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Concise One-step Synthesis of 4-Arylidene-1,3-oxazolidin-2-ones with Internal Propargylic Alcohols and Isocyanates†

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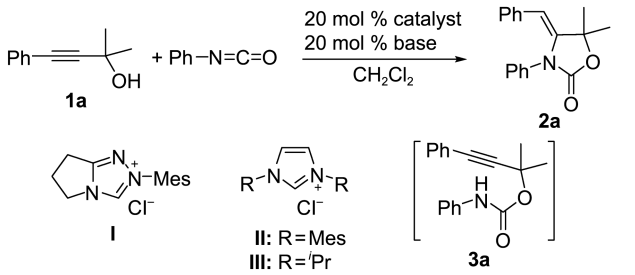
Oxazolidinones and their derivatives are widely used, as chiral synthons or chiral auxiliaries[1] and as bioactive scaffolds in numerous natural products.[2] Due to the importance of their structures, several methods for the synthesis of 1,3-oxazolidin-2-ones have been reported. Classical methods for formation of these heterocyclic rings involve condensation reactions between corresponding amino alcohols and carbonyl precursors such as phosgene, chloroformate and dialkyl carbonates. An alternative approach is the cyclization reaction of vinyl or propargyl carbamate catalyzed by base[3] or transition metal[4] catalyst, in which a variety of substituted oxazolidinones are obtained under milder conditions. Tamaru,[4a,b] Gagosz,[4c] and Schmalz[4d] reported the synthesis of 4-alkylidene-1,3-oxazolidin-2-one from *O*-propargyl carbamates using Cu(I) and Au(I) catalyst, whereas Chandrasekaran[3d] reported LiOH-catalyzed reaction method with DMF solvent. However, these procedures were mostly applied to the construction of 4-*methylene*-1,3-oxazolidin-2-one, and only a few 4-substituted methylene ones have been reported. Another method using CO_2 as a carbonyl source has also been developed,[5] and silver-catalyzed cycloaddition reactions involving internal propargylic alcohols and amines in supercritical CO_2 and formation of 2-oxoalkylcarbamate as a reaction intermediate have been recently disclosed by Jiang.[5e] In this context, concise catalytic methods for the direct synthesis of 4-substituted methylene oxazolidinones are presented as an atom economical and environmentally benign process using internal propargylic alcohols and isocyanates.

In the first series of experiments, to overcome the lower reactivity of internal propargylic alcohols compared to terminal ones,[5e] we investigated the cyclization reactions catalyzed by *N*-heterocyclic carbene catalysts, which are used for the activation of CO_2 in 1,3-dioxolan-2-ones synthesis with internal propargylic alcohols.[6] When the reaction was carried out with a catalytic amount (20 mol %) of triazolium catalyst **I** and DBU at 40 °C, a benzylidene oxazolidinone **2a** was obtained with 21% yield, accompanying a larger amount of carbamate intermediate **3a** (Table 1). Screening tests with imidazolium catalysts **II** and **III** revealed that 1,3-diisopropylimidazolium chloride and DBU co-catalyst efficiently catalyzed the oxazolidinone cyclization reactions. Based on these results, we performed a control experiment with only DBU base catalyst. Interestingly, we obtained highly effective synthesis of **2a** with 94% yield. It is noteworthy that previous reports on base-catalyzed oxazolidinone synthesis featured harsh conditions such as neat pyridine at 140 °C or two-step synthesis by *O*-propargyl carbamate formation (TEA/DMAP at 90 °C) followed by cyclization of the corresponding carbamates (LiOH in DMF). The use of weaker bases under identical conditions, as described in entries 7-9, was not efficient in terms of yield of **2a**, resulting in carbamate intermediate **3a** with unreacted propargylic alcohol substrate. Regarding the slightly different result with KO^{t}Bu in entry 10, we assume that the strong base completely and

Table 1. Optimization of conditions for benzylidene oxazolidinone synthesis[a]



Entry	Catalyst	Base	Temp. (°C)	Yield[b] (%)	Note[c]
1	**I**	DBU	40	21	**3a** (61)
2	**II**	DBU	40	79	
3	**III**	DBU	40	94	
4	**III**	TEA	40	6	**3a** (27)
5	–	DBU	40	94	
6[d]	–	DBU	r.t.	90	
7	–	DMAP	40	0[e]	**3a** (59)
8	–	DABCO	40	0[e]	**3a** (57)
9	–	TEA	40	0[e]	**3a** (35)
10	–	KO^{t}Bu	40	36[e]	**3a** (0)

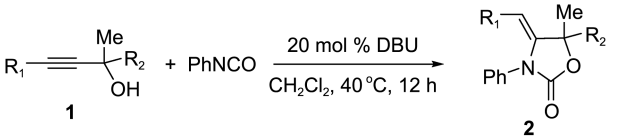
[a]Reactions and conditions: propargylic alcohol (**1a**: 0.4 mmol), PhNCO (0.6 mmol), NHC catalyst or base (0.08 mmol), CH_2Cl_2 (0.2 M), 12 h, under N_2, unless otherwise specified. [b]Isolated yield after chromatographic purification unless otherwise specified. [c]Carbamate intermediate was obtained (% yields in parentheses). [d]Reaction with 40 mol % of DBU in 20 h. [e]Determined by ^{1}H-NMR spectra.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

irreversibly deprotonated the alcohol protons, preventing the synthesis of carbamate **3a** and efficient proton shuttling.

Having identified the ideal conditions for the preparation of **2a**, we next investigated the synthesis of a variety of differently substituted oxazolidinones (Table 2). Preparation of the required internal propargylic alcohols was straightforward and was performed either by Sonogasira coupling with aryl iodide and 2-methyl-3-butyn-2-ol or alternatively via alkynylation with lithiated phenyl acetylene to various ketones. The presence of electron-donating groups conjugated to the triple bond led to an additional amount of PhNCO and DBU with an elongated reaction time (entries 2 and 3). The major isomer of the products was assigned by NOE measurement, and NOE interaction between the olefinic proton and methyl protons was used to identify the (*Z*)-configured isomer, indicating that addition to the alkynes proceeded predominantly in trans fashion. Internal propargylic alcohols containing electron-withdrawing halogen groups on an aryl ring were converted into corresponding oxazolidinones **2d-i** with good to excellent yield, and the reaction of substrate **1d** having a *p*-fluorophenyl group resulted in the exclusive formation of (*Z*)-isomer **2d** with 79% yield. Substrates bearing heterocycles such as thiophene and pyridine also were able to tolerate these reaction conditions (entries 10 and 11). We also examined the cyclization reaction involving substrates **1l** and **1m**, which have different spatial environment due to dialkyl substituents. These substrates also afforded the expected product with excellent yield, although introduction of the isopropyl substituent led to decreased reactivity, and therefore additional amounts of PhNCO, DBU, and DMF co-solvent were needed. We also found the reaction with terminal propargylic alcohol **1n** underwent uneventfully to afford 4-*methylene*-1,3-oxazolidin-2-one.

Table 2. DBU catalyzed arylidene oxazolidinone synthesis: substrate scope[a]



1 2

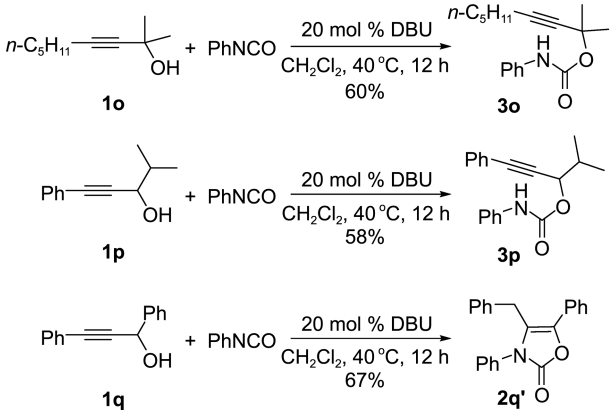
Entry	R_1	R_2	Product	*Z*/*E*[b]	Yield[c]
1	Ph	Me	**2a**	86:14	94
2[d]	4-MeC_6H_4	Me	**2b**	96:4	71
3[de]	4-MeOC_6H_4	Me	**2c**	90:10	36
4	4-FC_6H_4	Me	**2d**	>99:1	79
5	4-ClC_6H_4	Me	**2e**	78:22	86
6	4-BrC_6H_4	Me	**2f**	64:36	91
7	2-ClC_6H_4	Me	**2g**	69:31	79
8	3-ClC_6H_4	Me	**2h**	54:46	72
9	4-Cl-2-F-C_6H_4	Me	**2i**	63:37	89
10[f]	2-thienyl	Me	**2j**	>99:1	93
11	2-pyridyl	Me	**2k**	62:38	58
12	Ph	^{n}Pr	**2l**	76:24	93
13[de]	Ph	^{i}Pr	**2m**	63:37	95
14	H	Et	**2n**	–	96

[a]Reactions and conditions: propargylic alcohol (0.4 mmol), PhNCO (0.6 mmol), DBU (0.08 mmol), CH_2Cl_2 (0.2 M), 40 °C, 12 h, under N_2, unless otherwise specified. [b]Determined by ^{1}H-NMR of isolated product mixture. [c]Isolated yield of non-isolable *E*/*Z* isomers after chromatographic purification. [d]Reaction with 2 equiv of PhNCO and 40 mol % of DBU. [e]Reaction in CH_2Cl_2:DMF (4:1), 24 h. [f]Reaction in 5 h.

The substituents on the alkynyl and propargyl group delicately affected reactivity (Scheme 1). The reaction with *n*-butyl substituted alkyne **1o** resulted in the corresponding carbamate formation and this result can be understood by the lower reactivity of the electron-rich alkyne moiety toward the nucleophilic addition of the primary amine. Similar result obtained with secondary propargylic alcohols suggest that dialkyl substituents on the propargyl group were indispensible to the further cyclization of corresponding carbarmate intermediates. Cleanly obtained carbamates **3o-p** could be subjected to transition metal-catalyzed reactions to expand the substrate scaffold.[4] Interestingly, secondary propargylic alcohol with phenyl substituent (**1q**) could react smoothly under the given reaction conditions, and it is noteworthy that the obtained product was 4-benzyl-5-phenyloxazol-2-one (**2q'**), the isomer of 4-benzylideneoxazolidin-2-one.[5d]

Based on our experimental findings, a plausible mechanism for this oxazolidinone synthesis is conceived by the dual role of DBU base as follows: The carbamate intermediate is formed by an initial nucleophilic addition of the anionic oxygen of propargylic alcohol to the electrophilic carbon of isocyanate. The consecutive cyclization of carbamate intermediate is catalyzed by DBU-H^+ as a π-activator toward the alkyne moiety. The dual role of the conjugate acid (DBU-H^+) as a Brönsted acid and an alkyne-activator could give an account for the formation of the minor product, (*E*)-isomer, by the proximity effect.[7]

In summary, we have demonstrated that DBU base can serve as a potent catalyst for the synthesis of undiscovered arylidene oxazolidinones, and can be used for cyclization of internal propargylic alcohols and isocyanates in a mild one-step synthesis. In particular, the use of DBU has a significant advantage in oxazolidinone formation relative to previously reported basic conditions. Enantioselective hydrogenation of oxazolidinone products could build a wide vast of chiral synthons in asymmetric organic transformations.[8] The knowledge gained from base-catalyzed cyclization using iso-



Scheme 1. Substituent effect on the carbamate formation and cyclization reactions

cyanates is expected to contribute to the development of efficient nucleophilic catalysts for various heterocyclic ring formation reactions.

Experimental Section

General Procedure for Oxazolidinone Synthesis. Internal propargylic alcohol (0.4 mmol) in distilled CH_2Cl_2 (0.2 M) was treated with PhNCO (0.6 mmol) and DBU (0.08 mmol) at 40 °C under N_2 atmosphere. After stirring for 12 hours, the reaction mixture was concentrated and purified by silica column chromatography.

2a: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.06-6.98 (m, 5H), 6.90-6.82 (m, 3H), 6.66 (d, 2H, J = 6.6 Hz), 5.63 (s, 1H), 1.74 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.3, 142.3, 134.9, 133.2, 129.5, 128.3, 128.21, 128.17, 127.1, 127.0, 126.89, 126.86, 125.8, 125.7, 99.8, 83.1, 28.2; MS *m/z* (EI, relative intensity) 279 (M^+, 100), 234 (17), 220 (28), 132 (96), 117 (50); HRMS (EI) calcd for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1257.

2b: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.06-7.01 (m, 5H), 6.66 (d, 2H, J = 7.9 Hz), 6.54 (d, 2H, J = 7.9 Hz), 5.59 (s, 1H), 2.15 (s, 3H), 1.72 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.3, 141.6, 135.4, 135.0, 130.2, 128.15, 128.11, 127.9, 127.7, 126.7, 125.7, 99.9, 83.1, 28.2, 21.0; MS *m/z* (EI, relative intensity) 293 (M^+, 100), 278 (3), 248 (12), 234 (41), 146 (95), 131 (48); HRMS (EI) calcd for $C_{19}H_{19}NO_2$ (M^+) 293.1416, found 293.1418.

2d: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25-7.06 (m, 3H), 7.00-6.97 (m, 2H), 6.64-6.51 (m, 4H), 5.57 (s, 1H), 1.72 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.5, 159.3, 155.2, 142.6, 134.7, 129.8, 129.7, 129.3, 129.2, 128.3, 127.1, 125.9, 114.1, 113.8, 98.5, 83.1, 28.2; MS *m/z* (EI, relative intensity) 297 (M^+, 100), 252 (15), 238 (29), 165 (63), 150 (98), 135 (53); HRMS (EI) calcd for $C_{18}H_{16}FNO_2$ (M^+) 297.1165, found 297.1167.

2j: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.20-7.10 (m, 5H), 6.93 (d, 1H, J = 5.1 Hz), 6.50-6.48 (m, 1H), 5.99 (d, 1H, J = 3.7 Hz), 5.60 (s, 1H), 1.72 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.1, 142.7, 135.2, 129.9, 128.4, 127.3, 126.5, 125.9, 124.6, 92.5, 83.2, 28.1; MS *m/z* (EI, relative intensity) 285 (M^+, 100), 240 (7), 226 (20), 138 (94), 123 (31); HRMS (EI) calcd for $C_{16}H_{15}NO_2S$ (M^+) 285.0823, found 285.0815.

3a: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48-7.41 (m, 4H), 7.39-7.26 (m, 5H), 7.08-7.02 (m, 1H), 6.58 (br s, 1H), 1.84 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.6, 137.9, 131.8, 129.0, 128.3, 128.1, 123.2, 122.5, 118.5, 90.3, 84.0, 73.2, 29.3; MS *m/z* (EI, relative intensity) 279 (M^+, 2), 235 (3), 220 (4) , 160 (3), 143 (100), 128 (26); HRMS (EI) calcd for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1264.

3o: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 (d, 2H, J = 7.7 Hz), 7.30 (d, 2H, J = 7.7 Hz), 7.06-7.01 (m, 3H), 6.53 (br s, 1H), 2.21 (t, 2H, J = 7.1 Hz), 1.72 (s, 6H), 1.58-1.49 (m, 3H), 1.40-1.24 (m, 4H), 0.88 (t, 3H, J = 6.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.7, 138.1, 129.0, 123.1, 118.5, 84.9, 81.4, 73.4, 31.0, 29.6, 28.3, 22.2, 18.7, 14.0.

3p: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48-7.40 (m, 4H), 7.34-7.29 (m, 5H), 7.07 (t, 1H, J = 7.3 Hz), 6.71 (br s, 1H), 5.52 (d, 1H, J = 5.5 Hz), 2.19-2.13 (m, 1H), 1.29-1.25 (m, 1H), 1.13 (d, 3H, J = 6.8 Hz), 1.10 (d, 3H, J = 7.0 Hz).

2q': ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (d, 2H, J = 7.1 Hz), 7.43-7.31 (m, 7H), 7.23-7.21 (m, 2H), 7.12-7.07 (m, 2H), 7.01-6.98 (m, 2H), 3.93 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.1, 136.4, 135.8, 133.1, 130.0, 129.4, 129.1, 128.95, 128.87, 128.8, 128.4, 128.2, 127.9, 127.8, 127.7, 127.0, 124.9, 121.8, 104.3, 29.7.

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