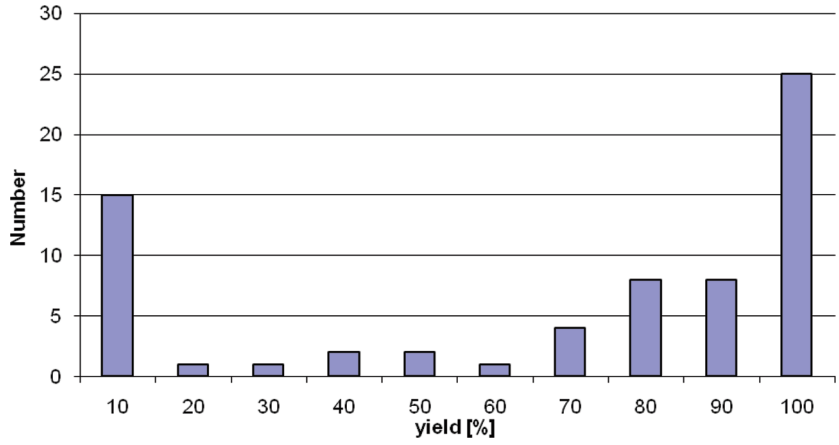
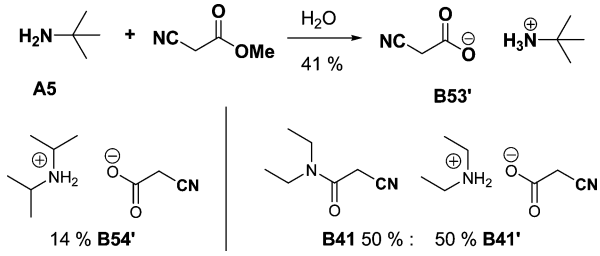


Figure 4. Isolated yield distribution.

Scheme 2. Bulky Amine Promoting Hydrolysis of Methyl Cyanoacetate



rotamers of the tertiary amide. For α-amino acid (**A37**), the zwitterionic structure makes the reaction fail.

Clearly, the above procedures allow for convenient, mild, and cheap access to a wide range of diverse cyanoacetamides. However, from the rare reports of their use in MCR chemistry it is not clear if the resulting amides are reactive in the corresponding parent MCRs of malondinitrile and cyanoaceticacidmethylester or if the different electronic and/or hydrogen bond donor propensity of the amides influence their reactivity and usefulness in these reactions.[26] For example, it is well-known that isocyanoacet*amides* in isocyanide-based MCRs react to give 5-amino-oxazoles,[31] whereas isocyanoaceticacid *esters* with the same components and under very similar reaction conditions give imidazolines.[32] Thinking in analogies in organic chemistry is very popular and often successful; on the other hand, often, different reactions resulting by introducing slight variations are not foreseeable. Therefore and having these cyanoacetamides in hand, several cyanoaceticacid ester MCRs and other reactions were examined. A key intermediate of cyanoacetamide chemistry is the Knoevenagel condensation product with aldehydes which was therefore investigated first. Not surprisingly, the condensation of these cyanoacetamides with aromatic aldehydes works well and generates single *E*-isomer products (Table 2).[33] The simple filtering of the formed precipitate offered products with very good purity.

Next we investigated the nucelophilic addition of dimedone onto the primary Knoevenagel condensation products. The condensation of these intermediates with 5,5-dimethylcyclohexane-1,3-dione works well under microwave conditions (Scheme 3). Further results and scope and limitations will be reported in a subsequent paper.

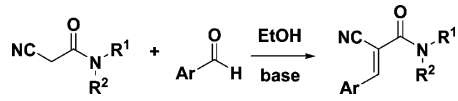
The G-3CR offers straight forward access to the important scaffold of 2-amino-thiophene. Due to the bioisosteric character of thiophenes to phenyl groups, the G-3CR 2-amino-3-carbonyl-thiphene can be regarded as bioisosters of anthranilic acids which are difficult to access in diversity. Due to the MCR character, however, the thiophenes are much more accessible. We investigated a recently reported G-3CR variant using mercaptoacetaldehyde and cyanoacetamide yielding 4,5-unsubstituted 2-amino-3-carbonyl-thiphenes.[34] Thus, compound **B51** reacts with mercaptoacetaldehyde dimer yielding thiophene **E1** in 50% yield (Scheme 4). Remarkably, the acetal substructure stays integer during this transformation. Further results and scope and limitations will be reported elsewhere.

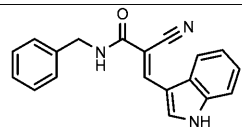
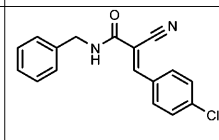
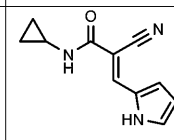
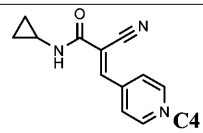
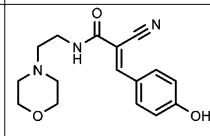
Additionally we discovered a new unprecedented MCR involving the three starting materials cyanoacetamide, aldehyde, and *N*-tosylacetophenone yielding 2-aminopyrroles. An exemplary conversion is shown in Scheme 5. The product is formed in 60% yield. Scope and limitations and further biological results of this new cyanoacetamide will be reported in due course.

On the basis of our parallel synthesis of a large number of cyanoacetamides, we punctually investigated their reactivity in different reactions and MCRs. The products of these conversions—in principle—can also be obtained by employing cyanoaceticacid methylester and a subsequent amidation reaction (path 1 in Scheme 6). However, from a parallel chemistry point of view the preparation of a library of aminoacetamides on a multigram preparative scale is advantageous for several reasons (path 2 in Scheme 6). First, the number of subsequent transformations of libraries should be minimized to avoid additional preparative steps and reduction of yields of final compounds. Second, the cyanoacetamide starting material library can be advantageously used for several combinatorial chemistry projects based on different MCRs and other transformations (Scheme 6).

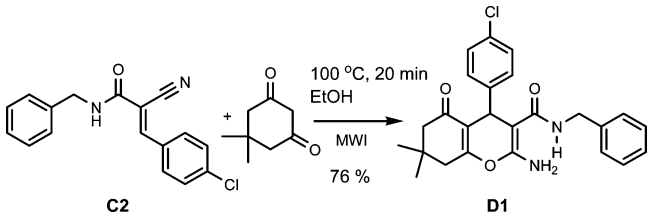
In conclusion, we described practical protocols for a one-pot amidation of cyanoaceticacid methylester on a multigram scale.[35] The protocols can lead to a high number of cyanoaceticacid amides using parallel chemistry techniques in often good to very good yields. The scope of the reaction is immense, however, limited to nonaromatic, not extremely bulky primary and secondary amines.

Table 2. Structures of Condensation Products of Cyanoacetamides and (Heter)Aromatic Aldehydes and Their Isolated Yields

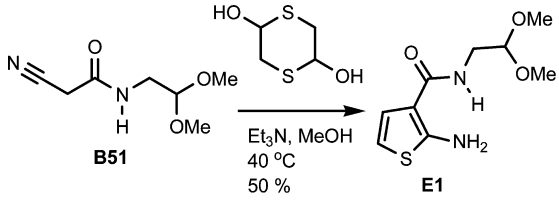


yield	structure	yield	structure	yield	structure
78	 **C1**	65	 **C2**	80	 **C3**
56	 **C4**	76	 **C5**		

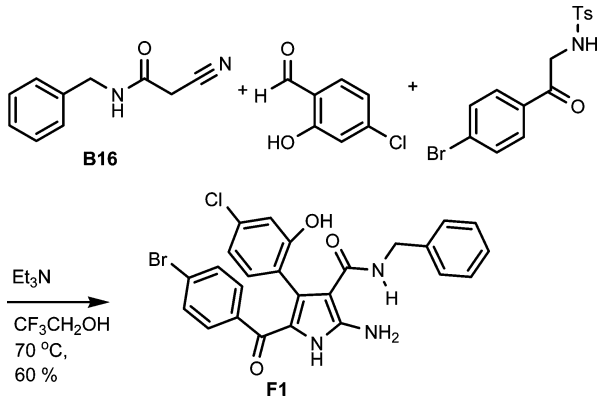
Scheme 3. Cyclization with Dimedone



Scheme 4. Gewald Reaction with Mercaptoacetaldehyde Dimer

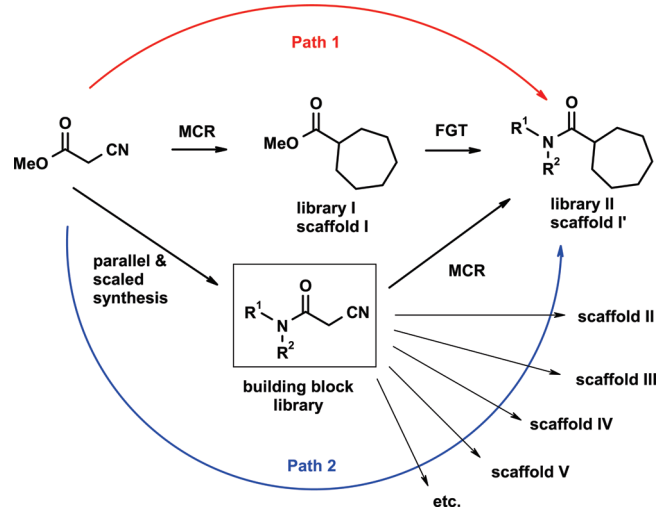


Scheme 5. New 2-Aminopyrroles Synthesis Involving Cyanoacetamide, Benzaldehyde, and N-Tosylacetophenone



The procedures are experimentally simple and allow for the cost efficient synthesis of these derivatives. Additionally, it can use cheap and bulk chemicals as starting materials including cyanoaceticacid methylester and primary and secondary amines, which after MCR derivatization in a next step can lead to many complex and potentially useful screening libraries. Amidation reactions were performed, and 52 examples have been successfully isolated and explicitly described, in addition to scope and limitations regarding the amine starting materials. The procedures described herein are significant due to the highly elaborated and widely published combinatorial, often MCR chemistry of cyanoaceticacid derivatives. Toward this end, we performed several types of transformations of single cyanoacetamides and could isolate the products in all cases in reasonable to very good yields. Thus, the resulting products are very useful building blocks for cyanoaceticacid-based MCR chemistry and will be of use in combinatorial and medicinal chemistry.

Scheme 6. Two Strategic Pathways for the Generation of MCR Scaffolds from Cyanoaceticesters[a]



[a] Pathway 1 comprises the initial MCR followed by postmodification (amidation). Pathway 2 comprises the initial generation of a starting material library of cyanoacetamides followed by different MCRs, thus leading to many scaffolds with less effort (functional group transformation (FGT)).

Further reports on the chemistry of this library of cyanoacetamide will follow in due course.

Experimental Section

2-Cyano-*N*-cyclopropylacetamide B1 (General Procedure). Methyl cyanoacetate (19.82 g, 200 mmol) and cyclopropanamine (**A1**, 11.42 g, 200 mmol) are added together into a 20 mL vial and stirred at room temperature. After 24 h, the precipitate is filtered and washed with cold diethyl ether then dried on vacuum to give the target product 20.39 g (82%) as a white solid. HR-MS (ESI-TOF) for $C_6H_8N_2O$ (M^+): found *m*/*z* 124.0637; calc mass 124.063. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.60−0.63 (2H, m), 0.85−0.88 (2H, m), 2.75−2.78 (1H, m), 3.37 (2H, s), 6.22 (1H, s) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.5, 114.8, 25.8, 23.3, 6.5 ppm.

(*E*)-*N*-Benzyl-2-cyano-3-(1*H*-indol-3-yl)acrylamide C1 (General Procedure). 1*H*-Indole-3-carbaldehyde (1.45 g, 10 mmol), *N*-benzyl-2-cyanoacetamide (**B16**, 1.74 g, 10 mmol), and catalyst piperidine (170 mg, 2 mmol) in 10 mL ethanol are added into a 20 mL vial. The reaction is heated to 60 °C oil bath for 8 h. Then, it is cooled to ambient temperature. The precipitate is filtered and washed with cold ethanol then dried on vacuum to obtain the title product 2.35 g (78%) as a yellow solid. ^{1}H NMR (*d*-DMSO, 600 MHz): δ 12.36 (s, 1H), 8.85 (s, 1H), 8.52 (s, 1H), 8.47 (s, 1H), 7.92 (s, 1H), 7.56 (s, 1H), 7.10−7.30 (m, 7H), 4.44 (s, 2H) ppm. ^{13}C NMR (*d*-DMSO, 150 MHz): δ 162.7, 142.8, 139.9, 136.5, 130.8, 128.8, 127.8, 127.6, 127.3, 123.8, 122.0, 119.2, 118.9, 113.2, 110.1, 97.6, 43.4 ppm.

2-Amino-*N*-benzyl-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxamide (D1). 5,5-Dimethylcyclohexane-1,3-dione (70 mg, 0.5 mmol), (Z)-*N*-benzyl-3-(4-chlorophenyl)-2-cyanoacrylamide (**C2**, 148 mg, 0.5 mmol) in 1 mL ethanol are added into a microwave oven reaction tube. The reaction is heated in the microwave oven at 100 °C for 10 min. The precipitate is filtered and washed with cold ethanol and dried on vacuum to obtain the title product 165 mg (76%) as a white solid. ^{1}H NMR (*d*-DMSO, 600 MHz): δ 11.31 (s, 1H), 8.99 (s, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 6.72 (d, J = 6.6 Hz, 2H), 5.05 (s, 1H), 4.80 (s, 1H), 4.36 (s, 1H), 4.34 (dd, J = 15.6, 7.2 Hz, 1H), 3.99 (dd, J = 15.6, 4.2 Hz, 1H), 2.00−2.40 (m, 4H), 1.03 (s, 6H) ppm. ^{13}C NMR (*d*-DMSO, 150 MHz): δ 164.8, 140.0, 138.6, 131.7, 130.6, 128.5, 128.5, 127.9, 127.2, 127.1, 118.9, 56.5, 31.7, 32.2, 26.0, 19.0 ppm.

2-Amino-*N*-(2,2-dimethoxyethyl)thiophene-3-carboxamide E1 (General Procedure). 2-Cyano-*N*-(2,2-dimethoxyethyl)acetamide (**B51**, 5 mmol, 860 mg), 1,4-dithiane-2,5-diol (380 mg, 2.5 mmol), and triethylamine (150 mg, 1.5 mmol) in 2.5 mL methanol are added into a 20 mL vial. The reaction is heated at 40 °C oil bath for 12 h. Then, the reaction is cooled to ambient temperature and extracted with dichloromethane (3 × 20 mL). The organic phase is dried with anhydrous sodium sulfate. After removal of the solvent on vacuum, the crude product is purified with silica gel chromatography (75% ethyl acetate in hexanes) to give the title compound 587 mg (51%) as a red solid. HR-MS (ESI-TOF) for $C_9H_{14}N_2O_3S$ (M^+): found *m*/*z* 230.0722; calc mass 230.0735. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.72 (d, J = 6.0 Hz, 1H), 6.23 (d, J = 6.0 Hz, 1H), 6.11 (s, 2H), 5.88 (s, 1H), 4.43−4.45 (m, 1H), 3.50−3.53 (m, 2H), 3.42 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.8, 161.0, 122.7, 108.7, 107.5, 103.4, 54.6, 40.7 ppm.

2-Amino-*N*-benzyl-5-(4-bromobenzoyl)-4-(4-chloro-2-hydroxyphenyl)-1*H*-pyrrole-3-carboxamide (F1). *N*-Benzyl-2-cyanoacetamide (**B16**, 35 mg, 0.2 mmol), *N*-(2-(4-bromophenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (0.2 mmol, 74 mg), 4-chloro-2-hydroxybenzaldehyde (32 mg, 0.2 mmol), and triethylamine (20 mg, 0.2 mmol) are added into 2 mL 2,2,2-trifluoroethanol. The reaction is heated to 70 °C for 12 h. Then, the reaction is cooled to ambient temperature. The precipitate is filtered and washed with cold ethanol and dried on vacuum to obtain the title product 63 mg (60%) as a yellow solid. HR-MS (ESI-TOF) for $C_{25}H_{19}BrClN_3O_3$; exact mass 523.0298; found 523.0295. ^{1}H NMR (*d*-DMSO, 600 MHz): δ 10.96 (s, 1H), 10.11 (s, 1H), 7.16−7.24 (m, 5H), 7.07 (d, J = 8.4 Hz, 1H), 6.93 (s, J = 7.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 1.8 Hz, 1H), 6.49 (dd, J = 7.8, 1.8 Hz, 1H), 6.29 (s, 2H), 5.77 (t, J = 5.4 Hz, 1H), 4.24 (dd, J = 15.6, 6.9 Hz, 1H), 4.17 (dd, J =15.6, 6.0 Hz, 1H) ppm. ^{13}C NMR (*d*-DMSO, 150 MHz): δ 182.7, 165.7, 156.4, 149.7, 139.1, 139.0, 134.0, 133.6, 130.3, 129.7, 128.6, 128.1, 127.2, 127.1, 123.4, 121.5, 120.5, 119.1, 115.7 ppm.

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Supporting Information Available. Experimental methods LC-MS of the products; NMR data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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