1-Hydroxy-2-methyl-2-propyl Isocyanide (HMPI) as a New Convertible Isocyanide for the Ugi Four-Component-Coupling Reaction

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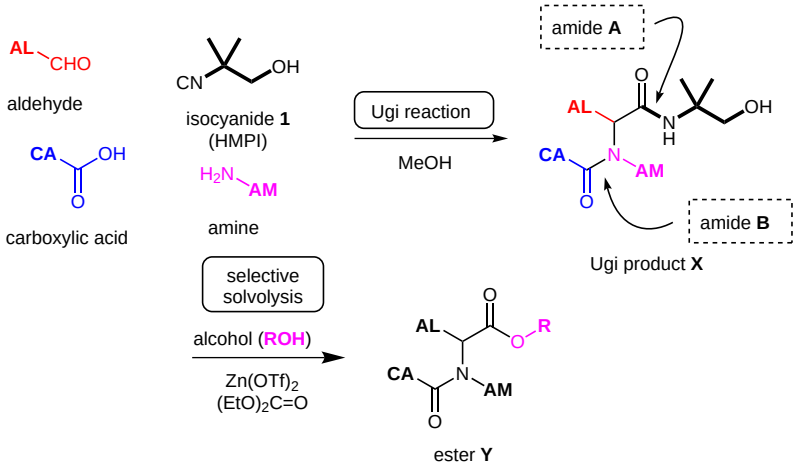
Abstract: The Ugi reaction is a useful four-component coupling reaction for α-(acylamino)amide. However, selective transformation of the two amides is generally difficult. Here, we report 1-hydroxy-2-methyl-2-propyl isocyanide (HMPI) as a new member of a 'convertible isocyanide' class used to solve the problem. HMPI is odorless and shows good reactivity in the Ugi reaction to give *N*-(1-hydroxy-2-methyl-2-propyl) amides, which are smoothly converted into esters upon $Zn(OTf)_2$-mediated solvolysis. Overall, structurally diverse α-amino acid esters are readily accessible in two steps by using HMPI.

Key words: amides, chemoselectivity, multicomponent reactions, zinc, esters

The Ugi reaction[1] is one of the most popular isocyanide-based multi-component coupling reactions (MCRs).[2] As a four-component coupling reaction of isocyanide with aldehyde, amine, and carboxylic acid, the Ugi reaction has been recognized as a promising methodology with which to construct α-(acylamino)amides in a one-pot operation. Furthermore, a structurally diverse collection of α-(acylamino)amides can be obtained by combination of various compounds as building blocks.[3] One of the problems of isocyanide-based MCRs is the difficulty in controlling the selective transformation of the amide functionality generated.[4] That is, chemoselective transformation of amide **A** (derived from the isocyanide component, see Scheme 1) in the presence of a second amide **B** (derived from the carboxylic acid) is often difficult to realize, and thus has been recognized as a significant challenge.

To realize the selective transformation, we have employed formation of *N*-Boc imide followed by alkaline methanolysis, in our synthetic study of AMPA receptor-selective antagonist IKM-159.[5] While the methodology is operative in most cases,[6] there are still problems; for example, the *N*-Boc group sometimes migrates intramolecularly to an intimate functional group such as the hydroxyl group under methanolic alkaline conditions.[7] On the other hand, several isocyanides have been developed to realize chemoselective transformation of amides derived from isocyanide components after MCRs. Such isocyanides, termed 'convertible isocyanide',[4] include Armstrong's 1-isocyanocyclohexene,[8] Ugi's 2-isocyano-2-methylpropyl carbonates,[9] Fukuyama's 2-isocyano-2-methylpropyl phenyl carbonate,[10] Kobayashi's 1-isocyano-2-(2,2-dimethoxyethyl)benzene,[11] and 2-nitrophenyl isocyanide,[12] and others.[13]

In this paper, we report our preliminary results on a new isocyanide **1** (1-hydroxy-2-methyl-2-propyl isocyanide, HMPI) as a novel entry for the convertible isocyanide. This convertible isocyanide is odorless[14] and structurally simple compared to the precedents, can be readily prepared, shows moderate to high reactivity in the Ugi four-



Scheme 1 Overview of the Ugi reaction followed by selective transformation using new isocyanide **1**

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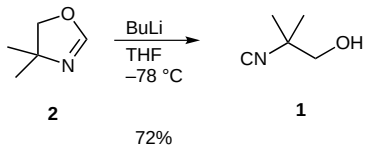
component coupling reaction, and can be directly and smoothly converted into esters without affecting another unfunctionalized amide moieties located elsewhere as, for example, amide **B** (see Scheme 1).

The overview of our strategy for the generation of α-acylaminoester **Y** through Ugi and post-Ugi reactions, by employing HMPI (**1**), is shown in Scheme 1. Here, the Ugi product **X** was expected to be converted into ester **Y** by $Zn(OTf)_2$-mediated solvolysis that was recently reported.[15] Since non-hydroxylated *N*,*N*-(dialkyl)amide has been reported to be inert under the solvolysis conditions, we anticipated that chemoselective transformation at amide **A** over amide **B** would be possible.

HMPI (**1**) has been reported in a polymer-bound form in 2005 for the study of polymer-bound Fischer tungsten carbene complexes.[16] Isocyanide **1** was not, however, isolated or characterized in solution phase. Therefore, the reactivity and usefulness of HMPI (**1**) in MCRs in the solution phase remained unknown.

HMPI (**1**) can be readily synthesized by treatment of the known oxazoline **2**[17] with BuLi (Scheme 2), according to the procedure for the synthesis of the *O*-phenyloxycarbonyl derivative reported by Ugi et al. in 1999.[9] The purification is performed by silica gel column chromatography (72% yield). Gratifyingly, **1** was found to be odorless.[18]



Scheme 2 Preparation of 1-hydroxy-2-methyl-2-propyl isocyanide (HMPI, **1**)

The Ugi reaction of HMPI (**1**) was then explored (Table 1). The reaction was performed in MeOH at between room temperature and 50 °C by mixing the four components in the ratio indicated.[19] Although the investigation was preliminary, we did not observe any clear influence of the ratio of the components on the reaction yield. With poorly reactive formic acid (entry 1), the Ugi reaction proceeded quite slowly at room temperature to provide **3X** in moderate yield (55%) after 40 hours. When the carboxylic acid component was changed to octanoic acid, which generally shows better reactivity, the yield improved to 66% **4X** (entry 2). With 2-aminoethanol as an amine component, the yield for **5X** was comparable (65%, entry 3). Diastereoselectivity was slightly induced when chiral amine 2-amino-2-(4-methoxyphenyl)ethanol[20] was employed (62%, dr 5:2; entry 4). Separation and structural analysis of the latter are under investigation.

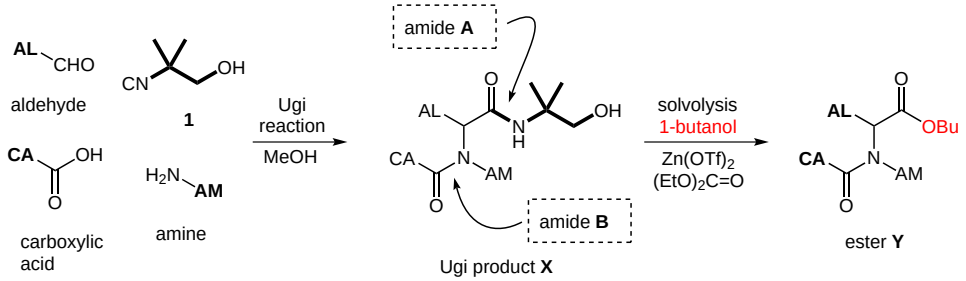
Domino Ugi/Diels–Alder (UDA) reaction was also attempted in the present study by using HMPI (**1**). Reported first by Paulvannan in 1999,[21] the UDA reaction employing acrylic acid derivative and 2-furaldehyde has been an important method with which to generate compound collections of 7-oxanorbornenes with appendage diversity.[22] He reported that the reaction between benzylamine, benzyl isocyanide, fumaric acid monoethyl ester, and 2-furaldehyde proceeds in 89% yield (structures not shown here).[21] Our results for two UDA reactions employing HMPI (**1**) are shown in Table 1 (entries 5 and 6). The UDA reactions were carried out at 50 °C to facilitate the Diels–Alder reaction. First, employment of HMPI (**1**) instead of benzyl isocyanide in the domino reaction gave 7-oxanorbornene **7X** in 56% yield as a single diastereomer (entry 5). The structure was determined by comparison to the known compound.[21] In this combination, **1** was shown to be less reactive than benzyl isocyanide.

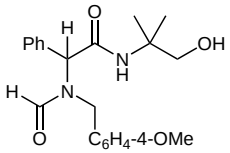
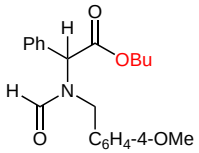
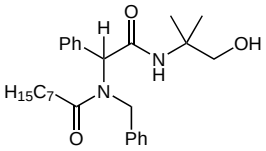
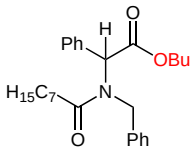
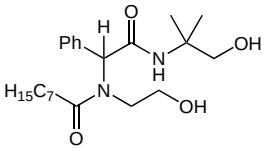
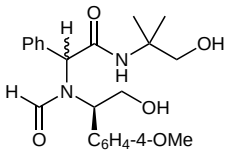
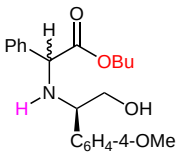
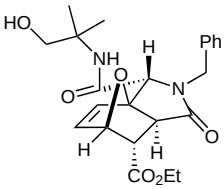
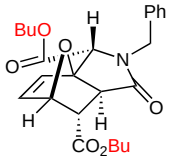
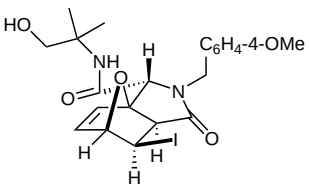
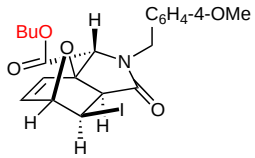
We had studied the UDA reaction employing *cis*-3-iodoacrylic acid[23] and 4-methoxybenzylamine as carboxylic acid and amine components, respectively, in combination with benzyl isocyanide and 2-furaldehyde to develop neuroactive agents.[5a,b] In those studies, we reported that the UDA reaction proceeded in 68% yield. When benzyl isocyanide was changed to HMPI (**1**) in the present study, 7-oxanorbornene **8X** was obtained in better yield (82%; Table 1, entry 6).

Solvolysis of the Ugi reaction products **3X**–**8X** was then investigated. Recently, the group of Mashima reported $Zn(OTf)_2$-catalyzed solvolysis of more simple *N*-(2-hydroxyethyl) amides by 1-butanol.[15] Since they demonstrated chemoselective solvolysis of peptides, we anticipated that solvolysis by 1-butanol would be realized at amide **A** of the Ugi products **X** (Table 1), and would be selective in some cases. All solvolysis reactions were carried out by using a catalytic amount (0.05 equiv) of $Zn(OTf)_2$ and two equivalents of diethyl carbonate $[(EtO)_2C{=}O]$ in 1-butanol at reflux temperature for 13–40 hours.[24] The results are summarized in Table 1. As shown in Table 1 (entry 1), butanolysis of diamide **3X** was achieved exclusively at the amide **A** moiety to give **3Y** in moderate yield (83% conversion, 62% isolated yield). No other products were observed. Complete selectivity was also observed for **4X** (Table 1, entry 2), which gave butyl ester **4Y** in 60% yield (>98% conversion), wherein the octanamide residue remained intact. Thus, an apparent reactivity difference between *N*-(2-hydroxy-1,1-dimethyl)ethyl amide (present as the amide **A**, Scheme 1) and other unfunctionalized amides (present as the amide **B**), in the $Zn(OTf)_2$-catalyzed butanolysis is clear (Table 1, entries 1 and 2).[15]

We next examined butanolysis of diamide **5X**, bearing *N*-(2-hydroxyethyl)-*N*-alkyl amide as the amide **B** moiety, which was originally derived from 2-aminoethanol used in the Ugi reaction (Table 1, entry 3). Here, bis-solvolysis at amides **A** and **B** was expected to serve as a new methodology for the generation of α-aminoesters, which have not been readily accessible by MCRs so far. However, after extensive exploration of the conditions required for simultaneous butanolysis of amides **A** and **B**, all attempts gave only complex mixtures and no product was isolated cleanly; the expected product that underwent bis-solvolysis was detected only in trace amounts (<5%) by LC–MS

Table 1 Ugi Reaction Using HMPI (**1**) followed by Solvolysis by 1-Butanol



Entry	Components used for Ugi reaction (equiv)	Product and yield (%) for Ugi reaction[a]	Product and yield (%) for solvolysis
1	benzaldehyde (2.0) HMPI (**1**) (1.0) formic acid (2.6) 4-methoxybenzylamine (2.0)	 **3X** (55)	 **3Y** (62,[a] 83[b])
2	benzaldehyde (1.5) HMPI (**1**) (1.4) octanoic acid (1.0) benzylamine (1.0)	 **4X** (66)	 **4Y** (60,[a] >98[b])
3	benzaldehyde (1.5) HMPI (**1**) (1.4) octanoic acid (1.0) ethanolamine (1.0)	 **5X** (65)	complex mixture
4	benzaldehyde (1.5) HMPI (**1**) (1.0) formic acid (2.0) 2-amino-2-(4-methoxyphenyl)ethanol (1.5)	 **6X** (62) dr = 5:2	 **6Y** (64,[a] 80[b]) dr = 5:2
5	2-furaldehyde (1.7) HMPI (**1**) (1.7) fumaric acid monoethyl ester (1.1) benzylamine (1.0)	 **7X** (56)	 **7Y** (44,[a] 75[b])
6	2-furaldehyde (1.5) HMPI (**1**) (1.5) *cis*-3-iodoacrylic acid (1.0) 4-methoxybenzylamine (1.0)	 **8X** (82)	 **8Y** (65,[a] 83[b])

[a] Isolated yield.
[b] Yield estimated from ^{1}H NMR spectroscopic analysis of the crude material.

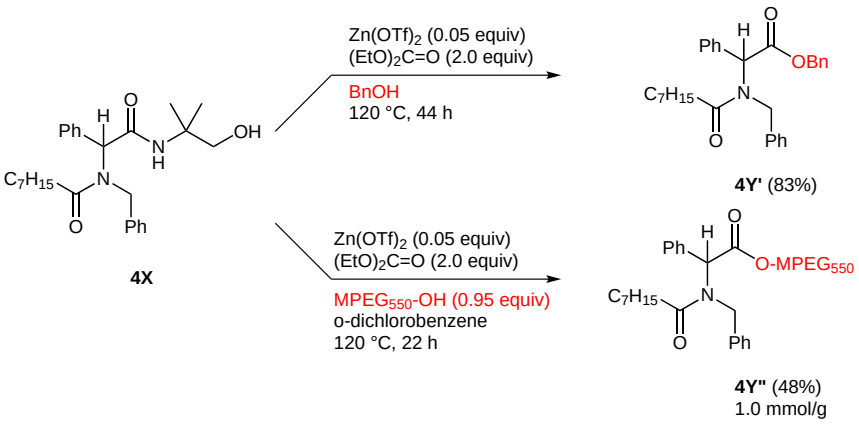
analysis. In Mashima's paper,[15] no solvolysis reaction was reported on 'hydroxylated *N*,*N*-dialkyl amide'. However, based on their proposed mechanism, which involves N,O-acyl rearrangement, solvolysis of amide **B** was expected to occur. We therefore next examined the butanolysis of diamide **6X**, bearing *N*-[2-hydroxy-1-(4-methoxyphenyl)]ethyl amide as amide **B**, which may smoothly undergo the N,O-acyl rearrangement via a five-membered transition state (entry 4). Gratifyingly, butanolysis of **6X** at both amides **A** and **B** was found to proceed cleanly, giving rise to **6Y** in 64% yield (80% conversion). In addition, the diastereomeric ratio was found to be retained, indicating that no epimerization had taken place. Here, the formyl group might enhance the reactivity of the butanolysis at amide **B**. It should also be noted that formation of cyclic carbamate was reported to take place by reaction between liberated 2-aminoethanol analogues and $(EtO)_2C{=}O$ after solvolysis.[15] Indeed, we generally detect 4,4-dimethyloxazolidin-2-one (structure not shown) derived from 2-methyl-2-aminopropanol released from the amide **A** moiety, in the product mixture. Product **6Y**, however, does not undergo cyclic carbamate formation (entry 4), indicating that the reactivity of the secondary amine is lower than the primary amine in oxazolidinone formation with $(EtO)_2C{=}O$.

The butanolysis of more complex 7-oxanorbornene analogues was next investigated (Table 1, entries 5 and 6). While butanolysis of the amide **A** moiety in **7X** cleanly proceeded (entry 5), transesterification at the ethyl ester moiety also took place to furnish dibutyl ester **7Y** in 44% yield (75% conversion). No other products were cleanly isolated. On the other hand, butanolysis of 7-oxanorbornene analogue **8X**, with a labile iodo group, provided butyl ester **8Y** in better yield (83% conversion, 65% upon isolation; entry 6). Although 7-oxanorbornenes are known to undergo aromatization,[25] it is worthy of note that no such side reaction was observed (entries 5 and 6), indicating the reaction conditions are mild. In general, bisbutanolysis provided the desired product in lower isolated yield (0–64%, entries 3–5) compared to monobutanolysis (60–65%, entries 1, 2, and 6).

Finally, solvolysis reactions using other alcohols were examined with diamide **4X**. It had been reported that 1-butanol (bp 117 °C) and 1-pentanol (bp 137 °C) are good solvolysis agents, whereas more volatile alcohols such as methanol and ethanol are inefficient. As shown in Scheme 3, we first examined benzyl alcohol (bp 203–205 °C) for solvolysis. To our delight, the reaction proceeded quite smoothly at 120 °C over 44 hours to give benzyl ester **4Y′** in the highest isolated yield (83%). Since benzyl ester can be readily transformed into carboxylic acid upon hydrogenolysis, this would serve as a promising methodology for the three-step synthesis of structurally diverse α-acylaminocarboxylic acids.

We further investigated the reaction with poly(ethylene glycol) methyl ether (MPEG-OH, average M_n ca. 550).[26] In this case, we needed to establish conditions for stoichiometric reaction. It was found that *o*-dichlorobenzene was suitable as solvent, and the amount of MPEG-OH could be reduced to 0.95 equiv relative to amide **4X**. The reaction was performed at 120 °C for 22 hours, then the mixture was directly subjected to silica gel flash column chromatography.[26a] Fractions that contain polymer were collected, and the loading yield was determined to be 48% (1.0 mmol/g) on the basis of ^{1}H NMR spectroscopic analysis.

In conclusion, we have demonstrated the synthesis and use of 1-hydroxy-2-methyl-2-propyl isocyanide (HMPI, **1**) in the Ugi four-component coupling reaction. HMPI (**1**) is odorless, and the coupling reaction, as well as that followed by Diels–Alder reaction, proceeded in reasonable yield. The products were selectively transformed into butyl esters under conditions mediated by $Zn(OTf)_2$. The solvolysis was chemoselective to *N*-(2-hydroxyethyl)amides, and bis-solvolysis was also demonstrated. Thus, HMPI (**1**) is an efficient convertible isocyanide that can be used for two-step synthesis of α-acylaminoesters and analogues. We also performed solvolysis with other agents such as benzyl alcohol and poly(ethylene glycol). Notably, the latter is expected to be useful for liquid-phase, rapid organic synthesis. Efforts are currently directed toward optimization of the reaction conditions to improve the isolated yield.



Scheme 3 Solvolysis of diamide **4X** for structurally diverse esters

Acknowledgment

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(14) To avoid isolation of unpleasant-smelling isocyanide, an in situ preparation method has been reported, see: El Kaim, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* **2009**, *7*, 3024.
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(18) Spectroscopic data for HMPI (**1**): IR (film): 3399, 2985, 2941, 2135, 1657 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.03 (br, 1 H), 3.38 (s, 2 H), 1.29 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 68.9, 58.9, 25.2 (×2). HRMS (ESI, +): *m*/*z* $[M + H]^+$ calcd for $C_5H_{10}ON$: 100.0762; found: 100.0764.
(19) To a stirred solution of aldehyde (0.0980 mmol) in methanol (0.5 mL) at r.t., were added amine (0.0650 mmol), carboxylic acid (0.0650 mmol), and HMPI (1, 9.0 mg, 0.091 mmol). After stirring at r.t. for 40 h, the mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (1 mL) and washed successively with sat. aq Na_2CO_3 (1 mL), sat. aq NH_4Cl (1 mL), and brine (1 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g; hexane–EtOAc) to give the Ugi product **X**.
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(24) A mixture of diamide **X** (0.011 mmol), zinc trifluoromethanesulfonate (0.20 mg, 0.00055 mmol), and diethyl carbonate (0.0027 mL, 0.022 mmol) in 1-butanol (0.200 mL) was heated to reflux with stirring for 39 h. The mixture was then concentrated under reduced pressure, dissolved in $CHCl_3$ (1 mL), and washed with water (1 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 1 mL) and the combined organic layer was washed with brine (1 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.6 g; hexane–EtOAc) to give butyl ester **Y**.
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