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Stereoselective Synthesis of Tetra-Substituted Olefins via Addition of Zinc Enolates to Unactivated Alkynes

Masaharu Nakamura,*,†,‡,§ Taisuke Fujimoto,‡ Kohei Endo,‡ and Eiichi Nakamura*,‡

Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and PRESTO, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan

nakamura@chem.s.u-tokyo.ac.jp

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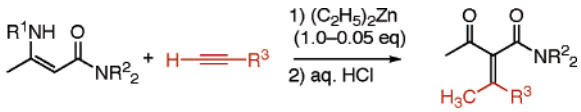
ABSTRACT

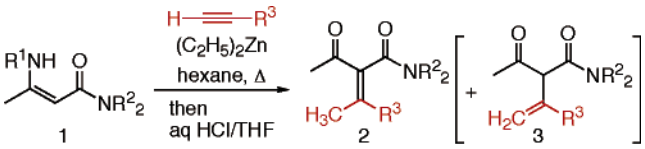


R^1 = allyl, butyl, 2-methoxyethyl; NR^2_2 = dialkylamino, morpholinyl
R^3 = aryl, alkyl

82 to 99% yield, 81:19 to> 99:1 stereoselectivity

In the presence of a stoichiometric or catalytic amount of diethylzinc, a *β*-aminocrotonamide undergoes sequential addition/isomerization reactions with 1-alkyne to produce, upon hydrolysis, an α-alkylidene *β*-dicarbonyl compound in a highly stereoselective manner. The method complements the conventional Knoevenagel synthesis of this class of compounds as to the choice of the starting material and the scope and stereochemistry of the product.

Condensation reactions of an active methylene compound with a carbonyl compound constitute a classical repertoire of synthetic chemists to achieve carbon chain extension. The Knoevenagel reaction is representative, producing an α-alkylidene carbonyl compound from an aldehyde or a ketone.[1] We report here that an equivalent operation can be achieved by starting with an alkyne instead of a carbonyl compound. Thus, a zinc enamide of a *β*-aminocrotonamide **1** adds smoothly to 1-alkyne to produce a tetra-substituted olefinic product **2** in high yield and with high *Z*-selectivity (Figure 1). The product structure corresponds to the one that would be derived from the Knoevenagel condensation of an active methylene compound with a ketone, which has been known to take place with low efficiency and with low stereoselectivity,[2,3] and hence the method reported in this Letter adds to the value of active methylene compounds in organic synthesis. The result provides further support for our conviction that metal enolates and enamides can serve for controlled carbometalation of unactivated alkenes and alkynes through judicious choice of the metal atom and reaction conditions.[4,5]



R^1= butyl, allyl, 2-methoxyethyl; NR^2_2 = dialkylamino, morpholinyl;
R^3 = aryl, alkyl

Figure 1. Zn-mediated alkylidenation of *β*-aminocrotonamide **1**.

† PRESTO, JST.
‡ The University of Tokyo.
§ masaharu@chem.s.u-tokyo.ac.jp.

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(3) (a) Farmer, E. H.; Ross, J. *J. Chem. Soc.* **1926**, 1570−1577. (b) Faucaud, A.; Person, H.; Robert, A. *Bull. Chim. Soc. Fr.* **1964**, 1873−1876.

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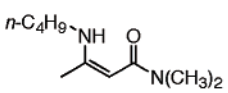
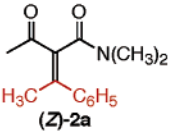
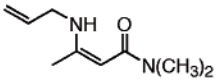
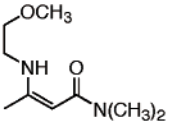
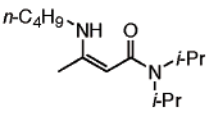
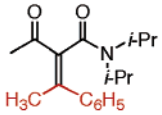
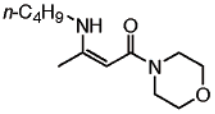
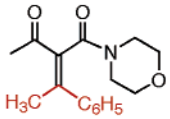
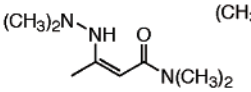
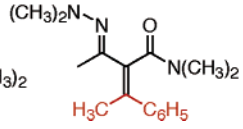
We recently reported that an active methylene compound undergoes indium-catalyzed addition to an alkyne to give a β,γ-unsaturated carbonyl compound.[5c] The reaction was mostly high-yielding for starting β-dicarbonyl compounds possessing only one acidic proton at the α position. When the starting material has two acidic α-protons, an α,β-unsaturated compound contaminates the major β,γ-unsaturated carbonyl product. We now report that the α,β-unsaturated compound can be made to form exclusively and with very high *Z*-stereoselectivity by the use of a β-aminocrotonamide **1** for coupling with an alkyne in the presence of diethylzinc.

After screening of the substrates and optimization of the reaction conditions, we found that simple heating of a mixture of **1a**, diethylzinc, and phenylacetylene followed by workup with dilute aqueous HCl (1 M, 1.5 equiv) gives exclusively the desired alkylidenation product (**2**) with high *Z*-stereoselectivity (up to 98:2 as in Table 1). A representative procedure is as follows. To 3-butylamino-*N*,*N*-dimethyl-2-butenamide **1a** (0.92 g, 5 mmol) was added dropwise a hexane solution of $(C_2H_5)_2Zn$ (1.0 M, 5.0 mL, 5 mmol) at room temperature. Phenylacetylene (2.8 mL, 25 mmol) was added at that temperature to produce a pale yellow solution. The reaction mixture was stirred at 70 °C for 8 h. After dilution with 5 mL of THF, to the reaction mixture was added aqueous HCl (1 M, 7.5 mL)[6] to effect hydrolysis of the imine group. Silica gel column chromatography gave the tetrasubstituted olefin **2a** (1.16 g, 96%) with the isomer ratio of 95:5 (entry 1, Table 1). The reaction was successful only by the use of the organozinc reagent[7] and did not take place by the use of lithium or magnesium compounds.

Table 1. Alkylidenation of Various β-Aminocrotonamides[a]

entry	crotonamide	product	% yield[b]	ratio (*Z*:*E*)[c]
1		 (*Z*)-**2a**	96[d] 98	95:5[d] 96:4
2		(*Z*)-**2a**	92	94:6
3		(*Z*)-**2a**	95	95:5
4			95	81:19
5			97	98:2
6[e]			98	72:28[f]

[a] The reaction was carried out on a 0.5 mmol scale by heating a mixture of a crotonamide, $(C_2H_5)_2Zn$, and a terminal alkyne (5 equiv) at 70 °C for 8 h unless otherwise noted. [b] Isolated yield. [c] Determined by GLC analysis. Stereochemistry of the major product was elucidated by an NOE experiment. [d] On a 5 mmol scale. [e] The hydrazono moiety could not be hydrolyzed under the conditions applied for imines. [f] Stereochemistry of the hydrazone moiety was determined to be *E*, based on the chemical shift values of the ^{1}H and ^{13}C NMR, and the ratio refers to the stereochemistry of the C−C double bond.

Other crotonamides possessing a different β-amino group take part equally well in the stereoselective alkylidenation reaction (entries 2 and 3). The use of a bulky diisopropylamide group lowered the stereoselectivity (entry 4). A tetrasubstituted olefin possessing a morpholinyl amide group, which is of potent synthetic utility,[8] was produced in 97% yield with 98:2 stereoselectivity (entry 5). The hydrazone compound in entry 6 resists hydrolysis and was isolated in 98% yield. The stereoselectivity eroded here because of a reason still unknown.

Table 2 summarizes the result of the addition reaction of the β-aminocrotonamide **1a** to a variety of alkynes. As shown in entries 1−3, the reactions with an aliphatic alkyne proceeded smoothly with high stereoselectivity (94:6 to 98:2), while the yields were slightly lower than those with aromatic alkynes. The reaction with an enyne substrate proceeded exclusively at the carbon−carbon triple bond to give an alkenylidene product in 89% yield with 98:2 selectivity (entry 4). With various aromatic alkynes, the corresponding alkylidenation products were obtained in excellent yield (94−99% yield) with high stereoselectivity (91:9 to 97:3).

Ortho-substitution on the aromatic ring lowers the selectivity, which may be due to steric repulsion (entries 6 and 8). Introduction of an electron-withdrawing group decreases the reaction rate, and efficient conversion required elongation of the reaction time (entries 9 and 10). Heteroaromatic alkynes also give an excellent result (entry 11).

We consider that the mechanism of the alkylidenation is essentially the same as the one proposed previously for the indium-catalyzed alkenylation reaction.[5c] A labeling experi-

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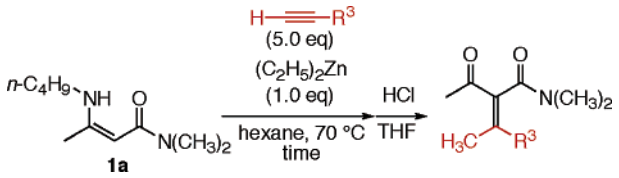
(6) Low stereoselectivity and incomplete mass balance were observed under some other hydrolysis conditions (e.g., AcOH/THF/H_2O, $Cu(OAc)_2$/H_2O/THF). Slightly excess amount of HCl is mandatory to prevent product isomerization.

(7) Combined use of a stoichiometric amount of $Zn(OTf)_2$ and NEt_3 or $In(OTf)_3$ and NEt_3 can promote the alkylidenation reaction (69% and 30% yield, respectively) to give a 1: 1 mixture of the geometrical isomers. See also ref 4b,c.

(8) Badioli, M.; Ballini, R.; Bartolacci, M.; Bosica, G.; Torregiani, E.; Marcantoni, E. *J. Org. Chem.* **2002**, *67*, 8938−8942.

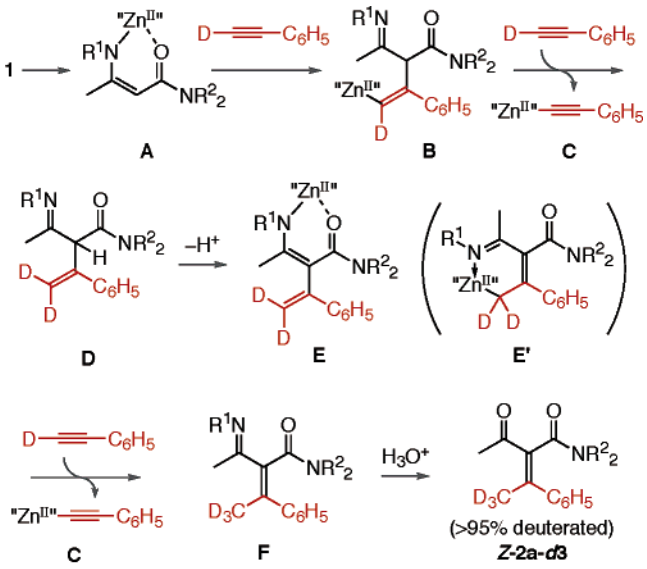
Table 2. Alkylidenation Reactions with a Variety of Alkynes



entry	R^3	time (h)	% yield[a]	ratio (Z:E)[b]
1	n-C_6H_{13}	24	82	98:2
2	CH_2OCH_3	24	87	94:6
3	$CH(OC_2H_5)_2$	24	90	98:2
4	1-cyclohexenyl	12	89	98:2
5	4-$CH_3OC_6H_4$	8	98	96:4
6	2-$CH_3OC_6H_4$	8	98	92:8
7	4-$CH_3C_6H_4$	8	99	97:3
8	2-$CH_3C_6H_4$	8	96	91:9
9	4-$CH_3OCOC_6H_4$	15	96	94:6
10	4-BrC_6H_4	10	99	95:5
11	5-n-C_8H_{17}-2-furyl	8	94	>99:1

[a] Isolated yield of the corresponding ketoamide obtained as a mixture of stereoisomers. [b] Determined by GLC analysis.

ment was therefore carried out. The reaction of **1b** with 1-deuterio-2-phenylyethyne gave, upon hydrolysis, the alkylidenation product Z-**2a**-d_3 (see Figure 2). Incorporation of



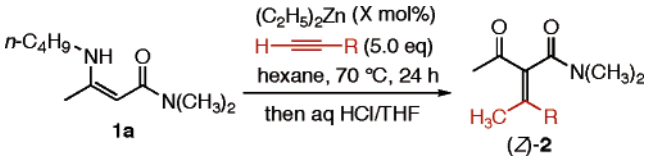
R^1: $CH_2CH_2OCH_3$, R^2: CH_3, "Zn^{II}": zinc countercation carrying an anionic ligand, such as ethyl, phenylethynyl or the enamide group. See supporting information for experimental details.

Figure 2. A possible reaction pathway.

three deuterium atoms at the methyl group (>95%) provides the following mechanistic scenario. A zinc enolate intermediate **A** that forms by the deprotonation of **1b** with diethylzinc adds to the alkyne to generate an alkenylzinc intermediate **B**. The deuteration of **B** takes place with the large excess phenylacetylene-d_1 to give alkynylzinc **C** and a neutral alkenylation product **D**. A N-zinc intermediate **E** forms via deprotonation of the active methyne proton in **D**. The second deuteration takes place at the γ-carbon by the labeled alkyne to generate a neutral β-imino-α-alkylidene amide **F** accompanied by the generation of alkynylzinc **C**. As shown in the catalytic alkylidenation described in the next paragraph, these protonation/deprotonation steps require a delicate balance of the acidity of the terminal proton of the alkyne substrate and the basicity of the alkynylzinc species. ^{1}H NMR measurement of the reaction mixture confirmed the in situ formation of the intermediate **F** (see Supporting Information). Thus, the high steroselectivity must be due to kinetic proton transfer from the relatively nonacidic acetylenic proton to N-zinc intermediate **E** or its tautomeric isomer **E′**, where the strong N−Zn interaction may account for the Z-selectivity of the product.[4g]

With the above mechanistic information in hand, we envisioned that the alkylidenation reaction can be effected by a catalytic amount of diethylzinc when the zinc enamide **A** is regenerated by deprotonation of **1** under the reaction conditions. This is indeed the case for aromatic alkynes but not for aliphatic alkynes, which possess a proton less acidic than those of the aromatic ones (vide supra). Table 3

Table 3. Catalytic Alkylidenation of **1a**



entry	X	R	% yield[a]	ratio (Z:E)[b]
1	50	C_6H_5	96	96:4
2	10	C_6H_5	93	96:4
3	5	C_6H_5	82	95:5
4	10	4-$CH_3OC_6H_4$	91	97:3
5	10	2-$CH_3OC_6H_4$	88	93:7
6	10	4-n-C_8H_{17}-2-furyl	86	>99:1

[a] Isolated yield for a mixture of isomers (Z)-**2a**, (E)-**2a**, and **3a**. [b] Determined by GLC analysis.

summarizes the results of the catalytic alkylidenation of β-aminocrotonamide **1**. The amount of the catalyst may be reduced to 5 mol % to obtain the alkylidenation product in acceptable yield at the expense of reaction rate. The catalytic reactions showed stereoselectivity either comparable or sometimes higher than that observed in the stoichiometric reactions (see Table 2, entries 5, 6, and 11).

In summary, we have developed a new alkylidenation reaction of active methylene compounds that can be used complementarily to the classic Knoevenagel reaction for the synthesis of fully substituted olefins. The key to the success is the facile intermolecular addition reaction of a metal enolate to a nonactivated alkyne, which can takes place with a stoichiometric or catalytic amount of Zn^{2+} countercation under basic conditions.

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

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