A Catalyst-Free, Convenient Construction of Eight-Membered [1,4]Oxazocane-5,8-dione Heterocycles from Aminoethanols with Divinyl Succinate

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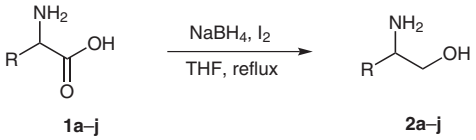
Abstract: A convenient protocol for the synthesis of [1,4]oxazocane-5,8-dione heterocycles by direct cyclization using 2-substituted aminoethanols and divinyl succinate without any catalysts and additives was established. This strategy is quite simple and effective to obtain eight-membered rings incorporating lactone and lactam functional groups.

Key words: aminoethanol, divinyl succinate, catalyst-free, [1,4]oxazocane-5,8-dione, cyclization

The preparation of medium-sized heterocycles has attracted much attention due to their wide applications such as biologically active natural products,[1] drug candidates,[2] materials,[3] and catalyst.[4] For example, many eight-membered heterocycles are very common in submarine species[5] or in drugs.[6] Approaches for the synthesis of eight-membered heterocycles were mostly available based on ring expansion,[7] ring-closing metathesis,[8] transannular cyclizations,[9] and metal-mediated ring cyclization.[10] However, the convenient construction of these heterocycles incorporating one or more heteroatoms remains a synthetic challenge for organic chemists.[11]

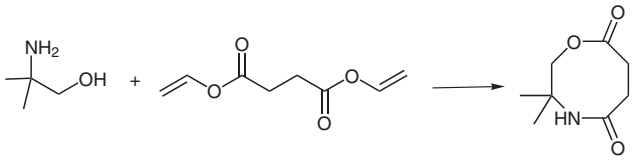
Eight-membered [1,4]oxazocane-5,8-dione heterocycles bearing oxazocane functional group are important intermediates of natural products[12] and expected to possess potent biological activities such as NK1 antagonists and non-narcotic analgesic drugs.[13] To date, a few approaches for the construction of the [1,4]oxazocane-5,8-dione heterocycles have been established. Aly[14] reported a strategy involving reaction of diethyl phthalate with *N*-tosyl-2-aminophenol derivatives to generate [1,4]oxazocane-5,8-dione heterocycles. Assoumatine and co-workers[12] reported analogous reactions of a succinate diester with amino alcohol derivatives through a multiple and complex process. Banfi and co-workers[15] transformed pyrroline derivatives into 2,5-functionalized pyrrolidines, which allowed an access to medium-sized bicyclic heterocycles by lactonization. However, no literature for the synthesis of medium-sized ring systems by simply direct cyclization reactions without any catalyst has been reported. Herein, we prepared a series of eight-membered heterocycles via catalyst-free cyclization reaction, which provided a convenient route for obtaining functionalized [1,4]oxazocane-5,8-dione heterocycles in moderate to high yields.

The starting aminoethanol derivatives were easily accessible from commercial amino acids using $NaBH_4$ and I_2 according to the routes previously reported (Scheme 1).[16] The pure aminoethanol analogues were obtained in yields ranging from 78% to 86% after purification by column chromatography.



1a–j 2a–j

Scheme 1 Reduction of amino acids. *Reagents and conditions*: $NaBH_4$, I_2, THF, reflux.



2a 3 4a

Scheme 2 Reaction of 2-amino-2-methyl-1-propanol with divinyl succinate

The reaction of 2-amino-2-methyl-1-propanol (**2a**) with divinyl succinate (**3**) was investigated in DMSO at 110 °C without any catalyst and additive (Scheme 2). The expected product was obtained after four hours and was characterized by ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and two-dimensional NMR techniques (HMQC). The structure was confirmed as an eight-membered heterocycle 3,3-dimethyl-[1,4]oxazocane-5,8-dione (**4a**).[17]

The reaction conditions were optimized using 2-amino-2-methyl-1-propanol (**2a**) as a model substrate (Scheme 2). Solvent often plays an important role in the reaction due to their different polarity and solubility of the reactant or product. Six conventional organic solvents were screened for the reaction of **2a** with divinyl succinate. The results (Figure 1) showed that highly polar solvents (DMSO and DMF), which enhanced the nucleophilicity of **2a** by hydrogen bond formation with the polar solvent,[18] efficiently promoted the reaction and a moderate yield of **4a** was obtained. In contrast, less polar or nonpolar solvents such

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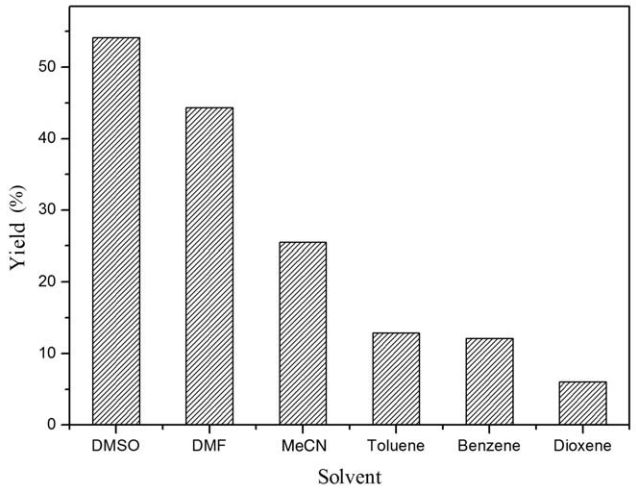


Figure 1 Influence of organic solvents on the yield of 2-amino-2-methyl-1-propanol with divinyl succinate. *Reagents and conditions*: 2-amino-2-methyl-1-propanol (2.5 mmol), divinyl succinate (3.0 mmol), organic solvent (5 mL), 80 °C, 6 h.

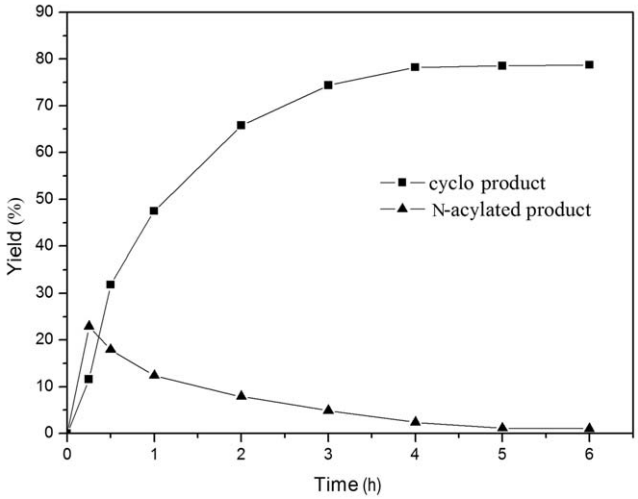


Figure 3 Time course of the reaction of 2-amino-2-methyl-1-propanol and divinyl succinate. *Reagents and conditions*: 2-amino-2-methyl-1-propanol (2.5 mmol), divinyl succinate (3.0 mmol), DMSO (5 mL).

as acetonitrile, dioxane, benzene, and toluene resulted in poor yields of **4a**. Therefore, DMSO was selected as solvent for the following reaction.

The influence of temperature on the reaction was investigated. The results are shown in Figure 2. When **2a** was treated with divinyl succinate in DMSO at different temperature ranged from 60 °C to 110 °C for two hours, the yield of **4a** increased from 28% to 55% (HPLC). When the temperature increased from 110 °C to 140 °C, there was no obvious influence on the yield. It showed that the reaction proceeded efficiently at 110 °C.

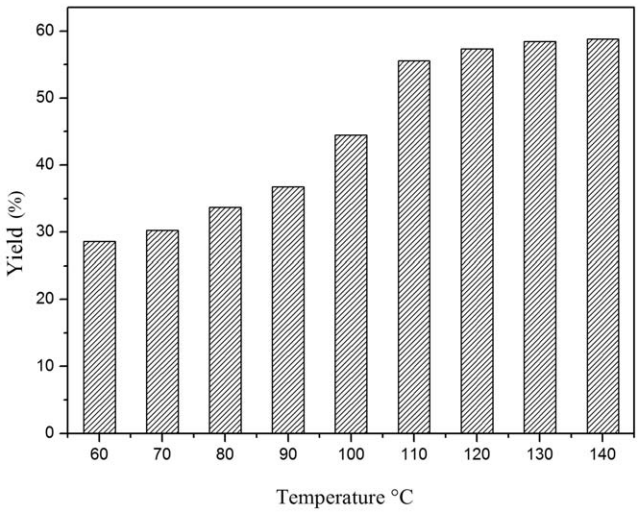
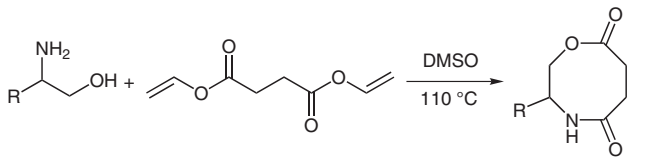


Figure 2 Influence of temperature on the yield of 2-amino-2-methyl-1-propanol with divinyl succinate. *Reagents and conditions*: 2-amino-2-methyl-1-propanol (2.5 mmol), divinyl succinate (3.0 mmol), DMSO (5 mL).

The time course of the reaction was also investigated. As shown in Figure 3, the whole reaction consisted of two steps, the N-acylation and O-acylation. It is well known that amines are more active than alcohols as nucleophiles. In fact, only the chain compound of N-acylation was detected and no chain product of O-acylation was observed during the reaction. Then the chain compound of N-acylation was followed by an intramolecular O-acylation reaction and transformed into cycloproduct 3,3-dimethyl-[1,4]oxazocane-5,8-dione (**4a**). The reaction reached equilibrium after four hours with 78% yield.

Table 1 Reaction of 2-Substituted Aminoethanol Derivatives with Divinyl Succinate in DMSO[a]



2a–k **4a–k**

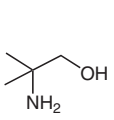
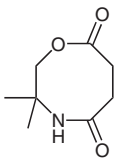
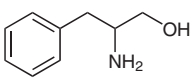
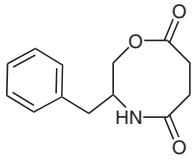
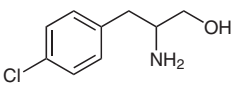
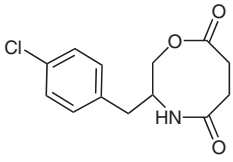
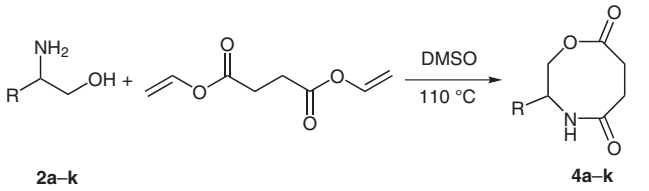
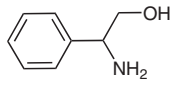
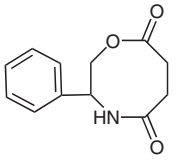
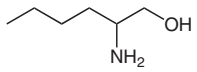
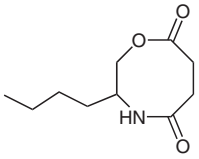
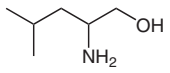
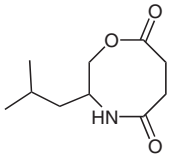
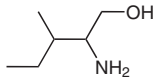
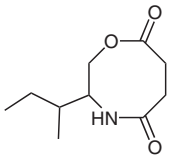
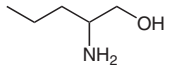
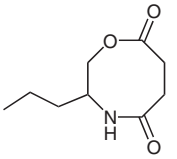
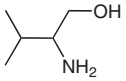
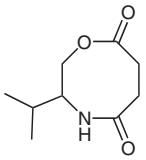
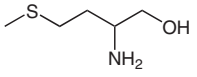
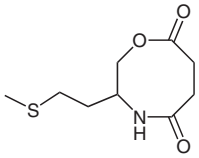
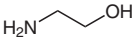
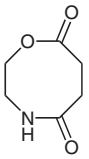
Entry	Substrate **2**[19]	Product **4**	Yield (%)[b]
1			73 (**4a**)
2			77 (**4b**)
3			67 (**4c**)

Table 1 Reaction of 2-Substituted Aminoethanol Derivatives with Divinyl Succinate in DMSO[a] (continued)



2a–k **4a–k**

Entry	Substrate **2**[19]	Product **4**	Yield (%)[b]
4			68 (**4d**)
5			75 (**4e**)
6			78 (**4f**)
7			69 (**4g**)
8			75 (**4h**)
9			72 (**4i**)
10			83 (**4j**)
11			61 (**4k**)

[a] Reagents and conditions: 2-substituted aminoethanols (20 mmol), divinyl succinate (24 mmol) in DMSO (20 ml) at 110 °C for 4 h.
[b] Isolated yield.

Next, the influence of chain length of divinyl dicarboxylates and the different diester dicarboxylates on the ring closure reaction with **2a** under identical reaction conditions was examined. Three divinyl dicarboxylates including divinyl succinate, divinyl adipate, and divinyl sebacate were investigated. Only divinyl succinate afforded the cycloproduct after four hours, while chain compounds of N-acylation were observed from the reaction between the other two divinyl dicarboxylates and **2a** after six hours. Furthermore, two diester dicarboxylates, dimethyl succinate and dimethyl adipate, were tested. After 24 hours no product was detected. The results showed that divinyl dicarboxylates and diester dicarboxylates with longer chains were unfavorable for the direct ring-closure reaction.

We then examined the generality of these conditions to other substrates. Results were summarized in Table 1. The reactions of three aromatic substituted aminoethanols with divinyl succinate were examined (entries 2–4, Table 1). 2-Benzyl aminoethanol generated the 3-benzyl-[1,4]oxazocane-5,8-dione in 77% yield. Compared with 2-benzyl aminoethanol, 2-(4-chlorobenzyl) aminoethanol showed lower reactivity than divinyl succinate in 67% yield. It demonstrated that the electron-withdrawing effect had influence on the reaction. A similar observation was obtained from 2-phenyl aminoethanol. We then examined the reactions of different aliphatic substituted aminoethanols. The yields ranged from 69% to 78% (entries 5–9). The different aliphatic substituted groups play a minimal role in the yields of the reactions. The 2-amino-4-methylsulfanyl-butan-1-ol also could generate 3-(2-methylsulfanylethyl)-[1,4]oxazocane-5,8-dione (entry 10) with high yield of 83%. The results showed that this protocol proved to be effective to form the [1,4]oxazocane-5,8-dione scaffolds from different substrated aminoethanols.

In summary, an efficient and convenient method for synthesis of eight-membered [1,4]oxazocane-5,8-dione derivatives was established. It is noteworthy that the procedure does not require any catalyst and can be efficiently achieved via a simply direct cyclization. This study is of significance in the synthesis of the interesting family of [1,4]oxazocane-5,8-dione scaffolds.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **Typical Procedure for the Synthesis of 3,3-Dimethyl-[1,4]oxazocane-5,8-dione (4a)**
2-Amino-2-methyl-1-propanol (20 mmol) was dissolved in DMSO (20 mL) and the divinyl succinate (24 mmol) was added. The reaction mixture was stirred at 110 °C and monitored by TLC. Upon completion of the reaction, the reaction gave a yellow solution which was purified by column chromatography (hexane–EtOAc, 1:1) to obtain the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81 (d, 2 H, *J* = 5.6 Hz), 3.57 (br s, 1 H), 2.66 (s, 4 H), 1.48 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 69.2, 62.8, 28.6, 22.1 ppm. ESI-MS: *m/z* = 193.8 $[M + Na]^+$. IR: 3440 (NH amide), 1772 (C=O amide), 1696 (C=O ester) cm^{-1}.
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