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An Ugi Reaction Incorporating a Redox-Neutral Amine C−H Functionalization Step

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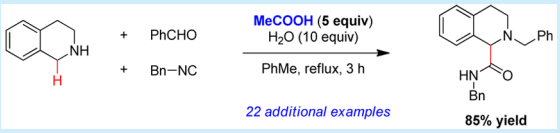
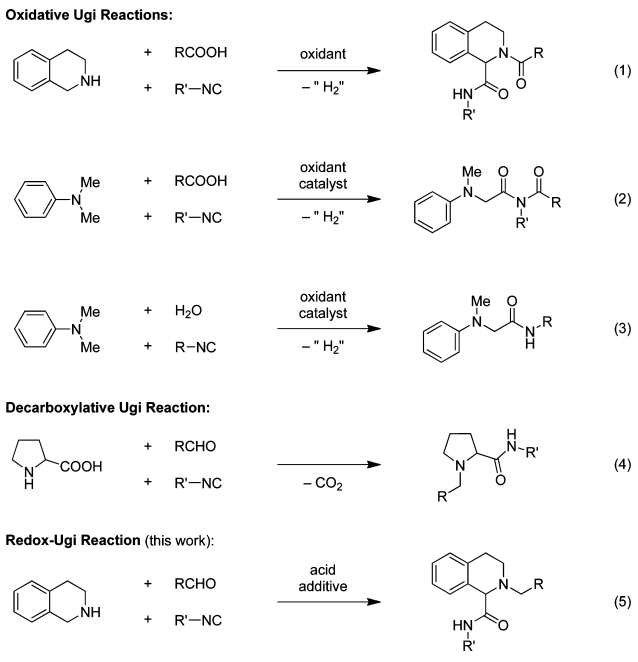
Supporting Information

ABSTRACT: Pyrrolidine and 1,2,3,4-tetrahydroisoquinoline (THIQ) undergo redox-neutral α-amidation with concurrent *N*-alkylation upon reaction with aromatic aldehydes and isocyanides. Reactions are promoted by acetic acid and represent a new variant of the Ugi reaction.



Ugi reactions are among the most powerful multicomponent transformations; their many variants provide rapid access to a remarkable wealth of structures.[1] Reactions of isocyanides with secondary amines and aldehydes/ketones represent a special case, as the prototypical Mumm rearrangement cannot take place.[2]

In recent years, a number of oxidative Ugi variants have been reported.[3] Secondary amines can be oxidized in situ to the corresponding imines, which subsequently participate in typical Ugi reactions that provide diamide products (eq 1). When



tertiary amines are used as starting materials, oxidation leads to iminium ions that are subsequently trapped by an isocyanide. In the presence of a carboxylic acid reaction partner, imides are obtained as the final products (eq 2). Alternatively, the intermediate nitrilium ion can be trapped by water, leading to the formation of aminoamides (eq 3). Mechanistically distinct from the reactions outlined in eqs 1−3, a decarboxylative version of the Ugi reaction was recently reported that employs proline as the starting material (eq 4).[4,5] Here, we report a new type of Ugi variant that enables the α-amidation of cyclic amines via redox-neutral α-C−H bond functionalization (eq 5).[6,7]

As part of a continuing program, our group developed a range of transformations that enable the redox-neutral α-C−H bond functionalization of amines.[8−10] As is commonly the case in a number of classic name reactions such as the Strecker, Mannich, and Friedel−Crafts reactions, these redox reactions involve the condensation of a secondary amine with an aldehyde/ketone in the presence of a (pro)nucleophile. C−H functionalization is achieved via an isomerization step in which azomethine ylides feature as reactive intermediates.[8a] Carboxylic acids play important roles as catalysts or promotors in most of these transformations. The scope of this chemistry was shown to be remarkably broad and includes intra- and intermolecular variants.

In order to determine whether our general concept is applicable to Ugi-type reactions with isocyanides as the nucleophiles, we selected pyrrolidine, fluorenone, and cyclohexyl isocyanide as test substrates. While we have recently identified 2,6-dichlorobenzaldehyde as an efficient carbonyl reaction partner for pyrrolidine in these types of transformations, it was subsequently shown by Jana et al. that fluorenone is particularly suitable to bring about redox-isomerization,[9c] a prerequisite for C−H functionalization. Key results of our initial survey are summarized in Table 1. Heating a 5:2:1 mixture of pyrrolidine, fluorenone, and cyclohexyl isocyanide under reflux in toluene resulted in the formation of desired product **1a** in trace amounts only (entry 1). Addition of acetic acid (20 mol %) allowed for the isolation of **1a** in 6% yield (entry 2). A gradual increase in the amount of acetic acid led to dramatically improved results, with 5 equiv proving optimal (entry 4). Xylenes, *n*-butanol, and DMF were inferior to toluene as the solvent (entries 6−8). 2-Ethylhexanoic acid and benzoic acid were also capable of promoting the title transformation but did so less effectively than

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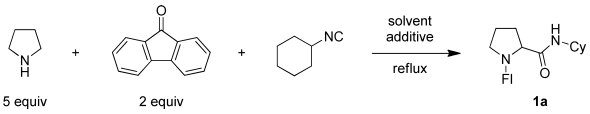
Table 1. Evaluation of Reaction Conditions[a]



entry	solvent (molarity)	additive (equiv)	time (h)	yield of **1a** (%)
1	PhMe (0.1)		36	trace
2	PhMe (0.1)	AcOH (0.2)	48	6
3	PhMe (0.1)	AcOH (1)	48	28
4	PhMe (0.1)	AcOH (5)	20	73
5	PhMe (0.1)	AcOH (10)	20	52
6	xylenes (0.1)	AcOH (5)	20	53
7	*n*-BuOH (0.1)	AcOH (5)	20	55
8[b]	DMF (0.1)	AcOH (5)	18	52
9	PhMe (0.1)	2-EHA (5)	20	32
10	PhMe (0.1)	BzOH (5)	20	63
11	PhMe (0.25)	AcOH (5)	18	89
12	PhMe (0.5)	AcOH (5)	15	75
13[c]	PhMe (0.25)	AcOH (5)	20	53
14[d]	PhMe (0.25)	AcOH (5)	20	85

[a]Reactions were performed with 0.5 mmol of cyclohexylisocyanide. Yields are isolated yields of chromatographically purified compounds. [b]Reaction was performed at 135 °C. [c]With 3 equiv of pyrrolidine. [d]With 10 equiv of H_2O.

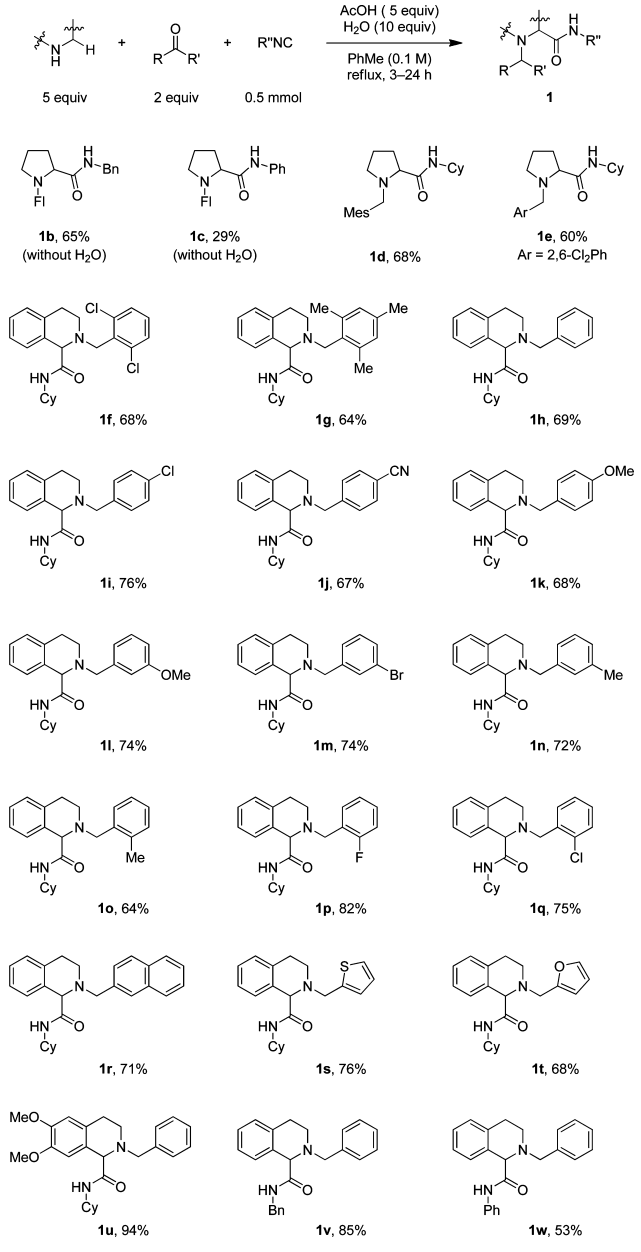
acetic acid (entries 9 and 10).[11] A significant improvement in efficiency was observed upon increasing the concentration from 0.1 to 0.25 M. In this instance, product **1a** was isolated in 89% yield (entry 11). A further increase in molarity to 0.5 led to a reduction in yield (entry 12). Lowering the amount of pyrrolidine from 5 to 3 equiv also led to a drop in yield (entry 13). Interestingly, addition of 10 equiv of water (later shown to be beneficial for most substrate combinations, vide infra) had little effect on the overall transformation (entry 14).[12]

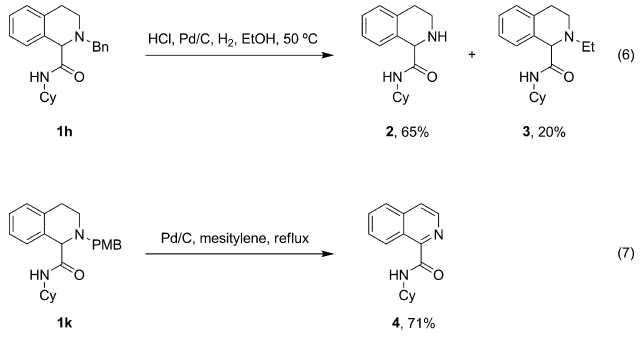
The scope of the new transformation was evaluated under the optimized conditions (Scheme 1). Isocyanides other than cyclohexyl isocyanide engaged in redox–Ugi reactions with pyrrolidine and THIQ. In addition to fluorenone, mesitaldehyde and 2,6-dichlorobenzaldehyde were viable substrates in reactions with pyrrolidine. The scope of the aldehyde in reactions with THIQ was found to be broad. Aromatic aldehydes with various substitution patterns provided moderate to good yields of amide products. Electron-donating and electron-withdrawing substituents in any ring position were well tolerated. In addition, heterocyclic aldehydes also participated in redox–Ugi reactions.

Selected redox–Ugi products were subjected to a number of subsequent transformations. Cleavage of the *N*-benzyl group in **1h** was achieved via hydrogenolysis to provide tetrahydroisoquinoline **2** in 65% yield. Interestingly, under the reaction conditions, *N*-ethyl product **3** was obtained as a byproduct in 20% yield (eq 6). Exposure of **1k** to Pd/C in the absence of hydrogen gas under reflux in mesitylene led to cleavage of the PMB group and aromatization of the ring system to provide isoquinoline **4** in 71% yield (eq 7).

In conclusion, we have demonstrated the ability of isocyanides to act as nucleophiles in Ugi-type reactions that incorporate an amine α-C–H bond functionalization step. This process is facilitated by simple acetic acid.

Scheme 1. Substrate Scope





■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data (PDF)
X-ray crystal structure of product **1k** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) No appreciable amount of product formation was observed with a range of other promoters, including Lewis acids such as LiCl and Cu(2-EH)$_2$.

(12) Please see the Supporting Information for additional optimization studies.

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