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One-Carbon Homologation of Primary Alcohols to Carboxylic Acids, Esters, and Amides via Mitsunobu Reactions with MAC Reagents

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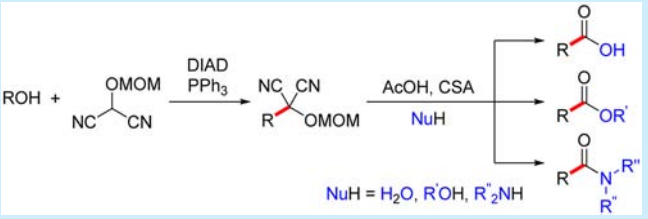
Supporting Information

ABSTRACT: A method is reported for the one-carbon homologation of an alcohol to the extended carboxylic acid, ester, or amide. The process involves the Mitsunobu reaction with an alkoxymalononitrile, followed by unmasking in the presence of a suitable nucleophile. The homologation and unmasking can even be performed in a one-pot process in high yield.

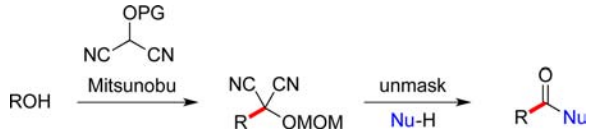


Extending the framework of a molecule by a single carbon is a commonly encountered task in chemical synthesis. This seemingly simple process can require anywhere from two to four steps, depending on the oxidation state of the starting functional group and that desired of the product. Given the importance of such elongations, numerous solutions have been developed for this task, most taking advantage of the rich chemistry of the carbonyl group.[1] For example, the transformation of a carboxylic acid to the corresponding one-carbon homologated derivative can be accomplished through the venerable Arndt−Eistert method, typically requiring a three-step reaction sequence.[2,3] The extension of an aldehyde or ketone carbonyl by one carbon can be achieved using the Wittig olefination or one of its many variants.[4,5] However, in contrast to the countless methods developed for the homologation of carbonyl groups, relatively few options are available to extend a primary alcohol by one carbon.[6] In the course of exploring the umpolung capability of alkoxymalononitrile reagents, termed masked acyl cyanide (MAC) reagents, for hydrogen-bonding-mediated enantioselective processes, we became interested in their potential for other useful transformations.[7,8] We report here that MAC reagents can serve as nucleophiles in Mitsunobu reactions, thereby allowing a net oxidative, one-carbon homologation of alcohols to their corresponding carboxylic acids, esters, and amides.

The standard protocol for extending an alcohol by one carbon calls for a three-step sequence: (1) conversion to a halide or sulfonate, (2) displacement by cyanide, and (3) hydrolysis to a primary amide or carboxylic acid. The current state of this homologation methodology is illustrated in the endgame to the elegant total synthesis of kingianin A by Lim and Parker.[9] Faced with the challenge of transforming two primary alcohols to their respective homologated secondary amides, the authors utilized a four-step sequence that proceeded in 31% overall yield.

In considering a direct and more general route for the homologation of primary alcohols, we recognized that the Mitsunobu reaction using a MAC reagent could provide a solution.[10,11] The mild reaction conditions, wide substrate scope, and high stereospecificity make the Mitsunobu one of the most commonly used reactions for C−O, C−S, and C−N bond formations. While the nucleophile substrate scope is broad with respect to oxygen, sulfur, and nitrogen species, that for carbon-based nucleophiles is rather limited, due in large part to the requirement for a relatively acidic pronucleophile ($pK_a \leq 15$, preferably <11).[10,12] Given the high acidity of malononitrile,[13] MAC reagents were expected to be effective as nucleophiles in the Mitsunobu reaction. A noteworthy advantage of the MAC reagent is their versatility, in that the intermediate can be unmasked to give either a carboxylic acid, an ester, or an amide (Scheme 1).[7,8]

Scheme 1. Plan for MAC−Mitsunobu Homologation



The initial studies to assess the feasibility of the above concept were carried out with phenethyl alcohol (**1a**) and revealed the importance of the order of addition of the reagents. When the MAC reagent was added before the alcohol, amination with the azodicarboxylate occurred to give the MAC-hydrazine dicarboxylate adduct.[14] On the other hand, the desired product was obtained cleanly when the MAC reagent was added last. Thus, treatment of a chilled solution (0 °C) of

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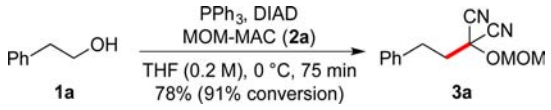
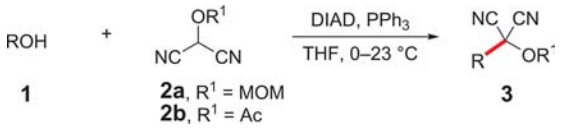
Ph_3P and phenethyl alcohol in THF with diisopropyl azodicarboxylate (DIAD) followed after 15 min by addition of MOM-protected hydroxymalononitrile (MOM-MAC, **2a**) afforded the desired product of C−C bond formation (**3a**) in 78% isolated yield (Scheme 2).[15] Comparable results were obtained in CH_2Cl_2. Further optimization improved the yield of **3a** to 82%.

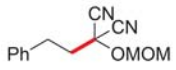
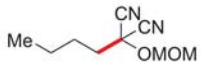
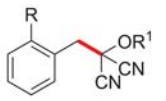
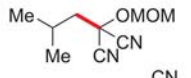
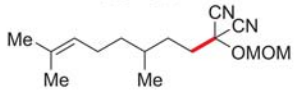
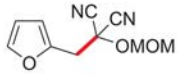
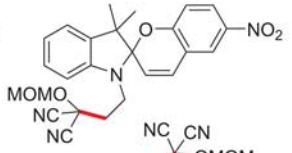
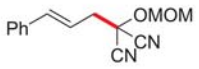
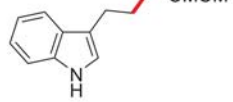
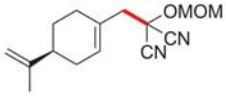
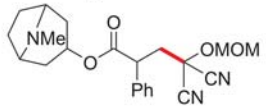
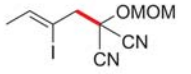
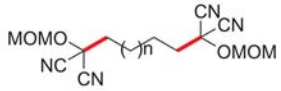
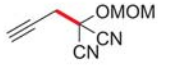
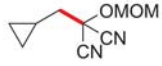
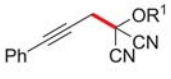
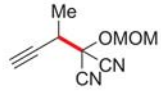
Scheme 2. Initial Result for MOM−Mitsunobu Reaction



The optimized reaction conditions were then applied to a broad selection of primary alcohols, and the MAC adducts were generally obtained in good to high yields (Table 1). Benzyl alcohol and 2-methyl benzyl alcohol performed well in the reaction. A few of these reactions were also carried out using the acetyl-protected MAC reagent (Ac-MAC, **2b**).[15] While effective, Ac-MAC generally provided adducts in lower yields than did MOM-MAC (cf., entries 2−5).[16] Furfuryl alcohol gave the expected homologation product in good yield. Three allylic alcohols were examined as substrates, and all afforded MAC-addition products in good yields, with none of the products of S_N2' displacement (entries 7−9). The Mitsunobu conditions were similarly effective for the two propargylic alcohols studied (entries 10−12). A small amount of the allenyl-MAC byproduct was observed with propargyl alcohol itself. Several unactivated primary alcohols were also subjected to the Mitsunobu conditions, and all performed well, although they required longer reaction times than cinnamyl or propargylic alcohols (entries 13−21). The indolic primary alcohol, tryptophol, produced the expected homologation product, **3n**, in 66% isolated yield (entry 17).[17] Of note is the double-Mitsunobu reaction with diol substrates, shown in entries 19 and 20. The lower yield with the first one, butanediol, may well

Table 1. Substrate Scope of Mitsunobu Reactions Using MAC Reagents



entry[a]	MAC adduct (3)		yield (%)[d]	entry[a]	MAC adduct (3)		yield (%)[d]
1		**3a**	82	13		**3j**	89
2[b]		**3b** R[1]=MOM, R=H	90	14		**3k**	69
3[b]		**3c** R[1]=MOM, R=Me	86				
4		**3b'** R[1]=Ac, R=H	68	15		**3l**	77
5		**3c'** R[1]=Ac, R=Me	78				
6[b]		**3d**	70	16[b]		**3m**	84
7[b]		**3e**	84	17		**3n**	66
8[c]		**3f**	81	18[b]		**3o**	86
9[b]		**3g**	80	19		**3p** n = 1	48
				20		**3q** n = 3	61
10[b]		**3h**	82	21		**3r**	80
11[b]		**3i** R[1]=MOM	91	22		**3s**	68
12		**3i'** R[1]=Ac	68				

[a]Reaction conditions: PPh_3, (1.1 equiv), DIAD (1.1 equiv), ROH (1.1 equiv), MAC (0.4 mmol), THF (2.0 mL), 0−23 °C. [b]PPh_3, (1.5 equiv), DIAD (1.5 equiv), ROH (1.5 equiv), MAC (0.4 mmol), THF (2.0 mL), 0−23 °C. [c]PPh_3, (1.3 equiv), DIAD (1.3 equiv), ROH (1.3 equiv), MAC (0.4 mmol), THF (2.0 mL), 0−23 °C. [d]Calculated based on MAC reagent used as the limiting reagent.

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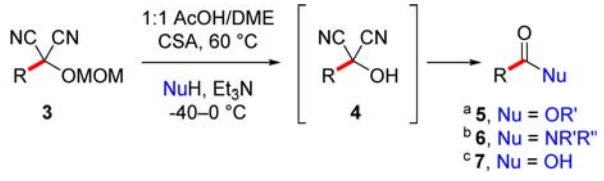
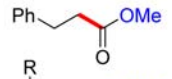
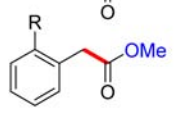
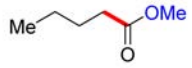
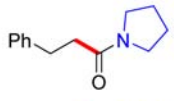
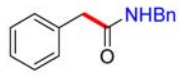
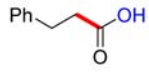
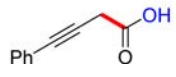
be due to the competing intramolecular cyclization to form tetrahydrofuran. The homologation of cyclopropyl carbinol proceeded uneventfully, without complications from conceivable rearrangements (entry 21). Secondary alcohols were generally not willing partners in the homologation, although 3-butyn-2-ol yielded the desired MAC-adduct **3s** in 68% yield (entry 22).[18]

To demonstrate fully the usefulness of the homologation methodology, we developed protocols for unmasking the MAC unit to reveal the one-carbon extended carboxylic ester, amide, or acid.[8] Treatment of an alcohol adduct with camphorsulfonic acid in a solution of acetic acid and DME produced a dicyanohydrin intermediate (**4**), which upon addition of methanol and triethylamine was converted to the methyl ester (**5**). Alternatively, addition of a primary or secondary amine to intermediate **4** gave the corresponding amide, **6**. Addition of water to intermediate **4** afforded the carboxylic acid, **7**. A selection of MAC adducts were subjected to the unmasking protocol, and the results are summarized in Table 2.

The oxidative homologation methodology was expected to be even more useful if the two steps were accomplished in a one-pot procedure, without isolation of the MAC adduct. In this regard, we were delighted to find that when benzyl alcohol was subjected to the Mitsunobu reaction followed by the unmasking protocol with benzyl amine as the nucleophile, secondary amide **6b** was formed in quantitative yield (Scheme 3). Unfortunately, the product had an R_f close to that of the hydrazine dicarboxylate byproduct of DIAD, necessitating tedious chromatographic separations. To circumvent the isolation difficulty, the Mitsunobu step was carried out using DMEAD, the hydrazine dicarboxylate byproduct of which is water soluble. Subsequent subjection to unmasking conditions with $EtNH_2$ as the nucleophile gave the corresponding ethylamide (**6b′**) in 85% isolated yield.[19] As hoped, the hydrazine byproduct of DMEAD was easily separated from **6b′**.

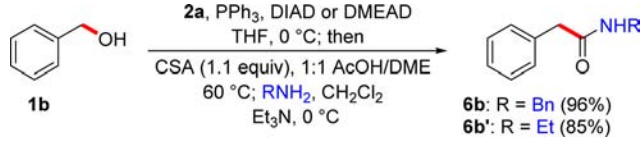
Table 2. Unmasking of Homologation Products



entry	3	NuH	ester/amide/acid		yield (%)
1	**3a**	MeOH		**5a**	80
2	**3b** (R = H)	MeOH		**5b**	80
3	**3c** (R = Me)	MeOH		**5c**	77
4	**3j**	MeOH		**5j**	87
5	**3a**	pyrrolidine		**6a**	98
6	**3b**	$BnNH_2$		**6b**	99
7	**3a**	H_2O		**7a**	99
8	**3i**	H_2O		**7i**	63 (80)[d]

[a]Reaction conditions: **3** (0.1–0.2 mmol), (*R*)-CSA (1.1 equiv), AcOH/DME (1:1, 0.5 M), 60 °C; then MeOH, Et_3N (20 equiv), −40 to 0 °C. [b]Same unmasking conditions, then CH_2Cl_2, amine (20 equiv), Et_3N (20 equiv), −40 to 0 °C. [c](*R*)-CSA (0.5–5.0 equiv), AcOH/H_2O (1:1, 0.2 M), 60 °C. [d]Based on recovered starting material (21%).

Scheme 3. One-Pot Conversion of an Alcohol to the Homologated Secondary Amide



The results described above demonstrate that the Mitsunobu reaction of MAC reagents followed by unmasking provides an efficient solution for the one-carbon homologation of primary alcohols. The versatility of the described methodology has a distinct advantage: the intermediate MAC adduct can be uncloaked to reveal either the extended carboxylic ester, the amide, or the acid. Although the two processes were generally carried out as separate steps, with isolation and purification of the intermediate MAC adduct, we have also demonstrated the feasibility of performing them sequentially in a one-pot process. We expect this methodology to provide effective solutions for homologation problems in complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00790.

Experiments and analytical data for new compounds are included (PDF)

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Notes

The authors declare no competing financial interest.

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(2) (a) Bachmann, W. E.; Struve, W. S. *Org. React.* **1942**, *1*, 38–62. (b) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.

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Table 1 contained errors in the version published ASAP on May 2, 2016; the correct version reposted May 3, 2016.

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