Tetrahedron Letters 53 (2012) 342–344

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Sequential [3+2] cycloaddition/rearrangement reaction of imidazolone nitrones and allenoates for the efficient synthesis of functionalized imidazolidinone

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ARTICLE INFO

Article history:
Received 24 July 2011
Revised 7 November 2011
Accepted 10 November 2011
Available online 18 November 2011

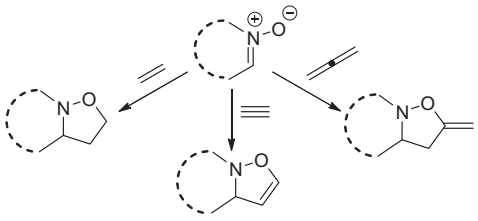
Keywords:
Cycloaddition
Rearrangement
Sequential reaction
Nitrone
Allenoate

ABSTRACT

Sequential [3+2] cycloaddition/rearrangement reaction of imidazolone nitrones and allenoates is described. The reaction was carried out in refluxing toluene to provide the methylene imidazolidinone derivatives in high yield. It provides a simple and convenient strategy for the synthesis of functionalized imidazolidinones.

1,3-Dipolar cycloaddition reaction is one of the most important methodologies and provides powerful tools for the synthesis of heterocycles from simpler starting materials.[1] Various 1,3-dipoles such as nitrone, azomethine ylide, azomethine imine, nitrile oxide, carbonyl ylide, azide, nitrile imine, carbonyl oxide, diazoalkane, and diazoacetate have been used for all kinds of target heterocycles.[1] Among these 1,3-dipoles, nitrone is a highly attractive one due to the extensive application of the corresponding cycloadduct.[2] Various dipolarophiles such as alkenes, alkynes, and allenes could undergo [3+2] cycloaddition with nitrones to furnish the useful heterocycles (Scheme 1).[2] The alkenes react with nitrones to give isoxazolidines. The alkynes undergo cycloaddition with nitrones to provide isoxazolines. The allenes have similar reaction mode as alkenes, leading to methylene isoxazolidine derivatives. While the cycloadditions of alkenes or alkynes and nitrones are widely used in organic synthesis, only a few examples of 1,3-dipolar cycloaddition of nitrones and allenoates have been reported to date.[3] Allenes contain highly valuable 1,2-propadiene system and are extremely versatile synthetic building blocks in modern synthetic chemistry.[4] Both C=C bonds are active positions for dipolar attack which can proceed with two opposite orientations, especially, allenes possessing electron-withdrawing substituents are very active to undergo dipolar cycloaddition. Generally, one of two C=C bonds in the functionalized allenes conducts the [3+2] cycloaddition to afford methylene isoxazoline derivatives, which can carry out rearrangement to provide new heterocyclic skeleton. By using this sequential reaction strategy, some very interesting heterocycles could be synthesized. For example, Padwa has used several electron-deficient allenes such as (phenylsulfonyl) allene to perform the [3+2] cycloaddition with nitrone, giving rise to the desired 5-exo-methylene substituted isoxazolidines, which underwent smooth rearrangement on thermolysis to produce 3-pyrrolidinones in high yield.[5] In order to develop this kind of sequential reaction to synthesize useful heterocycle molecules, we have explored the reactions between nitrones and allenes. Herein, we describe sequential [3+2] cycloaddition/rearrangement reaction of imidazolone nitrones with allenoates to furnish functionalized imidazolidinone (Scheme 2).

The imidazolone nitrones have extensively been utilized as 1, 3-dipoles in the cycloaddition reaction for the synthesis of various



Scheme 1. Classic [3+2] cycloaddition of nitrones with alkenes, alkynes, and allenes.

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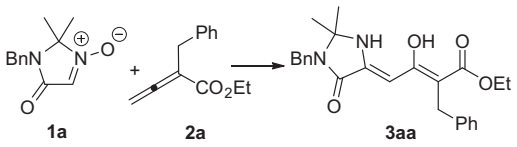
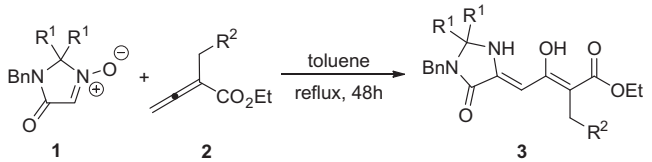
doi:10.1016/j.tetlet.2011.11.049



Scheme 2. The reaction was performed for screening reaction conditions.

Table 1
Sequential cycloaddition/rearrangement of imidazolone nitrones (**1**) and allenoates (**2**)[a]



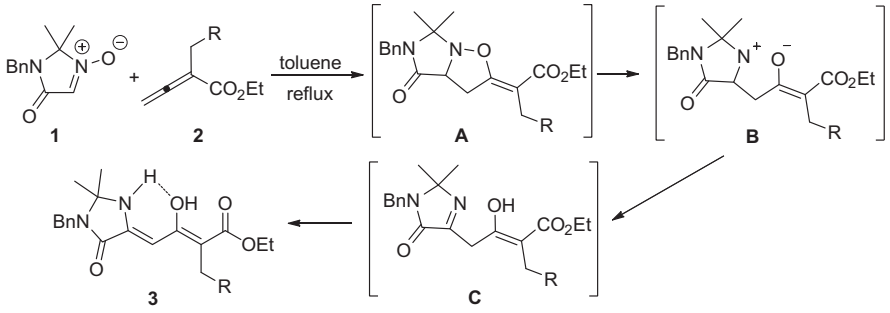
Entry	R^1	R^2	Product	Yield[b] (%)
1	Me (**1a**)	Ph (**2a**)	**3aa**	89
2	Me(**1a**)	2-MeC_6H_4 (**2b**)	**3ab**	81
3	Me(**1a**)	3-MeC_6H_4 (**2c**)	**3ac**	74
4	Me(**1a**)	4-MeC_6H_4 (**2d**)	**3ad**	81
5	Me (**1a**)	2-FC_6H_4 (**2e**)	**3ae**	73
6	Me (**1a**)	3-FC_6H_4 (**2f**)	**3af**	72
7	Me (**1a**)	4-FC_6H_4 (**2g**)	**3ag**	77
8	Me (**1a**)	2-ClC_6H_4 (**2h**)	**3ah**	82
9	Me (**1a**)	3-ClC_6H_4 (**2i**)	**3ai**	74
10	Me (**1a**)	4-ClC_6H_4 (**2j**)	**3aj**	80
11	Me (**1a**)	2-BrC_6H_4 (**2k**)	**3ak**	71
12	Me (**1a**)	3-BrC_6H_4 (**2l**)	**3al**	75
13	Me (**1a**)	4-BrC_6H_4 (**2m**)	**3am**	84
14	Me (**1a**)	H (**2n**)	**3an**	80
15	Me (**1a**)	Me (**2o**)	**3ao**	76
16	Me (**1a**)	Et (**2p**)	**3ap**	74
17	Et (**1b**)	Ph (**2a**)	**3ba**	70
18	*n*-Pr (**1c**)	Ph (**2a**)	**3ca**	66

[a] 5 equiv of allenoate were used. The excess allenoate was recovered by flash column chromatography.
[b] Isolated yield.

heterocyclic compounds.[6] Our initial attempts at the reaction of imidazolone nitrones with allenoates commenced with the reactions of 1-benzyl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-imidazole 3-oxide (**1a**) (Scheme 2). The imidazolone nitrone (**1a**) was treated with 2 equiv of ethyl 2-benzylbuta-2,3-dienoate (**2a**) in dichloromethane at room temperature. No new product was observed. The reaction was carried out in ethanol and benzene respectively, although the reaction mixture had been stirred at 80 °C for 120 h, the nitrone could not be consumed and no product was obtained. Considering that the reaction might need higher temperature to complete, the reaction was carried out in refluxing toluene for 48 h.[7] To our delight, the new product was obtained in a 58% yield. In order to improve the yield, 3, 4, 5, and 6 equiv of allenoate (**2a**) were used respectively, the corresponding 63%, 80%, 89%, and 90% yield was obtained. Obviously, the reaction yield was significantly improved with increased amount of allenoate. The excess allenoate probably drives first step of [3+2] cycloaddition to completion. However, 4–6 equiv of allenoate is too much for a practical reaction. Fortunately, the excess allenoate could be recovered in about an 80% yield by flash column chromatography and reused in the next case. Therefore, in next experiments, all reactions of imidazolone nitrones were carried out in refluxing toluene in the presence of 5 equiv of allenoates. By using ^{1}H NMR, ^{13}C NMR, and 2D NMR, the structure of new product was determined to be (*Z*)-methylene imidazolidinone (**3aa**), which was formed from the sequential cycloaddition/rearrangement reaction of imidazolone nitrone (**1a**) and allenoate (**2a**). The hydrogen-bond between hydroxyl and amine group stabilizes the product, favoring the (*Z*)-configuration of alkene.

A range of allenoates and three imidazolone nitrones were examined in the sequential cycloaddition/rearrangement reaction under the optimized reaction conditions (Table 1). A variety of allenoates underwent the sequential reaction with imidazolone nitrone (**1a**), providing the anticipated functionalized imidazolidinone in good to excellent yields (entries 1–16). Since the R^2 in allenoate is far away from the reacted double bond, the electron-donating or withdrawing substituent on benzene ring of aryl did not exert much influence on the course of the reaction. A variety of aryl-substituted allenoates underwent the reaction at reasonable rates (entries 1–13). After successful evaluation of the sequential reaction of aromatic allenoates with nitrone (**1a**), we were delighted to find out that aliphatic allenoates could also carry out the reaction in the refluxing toluene (entries 14–16). The sequential reaction of the aliphatic allenoate provided the corresponding products in comparable yields as aromatic allenoates. Two variants (**1b** and **1c**) of imidazolone nitrone (**1a**) worked well too, affording the corresponding products in satisfactory yields (entries 17–18). Since (*Z*)-methylene imidazolidinone products could be further functionalized, the sequential cycloaddition/rearrangement reaction would provide a generally applicable procedure for the synthesis of imidazolidinone derivatives, which are the key units of natural products and drug candidates.[8]

On the basis of the reported mechanistic studies,[5] the methylene isoxazoline derivatives from the reaction of nitrone and allene often underwent radical rearrangement under heated conditions. However, when the radical scavenger (1,4-dinitrobenzene) or radical inhibitor (hydroquinone) was used in the reaction, the sequential cycloaddition/rearrangement reaction could not be inhibited and the corresponding product was obtained in the nearly same yield as that in the absence of radical scavenger or inhibitor. According to this observation, a plausible pathway for the sequential reactions of the nitrone **1** and the allenoates **2** was presented in



Scheme 3. Postulated mechanism for sequential cycloaddition/rearrangement reaction.

Scheme 3. At high temperature, the allenoate and nitrone carry out [3+2] cycloaddition to give methylene tetrahydroimidazo [1,5-*b*]isoxazol-4(2*H*)-one **A**. Due to the thermal instability of **A**, a heterolytic cleavage of the N–O bond of **A** generates a zwitterionic intermediate **B**. Subsequent isomerization gives rise to the intermediate **C**. It undergoes rearrangement to lead to the formation of the final product **3**, which was stabilized by the hydrogen bond between amine and hydroxyl.

In conclusion, a simple and convenient strategy for the synthesis of functionalized imidazolidinones via sequential [3+2] cycloaddition/rearrangement reaction of imidazolone nitrones and allenoates has been developed. Using this method a range of functionalized imidazolidinones have been prepared from readily available starting materials. A variety of allenoates with various substituents are tolerated under the reaction conditions.

Acknowledgments

This work was financially supported by the startup research funding of China Agricultural University, Chinese Universities Scientific Fund (Nos. 2011JS029 and 2011JS031), the National Scientific and Technology Supporting Program of China (No. 2011BAE06B05-5), the National Natural Science Foundation of China (No. 21172253), the Key Technologies R&D Program of China, and Nutriechem Company.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.049.

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7. *General procedure for sequential [3+2] cycloaddition/rearrangement:* The nitrone **1a** (0.125 mmol, 1 equiv) was added to a solution of allenoate **2a** (0.625 mmol, 5 equiv) in 2 mL of toluene at room temperature, then the resulting mixture was stirred in the refluxing toluene for 48 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/hexanes = 1:2) to give the corresponding product **3aa** as a colorless oil. IR (film) ν_{max} 2962, 2930, 2873, 1736, 1701, 1585, 1456, 1401, 1365, 1298, 1260, 1221, 1181, 1149, 1095, 1029, 956, 921, 801, 708, 623, 582, 553, 496 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.17 (m, 10H), 6.24 (s, 1H), 5.03 (d, J = 1.0 Hz, 1H), 4.68–4.51 (m, 2H), 4.12–3.93 (m, 2H), 3.45–3.29 (m, 2H), 1.22 (d, J = 3.3 Hz, 6H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 162.2, 160.2, 140.5, 136.6, 135.6, 130.6, 128.7, 128.0, 127.9, 127.8, 126.8, 126.0, 83.5, 78.7, 61.5, 44.3, 42.4, 25.6, 25.5, 14.0; HRMS (ESI) calcd for $C_{25}H_{28}N_2O_4^+$ $[M]^+$ 420.2044, found 420.2040.
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