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2-Bromo-6-isocyanopyridine as a Universal Convertible Isocyanide for Multicomponent Chemistry

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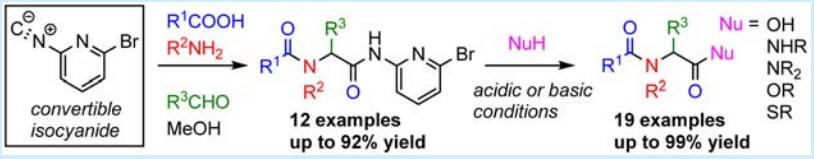
Supporting Information



ABSTRACT: The development of 2-isocyanopyridines as novel convertible isocyanides for multicomponent chemistry is reported. Comparison of 12 representatives of this class revealed 2-bromo-6-isocyanopyridine as the optimal reagent in terms of stability and synthetic efficiency. It combines sufficient nucleophilicity with good leaving group capacity of the resulting amide moiety under both basic and acidic conditions. To demonstrate the practical utility of this reagent, an efficient two-step synthesis of the potent opioid carfentanil is presented.

Drug discovery relies heavily on high-throughput screening of large compound collections which, in turn, requires efficient parallel synthesis methodologies for effective coverage of biological activity space. Isocyanide-based multicomponent reactions (IMCRs) such as the Ugi four-component reaction (Ugi 4CR, Scheme 1) are of tremendous importance in this area because of their high efficiency and variability.[1] Clever design of inputs with various reactivity handles opens possibilities for postmodification of the IMCR products to generate arrays of new scaffolds such as heterocycles and macrocycles.[2]

Scheme 1. Application of a Convertible Isocyanide in the Ugi 4CR

One important drawback of IMCRs is the limited commercial availability of many isocyanides, particularly with biologically relevant functional groups, compared to the exceedingly wide availability of other IMCR components (carboxylic acids, ketones/aldehydes, and amines).[3] In addition, the isocyanide input generally results in a very stable secondary amide, which makes further synthetic manipulation at this site challenging.

In 1962, Ugi and Rosendahl described the use of cyclohexenyl isocyanide (**I**, R = H) in the Ugi 4CR and subsequent conversion of the product to a primary amide. In 1995, Armstrong introduced the concept of a *convertible isocyanide* (Scheme 1).[4] In the ideal case, this (universal) isocyanide can substitute all other isocyanides, since it can be converted after the IMCR into any other functional group, e.g., another amide, a (thio)ester, or a carboxylic acid. As a result, the synthesis, purification and handling of custom isocyanides can be avoided, while a host of functional groups can be introduced by post-MCR transformations, greatly expanding the molecular diversity of the products beyond the typical secondary amides. Over the past two decades, several convertible isocyanides have been developed[5] (Figure 1), but all suffer from limitations such as (a) the isocyanides require lengthy, tedious synthetic routes; (b) the isocyanides themselves are unstable/difficult to handle; (c) the conversion to different functional groups is rather limited; (d) functional groups in the isocyanide moiety are incompatible with various standard manipulations; (e) the IMCR requires a workup before cleavage of the secondary

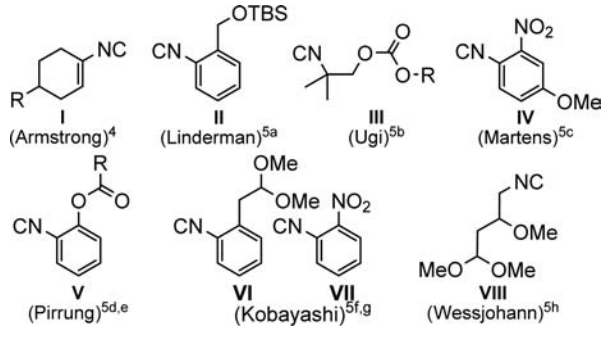


Figure 1. Selected examples of convertible isocyanides **I**–**VII**.

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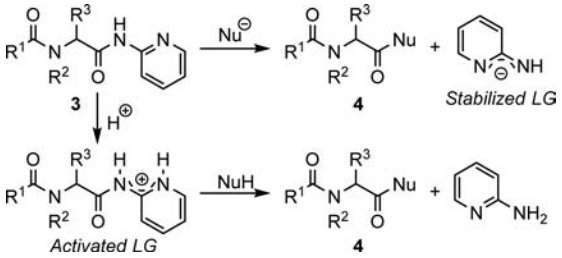
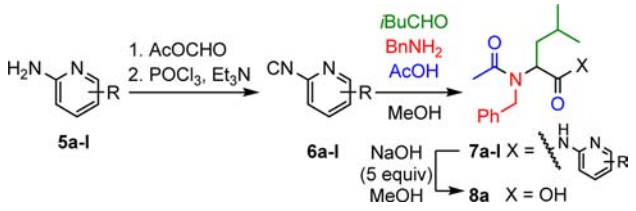
amide; and (f) cleavage of the convertible isocyanides requires a tedious multistep transformation. In light of our continued interest in the application of isocyanide-based reactions, we embarked on the quest of finding a truly practical convertible isocyanide which is sufficiently nucleophilic to react with a broad range of other inputs in various IMCRs, but also generates an electrophilic amide carbonyl upon the IMCR. We envisioned that 2-isocyanopyridines could be suitable candidates as the resulting *N*-2-pyridyl amide is a good leaving group under both basic and acidic conditions (Scheme 2).

Scheme 2. Proposed Cleavage of *N*-Pyridylamides under Basic and Acidic Conditions



Basic cleavage would lead to a negatively charged aminopyridine species in which the charge is stabilized by the pyridine ring, whereas protonation of the pyridine ring enhances both the leaving group capability of the amine and the electrophilicity of the amide (potentially via münchnones as described by Armstrong).[4b] Although there are scattered reports on the synthesis,[6] dimerization,[7] and metal complexes[8] of 2-isocyanopyridines, their use in IMCRs is limited to only three examples.[9] Given their proposed potential as convertible isocyanides, we set out to synthesize a set of 12 monosubstituted 2-isocyanopyridines from the corresponding commercial 2-aminopyridines (Table 1). These isocyanides were then reacted with isovaleraldehyde, benzylamine, and acetic acid to afford the Ugi products **7a–l**. Finally, compounds **7a–l** were subjected to mild hydrolysis conditions (5 equiv of aq NaOH, MeOH, rt) to give carboxylic acid **8a**.[10] The results, summarized in Table 1, clearly indicate that 2-bromo-6-isocyanopyridine (**6l**) is the optimal isocyanide in all respects (ease of synthesis, reactivity in the Ugi 4CR, and hydrolysis of the resulting secondary amide). Importantly, **6l** is an easy-to-handle solid that is stable for months at −18 °C and soluble in most common organic solvents. To evaluate the applicability of isocyanide **6l** in the Ugi 4CR, we reacted it with a set of chemically diverse amines, aldehydes, and carboxylic acids (Scheme 3) under standard Ugi conditions (MeOH, rt, 48 h).

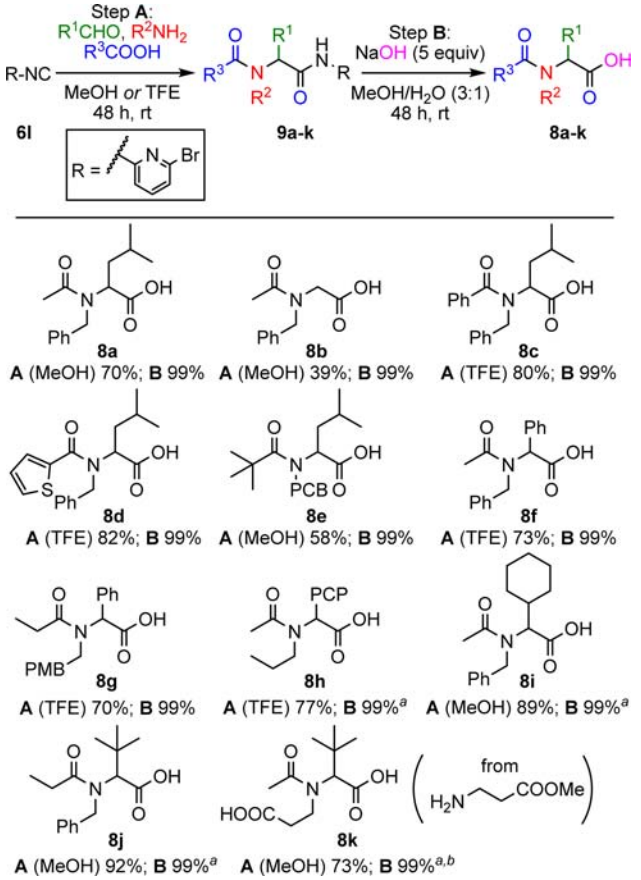
Table 1. Selection of Optimal Convertible Isocyanide



entry	R	6	yield of 6 (%)	7	yield of 7 (%)	yield of 8a[a] (%)
1	3-CH_3	**6a**	43	**7a**	66	48
2	3-Br	**6b**	71	**7b**	41	63
3	4-CH_3	**6c**	12	**7c**	66	52
4	4-Br	**6d**	44	**7d**	65	95
5	5-CH_3	**6e**	57	**7e**	58	21
6	5-F	**6f**	27	**7f**	58	23
7	5-Cl	**6g**	35	**7g**	62	73
8	5-Br	**6h**	62	**7h**	76	81
9	5-CF_3	**6i**	42	**7i**	15	n.d.
10	6-CH_3	**6j**	49	**7j**	62	55
11	6-Cl	**6k**	54	**7k**	65	95
12	**6-Br**	**6l**	**70**	**7l**	**70**	**96**

[a]Yield determined by GC.

Scheme 3. Applicability of Isocyanide 6l in the Ugi 4CR



[a]Deprotection requires elevated temperatures (50 °C) or prolonged reaction time. [b]The methyl ester was also hydrolyzed under the reaction conditions. PCB = *p*-chlorobenzyl; PCP = *p*-chlorophenyl; PMB = *p*-methoxybenzyl.

Pleasingly, all examined combinations provided the Ugi products **9a–k** in moderate to excellent yields (39–92%). Reactions with (hetero)aromatic carboxylic acids (to give **8c** and **8d**) and aromatic aldehydes (to give **8f–h**) gave low conversion under the standard reaction conditions. However, the yields were greatly improved using the more activating solvent 2,2,2-trifluoroethanol (TFE).[11]

We then converted Ugi products **9a–k** to the corresponding carboxylic acids under mildly basic conditions. Carboxylic acids are the most versatile intermediates since standard methodologies allow their further elaboration to, e.g., (thio)esters and amides. In most cases, the hydrolysis proceeded very cleanly in quantitative yield at room temperature (**8a–g**). For sterically more demanding substrates (**8h–k**), higher temperatures (up

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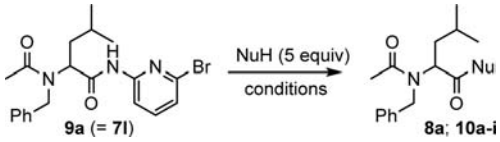
to 50 °C) or longer reaction times were required. Notably, the mild hydrolysis conditions tolerate a variety of functional groups. As expected, however, esters are saponified (**8k**). Since both the Ugi and the hydrolysis reaction require the same solvent, we envisioned a one-pot IMCR/hydrolysis procedure (MeOH, rt; then 5 equiv of aq NaOH). To our delight, we obtained the hydrolyzed Ugi product **8a** in similar yield as the two-step procedure (67% vs 70%). Advantageously, **8a** could be purified by simple acid−base extraction, thereby avoiding the need for column chromatography.

Next, we investigated the transformation of the secondary amide of **9a** (**7l**) into other functionalities. Switching from NaOH to NaOMe under anhydrous conditions furnished the corresponding methyl ester **10a** (Table 2, entry 2). To our delight, addition of 5 equiv of *n*-butylamine or pyrrolidine provided the corresponding secondary and tertiary amide **10b** and **10c**, respectively (entries 3 and 4). However, the use of a less nucleophilic secondary amine (morpholine, entry 5) did not provide the desired product.

Table 2. Substitution of the 2-Pyridylamido Group by Various Nucleophiles



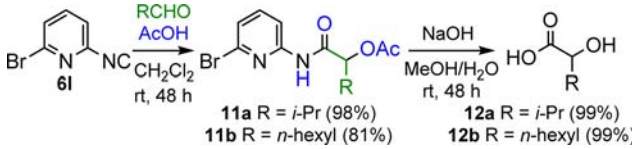
entry	NuH	product	yield (%)	cond[a]
1	H_2O	**8a**	99	A
2	MeOH	**10a**	80	A
3	*n*-$BuNH_2$	**10b**	61	A
4	pyrrolidine	**10c**	70	A
5	morpholine	**10d**	0[b]	A
6	H_2O	**8a**	99	B
7	MeOH	**10a**	99	B
8	*n*-BuOH	**10e**	99	B
9	*i*-PrOH	**10f**	99	B
10	3-butyn-1-ol	**10g**	65[c]	B
11	EtSH	**10h**	86[d]	B

[a]Reaction conditions: (A) NaOMe (5 equiv) in MeOH, 3 Å MS, 50 °C, 24 h; (B) NuH (5 equiv), HCl (5 equiv), CH_2Cl_2/Et_2O, rt, 16 h. [b]Only the methyl ester was observed in ^{1}H NMR. [c]2 equiv of the corresponding alcohol was used. [d]EtSH was used as a cosolvent.

As proposed in Scheme 2, protonation should enhance the electrophilicity of the amide as well as the leaving group capability of the pyridylamine. As envisioned, performing the acid-mediated conversion in the presence of 5 equiv of nonbasic nucleophiles such as water (entry 6), alcohols (entries 7−10) or thiols (entry 11) provided the corresponding carboxylic acid, ester or thioester respectively in good-to-excellent yields (61−99%). Notably, thioesters are versatile intermediates with great potential in chemical biology by means of native chemical ligation (NCL).[12] Our Ugi/thioesterification method can provide easy access to synthetic peptide thioesters bearing various labels. The generality of this approach is an important synthetic advantage. Even less nucleophilic alcohols, such as 3-butyn-1-ol (entry 10), in only moderate excess (2 equiv) afford the corresponding ester in reasonable yield. Unfortunately, the use of carbon nucleophiles (e.g., indole) did not lead to the desired ketones.

To evaluate the potential of convertible isocyanide **6l** in other IMCRs, we reacted it with acetic acid and either isobutyraldehyde or *n*-hexanal to give the corresponding Passerini products **11a** and **11b** in 98% and 81% yield, respectively (Scheme 4). Subsequent hydrolysis quantitatively afforded the α-hydroxycarboxylic acids **12a** and **12b**.

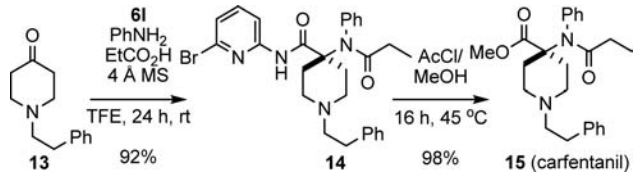
Scheme 4. Synthesis of α-Hydroxycarboxylic Acids via Passerini Reaction of 6l



An additional advantage of **6l** over most other convertible isocyanides is the fact that the *N*-substituent remains intact after conversion of the IMCR product. This offers opportunities for overall recyclability by recovery of the final cleavage products and excess reactants containing the 2-amino-6-bromopyridine moiety. Thus, we performed a full recovery cycle starting from 2-amino-6-bromopyridine (**5l**; Scheme S3). After quantitative *N*-formylation, dehydration proved incomplete but allowed recovery of the majority of the unreacted formamide. The Ugi 4CR leading to **7l**/**9a** proceeded optimally with a slight excess of **6l**, and unreacted **6l** could be quantitatively recovered. In the final methanolysis, **5l** was isolated in 91% yield. Combining the various recovered fractions led to an overall recovery of 83%, making our novel reagent the first convertible isocyanide that is easily recycled.

As a demonstration of the practicality of our new reagent, we applied it to the efficient synthesis of carfentanil (**15**).[13] This synthetic opioid, which is ∼100000 times more potent than morphine,[14] is plausibly accessible via the Ugi 4CR of **6l**, commercial ketone **13**, aniline, and propionic acid followed by methanolysis (Scheme 5). To our delight, the Ugi 4CR smoothly afforded **14** in excellent yield (92%). Acidic methanolysis (AcCl/MeOH, 45 °C) then gave carfentanil in near-quantitative yield (98%).

Scheme 5. Synthesis of the Potent Opioid Carfentanil



In conclusion, we have successfully developed 2-bromo-6-isocyanopyridine as a novel convertible isocyanide. Compared to existing convertible isocyanides, our reagent performs better in terms of accessibility, convertibility of the IMCR primary scaffold, and regeneration/recycling. The most important advantage is the facile and versatile diversification of IMCR products at a site that is relatively chemically inert: the secondary amide originating from the isocyanide input in Ugi-type reactions can be converted (in the same pot) to a diverse set of functional groups under two sets of complementary reaction conditions. As a consequence, we believe that this novel reagent has unmatched synthetic potential and can play an important part in multicomponent applications.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00091.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): VU Amsterdam has filed a patent application on 2-isocyanopyridines and their use in multicomponent reactions as well as transformation of the resulting products from which the authors may receive royalty payments.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The blue R^1 groups in Scheme 3 were changed to R^3 on February 10, 2016.

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