

University of Groningen

Leuckart-Wallach Route Toward Isocyanides and Some Applications

Neochoritis, Dinos; Zarganis Tzitzikas, Tryfon; Stotani, Silvia; Domling, Adrian; Herdtweck, Eberhardt; Khoury, Kareem; Dömling, Alex

Published in:
Acs combinatorial science

DOI:
[10.1021/acscombsci.5b00066](https://doi.org/10.1021/acscombsci.5b00066)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Neochoritis, D., Zarganis Tzitzikas, T., Stotani, S., Domling, A., Herdtweck, E., Khoury, K., & Dömling, A. (2015). Leuckart-Wallach Route Toward Isocyanides and Some Applications. *Acs combinatorial science*, 17(9), 493-499. <https://doi.org/10.1021/acscombsci.5b00066>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

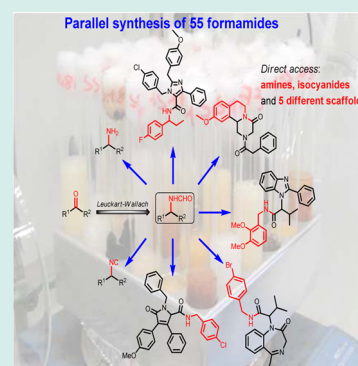
Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Leuckart–Wallach Route Toward Isocyanides and Some Applications

Constantinos G. Neochoritis,[†] Tryfon Zarganes-Tzitzikas,[†] Silvia Stotani,[†] Adrian Dömling,[‡] Eberhardt Herdtweck,[§] Kareem Khoury,[‡] and Alexander Dömling^{*,†}[†]Department of Drug Design, University of Groningen, A. Deusinglaan 1, Groningen 9700AV, The Netherlands[‡]Carmolex, Inc., Pittsburgh, Pennsylvania 15219, United States[§]Institut für Anorganische Chemie, Technische Universität München, 80333 München, Germany

Supporting Information

ABSTRACT: Isocyanide-based multicomponent reactions (IMCR) are among the most important chemical reactions to efficiently generate molecular diversity and have found widespread use in industry and academia. Generally, isocyanides are synthesized in 1–2 steps starting from primary amines. Here, we provide experimental detail on an alternative approach toward formamides and, thus, isocyanides via the Leuckart–Wallach reaction in an improved variation. The resulting >50 synthesized and characterized formamides are useful starting materials for IMCR, as well as other chemistries. The advantage of using the Leuckart–Wallach pathway to formamides and isocyanides is the lower price, on average, of the starting materials, as well as their differential and complementary structural diversity, as compared to the primary amine pathway.



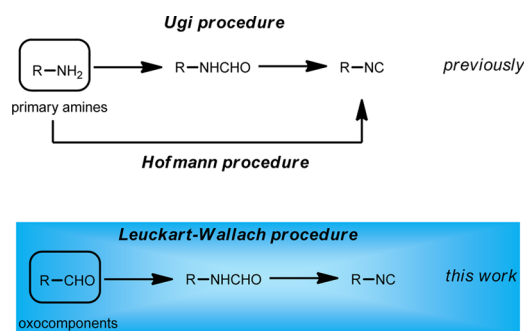
KEYWORDS: Leuckart–Wallach, formamides, isocyanides, IMCR, Ugi

INTRODUCTION

Atom economy, efficiency, diversity, and complexity: Four terms that multicomponent reactions (MCRs) fulfill and represent more than any other type of reactions.^{1–4} Recently, MCR has reached a “golden era” as an increasing number of researchers understand the deeper principles and applications behind this chemistry. The scaffold diversity of MCRs and the window in chemical space has been undoubtedly recognized by the synthetic community in industry and academia as a preferred method to design and discover pharmaceutically active compounds.⁵ Isocyanide-based multicomponent reactions (IMCRs) belong to the most important reactions of their kind giving easy access to biologically relevant compounds and libraries. Ugi and Passerini reactions are the most famous IMCRs with extended application in drug discovery.⁶ It is unquestionable that IMCRs are based on the isocyanide moiety and therefore preparative isocyanide synthesis is extremely important. The majority of isocyanide syntheses use the classical 2-step sequence described by Ugi: primary amine \Rightarrow formamide \Rightarrow isocyanide.⁷ The Hoffman procedure of carbene-mediated isocyanide formation directly from primary amines is also popular since the introduction of phase transfer catalysis (Scheme 1).⁸

Formamides are at a unique position in the IMCRs, since they are by far the most important precursors for isocyanides. Herein, we want to give experimental details and exemplify a new route toward isocyanides through formamides on the basis of the Leuckart–Wallach procedure. Thus, we employ a wide variety of oxo components into the isocyanide synthesis through their reductive amination with formamide and formic

Scheme 1. Leuckart–Wallach Route to Isocyanides



acid (Scheme 2). Moreover, we provide further synthetic applications, including an expansion of our recently introduced in situ isocyanide method,⁹ trying to give a well-rounded aspect of this novel pathway.

RESULTS AND DISCUSSION

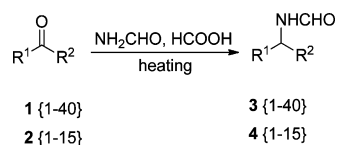
Demonstrating the effectiveness and applicability of our method, we synthesized 55 different formamides from their corresponding carbonyl compounds. The oxo components were carefully chosen to include various aliphatic and aromatic aldehydes with different substituents, both EWG and EDG,

Received: April 28, 2015

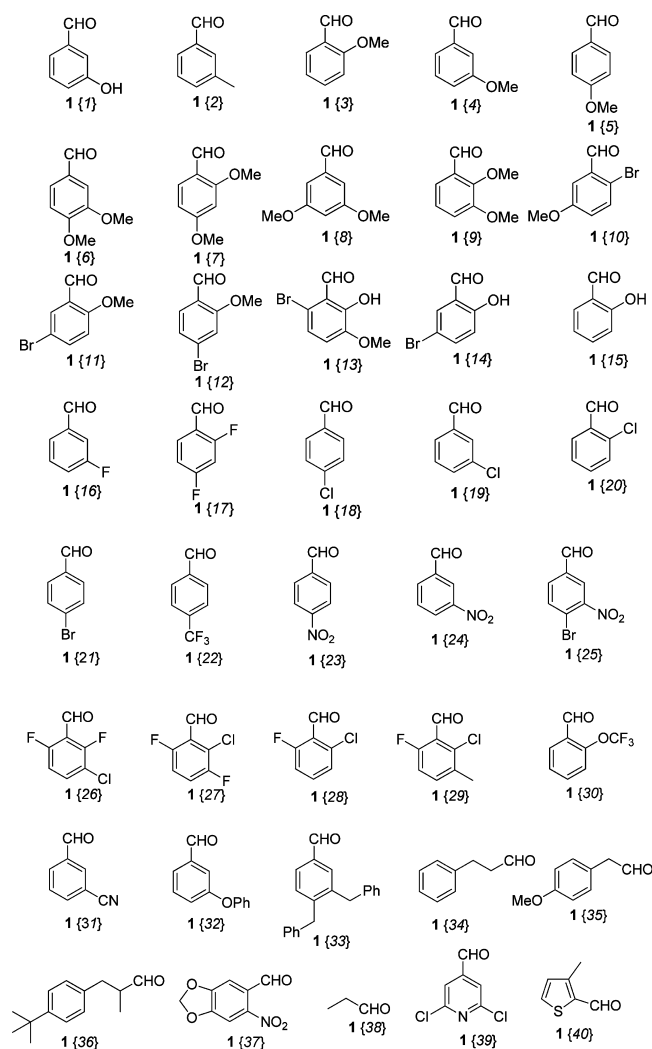
Revised: June 8, 2015

Published: July 30, 2015

Scheme 2. Leuckart–Wallach Reaction Using Formamide and Formic Acid as the Reductive Agent from the Corresponding Oxo Component



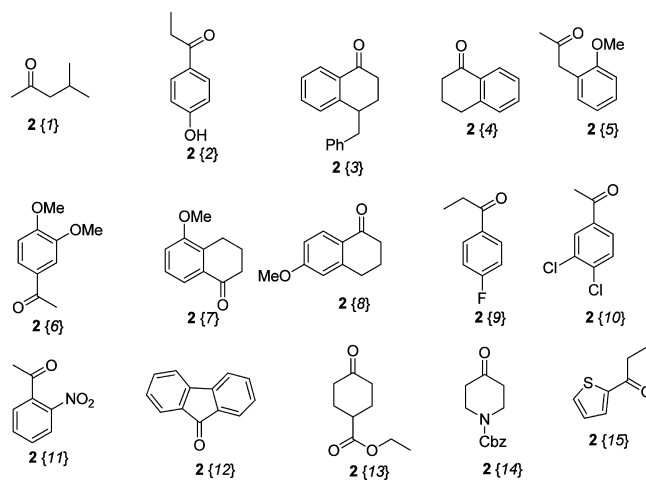
Scheme 3. Chemset 1 Consisting of Aldehydes



and heterocycles (chemset 1). Moreover, ketones with aromatic, aliphatic and heterocyclic substituents were employed (chemset 2).

The formamides (chemsets 3 and 4) were prepared either in parallel, using suitable metal block heaters (*SI movie*, photos in *Supporting Information*) or under microwave irradiation (*Table 1*). A typical experimental procedure by conventional heating involves the addition of the corresponding oxo component (1 equiv) in a solution of formamide (12 equiv) with formic acid (5 equiv) and refluxing at 160–180 °C for 1–2 h. In the case of microwave irradiation, the reaction time is drastically shortened as the reaction is completed, in most of the substrates, in 3 min. Carbon dioxide emission was observed during the procedure which ceased upon completion and after an aqueous workup the desired formamide is isolated with no

Scheme 4. Chemset 2 Consisting of Ketones



further purification in many of the cases. The reaction is scalable (*Table 1*, substrates were indicated in 20 mmol scale) (by conventional heating) with good to excellent yields and has been performed on a 50 g scale, to produce 3{28} and 3{31}. The method is applicable to both aromatic and aliphatic derivatives whereas many functional groups (like hydroxyl, nitro, ester groups, ether bonds, and heterocycles) are compatible with the reaction conditions allowing for further modifications or transformations. The formation of the formamides from the tetralones (2{3}, 2{4}, 2{7}, 2{8}) and various heterocycles are particularly noteworthy given their great biological importance.^{10–14}

Having in hand, this diversity and complexity of formamides, which often are very difficult to produce through previously described methods, we wanted to go a step further. Demonstrating the generality of our procedure, we employed the Leuckart–Wallach procedure in the synthesis of isocyanides, amines, and novel IMCR-based compounds through our recently published *in situ* isocyanide method (*Scheme 5*).⁹

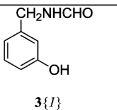
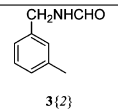
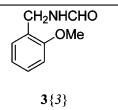
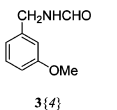
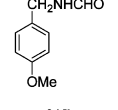
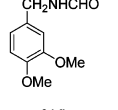
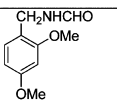
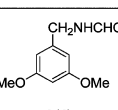
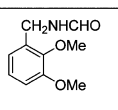
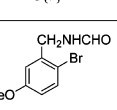
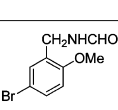
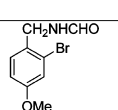
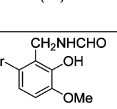
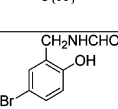
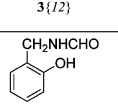
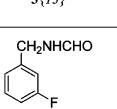
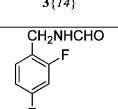
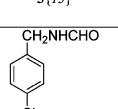
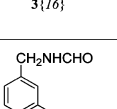
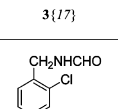
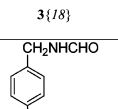
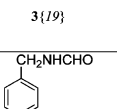
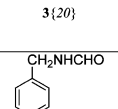
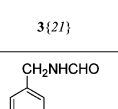
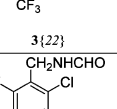
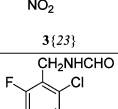
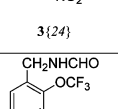
Isocyanides 5(3{3,26,27,30,31,37,40}, 4{11}) (chemset 5) were synthesized under the common dehydration conditions (POCl₃, Et₃N). These isocyanides are preferentially produced from their oxo components and not from the primary amines due to both availability and pricing considerations. In addition, isocyanide 5(3{37}) is worth mentioning because it can be used for the synthesis of photo inducible probes, a recently emerging research area.¹⁵

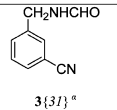
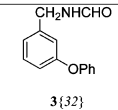
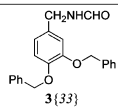
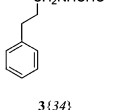
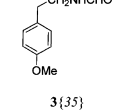
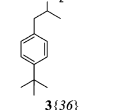
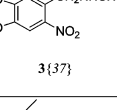
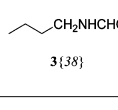
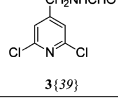
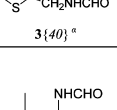
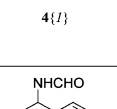
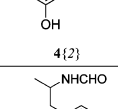
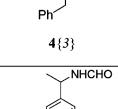
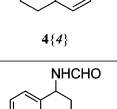
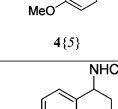
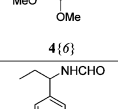
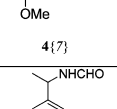
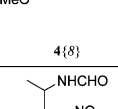
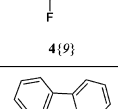
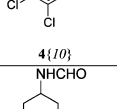
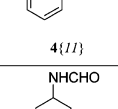
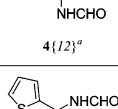
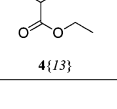
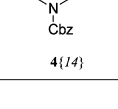
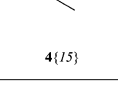
Similarly, the corresponding formamides after treatment with HCl (5 N in dioxane) gave access to the amines 6(3{10},4{5}) in excellent yields. Compound 6(3{10}), for example would cost \$428 for 1 g and is only available through one supplier, EnamineBB. However, the corresponding aldehyde 1{10} costs \$28 for 5 g and is available through multiple suppliers (AK Scientific, CombiBlocks, and OxChem).

It was possible to get the crystal structures of formamides 3{21} and 3{37} along with the corresponding isocyanide 5(3{37}). As expected the isocyanide adopts a linear conformation of the N1–C1 bond and the formamides occupy a (Z) position relative to the carbonyl oxygen.

Lastly, we synthesized 5 different compounds (*Scheme 5*) based on different MCR scaffolds with a sequence of two steps without isolating the isocyanide. The first step for all 5 different scaffolds is a classical Ugi four component reaction (U4CR) and then a postmodification step that gives access to important

Table 1. Formamides Synthesized (Chemsets 3 and 4) via Leuckart–Wallach Reactions Either by Conventional Heating or Microwave Irradiation

Chemsets 3,4	Yield (%)	Chemsets 3,4	Yield (%)	Chemsets 3,4	Yield (%)
	71		73		44
	87 (85) ^b		55		53 (75) ^b
	60		61		53
	66		82		69
	43		43 (80) ^b		44
	50		79		68
	78		59		48 (95) ^b
	62		52 (91) ^b		60
	85		94 (46) ^b		81

Chemsets 3,4	Yield (%)	Chemsets 3,4	Yield (%)	Chemsets 3,4	Yield (%)
	92		89		58
	58		90		60 (57) ^b
	40		80		45
	87 (85) ^b				
	45		69		55
	64 (45) ^b		62		56
	45		53		75
	66		54		87
	51		60		59

^aThe reaction performed in 20 mmol scale. ^bThe reaction performed in MW.

and diverse scaffolds in medicinal chemistry. Compound 7 is a tetrasubstituted imidazole bearing an isocyanide side chain, that is only possible to synthesize via the Leuckart–Wallach procedure using the appropriate formamide (4{9}) since the corresponding primary amine is not commercially available. The first step of the sequence, the Ugi reaction, proceeded nicely with in situ formation of the isocyanide (compound 7a) followed by the cyclization to the imidazole which was accomplished with the use of ammonium acetate and acetic acid under reflux conditions with excellent yield.¹⁶ The second derivative 8 can be assembled by performing a Pictet–Spengler reaction with the appropriate Ugi product 8a.^{17–19} In this case the necessary isocyanide is produced in situ from the corresponding formamide (3{35}), while the cyclization reaction was performed in methanesulfonic acid at 60 °C for 24 h to

yield the final compound. Substituted benzimidazoles are often used in medicinal chemistry.²⁰ Compound 9 is a disubstituted benzimidazole that can be produced with the so-called Ugi deprotection–cyclization methodology.²¹ In this case a mono Boc protected ortho-phenylenediamine is used as an amine component in the Ugi reaction (compound 9a) along with the in situ generated isocyanide (3{9}) which can only be synthesized via the Leuckart–Wallach procedure since the corresponding amine is not commercially available. The deprotection–cyclization step was performed under microwave conditions giving the final product in excellent yield. Compounds such as 10 were first synthesized in our group giving access to a large variety of substituted 1,4-benzodiazepines.^{22,23} The synthetic route for such a compound consists of an Ugi reaction with a substituted 2-aminoacetophenone as an

Scheme 5. Applications of the Formamides and Synthesis of Isocyanides, Amines, and Five Different MCR Scaffolds with Their Overall Yields

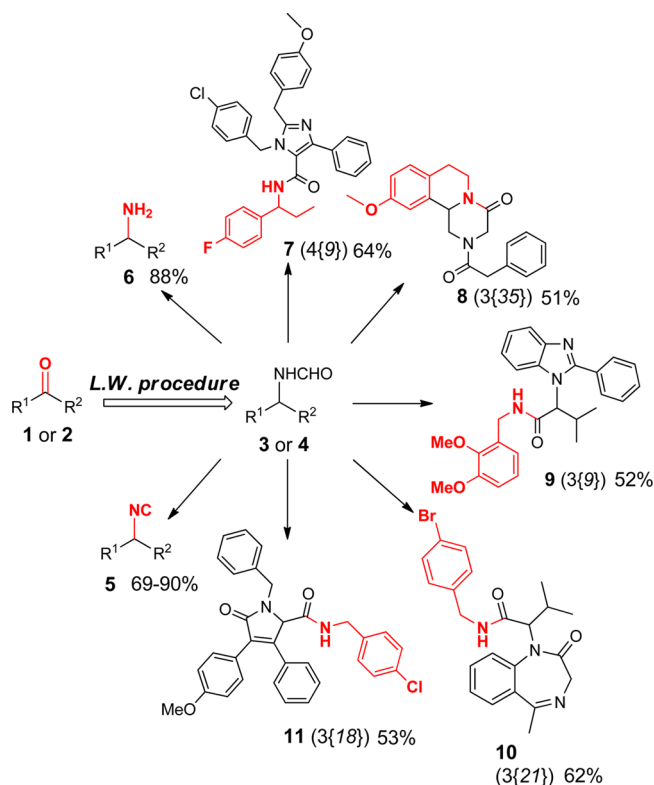
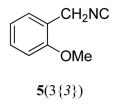
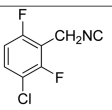
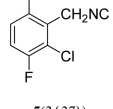
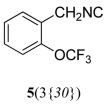
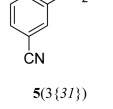
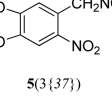
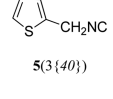
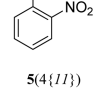


Table 2. Isocyanides Synthesized (Chemset 5) from Selected Formamides

Chemsets 5	Yield (%)	Chemsets 5	Yield (%)
	85		82
	90		82
	81		88
	75		69

amine component (compound 10a) which in a second step of Boc-deprotection, cyclizes to the corresponding 1,4-benzodiazepine. The isocyanide component was produced in situ from its formamide precursor (3{21}). In this case, the option to produce the isocyanide via the benzylamine would be very pricy (101\$/1g instead of 32\$/10g for 4-bromobenzaldehyde).

Scheme 6. Amines Synthesized (Chemset 6) from Selected Formamides

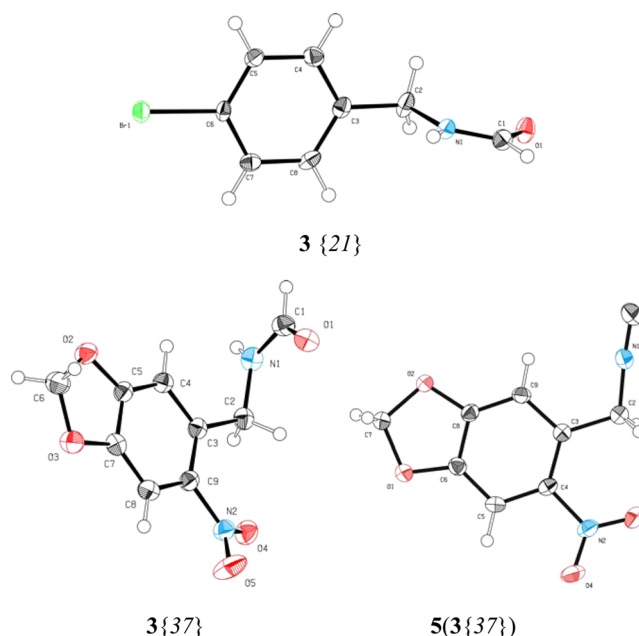
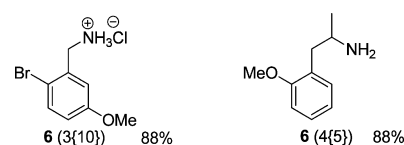


Figure 1. Ortep drawing with 50% ellipsoids.

Finally the pyrrolinone compound 11 was synthesized using an Ugi reaction as a primary step followed by an aldol reaction.²⁴ It was performed under microwave conditions using DIPA as base for this specific cyclization giving the final product in 75% yield.

The biggest advantage of the herein described method is the lower price of the oxo components on average and their differential and complementary structural diversity as compared to the primary amine pathway. Indeed, after the application of few criteria (see [Supporting Information](#)), we found and searched the emolecule Plus database finding 93 521 oxo components and 142 020 primary amines from which 106 963 from the latter and 53 577 of the former were available for purchase through the emoleculeBB Web site. After a second round of criteria, affording relatively fast shipments and similarity comparisons (oxo and primary amine compounds that would create the same isocyanide, see [Supporting Information](#)), 7857 unique amines (out of 11 339) and 11 033 (out of 13 487) unique oxo components were found, with an additional 3482 equiv oxo and amine compounds. As it is illustrated in [Charts 1–3](#), we can conclude that comparing the amines and oxo components that would create the same isocyanide (equivalent), the oxo compounds are on average \$75/gram cheaper ([Chart 1](#)). This is also true in the case of the unique compounds, which again show the oxo components are on average \$70/gram cheaper ([Chart 2](#)).

It is worth mentioning that the physical properties of the unique oxo components compared to the unique primary amines seem to be equivalent with the exception of logP, which was slightly higher in the case of oxo components

Chart 1. Comparison of Price and Quantity of the “Equivalent” and “Unique” Amines and Oxo Components

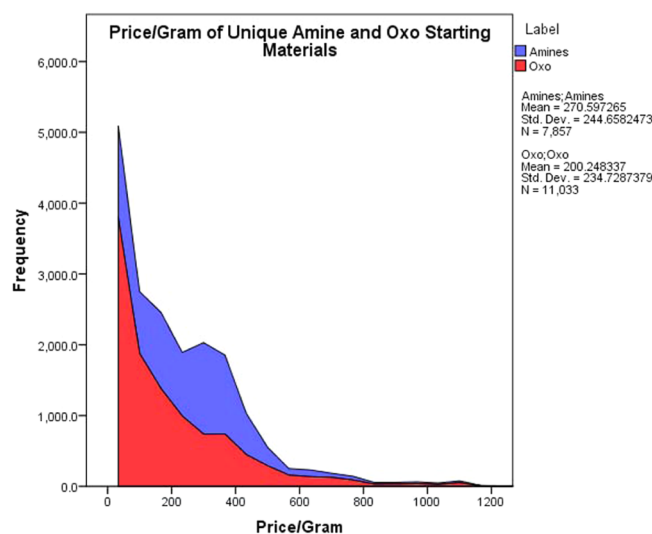
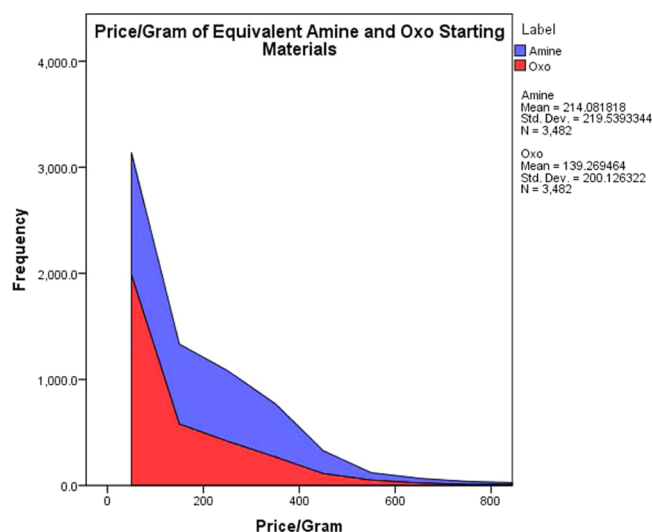
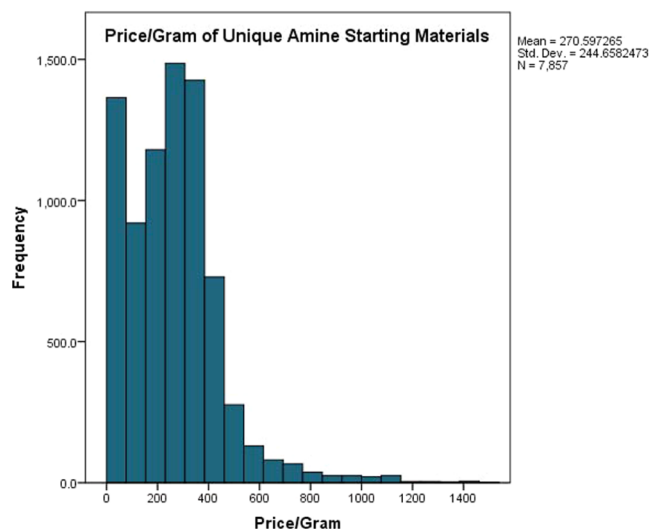
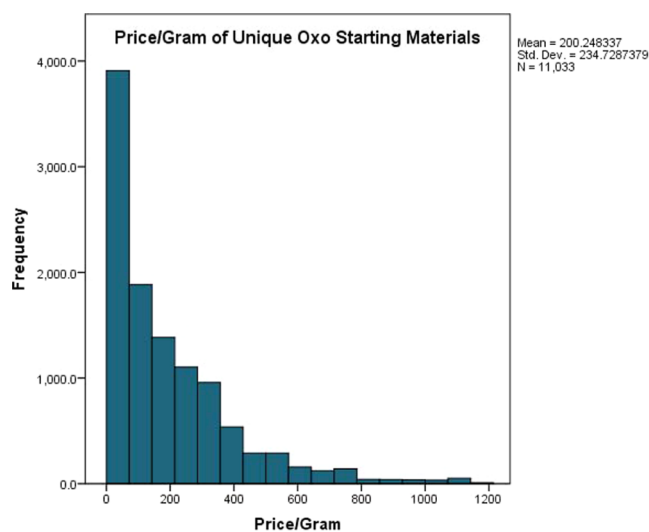


Chart 2. Comparison of Price and Quantity of the “Unique” Amines and Oxo Components



(Chart 3); however, this can likely be attributed to the fact that the amine functionality has a lower logP than the oxo C=O group. While there is a subset of isocyanides which would only be available through the amine synthesis (i.e., tertiary or aromatic amines), the quantity of the unique oxo compounds shows that our new method for developing isocyanides is complementary and not redundant to the previously described amine method. When looking at the price comparison of the equivalent amine/oxo compounds, the average price decrease makes this method even more desirable.

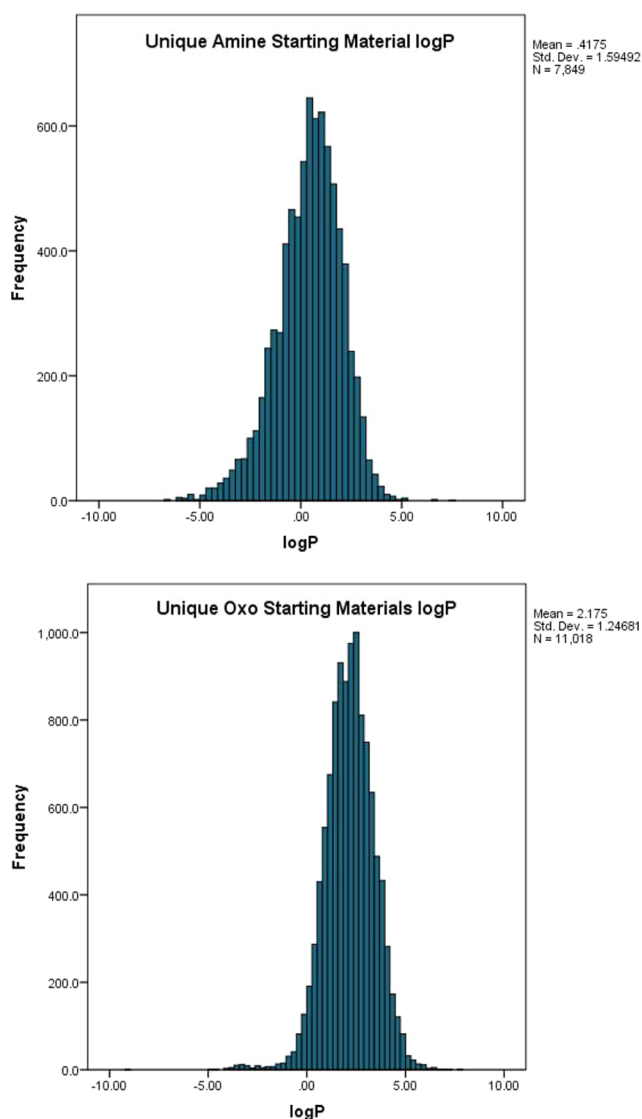
EXPERIMENTAL PROCEDURES

Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer (^1H NMR (500 MHz), ^{13}C NMR (126 MHz)). Chemical shifts for ^1H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double of doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR were reported in ppm relative to the solvent peak. Thin layer chromatography was performed on Fluka precoated silica gel plates

(0.20 mm thick, particle size 25 μm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 \AA , 230–400 mesh) and on a Reveleris X2 Flash Chromatography, using Grace Reveleris Silica flash cartridges (12 g). Reagents were available from commercial suppliers (Sigma-Aldrich, ABCR, Acros and AK Scientific) and used without any purification unless otherwise noted. All microwave irradiation reactions were carried out in a Biotage Initiator Microwave Synthesizer. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semiprep 15 SFC-MS instrument.

Typical Procedure for the One-Pot Synthesis of Compound 3{31}. A solution of 3-cyanobenzaldehyde (2.0 mmol) in formamide (100.0 mmol) and formic acid (10.0 mmol) was irradiated in a microwave oven at 180 $^\circ\text{C}$ for 3 min. After cooling down, extractions with dichloromethane (3×30 mL) followed. The organic layer was separated, washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica gel eluted with hexane-ethyl acetate (1:2) afforded the formamide 3{31} as a white solid in 92% yield. $R_f = 0.42$ (EtOAc/P.S 1:1)

Chart 3. Comparison of logP of the “Unique” Amines and Oxo Components



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscmbosci.5b00066.

Parallel synthesis of formamides (AVI)

General procedures, characterization data of all the compounds, and crystallographic data(PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.s.domling@rug.nl. Phone: +491603706633.

Author Contributions

The manuscript was written through contributions of all authors. C.N., T.T., and S.S. performed wet/lab chemistry experiments; K.K. and A.D. performed computational analyses.

Funding

The work was financially supported from the NIH (1R21GM087617, 1R01GM097082, and 1P41GM094055) and by Innovative Medicines Initiative (grant agreement no. 115489).

Notes

The authors declare no competing financial interest.

■ REFERENCES

- Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* **2006**, *106*, 17–89.
- Hulme, C.; Dietrich, J. Emerging Molecular Diversity from the Intra-Molecular Ugi Reaction: Iterative Efficiency in Medicinal Chemistry. *Mol. Diversity* **2009**, *13*, 195–207.
- Dömling, A.; Ugi, I. Multicomponent Reactions with Isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39* (18), 3168–3210.
- Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Multicomponent Reaction Design in the Quest for Molecular Complexity and Diversity. *Angew. Chem., Int. Ed.* **2011**, *50* (28), 6234–6246.
- Dömling, A.; Wang, W.; Wang, K. Chemistry and Biology Of Multicomponent Reactions. *Chem. Rev.* **2012**, *112* (6), 3083–3135.
- Koopmanschap, G.; Ruijter, E.; Orru, R. V. Isocyanide-Based Multicomponent Reactions towards Cyclic Constrained Peptidomimetics. *Beilstein J. Org. Chem.* **2014**, *10*, 544–598.
- Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. Isonitrile Syntheses. *Angew. Chem., Int. Ed. Engl.* **1965**, *4* (6), 472–484.
- Weber, W. P.; Gokel, G. W.; Ugi, I. K. Phase Transfer Catalysis in the Hofmann Carbylamine Reaction. *Angew. Chem., Int. Ed. Engl.* **1972**, *11* (6), 530–531.
- Neochoritis, C. G.; Stotani, S.; Mishra, B.; Dömling, A. Efficient Isocyanide-Less Isocyanide-Based Multicomponent Reactions. *Org. Lett.* **2015**, *17* (8), 2002–2005.
- Nyangulu, J. M.; Nelson, K. M.; Rose, P. A.; Gai, Y.; Loewen, M.; Loughheed, B.; Quail, J. W.; Cutler, A. J.; Abrams, S. R. Synthesis and Biological Activity of Tetralone Abscisic Acid Analogues. *Org. Biomol. Chem.* **2006**, *4* (7), 1400–1412.
- Fournet, A.; Barrios, A. A.; Muñoz, V.; Hocquemiller, R.; Roblot, F.; Cavé, A. Antileishmanial Activity of a Tetralone Isolated from *Ampelocera Edentula*, a Bolivian Plant Used as a Treatment for Cutaneous Leishmaniasis. *Planta Med.* **1994**, *60* (1), 8–12.
- De Andrade-Neto, V. F.; Da Silva, T.; Lopes, L. M. X.; Do Rosário, V. E.; de Pilla Varotti, F.; Krettli, A. U. Antiplasmodial Activity of Aryltetralone Lignans from *Holostylis Reniformis*. *Antimicrob. Agents Chemother.* **2007**, *51* (7), 2346–2350.
- Messiano, G. B.; da Silva, T.; Nascimento, I. R.; Lopes, L. M. X. Biosynthesis of Antimalarial Aryltetralone Lignans from *Holostylis Reniformis*. *Planta Med.* **2008**, *74* (09), SL72.
- Ai, W.; Lin, X.; Wang, Z.; Lu, X.; Mangaladoss, F.; Yang, X.; Zhou, X.; Tu, Z.; Liu, Y. Cladosporone A, A New Dimeric Tetralone from Fungus *Cladosporium* Sp. KcFL6' Derived of Mangrove Plant *Kandelia Candel.* *J. Antibiot.* **2015**, *68* (3), 213–215.
- Szymański, W.; Velema, W. A.; Feringa, B. L. Photocaging of Carboxylic Acids: A Modular Approach. *Angew. Chem., Int. Ed.* **2014**, *53* (33), 8682–8686.
- Zhang, C.; Moran, E. J.; Woiwode, T. F.; Short, K. M.; Mjalli, A. M. Synthesis of Tetrasubstituted Imidazoles via α -(N-Acyl-N-Alkylamino)- β -Ketoamides on Wang Resin. *Tetrahedron Lett.* **1996**, *37* (6), 751–754.
- Wang, W.; Ollio, S.; Herdtweck, E.; Dömling, A. Polycyclic Compounds by Ugi-Pictet-Spengler Sequence. *J. Org. Chem.* **2011**, *76* (2), 637–644.
- Liu, H.; Dömling, A. Efficient and Diverse Synthesis of Indole Derivatives. *J. Org. Chem.* **2009**, *74* (17), 6895–6898.
- Liu, H.; William, S.; Herdtweck, E.; Botros, S.; Dömling, A. MCR Synthesis of Praziquantel Derivatives. *Chem. Biol. Drug Des.* **2012**, *79* (4), 470–477.
- Richter, H. G. F.; Benson, G. M.; Bleicher, K. H.; Blum, D.; Chaput, E.; Cleemann, N.; Feng, S.; Gardes, C.; Grether, U.; Hartman, P.; Kuhn, B.; Martin, R. E.; Plancher, J. M.; Rudolph, M. G.; Schuler, F.; Taylor, S. Optimization of a Novel Class of Benzimidazole-Based Farnesoid X Receptor (FXR) Agonists to Improve Physicochemical and ADME Properties. *Bioorg. Med. Chem. Lett.* **2011**, *21* (4), 1134–1140.

(21) Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. Two-Step Solution-Phase Synthesis of Novel Benzimidazoles Utilizing a UDC (Ugi/de-Boc/cyclize) Strategy. *Tetrahedron Lett.* **2001**, *42* (30), 4959–4962.

(22) Huang, Y.; Khoury, K.; Chanas, T.; Dömling, A. Multi-component Synthesis of Diverse 1,4-Benzodiazepine Scaffolds. *Org. Lett.* **2012**, *14* (23), 5916–5919.

(23) Azuaje, J.; Pérez-Rubio, J. M.; Yaziji, V.; El Maatougui, A.; González-Gomez, J. C.; Sánchez-Pedregal, V. M.; Navarro-Vázquez, A.; Masaguer, C. F.; Teijeira, M.; Sotelo, E. Integrated Ugi-Based Assembly of Functionally, Skeletally, and Stereochemically Diverse 1,4-Benzodiazepin-2-Ones. *J. Org. Chem.* **2015**, *80* (3), 1533–1549.

(24) Xu, Z.; De Moliner, F.; Cappelli, A. P.; Hulme, C. Ugi/Aldol Sequence: Expeditious Entry to Several Families of Densely Substituted Nitrogen Heterocycles. *Angew. Chem., Int. Ed.* **2012**, *51* (32), 8037–8040.