The Leuckart-Wallach Route Towards Isocyanides and Some Applications

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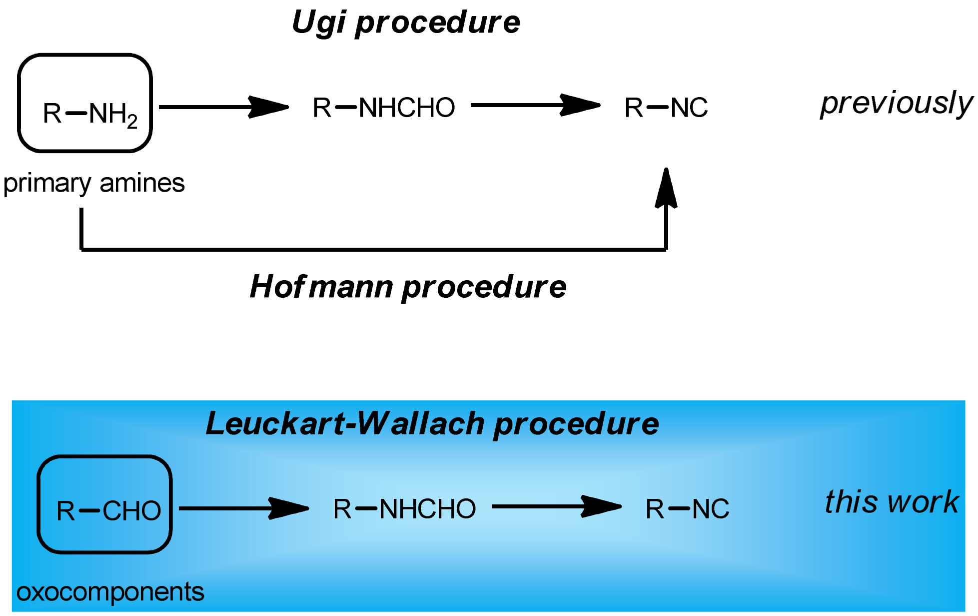
KEYWORDS. Leuckart-Wallach, formamides, isocyanides, IMCR, Ugi

ABSTRACT. Isocyanide-based multicomponent reactions (IMCR) are amongst 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 towards 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.

INTRODUCTION

Atom economy, efficiency, diversity and complexity: Four terms that multi-component 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 multi-component 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 ⇨ formamide ⇨ 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]



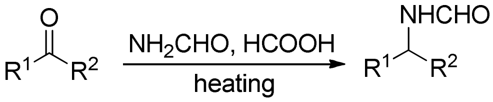
Scheme 1. The Leuckart-Wallach route to isocyanides.

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 towards isocyanides through formamides based on 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 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

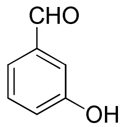
EWG and EDG, and heterocycles (chemset 1). Moreover, ketones with aromatic, aliphatic and heterocyclic substituents were employed (chemset 2).



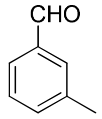
1 {1-40} **3** {1-40}

2 {1-15} **4** {1-15}

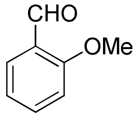
Scheme 2. The Leuckart-Wallach reaction using formamide and formic acid as the reductive agent from the corresponding oxo component.



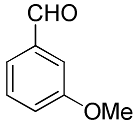
1 {*1*}



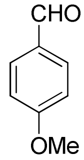
1 {*2*}



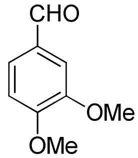
1 {*3*}



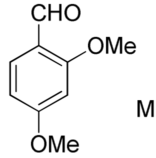
1 {*4*}



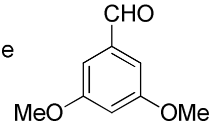
1 {*5*}



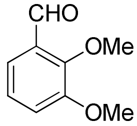
1 {*6*}



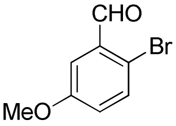
1 {*7*}



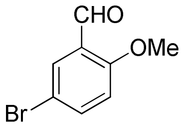
1 {*8*}



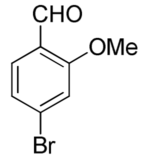
1 {*9*}



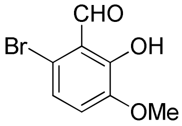
1 {*10*}



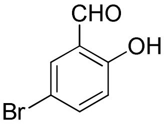
1 {*11*}



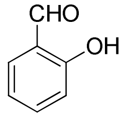
1 {*12*}



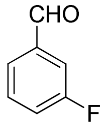
1 {*13*}



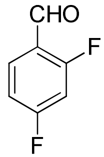
1 {*14*}



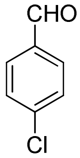
1 {*15*}



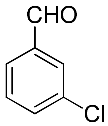
1 {*16*}



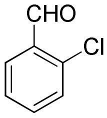
1 {*17*}



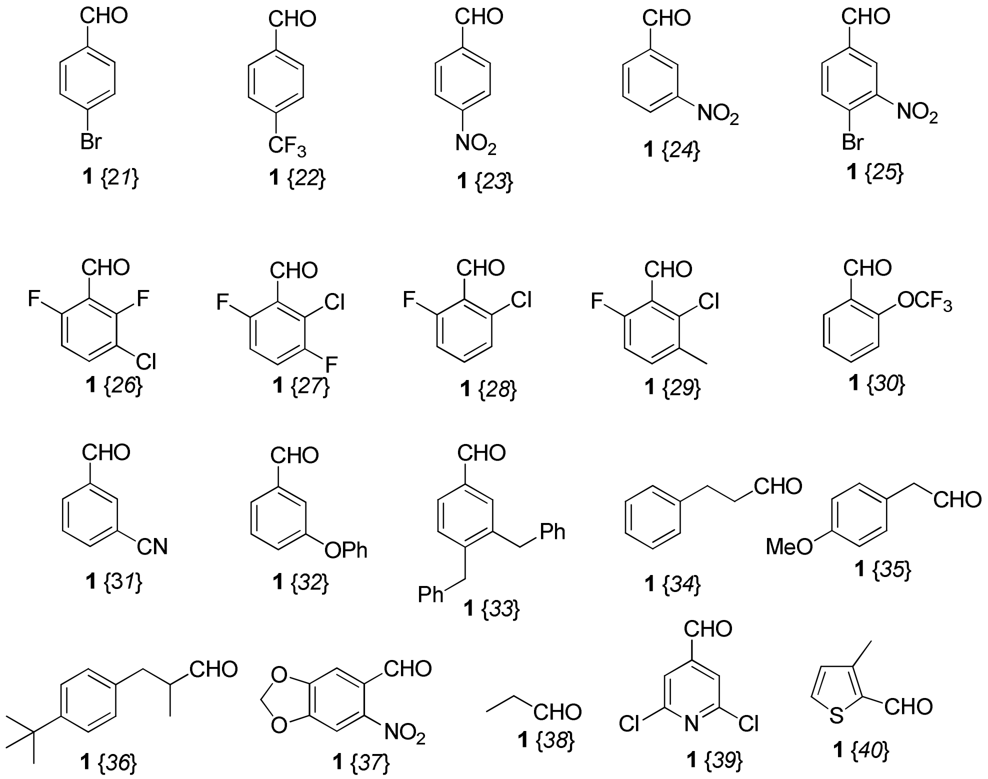
1 {*18*}



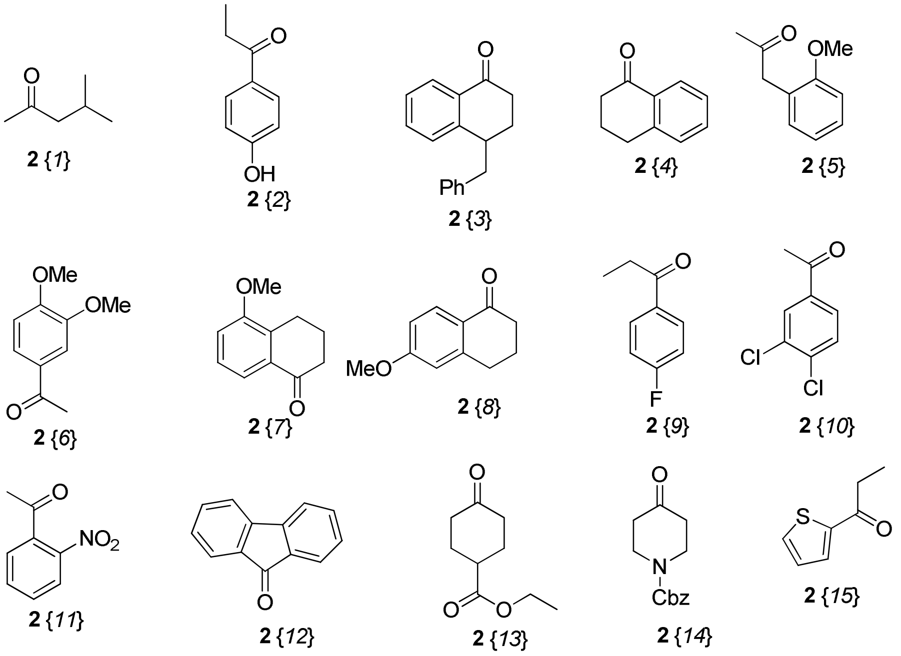
1 {*19*}



1 {*20*}



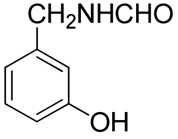
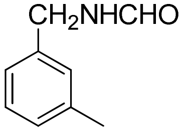
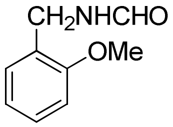
Scheme 3. The Chemset 1 consisting of aldehydes.

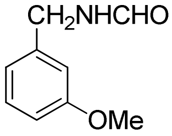
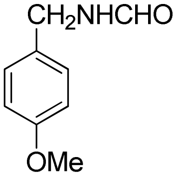
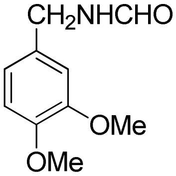
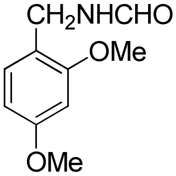
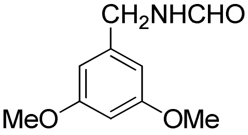
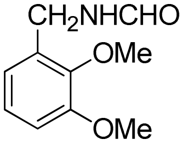
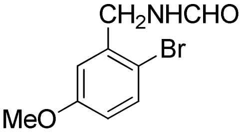
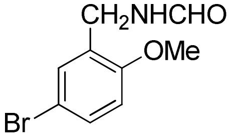
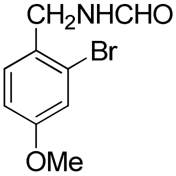
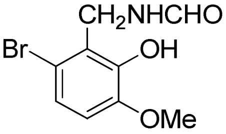
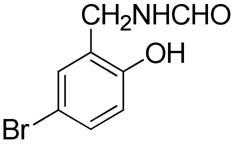
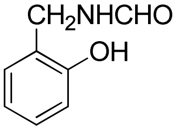
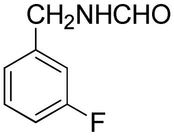
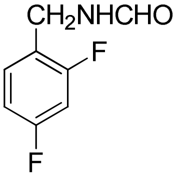
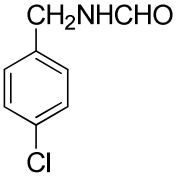
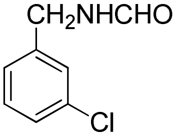
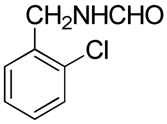
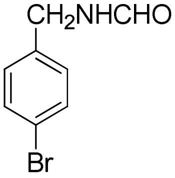


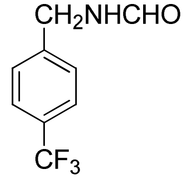
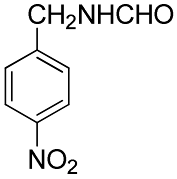
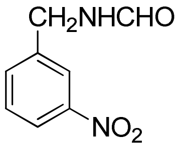
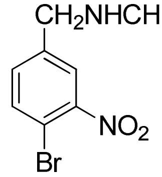
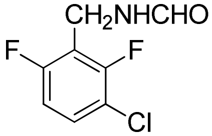
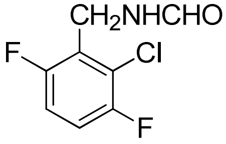
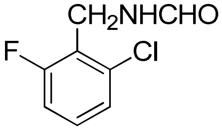
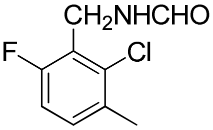
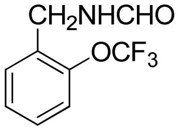
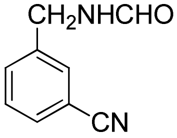
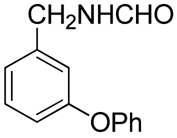
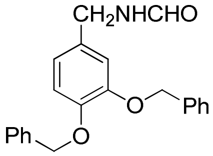
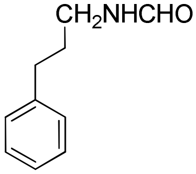
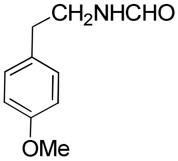
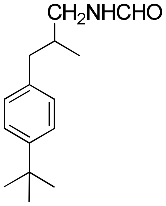
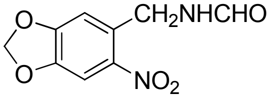
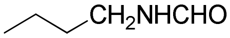
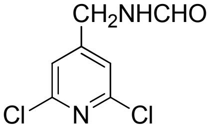
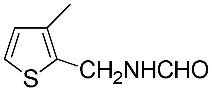
Scheme 4. The Chemset 2 consisting of ketones.

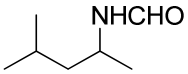
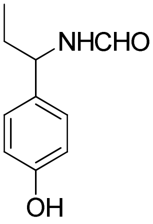
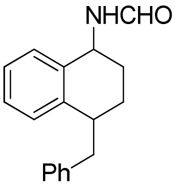
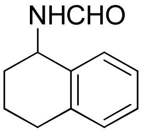
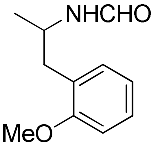
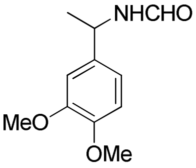
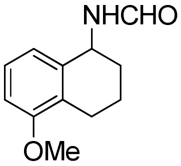
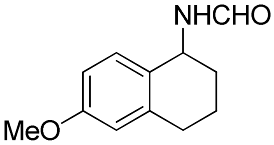
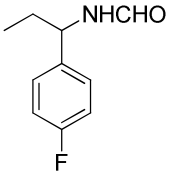
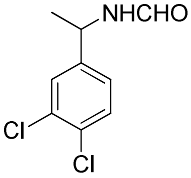
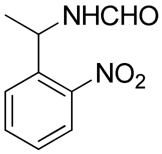
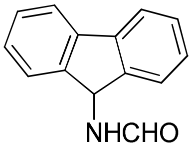
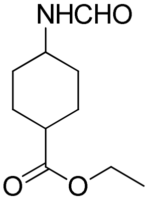
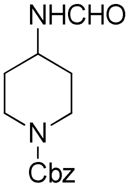
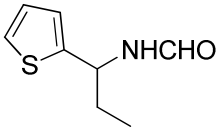
The formamides (chemsets 3,4) were prepared either in parallel, using suitable metal block heaters (SI movie, photos in supporting information) or under microwave irradiation (Table 1). A typical experimental procedure by conventional heating involves the addition of the corresponding oxo component (1 equiv.) in a solution of formamide (12 equiv.) with formic acid (5 equiv.) and refluxing at 160-180 ^{o}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 minutes. Carbon dioxide emission was observed during the procedure which ceased upon completion and after an aqueous workup the desired formamide is isolated with no 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]

Table 1. Formamides synthesized (Chemsets **3**,**4**) via Leuckart-Wallach reactions either by conventional heating or microwave irradiation.

Chemsets 3,4	**Yield (%)**	**Chemsets 3,4**	**Yield (%)**	**Chemsets 3,4**	**Yield (%)**
 **3**{*1*}	71	 **3**{*2*}	73	 **3**{*3*}	44

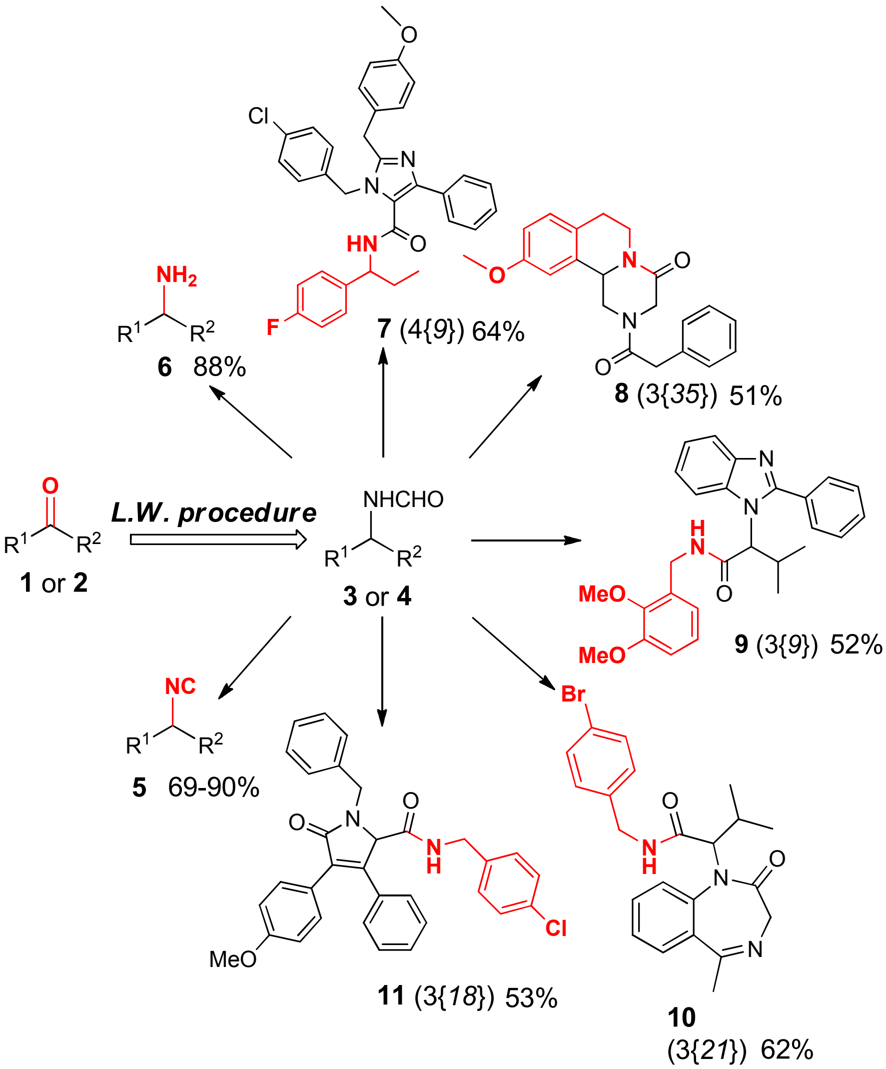
 **3**{*4*}	87 (85)^{b}	 **3**{*5*}	55	 **3**{*6*}	53 (75)^{b}
 **3**{*7*}	60	 **3**{*8*}	61	 **3**{*9*}	53
 **3**{*10*}	66	 **3**{*11*}	82	 **3**{*12*}	69
 **3**{*13*}	43	 **3**{*14*}	43 (80)^{b}	 **3**{*15*}	44
 **3**{*16*}	50	 **3**{*17*}	79	 **3**{*18*}	68
 **3**{*19*}	78	 **3**{*20*}	59	 **3**{*21*}	48 (95)^{b}

 **3**{*22*}	62	 **3**{*23*}	52 (91)[b]	 **3**{*24*}	60
 **3**{*25*}	68	 **3**{*26*}[α]	91 (60)[b]	 **3**{*27*}[α]	83 (95)[b]
 **3**{*28*}[α]	85	 **3**{*29*}[α]	94 (46)[b]	 **3**{*30*}[α]	81
 **3**{*31*}[α]	92	 **3**{*32*}	89	 **3**{*33*}	58
 **3**{*34*}	58	 **3**{*35*}	90	 **3**{*36*}	60 (57)[b]
 **3**{*37*}	40	 **3**{*38*}	80	 **3**{*39*}	45
 **3**{*40*}[α]	87 (85)[b]				

 **4**{*1*}	45	 **4**{*2*}	69	 **4**{*3*}	55
 **4**{*4*}	64 (45)[b]	 **4**{*5*}	62	 **4**{*6*}	56
 **4**{*7*}	45	 **4**{*8*}	53	 **4**{*9*}	75
 **4**{*10*}	66	 **4**{*11*}	54	 **4**{*12*}[a]	87
 **4**{*13*}	51	 **4**{*14*}	60	 **4**{*15*}	59

[a] The reaction performed in 20 mmol scale; [b]The reaction performed in MW

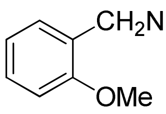
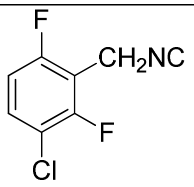
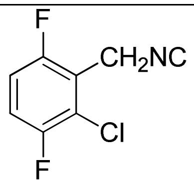
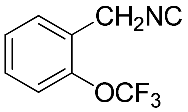
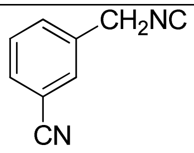
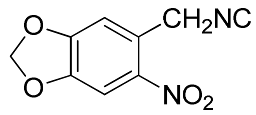
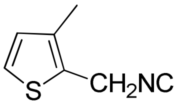
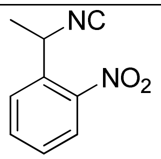
Having in hand, this diversity and complexity of formamides, which often are very difficult to produce through previously described methods, we wanted to go a step further. Demonstrating the generality of our procedure, we employed the Leuckart-Wallach procedure in the synthesis of isocyanides, amines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



Scheme 5. Applications of the formamides and synthesis of isocyanides, amines and five different MCR scaffolds with their overall yields.

Isocyanides **5**(**3**{*3*, *26*, *27*, *30*, *31*, *37*, *40*},**4**{*11*}) (chemset 5) were synthesized under the common dehydration conditions ($POCl_3$, Et_3N). 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 worthwhile mentioning as it can be used for the synthesis of photo inducible probes, a recently emerging research area.[15]

Table 2. Isocyanides synthesized (Chemset **5**) from selected formamides.

Chemsets 5	**Yield (%)**	**Chemsets 5**	**Yield (%)**
 **5**(3{*3*})	85	 **5**(3{*26*})	82
 **5**(3{*27*})	90	 **5**(3{*30*})	82
 **5**(3{*31*})	81	 **5**(3{*37*})	88
 **5**(3{*40*})	75	 **5**(4{*11*})	69

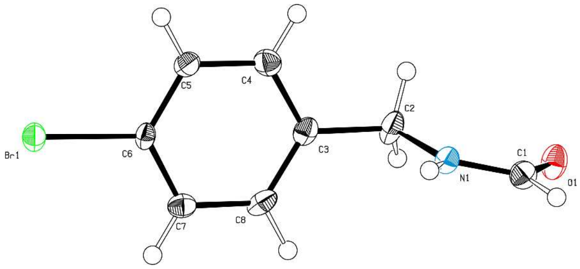
Similarly, the corresponding formamides after treatment with HCl (5N in dioxane) gave access to the amines **6**(3{*10*},4{*5*}) in excellent yields. Compound **6**(3{*10*}, for example would cost $428 for 1 g, and is only available through one supplier, EnamineBB. However the corresponding aldehyde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

6 (3{10}) 88%

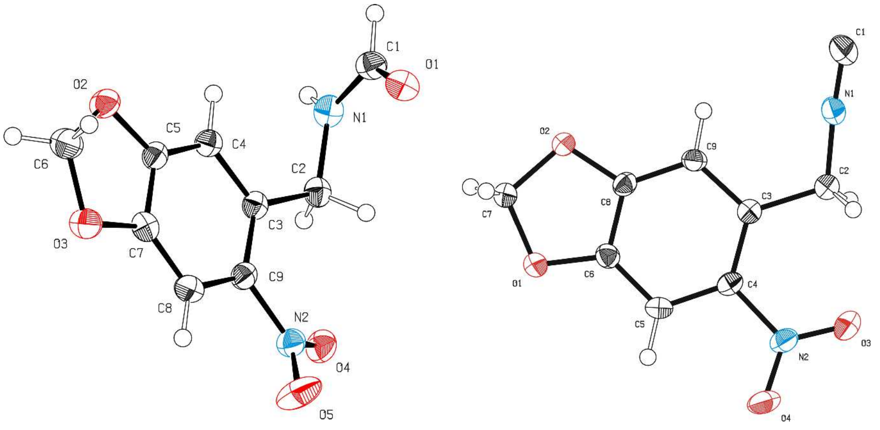
6 (4{5}) 88%

Scheme 6. Amines synthesized (Chemset **6**) from selected formamides.

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.



3 {*21*}



3{*37*} **5**(**3**{*37*})

Figure 1. Ortep drawing with 50% ellipsoids.

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 post-modification step that gives access to important 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 methanesulphonic 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 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). 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 SI), 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 website. 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 SI), 7857 unique amines (out of 11,339) and 11,033 (out of 13,487) unique oxo components were found, with an additional 3,482 equivalent oxo and amine compounds. As it is illustrated in the following charts, 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).

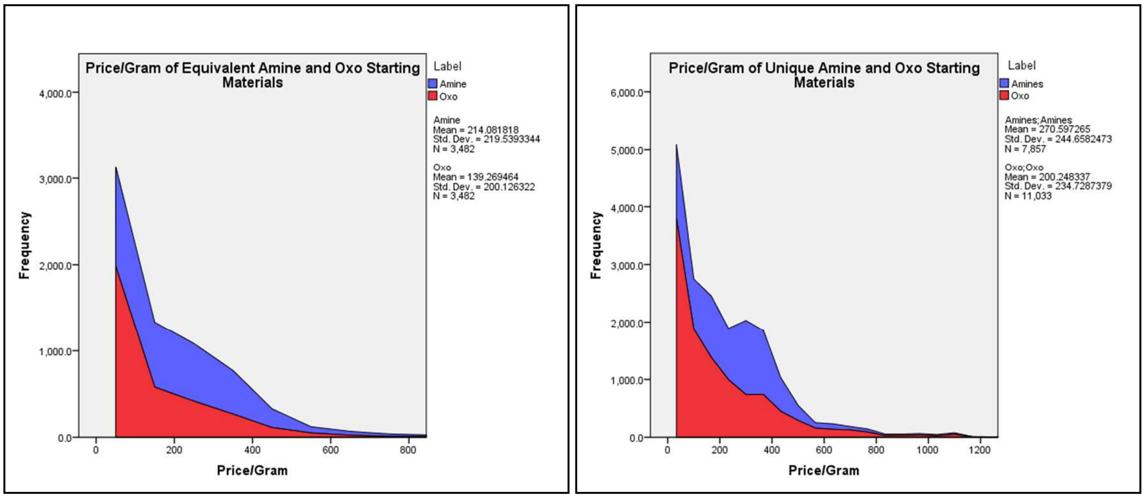


Chart 1. Comparison of price and quantity of the "equivalent" and "unique" amines and oxo components.

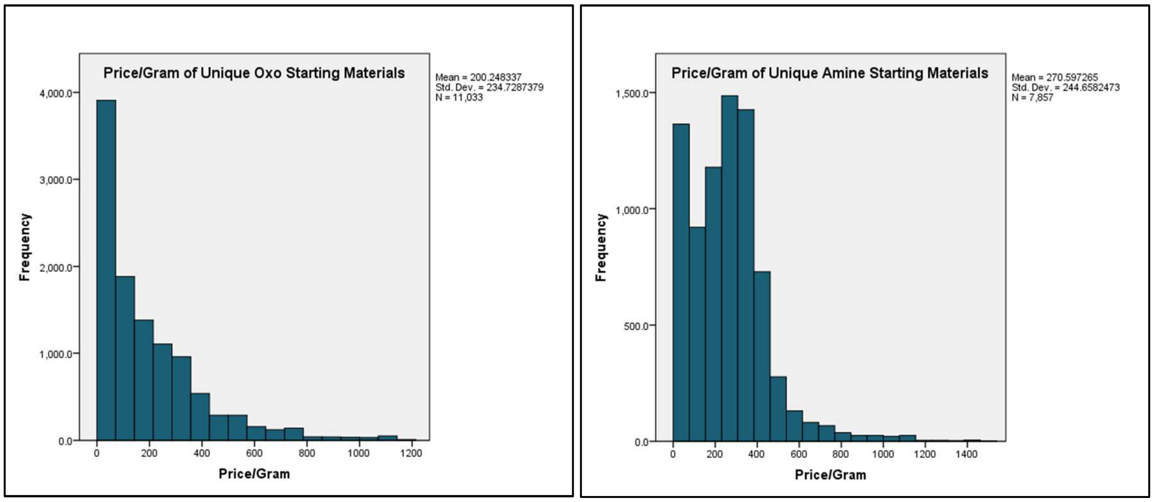


Chart 2. Comparison of price and quantity of the "unique" amines and oxo components.

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 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.

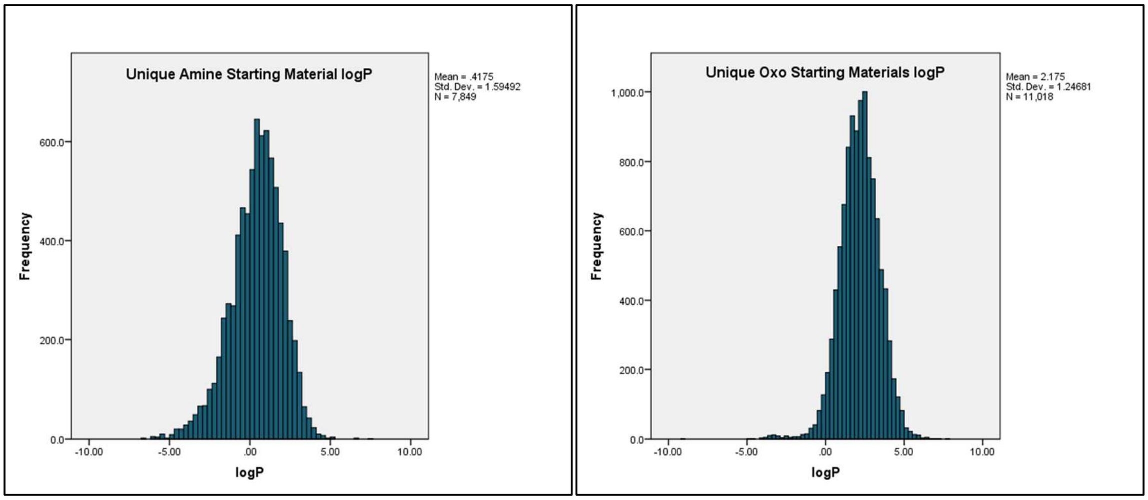


Chart 3. Comparison of logP of the “unique” amines and oxo components.

EXPERIMENTAL PROCEDURES

Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)}. Chemical shifts for ^{1}H 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 Å, 230 - 400 mesh) and on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). 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 Semi-prep 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 °C for 3 min. After cooling down, extractions with dichloromethane (3x30 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)

ASSOCIATED CONTENT

General procedures, characterization data of all the compounds, crystallographic data and a multimedia file (AVI) are included as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. CN, TT and SS performed wet/lab chemistry experiments; KK and AD performed computational analyses.

Funding Sources

The work was financially supported from the NIH (1R21GM087617, 1R01GM097082, and 1P41GM094055) and by Innovative Medicines Initiative (grant agreement n° 115489).

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Formamides as the most important precursors of isocyanides, have a unique position in IMCRs. We report a novel route to access them through oxo components in a one-pot, parallel and easily applied procedure. Moreover, we provide further synthetic applications, demonstrating the general applicability and effectiveness of our method.