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2-Nitrobenzyl Isocyanide as a Universal Convertible Isocyanide

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Abstract

2-Nitrobenzyl isocyanide is reported as a universal convertible isocyanide with extensive applicability in both Ugi four-component reaction (Ugi-4CR) and Ugi-tetrazole reaction. The cleavage of this isocyanide from 17 examples in both acidic and basic conditions is presented. Additionally, this isocyanide has various handling and synthetic advantages, as it is easy to prepare, odorless, stable, and easy to handle as a solid.

Keywords

convertible isocyanide; multicomponent reactions; tetrazole; ugi-4cr; ugi-tetrazole reaction

Multicomponent reactions are considered ideal reactions owing to a wide range of advantages, such as simplicity, high efficiency, green nature, and time efficacy.^[1] The isocyanide-based multicomponent reaction (IMCR) is a promising synthetic methodology for the synthesis of peptidomimetics and peptides with broad applications in pharmaceutical and organic industries.^[2] The Ugi reaction is the most extensively studied and widely used IMCR, which directly accesses bis-amides or more complex structures by means of substrate modification and post-condensations.^[3,4]

However, the IMCR has several drawbacks, such as the commercial availability of a rather small number of isocyanides and their notorious stench that makes handling unpleasant. Moreover, isocyanide stability and synthesis are always key concerns. One of the solutions to these problems is the use of so-called convertible isocyanides, which can be easily transformed to other functional groups such as acids, esters or amides. This consequently circumvents the use of specific isocyanides to gain similar molecular diversity and complexity. In 1963, Ugi and Rosendahl reported the first convertible isocyanide, cyclohexenyl isocyanide, which was also called Armstrong isocyanide later on.^[5] Subsequently, a plenty of convertible isocyanides have been reported in Ugi-4CR^[6] or Ugi-tetrazole four-component reaction (Ugi-T-4CR),^[7] which are cleavable under acidic or basic

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Conflict of interest

The authors declare no conflict of interest.

conditions, or sometimes require multistep methods. The use of these convertible isocyanides became a considerable step in the synthesis of peptidomimetics and natural products. Some convertible isocyanides are also reported in Groebke—Blackburn—Bienaymé CR.^[8]

Despite the increasing popularity of using convertible isocyanides for further molecular modification, these isocyanides suffer from major disadvantages, such as lengthy synthesis, instability, incompatibility with more delicate substrates, laborious workup and multistep cleavage. Furthermore, these isocyanides are only applicable in one type of reaction (either Ugi-4CR or Ugi-tetrazole reactions). Thus, the development of a “truly universal convertible isocyanide”, which could be applicable in both Ugi-4CR and Ugi-T4CR, and also cleavable under more than one condition remains a significant challenge.

Herein, we report the 2-nitrobenzyl isocyanide as a truly universal convertible isocyanide that is applicable not only in Ugi-4CR, but also in Ugi-tetrazole reactions, and is also cleavable under both acidic and basic conditions (Figure 1).

The 2-nitro benzyl group is prevalent in a variety of synthetic transformations, mainly because of its photocleavable nature.^[9] It is also used in the preparation of polymers^[10] and natural products.^[1c,11] Nonetheless, the use of 2-nitrobenzyl isocyanide as a convertible isocyanide has not been sufficiently explored, with the exception of only one example of photo-cleavable isocyanide (sunlight for 5 days) in polymers.^[12]

We envisioned the use of this isocyanide as an extensively practical convertible isocyanide in both acidic and basic conditions.^[13] At first, the Ugi-tetrazole reaction product was chosen as the model substrate to verify this hypothesis. Recently, our group reported a basic condition (LiOH in THF:H₂O) for the cleavage of β -cyanoethyl isocyanide.^[7a] Therefore, we started our optimization by using similar conditions and attempted to cleave the 2-nitrobenzyl group from the Ugi-tetrazole product (Table 1). Unfortunately, no product was formed under these conditions (Table 1, entry 1). Further increases in the temperature, even to reflux overnight, did not show any effect on reaction, and the starting material still remained intact. Meanwhile, changing the solvent to acetonitrile was also ineffective which indicated that LiOH was not applicable for this isocyanide cleavage (Table 1, entry 4). Next, we screened different bases and different conditions. The reaction with NaOH in toluene did not form any product, but trace product formation occurred in acetonitrile, while starting material remained intact in the acetonitrile/water system.

Remarkably, the increase of NaOH equivalence to 20% efficiently promoted the reaction, with a promising reaction conversion. From further evaluation, we found that the 20% aqueous NaOH in MeOH/water under reflux conditions gave an excellent yield of 90% (Table 1, entry 11). Aiming for milder conditions instead of reflux, we next screened KOtBu in different solvents. To our delight, superior conditions were found in acetonitrile. With only 4 equivalents of KOtBu at room temperature, we obtained a 63% yield (Table 1, entry 14). The reaction worked best in THF with an 84% yield (Table 1, entry 15).

With these optimized conditions in hand, we next examined the scope of this convertible isocyanide in various Ugi-tetrazole products (Table 2). This isocyanide was moderate to

good in the Ugi-tetrazole reactions and was compatible with diverse substrates under the optimized conditions. The aliphatic butyl amine substrate gave a moderate deprotection yield of 45% (Table 2, entry **1b**). Aromatic amines with electron-withdrawing/-donating functionalities provided excellent yields (Table 2, entries **1c–1e**). Secondary amines and cyclic heterocycles gave moderate to good yields ranging from 62 to 69% (Table 2, entries **1f–1h**). Heterocycles, such as 2-amino pyridine and indole, also worked well (Table 2, entries **1i–1j**).

Different aldehydes were also compatible with this protocol. Aliphatic aldehydes, such as phenylacetaldehyde, butyraldehyde, and isobutyraldehyde, worked well with 84, 91, and 99% yields, respectively. Aromatic aldehydes with electron-withdrawing/-donating functionalities resulted in moderate to good yields (Table 2, entries **1b**, **1f**, **1g**, and **1j**). Ketones, for example, cyclohexanone and acetone afforded the products in 55 and 99% yields, respectively (Table 1, entries **1e** and **1i**).

We next sought to cleave this 2-nitrobenzyl group from the Ugi-4CR products. When the Ugi-4CR product was treated under the optimized conditions, no cleavage was detected. Nevertheless, using NaOH instead of KOtBu to cleave the 2-nitrobenzyl group was successful. A 38% yield (**4a**) was obtained with 5 equivalents of NaOH at 60°C. However, the yield did not improve even when the reaction was heated to reflux in 20% NaOH.

Afterward, we attempted to achieve a one-step transformation of this convertible isocyanide to the acid or ester from Ugi-4CR products under acidic conditions. After screening different temperatures, we observed that cleavage in acid worked best with 1 N HCl under reflux conditions and provided the free acids in 51 and 62% yield (Scheme 1, entries **4a** and **4b**). Here aliphatic and aromatic substituents on Ugi-4CR products displayed comparable results. Furthermore, with the purpose of a one-step acidic esterification, 4 N HCl in dioxane was used, and the desired product was obtained in good yields (Scheme 1, entries **4c–4g**). Under acidic esterification conditions, we observed that aromatic substitution on the α carbon afforded the ester product in 70% yield (Scheme 1, entry **4c**). Aromatic amines enclosing Ugi-4CR products also performed well (70 and 87% yield). Benzoic acid was also effective with 76% yield (Scheme 1, entry **4f**).

In conclusion, the current findings add to a growing body of literature on convertible isocyanides. This isocyanide could be called a universally convertible isocyanide owing to its application in more than one reaction types. Advantages include an easy synthesis, the fact that they are odorless, good yields during Ugi reactions and also in deprotection steps. We believe that this isocyanide will provide a good choice in multi-component reactions as a convertible isocyanide.

Experimental Section

General procedure for the synthesis of 2-nitrobenzyl isocyanide (gram scale):

2-Nitrobenzaldehyde (199 mmol, 30 g), formamide (240 mmol, 95 mL) and formic acid (160 mmol, 60 mL) were transferred into a 500 mL round-bottom flask. The flask was placed in an oil bath and the reaction mixture was heated at 180°C for 5 h. After cooling

down, the mixture was extracted with CH₂Cl₂ (3×200 mL). The organic layer was separated, washed with water, dried with MgSO₄, filtered and concentrated in vacuo. Flash chromatography on silica gel (hexane/EtOAc, 1:2) afforded the corresponding formamide as a brown solid (18.86 g, 105 mmol, 53%).

To a solution of *N*-(2-nitrobenzyl)formamide (18.1 g, 100 mmol) in CH₂Cl₂ (200 mL) was added Et₃N (400 mmol, 4.0 equiv, 55.7 mL). The mixture was cooled to –5°C, after which POCl₃ (100 mmol, 1.0 equiv, 9.3 mL) was added dropwise over 60 min, while maintaining the temperature below 0°C. After the addition, the reaction was stirred at room temperature for 4 h. A saturated solution of Na₂CO₃ was then added carefully. The organic layer was separated, and the water layer was extracted with CH₂Cl₂. The combined organic layers were washed with water, dried over MgSO₄, and concentrated in vacuo. The product was purified by silica gel flash chromatography (CH₂Cl₂), and after the solvent was evaporated, it was isolated as a pale yellow solid (14.07 g, 87 mmol, 87%).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Applicable in U-4CR

acidic cleavage

acidic cleavage

acidic cleavage

basic cleavage

basic cleavage

acidic / basic cleavage

multistep cleavage

multistep cleavage

multistep cleavage

Applicable in Ugi-tetrazole

acidic cleavage

acidic cleavage

acidic cleavage

basic cleavage

This Universal Convertible Isocyanide:

Applicable in Ugi-tetrazole and U-4CR

Cleavable in acidic and basic conditions

Figure 1.
Convertible isocyanides.

4aA 91%; B 51%^[a] **4b**A 99%; B 62%^[a] **4c**A 58%; B 70%^[b] **4d**A 63%; B 77%^[b] **4e**A 96%; B 70%^[b] **4f**A 96%; B 76%^[b] **4g**A 91%; B 87%^[b]**Scheme 1.**

Substrate scope of deprotection from Ugi-4CR products. [a] Deprotection using 1 N HCl and H₂O/MeOH (3:1) as a solvent; [b] Deprotection carried out in 4 N HCl in dioxane and MeOH as solvent.

Table 1.

Reaction optimizations.

Entry	Base	Equiv	Solvent	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[a]
1	LiOH	2	THF/H ₂ O	RT	2	-
2	LiOH	2	THF/H ₂ O	60	2	-
3	LiOH	2	THF/H ₂ O	reflux	12	-
4	LiOH	2	CH ₃ CN	RT	48	-
5	NaOH	2	toluene	RT	12	-
6	NaOH	2	CH ₃ CN	RT	12	trace
7	NaOH	2	CH ₃ CN/H ₂ O	RT	12	-
8	NaOH	2	THF	RT	12	n.d.
9 ^[b]	NaOH	> 10	CH ₃ CN	RT	12	32
10 ^[b]	NaOH	8	MeOH	reflux	12	69
11 ^[b]	NaOH	>10	MeOH/H ₂ O	reflux	6	90
12	KO ^{<i>t</i>} Bu	1	CH ₃ CN	RT	12	n.d.
13	KO ^{<i>t</i>} Bu	2	CH ₃ CN	RT	48	n.d.
14	KO ^{<i>t</i>} Bu	4	CH ₃ CN	RT	12	63
15	KO ^{<i>t</i>} Bu	4	THF	RT	12	84

^[a]Yield of isolated product **2a**;^[b]20% NaOH used. n.d.=not determined.

Table 2.

Yields of the Ugi products (**1**) and deprotected 5-substituted 1*H*-tetrazoles^[a]

entry	amine	aldehyde/ketone	1	2 Yield [%] ^[b]
a			53	84
b			86	45
c ^[c]			30	91
d			41	99
e			40	99
f			30	69
g			81	62
h			58	63
i			55	55
j			60	84

^[a] The reaction was carried out using an aldehyde (1.0 mmol), an amine (1.0 mmol), isocyanide (1.0 mmol) and TMS-azide (1.0 mmol) in 1 mL MeOH;

^[b] Yield of isolated products **1** and **2**;

^[c] The reaction required 24 h.