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Regioselective Tandem *N*-Alkylation/ *C*-Acylation of β,γ-Alkynyl α-Imino Esters

Isao Mizota, Yuri Matsuda, Satoshi Kamimura, Hirotaka Tanaka, and Makoto Shimizu*

Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan

imizota@chem.mie-u.ac.jp; mshimizu@chem.mie-u.ac.jp

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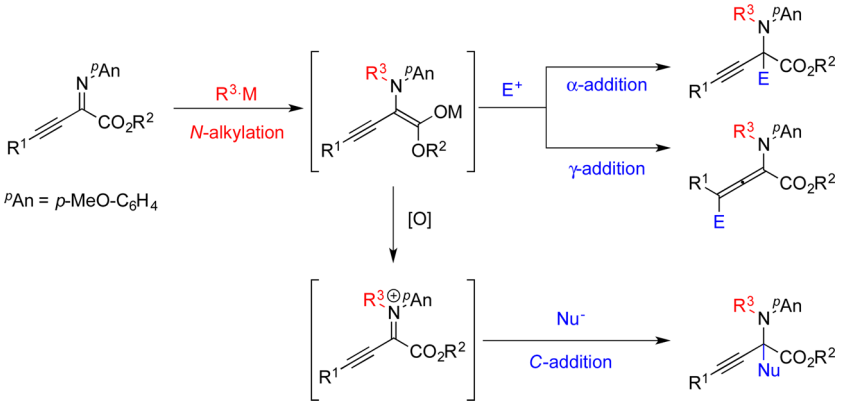
ABSTRACT



A new synthesis of α-quaternary alkynyl amino esters and allenoates was developed utilizing umpolung *N*-addition to β,γ-alkynyl α-imino esters followed by regioselective acylation. The reaction exhibits broad substrate generality and unique regioselectivity. Moreover, synthesis of α-quaternary alkynyl amino esters was also carried out via oxidation of the intermediary enolate followed by alkylation.

Quaternary α-amino acids are an interesting class of nonproteinogenic acids and also powerful enzyme inhibitors. Their synthesis is very important, and several methods have been developed.[1] In particular, β,γ-alkynyl α-amino acids represent important optically active nonproteinogenic α-amino acids. It is known that introduction of α-ethynyl substituents to certain natural amino acids can convert their biological properties from enzyme substrates to enzyme-activated irreversible inhibitors with potential therapeutic utility.[2c] However, the synthesis of β,γ-alkynyl α-amino acid derivatives is a challenging topic, and to our knowledge only limited examples are available.[2] Yet, although allenoates are also useful precursors to important biologically active compounds,[3] only a few general synthetic methods exist.[4]

An umpolung of an α-imino ester is difficult due to the electronegativity of the imino group.[5] Our laboratory has developed umpolung reactions of α-imino esters,[6] and we have recently reported a new type of C−C bond formation using the *N*-alkylation followed by the Claisen rearrangement to give γ,δ-unsaturated amino esters.[6e] However, it is still of interest for us to construct C−C bonds via alkylation of the enolate formed in situ by *N*-alkylation. Herein, we report a one-pot tandem synthesis of α-quaternary

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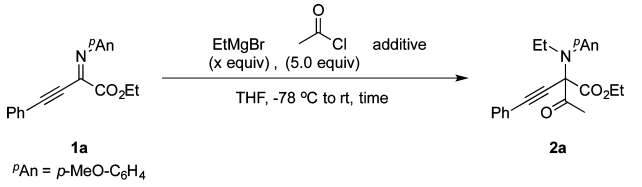
alkynyl amino esters and allenoates using an umpoled *N*-addition to a β,γ-alkynyl α-imino ester followed by electrophilic α- or γ-addition. Moreover, we also found an alternative α-quaternary alkynyl amino ester synthesis utilizing the addition to the iminium salts formed by the oxidation of the intermediary enolates.

As an initial reaction, ethyl-2-((4-methoxyphenyl)imino)-4-phenylbut-3-ynoate **1a** first reacted with ethylmagnesium bromide and subsequently with acetyl chloride in THF at −78 °C to rt for 24 h (Table 1, entry 1).[5b] Gratifyingly, the reaction proceeded as expected to give the desired α-addition product **2a** in 64% yield. To find optimum reaction conditions, we next screened the amount of Grignard reagent, additives, and reaction times, which are summarized in Table 1. First, the amount of nucleophile was examined (entries 1−3). An excess of Grignard reagent led to a slight improvement in the yield of **2a** (entries 2 and 3). Additives such as molecular sieves 4 Å, 1,10-phenanthroline, TMEDA, and TMSCl were not effective (entries 4, 10−12), while shortening the reaction time increased the product yields (entries 5 and 6). These results indicated that **2a** was relatively unstable under the reaction conditions. The amount of Grignard reagent was next reexamined (entries 7−9), and a satisfactory product yield was obtained using 1.1 equiv of Grignard reagent in THF at −78 °C to rt for 30 min (entry 8).

The scope of substrates, electrophiles, and nucleophiles was next examined under the optimized reaction conditions, and the results are summarized in Table 2. Use of acetyl bromide was not effective in this reaction (entry 2). Acyl chlorides having linear aliphatic groups such as acetyl and propionyl chlorides underwent the desired reaction to give the products **2a**, **2b** in high yields (entries 1 and 3), while those having branched aliphatic groups such as isobutyryl and pivaloyl chlorides decreased the yield or gave no product, presumably because of the steric hindrance (entries 4 and 5). Aromatic and heteroaromatic acid chlorides also afforded the desired products **2e**, **2f** in moderate to high yields (entries 6 and 7). Ethyl chloroformate and crotonoyl chloride gave the products **2g**, **2h** in high yields (entries 8 and 9). The substrates having

Table 1. Optimization of *N*-Ethylation/α-Acetylation[a]



entry	*x* equiv	additive	time (h)	yield (%)[b]
1	1.5	none	24	64
2	2.0	none	24	69
3	3.0	none	24	66
4	2.0	MS 4 Å (1.3 g/mmol)	24	59
5	2.0	none	2	69
6	2.0	none	0.5	74
7	1.5	none	0.5	80
8	1.1	none	0.5	79
9	1.0	none	0.5	70
10	1.1	1,10-phenanthroline (0.7 equiv)	0.5	66
11	3.0	TMEDA (3.0 equiv)	24	57
12	1.1	TMSCl (1.1 equiv)	0.5	65

[a] The reaction was carried out according to the general procedure (Supporting Information (SI)). [b] Isolated yield.

aromatic substituents with electron-withdrawing groups or an aliphatic substituent afforded the desired products **2i**−**k** in high yields (entries 10−12). We also found that silyl substituents were efficient for this reaction to give the products **2l**−**p** in high yields (entries 13−17). The substrate with a thienyl group gave the product **2q** in 70% yield (entry 18), while other nucleophiles such as methyl- and benzylmagnesium bromides gave the products in moderate to good yields (entries 19 and 20).

Since α-addition proceeded regioselectively, we next studied γ-addition to give allenyl enolates. Although we examined various reaction conditions, *e.g.*, use of various electrophiles and addition of some ligands to weaken the O−Mg bond of magnesium enolate, the α-adduct was obtained in all cases. Finally we obtained the γ-product **3a** in 18% yield, when CH_2Cl_2 was used as a solvent (Table 3, entry 1). In this context, addition of a Lewis acid, $BF_3 \cdot OEt_2$, was next investigated, and the yield of γ-adduct **3a** was improved to 44% (entry 2). Although use of $ZnCl_2$ or $AlCl_3$ was not effective (entries 4 and 5), it was found that $MgBr_2$ was an appropriate Lewis acid to promote γ-addition, and the combined use of THF and $MgBr_2$ gave the best result (entry 8). Use of $MgCl_2$ worked equally well (entry 9).

The scope of the reaction was next examined, and the results are summarized in Table 4. Under the optimum reaction conditions (Conditions A, see the equation), aromatic and heteroaromatic acyl chlorides afforded the desired products **3a**, **3b**, **3f**, **3k** in good to high yields (entries 1, 3, 9, and 15). However, when aliphatic acyl chlorides were used, the γ-products **3c**, **3d** were not obtained at all (entries 4 and 6). As compared with the results obtained under the conditions A, the yields of **3a**, **3f**, and

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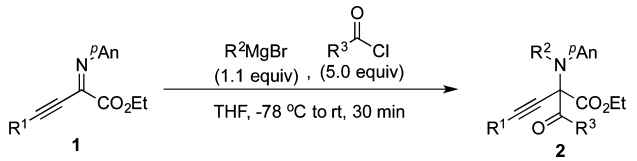
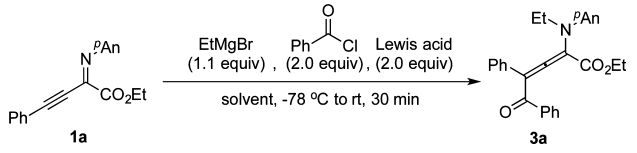
Table 2. Tandem *N*-Alkylation/α-Acylation[a]



entry	R^1	R^2	R^3	product	yield (%)[b]
1	Ph	Et	Me	**2a**	79
2[c]	Ph	Et	Me	**2a**	56
3	Ph	Et	Et	**2b**	78
4	Ph	Et	^{i}Pr	**2c**	32
5	Ph	Et	^{t}Bu	**2d**	0
6	Ph	Et	Ph	**2e**	75
7	Ph	Et	2-furyl	**2f**	54
8	Ph	Et	OEt	**2g**	80
9	Ph	Et	$CH_3CH{=}CH$-	**2h**	92
10	3-FC_6H_4-	Et	Me	**2i**	80
11	4-ClC_6H_4-	Et	Me	**2j**	83
12	1-cyclohexenyl	Et	Me	**2k**	76
13	TIPS	Et	Me	**2l**	85
14	TIPS	Et	Ph	**2m**	88
15	TIPS	Et	2-thienyl	**2n**	98
16	TES	Et	Ph	**2o**	87
17	TES	Et	2-thienyl	**2p**	quant
18	2-thienyl	Et	OEt	**2q**	70
19	Ph	Me	Me	**2r**	73
20	Ph	Bn	Me	**2s**	41

[a] The reaction was carried out according to the general procedure (SI). [b] Isolated yield. [c] Acetyl bromide was used instead of acetyl chloride.

Table 3. Optimization of *N*-Ethylation/γ-Benzoylation[a]

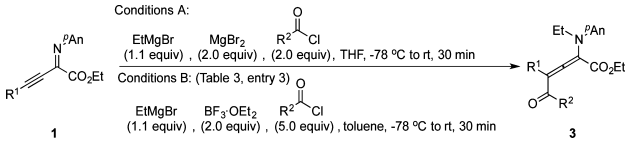


entry	solvent	Lewis acid	yield (%)[b]
1[c]	CH_2Cl_2	none	18
2[c]	CH_2Cl_2	$BF_3{\cdot}OEt_2$	44
3	toluene	$BF_3{\cdot}OEt_2$	54
4	toluene	$ZnCl_2$	0
5	toluene	$AlCl_3$	0
6	toluene	$MgBr_2$	61
7	EtCN	$MgBr_2$	61
8	THF	$MgBr_2$	82
9	THF	$MgCl_2$	79

[a] The reaction was carried out according to the general procedure (SI). [b] Isolated yield. [c] Acetyl chloride (5.0 equiv) was used instead of benzoyl chloride.

3k decreased under the conditions B (entries 2, 10, 16), while the γ-products **3c** and **3d** were obtained in moderate yields under conditions B (entries 5 and 7). These results indicate that when benzoyl chloride was used, the Lewis acidity of $MgBr_2$ was suitable for the in situ formation of an acylium ion, whereas the use of $BF_3{\cdot}OEt_2$ led to decomposition of the product, perhaps due to an increased Lewis acidity. When aliphatic acid chlorides were used, the relatively slow formation of acylium ions by $MgBr_2$ would reflect the results.[7] It should be noted that silyl substituted imino esters gave the α-adducts exclusively in high yields (entries 18−20). Although the selectivity of α- to γ-addition is not readily explained, we presume that the γ-addition would proceed via orbital control in the presence of a Lewis acid due to lowering the LUMO level by forming an acylium ion to overlap the HOMO of the γ-carbon well.[8]

Table 4. Tandem *N*-Alkylation/γ-Acylation[a]



entry	R^1	R^2	conditions	product	yield (%)[b]
1	Ph	Ph	A	**3a**	82
2[c]	Ph	Ph	B	**3a**	54
3	Ph	2-thienyl	A	**3b**	86
4[c,d]	Ph	Me	A	**3c**	0
5	Ph	Me	B	**3c**	54
6	Ph	Et	A	**3d**	0
7	Ph	Et	B	**3d**	42
8[e]	Ph	$CH_3CH{=}CH$-	B	**3e**	40
9[f]	2-thienyl	Ph	A	**3f**	82
10[e]	2-thienyl	Ph	B	**3f**	46
11[e]	2-thienyl	2-thienyl	B	**3g**	42
12	3-FC_6H_4-	Me	B	**3h**	28
13[g]	3-FC_6H_4-	Ph	B	**3i**	36
14	4-ClC_6H_4-	Me	B	**3j**	13
15	1-cyclohexenyl	Ph	A	**3k**	63
16[g]	1-cyclohexenyl	Ph	B	**3k**	50
17	1-cyclohexenyl	Me	B	**3l**	36
18	TES	Ph	A	**2m**[h]	83
19	TIPS	Ph	A	**2n**[h]	86
20	TIPS	2-thienyl	A	**2o**[h]	85

[a] The reaction was carried out according to the general procedure (SI). [b] Isolated yield. [c] Acyl chloride (5.0 equiv) was used. [d] Toluene was used as a solvent. [e] THF was used as a solvent. [f] Reaction was carried out in the absence of Lewis acid. [g] Acyl chloride (2.0 equiv) was used. [h] α-Addition product (see Table 2).

In our preliminary experiment, which was a simple *N*-ethylation of β,γ-alkynyl-α-imino ester **1a** with Et_2Zn, we found that the *N*-ethylation product was unstable in the presence of a proton source due to an isomerization to the allene.[9] When the *N*-ethylation reaction was carried out with Et_2Zn (3.0 equiv), after the normal workup, the

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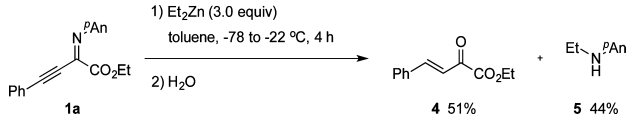
ketoester **4** and *N*-ethyl-4-methoxyaniline **5** were obtained instead of the *N*-ethylated product in moderate yields (Scheme 1). Since introduction of a substituent into the imino carbon in situ should inhibit the tautomerization to an allene, we next examined a further alternative synthesis of α-quatenary alkynyl amino esters utilizing sequential *N*-alkylation/oxidation/nucleophilic addition to *β*,*γ*-alkynyl-α-imino ester **1**.

Scheme 1. *N*-Ethylation to α-Alkynyl Imino Ester



As an initial reaction, ethyl-2-((4-methoxyphenyl)imino)-4-phenylbut-3-ynoate **1a** first reacted with 1.2 equiv of EtMgBr in THF at −78 °C to rt for 20 min followed by oxidation with DBDMH (1,3-dibromo-5,5-dimethylhydantoin) at rt for 10 min and treatment with another 3.0 equiv of EtMgBr at −78 °C to rt for 6 h. Unfortunately the desired product was not obtained at all. Therefore, a series of reaction conditions such as the amount of Grignard reagent, oxidants, temperatures, Lewis acids, reaction times, and substrates were examined in detail.[10] As a result, the desired products **6a**−**d** were obtained in a maximum 49% yield (Scheme 2). Among the substrates examined, the one with the terminal silyl group gave the desired product **6e** in good yield.

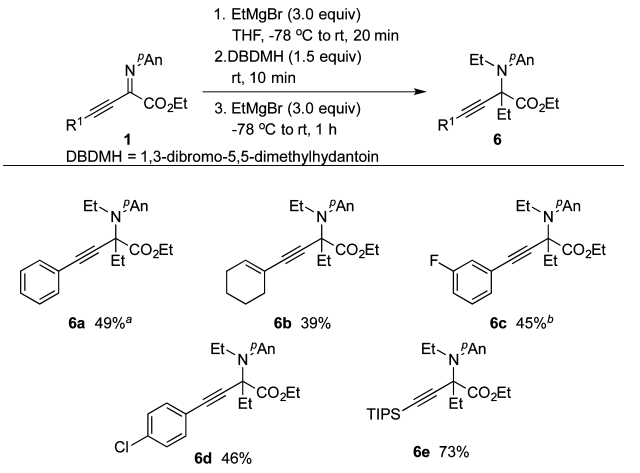
A proposed reaction mechanism is shown in Scheme 3. First, *N*-ethylation of the imino ester **1** generates the magnesium enolate **A**. Under basic conditions, the enolate reacts with an electrophile at the α-position to give the alkynyl amino ester **2**, while, under Lewis acidic conditions, the enolate reacts with the acylium ion derived from acyl chloride with a Lewis acid at the *γ*-position through orbital control to provide the allenyl esters **3**. In the cases with DBDMH as an oxidant, the enolate **A** is oxidized to give an iminium salt as intermediate **B**, which reacts with another equivalent of EtMgBr to give the alkynyl amino ester **6**.

In summary, we have developed a one-pot synthesis of α-quatenary alkynyl amino esters and allenoates using umpolung *N*-alkylation of *β*,*γ*-alkynyl α-imino esters followed by nucleophilic α- or *γ*-addition. This method has unique regioselectivity and provides important α-quaternary alkynyl amino acids in good yields. Moreover,

(9) The α-addition product could not be isolated on silica gel TLC instead of silica gel column chromatography due to decomposition under acidic conditions. See for example: Yamamoto, Y.; Hayashi, H. *Tetrahedron* **2007**, *63*, 10149.

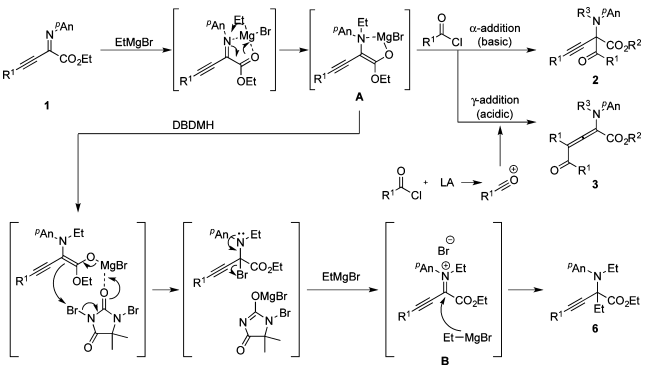
(10) See the SI for more detailed examination of reaction conditions.

Scheme 2. Tandem *N*,*C*-Diethylation via an Iminium Salt



[a] $PhI(OAc)_2$ (3.0 equiv), 6 h. [b] Reaction time was 22 h.

Scheme 3. Plausible Mechanism



we also show the synthesis of α-quaternary alkynyl amino esters utilizing a *β*,*γ*-alkynyl α-imino ester with a terminal silyl group via an intermediary iminium salt formed by the oxidation of the amino ester enolate.

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Supporting Information Available. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.