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Synthesis of *N*-substituted-4-methylene-oxazolidinones via base-catalyzed cyclization of propargylic alcohols with *p*-toluenesulfonyl isocyanate

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Abstract

A practical method is developed for the synthesis of oxazolidinone derivatives, an important class of heterocyclic compounds. The effect of bases and solvents on this cyclization reaction is discussed and a simple new base–solvent system (triethylamine in toluene) is found to be the most effective. The reaction conditions developed here are mild and no by-products are observed. Moreover, using optimized conditions, a number of differently substituted propargylic alcohols are cyclized to the corresponding *N*-substituted-4-methylene-oxazolidinones in yields of up to 99%.

Keywords

base-catalyzed, cyclization, oxazolidinones, propargylic alcohols, *p*-toluenesulfonyl isocyanate

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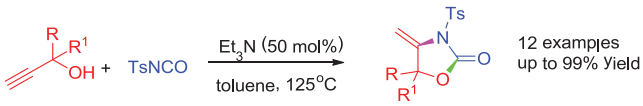

Introduction

Oxazolidinones, an important class of heterocyclic compounds, are ubiquitous in natural products and materials. As important intermediates in organic synthesis, they are widely used to construct the skeletons of diverse pharmaceuticals.[1–4] Among the numerous oxazolidinones, *N*-substituted-4-methylene-oxazolidinones usually show excellent antibacterial and anticancer properties. Consequently, there is increasing interest being paid toward the synthesis of *N*-substituted-4-methylene-oxazolidinones.[5–11] Most of these approaches are focused on nucleophilic cyclization via transition-metal-catalyzed strategies. However, the high catalyst loading in some of these processes results in a high economic cost.[12–16] In addition, the residual heavy transition metals in the final products also present a major problem. Therefore, the development of efficient strategies and transition-metal-free processes for the assembly of oxazolidinones is an important target in organic synthesis.

The transformation of alkynes via nucleophilic addition, especially for oxygen or nitrogen heteroatoms, is endowed with great synthetic value. Although this strategy has been used to construct oxazolidinone derivatives through intermolecular or intramolecular nucleophilic addition of acetylenic triple bonds with nitrogen components, examples are still scarce. Zhang and co-workers[17] reported a new route for the synthesis of *N*-substituted-4-methylene-oxazolidinones via the carbonylation of propargylic alcohols with amines using

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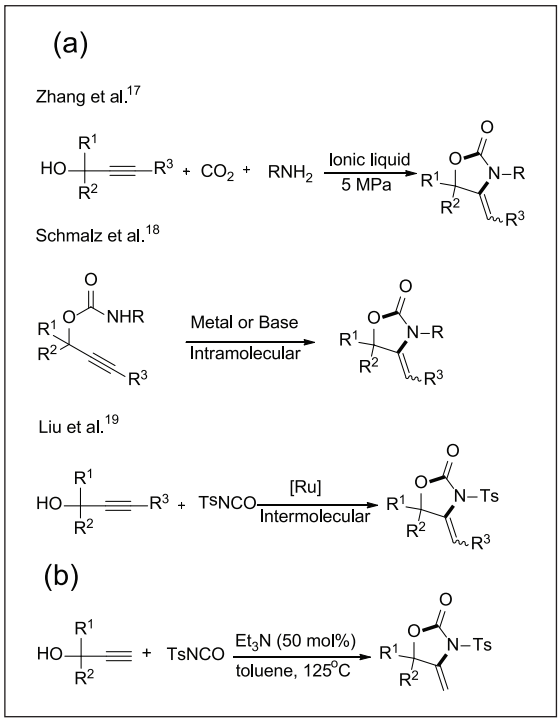


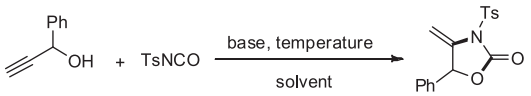
Scheme 1. Synthesis of *N*-substituted-4-methylene-oxazolidinones: (a) Previous work and (b) this work.

CO_2 as the carbonyl source under high pressure, high temperature, and in the presence of ionic liquids. The reaction occurs via intramolecular nucleophilic addition of the acetylenic triple bond with the amino component (Scheme 1(a)). Schmalz et al.[18] have provided some simple routes to furnish *N*-substituted-4-methylene-oxazolidinones via cyclization of *o*-propargyl carbamates under palladium, gold, and base-catalyzed conditions (Scheme 1(a)). Liu et al.[19] have developed transition-metal-catalyzed protocols for producing oxazolidinones via domino intermolecular nucleophilic addition between propargylic alcohols and *p*-toluenesulfonyl isocyanate. Herein, we describe a facile, one-pot preparation of 4-alkylideneoxazolidinones having an *N*-tosyl group. The reactions proceed under mild conditions in good yields starting from propargylic alcohols and *p*-toluenesulfonyl isocyanate in the presence of a catalytic amount of triethylamine (Scheme 1(b)). This proved to be an efficient method for preparing oxazolidinones by *exo*-cycloisomerization of propargylic carbamates catalyzed by a base.

Results and discussion

Initially, the cyclization of 1-phenylprop-2-yn-1-ol (see the Supporting Information for details) (**1a**) with *p*-toluenesulfonyl isocyanate (**2**) was selected for optimization of the reaction conditions. As shown in Table 1, our investigation started with the attempted cyclization of substrate **1a** with **2** in toluene at 125°C in the presence of KO*t*Bu as the base in a sealed Schlenk tube, leading to the desired product **3a** 59% isolated yield (entry 1). This result encouraged us to develop a transition-metal-free system to synthesize oxazolidinones. A series of other bases were tested; however, K_2CO_3 and 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) did not give the desired product

Table 1. Optimization of the reaction conditions.[a]



1a 2 3a

Entry	Base	Solvent	Temperature (°C)	Yield (%)[b]
1	KO*t*Bu	Toluene	125	59
2	K_2CO_3	Toluene	125	Trace
3	DBU	Toluene	125	Trace
4	DABCO	Toluene	125	75
5	Et_3N	Toluene	125	98
6	DIPEA	Toluene	125	95
7	Et_3N	DCE	125	96
8	Et_3N	THF	125	45
9	Et_3N	Toluene	100	95
10	Et_3N	Toluene	80	33

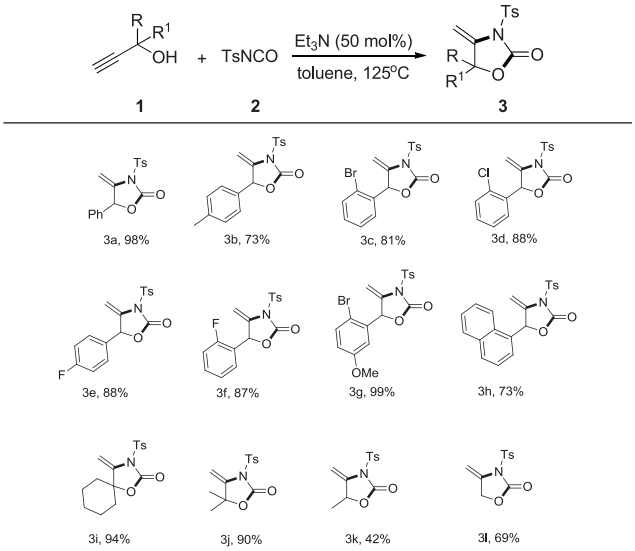
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DABCO: 1,4-diazabicyclo[2.2.2] octane; DIPEA: *N, N*-diisopropylethylamine; DCE: 1,2-dichoroethane; THF: tetrahydrofuran.
[a]Reaction conditions: **1a** (0.30 mmol), **2** (0.45 mmol), base (50 mol%), solvent (2 mL), Ar atmosphere.
[b]Isolated yield.

(entries 2 and 3). Next, 1,4-diazabicyclo[2.2.2] octane (DABCO), Et_3N, and *N, N*-diisopropylethylamine (DIPEA) were examined as bases (entries 4–6). Surprisingly, Et_3N was found to give the best result with a 98% yield of **3a** being obtained (entry 5). In light of these results, solvents such as 1,2-dichoroethane (DCE) and tetrahydrofuran (THF) were screened (entries 7 and 8). A 96% yield of **3a** was obtained when DCE was used, while a 45% yield of **3a** was afforded in THF. The results indicated that toluene was the best solvent for this cyclization. Among the reaction temperatures tested, relatively low yields were obtained when the reaction was carried out at 100°C and 80°C (entries 9 and 10). Thus, the optimized reaction conditions were as follows: **1a** (0.30 mmol), **2** (0.45 mmol), Et_3N (0.5 equiv.), toluene (2 mL), 125°C.

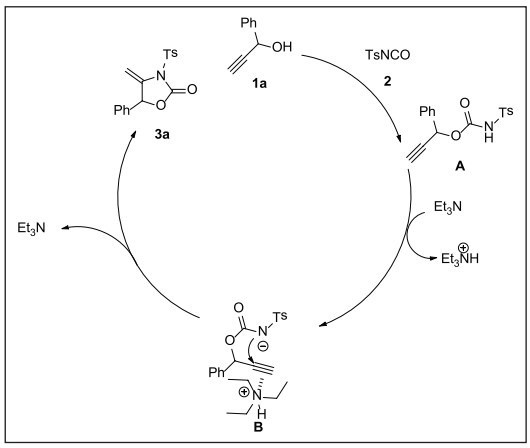
With optimized conditions in hand, the scope of the cyclization of *p*-toluenesulfonyl isocyanate with various propargylic alcohols was investigated, and the results are summarized in Table 2. First, a number of 1-arylprop-2-yn-1-ols were evaluated, and they were all found to be suitable substrates for the cyclization with *p*-toluenesulfonyl isocyanate (**2**) under the standard conditions. For instance, when substrate **1b** bearing a methyl group was treated with **2** and Et_3N at 125°C, oxazolidinone **3b** was formed in 73% yield. Substrates **1c–g** containing halo and methoxy groups were also well tolerated under the same conditions. Subsequently, the reaction of **1h** with **2** was conducted smoothly in 73% yield under the optimized conditions. We were happy to observe that 1-cyclohexylprop-2-yn-1-ol (**1i**) could also react with **2** efficiently in 94% yield. 2-Methylbut-3-yn-2-ol (**1j**) was treated with **2** to afford the corresponding product **3j** in 90% yield. A 42% yield of 5-methyl-4-methylene-3-tosyloxazolidin-2-one (**3k**) was obtained in the reaction of substrate **1k** with **2**. Finally, 4-methylene-3-tosyloxazolidin-2-one (**3l**) was obtained in 69% yield.

Based on the above results and previous reports, a proposed reaction mechanism is shown in Scheme 2. First,

Table 2. Screening the scope of propargylic alcohols **1**.[a]



[a]Reaction conditions: **1** (0.30 mmol), **2** (0.45 mmol), Et_3N (50 mol%), toluene (2 mL), 125°C, Ar atmosphere, 8 h.



Scheme 2. Proposed mechanism.

1-phenylprop-2-yn-1-ol (**1a**) undergoes addition with *p*-toluenesulfonyl isocyanate (**2**) to yield intermediate **A**. Next, the amine proton of **A** is abstracted by Et_3N to produce intermediate **B**. Subsequent, intramolecular nucleophilic addition of the nitrogen anion to the acetylenic triple bond via *exo*-cycloisomerization with the protonation yields oxazolidinone **3a**.

Conclusion

In conclusion, we have developed a mild and general cascade reaction of propargylic alcohols with *p*-toluenesulfonyl isocyanate for the synthesis of *N*-substituted-4-methyleneoxazolidinones. In the presence of a base–solvent system (triethylamine in toluene), a broad range of propargylic alcohols was tolerated in the present method. Notably, oxazolidinones are an important skeleton in natural products and exhibit a broad range of biological activities. Further work to probe the detailed mechanism and apply this reaction in organic synthesis is currently underway.

Experimental

Typical experimental procedure for the synthesis of 4-methylene-5-phenyl-3-tosyloxazolidin-2-one (**3a**)[20]:

A dried 25 mL Schlenk tube equipped with a stir bar was loaded with **1a** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv.), Et_3N (0.1 mmol, 0.5 equiv.), and toluene (2 mL) under an Ar atmosphere. The mixture was then stirred under argon at 125°C for 8 h. After cooling to room temperature and concentrating in vacuum, the residue was purified through column chromatography to afford the pure product. Yellow solid, m.p.: 69–72°C, 1H NMR (nuclear magnetic resonance) (500 MHz, $CDCl_3$, 25°C): $\delta = 7.96$ (d, $J = 8.0$ Hz, 2H), 7.32–7.38 (m, 5H), 7.17 (d, $J = 7.0$ Hz, 2H), 5.78 (t, $J = 4.0$ Hz, 1H), 5.61 (t, $J = 5.5$ Hz, 1H), 4.37–4.38 (m, 1H), 2.46 (s, 3H); 13C NMR (125 MHz, $CDCl_3$, 25°C): $\delta = 150.8, 146.3, 139.3, 135.7, 134.1, 129.9, 129.8, 128.9, 128.0, 127.0, 93.8, 80.1, 21.6$; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO_4S$ $[M + H]^+$: 330.0790, found: 330.0803.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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