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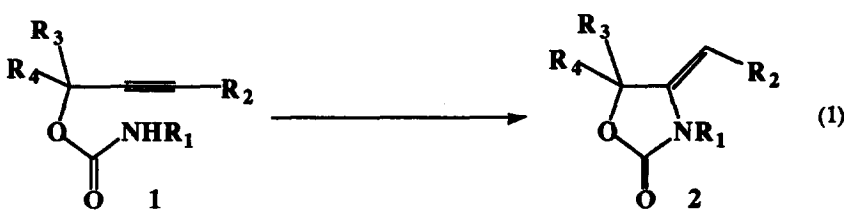
Convenient Synthesis of Densely Functionalized N-Substituted 4-Methylene-2-oxazolidinone

M. Kimura, S. Kure,[1] Z. Yoshida,[1] S. Tanaka, K. Fugami, and Y. Tamaru*
Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Bunkyo-Machi, Nagasaki 852, Japan

Summary: O-Propargyl carbamates 1 undergo an intramolecular nucleophilic addition to acetylenic bond at the nitrogen atom to furnish 4-methylene-2-oxazolidinones 2 in good yields in the presence (Cu^+ for R_1 = *p*-toluenesulfonyl, Ag^+ for R_1 = acyl) or absence (for R_1 = alkyl and aryl) of a transition metal catalyst.

Nucleophilic addition reaction of alkoxide to acetylene is synthetically useful, because this reaction alters the electrophilic acetylenic C-C bond to the nucleophilic C-C bond of vinyl ether. Accordingly many modifications have been developed in pursuit of the milder conditions, the higher regio- and stereoselectivities, and better yields, employing carboxylic acid[2] or carbamic acid[3] as an oxygen nucleophile and a transition metal as a catalyst (e.g., copper and ruthenium).

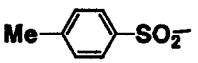
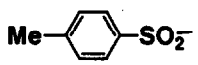
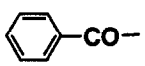
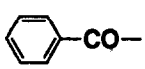
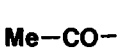
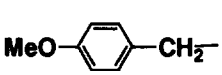
Here we would like to report that the nitrogen atom of O-propargyl carbamates 1 serves as a nucleophile and intramolecularly adds to triple bond to form 4-methylene-2-oxazolidinones 2. The reaction is highly dependent on the kind of the substituent (R_1) on the nitrogen. However, by the selection of an appropriate base and/or metal catalyst, 2 could be obtained in good yields, irrespective of R_1 (equation 1).



(1)

The reactivity of the parent carbamate 1 (R_2 = R_3 = R_4 = H) was fully examined by changing the electronic nature of the R_1 substituents (Table 1). Inspection of Table 1 suggests that the reaction can be grossly classified into three categories. The first is the reaction of 1 with R_1 = *p*-toluenesulfonyl. In this case, the reaction proceeds smoothly in the presence of catalytic amounts of CuCl and Et_3N (0.1 equivalents each). These two components are essential. No cyclization takes place in the absence of either CuCl (entry 2) or triethylamine. Other metal salts than CuCl were examined under the similar

Table I. Cyclization of O-Propargyl Carbamate 1 ($R_2 = R_3 = R_4 = H$) with Varying R_1[1]

entry	carbamate 1 ($R_2 = R_3 = R_4 = H$) R_1		metal catalyst	base	reaction conditions[2]	isolated yield of 2
1		1a	CuCl	Et_3N	r.t., 24 h; refl., 12 h	2a: 94%
2		1a	none	Et_3N	r.t., 45 h	2a: 0%
3		1b	CuCl	t-BuOK	r.t., 24 h	2b: 32%
4		1b	AgNCO	t-BuOK	r.t., 24 h	2b: 71%
5		1c	CuCl	t-BuOK	r.t., 48 h; refl., 9 h	2c: 77%
6		1c	AgNCO	t-BuOK	r.t., 20 h; refl., 2 h	2c: 89%
7		1c	none	t-BuOK	r.t., 24 h; refl., 3 h	2c: 0%
8		1d[3]	AgNCO	t-BuOK	r.t., 30 h	2d: 81%
9		1e	CuCl	t-BuOK	r.t., 24 h; refl., 20 h	2e: 95%
10		1e	none	t-BuOK	r.t., 24 h	2e: 91%
11		1f	none	t-BuOK	r.t., 20 h	2f: 99%
12		1g	CuCl	t-BuOK	r.t., 24 h; refl., 18 h	2g: 86%
13		1g	none	t-BuOK	r.t., 20 h	2g: 93%

1) Reactions, except for entry 8, were undertaken by using 1 (1.0 mmol) and a base (0.1 mmol) in the presence or absence of a metal salt (0.1 mmol) in dry THF (5 mL) under a nitrogen atmosphere. For entry 8, AgNCO (0.13 mmol) and KO^tBu (0.2 mmol) were applied.
2) Except for entry 7, the reaction proceeded to substantial extent at room temperature. In order to attain the completion, the mixture was refluxed for the additional period of time indicated.
3) *trans* crotonoyl was used.

conditions to entry 1, Table 1. Among them, $ZnCl_2$, $PdCl_2$, and Ru(COD)(COT) showed marginal success, providing **2a** in 69, 46, and 54% isolated yields, respectively. The second group is the reactions for R_1 = acyl. In this case the above CuCl-Et_3N catalytic system was completely ineffective and no expected **2** were detected. A combination of CuCl and a stronger base, such as KO^{t}Bu, improved the reaction considerably (entries 3 and 5). However, the more satisfactory results were obtained by the use of Ag salt as a catalyst in place of Cu salt (entries 4, 6, and 8). The third case is for R_1 = aryl and alkyl, where the cyclization proceeded smoothly at room temperature only in the presence of KO^{t}Bu as a catalyst. In the reactions belonging to this category, CuCl seems to retard the reaction (entries 9 and 12), which makes sharp contrast to the result in entry 7.

Next, we examined the scope of the reaction varying the substituents R_2 - R_4, setting R_1 = *p*-toluenesulfonyl invariable (Table 2). It may be clearly seen from Table 2 that the higher the number of substitution at the propargylic position, the higher the reactivity. The results of entries 6 - 8 indicate that the present reaction is applicable not only for the terminal alkynyl carbamates but also for the internal alkynyl carbamates, though requiring the longer reaction times for the completion of the reaction, compared with the corresponding terminal ones. The reaction was highly stereoselective and only single stereoisomers were detected. The structure was assigned to be Z on the basis of the NOE experiments.[4]

The products obtained here are densely functionalized molecules with stereochemically defined enamine and protected allylic alcohol moieties. The enamine moiety, for example, may serve as an active component for **2d**, **2f**, and **2g** to undergo

Table 2. Cyclization of O-Propargyl Carbamate **1** (R_1 = tosyl) with Varying R_2, R_3, and R_4[1)]

entry	carbamate **1** (R_1 = tosyl)	reaction time	isolated yield of **2**
1	**1a**: $R_2 = R_3 = R_4 = H$	1 day	**2a**: 91%
2	**1h**: $R_2 = R_3 = H$, $R_4 = Me$	2 h	**2h**: 94%
3	**1i**: $R_2 = R_3 = H$, $R_4 = Et$	2 h	**2i**: 95%
4	**1j**: $R_2 = H$, $R_3 = R_4 = Me$	2 h	**2j**: 94%
5	**1k**: $R_2 = H$, R_3-$R_4 = (CH_2)_5$	1 h	**2k**: 96%
6	**1l**: $R_2 = Me$, $R_3 = R_4 = H$	21 h	**2l**: 93%
7	**1m**: $R_2 = R_3 = Me$, $R_4 = H$	7 h	**2m**: 78%
8	**1n**: $R_2 = MeC{=}CH_2$, $R_3 = R_4 = H$	42 h	**2n**: 16%

1) Reactions were undertaken by using **1** (1.0 mmol), CuCl (0.1 mmol), and Et_3N (0.1 mmol) in dry THF (5 mL) at reflux under a nitrogen atmosphere.

intramolecular enamine-enone Michael addition reaction, intramolecular Friedel-Crafts alkylation (e.g., via protonation of emanine), and aza-Claisen rearrangement, respectively.

Typically the reaction was performed as follows (entry 5, Table 2): A flask containing **1k** (321 mg, 1.0 mmol) and CuCl (10 mg, 0.1 mmol) is purged with nitrogen and then dry THF (5 mL) and triethylamine (14 μL, 0.1 mmol) are introduced via syringes. The homogeneous mixture is stirred for 1 hour at an ambient temperature, and then diluted with ethyl acetate (50 mL), washed with aq. $NaHCO_3$. The reaction is monitored with TLC (benzene - ethyl acetate 16:1, v/v). The organic phase is dried over $MgSO_4$ and condensed to give waxy solid, which is purified by means of column chromatography over silica gel (benzene - ethyl acetate gradient) to give **2k** as colorless solid in 96% yield: mp. 89.5 - 90.0 °C; IR (KBr disk) 1780 (s), 1680 (s), 1370 (s), 1300 (s), 1260 (s), 1180 (s), 1100 (s), 810 (m), 700 (m), 670 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10 (m, 10 H), 2.45 (s, 3 H), 4.41 (d, J = 2.9 Hz, 1 H), 5.50 (d, J = 2.9 Hz, 1 H), 7.33 (d, J = 8.3 Hz, 2 H), 7.93 (d, J = 8.3 Hz, 2 H). Anal. Calcd for $C_{16}H_{19}O_4NS$: C, 59.79; H, 5.96; N, 4.36; S, 9.98. Found: C, 59.76; H, 5.84; N, 4.35; S, 10.03.

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References and Notes

(1) Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Sakyo, Kyoto 606, Japan.

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(4) One of the olefinic protons of **2a** resonates at lower field by ca. 1 ppm (δ 5.53 ppm) than the other proton (δ 4.57 ppm). Irradiations at *ortho* protons of phenyl ring and C_5 methylene protons caused the increment of the area intensities of the former and the latter olefinic protons, respectively, which indicates that phenyl and the olefinic proton resonating at the lower field sterically locate in a close proximity. Judging from the chemical shift of the olefinic proton (δ 5.27 ppm), the structure of **2l** was determined to be Z, which was further supported by the increment of the area intensities of the olefinic proton by irradiation of C_5 methylene protons.

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