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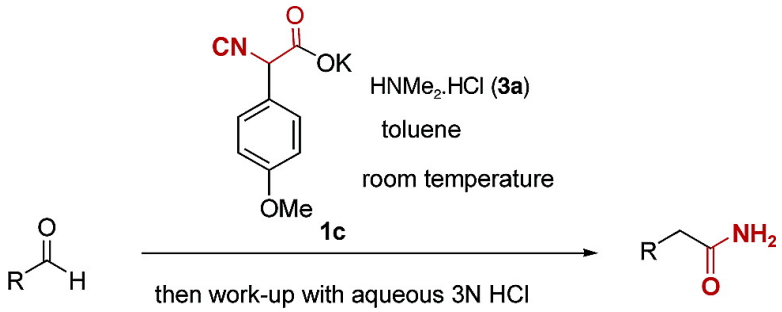

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Mild Oxidative One-Carbon Homologation of Aldehyde to Amide

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Homologation of carbonyl compounds by one-carbon extension is a demanding transformation in organic synthesis.[1,2] While several methods exist for the one-carbon homologation of carboxylic acid derivatives, including the classic Arndt−Eister reaction,[3] Kowalski's ester homologation,[4] and Barton's radical reaction,[5] methods allowing the oxidative homologation of an aldehyde to carboxylic acid derivatives are rare.[6] In connection with our ongoing project aiming at the development of novel multicomponent reactions, we recently reported a three-component synthesis of di- and tripeptides based on the unique reactivity of isocyano acetic acid (**1**, eq 1, Scheme 1).[7−9] Further expanding the generality of this reaction, we found that the reaction of cyclohexanal **2a** with hydrochloride salt of dimethylamine **3a** and potassium salt of α-phenyl-α-isocyano acetic acid (**1a**, R = H) gave predominantly *N*-acyl α-imino amide **5a** together with a small amount of dipeptide (5%). Compound **5a** is isolable but can be directly converted into amide **6a** and ketoamide **7a** upon acidic workup (3 N HCl) (eq 2, Scheme 1). The overall process represented a first example of one-pot homologation of an aldehyde to amide. The mild reaction conditions and the intriguing mechanistic issue in conjunction with the general lack of this type of homologation procedure prompted us to examine in detail this unprecedented transformation and report herein our preliminary results.

Preliminary experiments indicated that the combined use of the hydrochloride salt of dimethylamine (**3a**) and α-aryl-substituted α-isocyano acetic acid (**1a**) is a prerequisite in order to drive the reaction toward the formation of α-acylimino amide **5a**, hence **6a**. Use of any other amines or any other isonitriles (**1**, R_1 = alkyl) led only to the formation of dipeptide (**4**, eq 1). The omission of the hydrochloride salt of dimethylamine (**3a**) led to no reaction, indicating its unique role in this reaction. To further optimize the reaction conditions, we investigated the effect of solvent and the structure of **1** by varying the metal counterion and the aromatic substituents. As is seen from Table 1, the reaction proceeded smoothly in both nonpolar aprotic solvent (toluene, entry 1) and polar protic solvent (MeOH, entry 3), but a highly polar aprotic solvent, such as DMSO, was a poor medium for the present transformation (entry 4). Although both methanol and toluene were suitable reaction media, the reaction appeared generally more complex in the former solvent due to the concurrent formation of both keto amide (**7**) and keto ester. As far as the structure of isonitrile was concerned, the introduction of a fluorine atom into the phenyl ring decreased significantly the reaction efficiency (compound **1b**, R = 2-F, entries 5 and 6), while the presence of an electron-donating group (**1c**, R = 4-OMe) on the aromatic ring resulted in an increase of the product yield (entry 7). Further increasing the electron density (**1d**) of the aromatic ring did not have significant impact on the reaction outcome (entry 11). The metal counterion can also influence the reaction efficiency. Thus, with the same isonitrile (**1c**)[10] under otherwise identical conditions,

Scheme 1. One-Carbon Homologation of Aldehyde to Amide

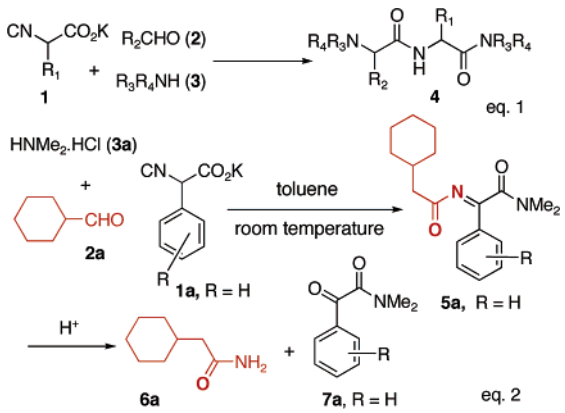

Table 1. Oxidative Homologation of Aldehyde, Optimization of Reaction Parameters[a]

entry	R in **1**	solvent	M	yield (%)[b]
1	H	toluene	K	63
2	H	THF	K	47
3	H	MeOH	K	62
4	H	DMSO	K	7
5	2-fluoro	toluene	K	32
6	2-fluoro	MeOH	K	24
7	4-methoxy	toluene	K	71
8	4-methoxy	MeOH	K	65
9	4-methoxy	toluene	Li	53
10	4-methoxy	toluene	Cs	77
11	3,4-dimethoxy	toluene	K	69
12	4-methoxy	toluene	K	81[c]

[a] General conditions: molar ratio **2a**/**3a**/**1** = 1/1.2/1.2, room temperature, 15 h, concentration = 0.5 M, then, 3 N HCl, 1 h. [b] Yields refer to the mass isolated after silica gel chromatography. [c] Additional 2 equiv of **3a** and Et_3N was introduced after 5 h.

the yield of homologation product increased going from lithium (entry 9) to potassium (entry 7) to cesium (entry 10).[11] However, the hygroscopic nature of the cesium salt made it less practical than the corresponding potassium salt. Overall, in terms of the simplicity of manipulation and product purification, the conditions outlined in entry 7 (**1c**, **3a**, toluene, room temperature, then workup with 3 N HCl) turned out to be optimal for the one-carbon homologation of aldehyde. The yield can be further increased by addition of 2 equiv of **3a** and Et_3N each in the course of the reaction (entry 12).

Having identified reagent combination as well as reaction conditions, we carried out an initial survey of substrate scope. As shown in Table 2, both aliphatic (entries 1, 2, 13, and 14 and eq 2) and aromatic aldehydes (entries 7−12), including those with an electron-withdrawing and electron-donating group, are suitable substrates. Naphthaldehyde and pyridine carboxyaldehyde were also homologated (entries 11 and 12). Chiral aldehydes, such as (*S*)-(−)-citronellal (**2n**), have been transformed into **6n** without

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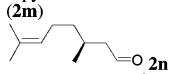
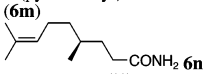
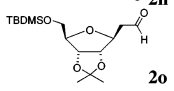
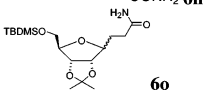
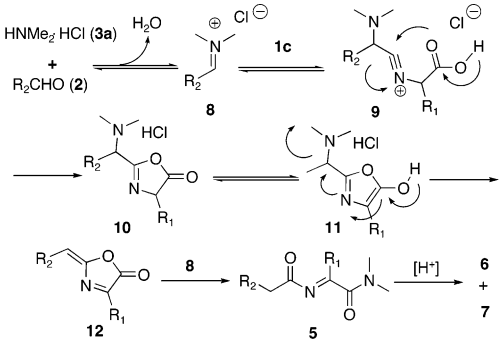
Table 2. Examples of Oxidative One-Carbon Homologation[a]

Entry	Aldehyde	Amide	Yield[b]
1	$C_6H_{13}CHO$ (**2b**)	$C_6H_{13}CH_2CONH_2$ (**6b**)	55 %
2	Me_2CHCHO (**2c**)	$Me_2CHCH_2CONH_2$ (**6c**)	72%
3	cyclohexanone (**2d**)	c-$C_6H_{11}CONH_2$ (**6d**)	61 %
4	cyclopentanone (**2e**)	c-$C_5H_9CONH_2$ (**6e**)	50%
5	4-Ph-cyclohexanone (**2f**)	4-Ph-c-$C_6H_{10}CONH_2$ (**6f**)	56 %[c]
6	Pentanone-3 (**2g**)	—	0%
7	PhCHO (**2h**)	$PhCH_2CONH_2$ (**6h**)	67 %
8	3-Br-benzaldehyde (**2i**)	4-Br-phenylacetamide (**6i**)	51 %
9	3-NO_2-benzaldehyde (**2j**)	3-NO_2-phenylacetamide (**6j**)	52 %
10	3-MeO-benzaldehyde(**2k**)	3-MeO-phenylacetamide(**6k**)	51 %
11	2-naphthaldehyde (**2l**)	2-(naphthalen-2-yl)-acetamide (**6l**)	61%
12	3-pyridine carboxaldehyde (**2m**)	2-(pyridin-3-yl)acetamide (**6m**)	55%
13	 **2n**	 **6n**	53 %
14	 **2o**	 **6o**	45%[c]

[a] All reactions were run in toluene at room temperature in the presence of the hydrochloride salt of dimethylamine and potassium salt of α-*p*-methoxy-α-isocyano acetic acid (**1c**). [b] Yields refer to the mass isolated after silica gel chromatography. [c] Isolated as a mixture of two diastereomers.

Scheme 2. From Aldehyde to Amide, a Mechanistic Hypothesis



racemization. When **2o** was subjected to the same reaction conditions, two separable diastereomers **6o** were produced most probably via a sequence of β-elimination and intramolecular Michael addition process (entry 14). Cyclic ketone can be homologated (entries 3 and 4), but aliphatic ketone failed to participate in the reaction (entry 6).

A plausible mechanism for the formation of the compound **5** is shown in Scheme 2. The condensation of the ammonium ion **3a** with aldehyde **2** would give the iminium **8** that would be trapped by nucleophilic addition of isonitrile to provide the putative isonitrilium intermediate **9**. Intramolecular addition of carbonyl oxygen would lead to oxazolone **10**, which would be in equilibrium with 5-hydroxyoxazole **11**. Depending on the nature of the substituent R_1, the subsequent reaction diverged. In the case of an alkyl group, the oxazolone **10** may exist predominantly over 5-hydroxyoxazole **11**. Nucleophilic attack of amine would then provide the dipeptide **4**. However, when R_1 is an aryl group, the equilibrium between **10** and **11** should shift toward the latter species due to the increased acidity of the proton α to the carbonyl function and additional stabilization offered by the conjugation with the aromatic ring. The 1,6-elimination of the ammonium ion assisted by the 5-hydroxy group from **11** would lead to the pseudooxazolone **12**. This process was apparently favored over reprotonation, which is anyway degenerative since the oxazolone **10** would tautomerize back to the resonance-stabilized hydroxyoxazole **11**. Ring opening of pseudooxazolone **12** by dimethylamine would afford the *N*-acyl imino amide **5**.[12] To validate this mechanistic proposal, authentic pseudooxazolone **12e** ($R_1 = R_2 =$ Ph) was synthesized from readily available mandelic acid and phenylglycine.[13] Simply mixing **12e** and **3a** in toluene in the presence of triethylamine produced **5e** in 90% yield. This control experiment revealed that pseudooxazolone could well be the intermediate of the present homologation procedure.

In summary, we have developed a novel method for oxidative homologation of aldehyde to amide. The reaction is realized under very mild conditions using readily accessible reagents. While multicomponent reaction (MCR) is gaining popularity for creating the structural complexity and diversity,[14] we demonstrated herein that research on MCR can also lead to the discovery of new fundamental transformations. In the present case, α-*p*-methoxyphenyl-α-isocyano acetic acid served as donor of the $CONH_2$ function to aldehyde, while the dimethylamine acted only as a shuttle molecule to initiate/terminate the sequence and to mediate the internal redox process of one of the three-component adducts. Further studies on the scope and limitations of this new reaction are underway.

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Supporting Information Available: Experimental procedures and product characterization for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Compound **1c** is synthesized in four steps from commercially available and inexpensive 4-hydroxy phenylglycine. Racemic aryl glycine is synthesized by Strecker reaction from the corresponding aromatic aldehyde.
(11) Prepared by saponification of the corresponding ester with a stoichiometric amount of LiOH, KOH, and CsOH and used without purification.
(12) The crude reaction mixture of **1c**, **3a**, and **2a**, after quenching with water, was subjected to GC/MS analysis. Besides **5a** (82%), pseudooxazolone **12a** (6%) and dipeptide **4a** (R_1 = 4-MeO-phenyl, $R_2 = C_6H_{13}$, $R_3 = R_4$ = Me, 9%) have been detected. However, the dipeptidic acid resulting from the ring opening of oxazolone **10** by water was not observed (for details, see Supporting Information). Pseudooxazolone **12a** and dipeptide **4a** have also been isolated from the reaction mixture by preparative TLC.
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