Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

One-pot synthesis of isoxazoles from enaminones: an application of Fe(II) as the catalyst for ring expansion of 2*H*-azirine intermediates

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ARTICLE INFO

Article history:
Received 9 June 2013
Revised 1 August 2013
Accepted 20 August 2013
Available online xxxx

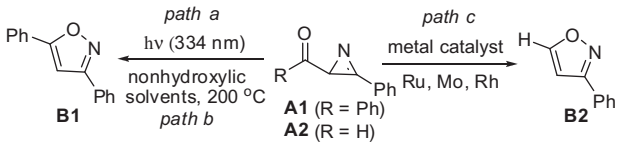
Keywords:
One-pot synthesis
Isoxazoles
Enaminones
$FeCl_2$-catalyzed ring expansion
2*H*-Azirine

ABSTRACT

We report an application of $FeCl_2$ as an inexpensive, nontoxic, and efficient catalyst in a clean ring expansion reaction of 2*H*-azirine derivatives, an intermediate formed through the $PhI(OAc)_2$-mediated azirination of readily available enaminones. An alternative one-pot protocol for the synthesis of various substituted isoxazoles from their corresponding enaminones has been further established based on this reaction, and herein described.

Isoxazole skeleton, ubiquitous in natural products and pharmaceuticals, is a key heterocyclic motif that is responsible for a broad spectrum of biological and pharmacological activities, and has become a key substructure in drug design.[1] The biological activities' studies on the agents containing functionalized isoxazole and derivatives have stimulated a significant interest in developing novel synthetic methods for their syntheses. Among versatile diverse strategies ranging over numerous reaction types and starting materials,[2] ring expansion of 2*H*-azirine compounds via rearrangement has been considered as a unique and attractive approach to access this important class of heterocycles.[3]

In 1972, Singh et al.[4] reported the photo rearrangement of 2*H*-azirines which afforded isoxazoles or oxazoles, depending on the wavelength applied. For example, irradiation of 2-benzoyl-3-phenyl-2*H*-azirine **A1** with 334 nm light afforded almost exclusively its corresponding isoxazole **B1** (Scheme 1, path a). The same conversion of 2*H*-azirines to isoxazoles could also be achieved via the thermal rearrangement in nonhydroxylic solvents at high temperature. For example, on heating in nonhydroxylic solvents at 200 °C, 2*H*-azirine **A1** produced its corresponding isoxazole **B1** in 30% yield (Scheme 1, path b).[5] The rearrangement of 2*H*-azirines into isoxazoles could also be mediated by some metal catalysts such as Grubbs' ruthenium–carbene complexes,[3](b,c) or $Mo(CO)_6$[6] (Scheme 1, path c). Recent findings by Ray et al.[7] revealed that the



Scheme 1. Existing methods for rearrangement of 2*H*-azirines into isoxazoles or isoxazoles to 2*H*-azirines.

application of rhodium acetate dimer ($Rh_2(OAc)_4$) in nonpolar solvents could realize the conversion of 2*H*-azirine **A2** to isoxazoles **B2** (Scheme 1, path c). Considering the cost and toxicity of the above metal catalysts, it is evidently much desired to identify cheaper and less or nontoxic transition metal catalysts for realizing the same rearrangement of 2*H*-azirines into isoxazoles. In this Letter, we report the discovery of an one-pot protocol, where the commonly known Fe(II) salt served as an efficient catalyst in carrying out the ring expansion reaction of the 2*H*-azirine intermediates to form their corresponding isoxazoles in a controlled and specific manner (Scheme 2, path a).

It is worth pointing out that this process is indeed the reverse reaction of Auricchio's work,[8] in which a $FeCl_2$-catalyzed isomerization of isoxazole **B3** to azirine **A3** was realized (Scheme 2, path b). It is apparent that the substrate type we have applied thermodynamically favors the rearrangement of azirine into isoxazole.[9]

In our previous studies, we reported that, upon treatment with hypervalent iodine reagent, that is, phenyliodine (III) diacetate (PIDA), enaminone 2′ underwent azirination to give 2*H*-azirine

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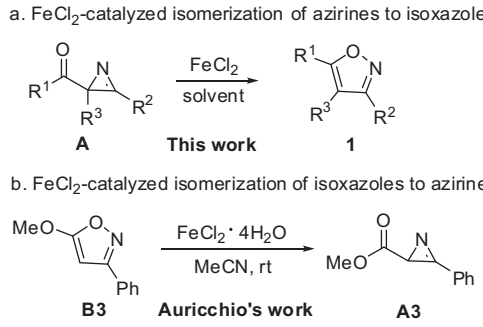
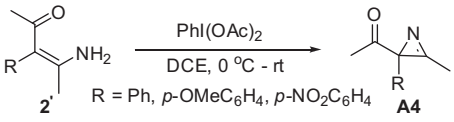
0040-4039/$ - see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2013.08.079



Scheme 2. Substituent-dependant $FeCl_2$-mediated isomerization between 2*H*-Azirines and isoxazoles.

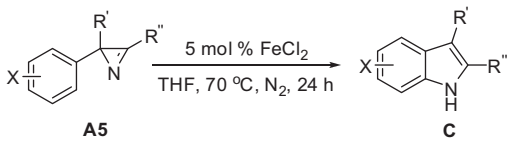


Scheme 3. PIDA-mediated azirination of enaminones previously reported (our previous work).

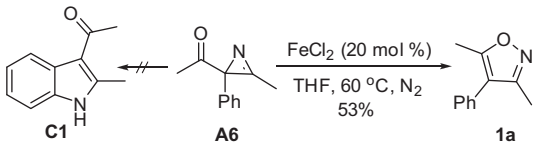
A4 (Scheme 3).[10] In 2009, Zheng et al.[11] described the $FeCl_2$-catalyzed ring opening of 2*H*-azirines **A5** to form 2,3-disubstituted indoles **C** (Scheme 4).

Inspired by these results, we set out to investigate the conversion of the 2*H*-azirine intermediate **A6**, obtained through the azirination of enaminone **2a**, to its corresponding indole product **C1** using the conditions described by Zheng. Unexpectedly, the product was found to consist of exclusively the isoxazole **1a**, in 53% of yield, upon treatment of **A5** with $FeCl_2$ in THF at 60 °C under a nitrogen atmosphere, with no formation of the expected indole product **C1** (Scheme 5). Although unexpected, this finding opened the door for us to establish an alternative protocol to access a variety of isoxazoles via the $FeCl_2$-catalyzed ring expansion of their corresponding 2-acyl-2*H*-azirine compounds.

Our next focus was on developing a one-pot protocol for the synthesis of isoxazoles **1** from enaminones **2** through the azirination reaction of **2** mediated by $PhI(OAc)_2$ followed by Fe(II)-catalyzed ring expansion of the generated 2*H*-azirines. The main task naturally involved the identification of a suitable solvent which would allow high yields for both steps. Substrate **2a** was used to further screen the optimal reaction conditions (Table 1). Among the solvents being screened, DCE and MeOH were found to be the best ones for the azirination step, but unfortunately unsuitable for the second step of ring opening of the generated 2*H*-azirine intermediate (Table 1, entry 1). Only trace amounts of the products were observed when both steps were carried out in DCE or 1,4-dioxane at room temperature (Table 1, entries 2 and 3). Further studies showed that carrying out both reactions under reflux in 1,4-dioxane, provided the desired isoxazole **1a** in 21% yield (Table 1, entry 4). Delightedly, we found that the introduction of some bases, such as sodium carbonate or sodium hydroxide greatly

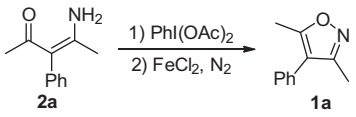


Scheme 4. $FeCl_2$-catalyzed rearrangement of 2*H*-azirines into indoles (Zheng's work).



Scheme 5. The discovery of rearrangement of 2*H*-azirine **A6** into isoxazole **1a**.

Table 1
Condition optimization of one-pot synthesis of isoxazole **1a** from enaminone **2a**[a]



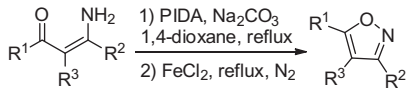
Entry	Additive (equiv)	Base (equiv)	Solvent	Temp (°C)	Time[b] (h)	Yield[c] (%)
1	$FeCl_2$ (1.0)	—	MeOH	rt	24	10
2	$FeCl_2$ (1.0)	—	DCE	rt	24	Trace
3	$FeCl_2$ (1.0)	—	1,4-Dioxane	rt	24	Trace
4	$FeCl_2$ (1.0)	—	1,4-Dioxane	Reflux	2	21
5	$FeCl_2$ (1.0)	Na_2CO_3 (2.0)	1,4-Dioxane	Reflux	2	77
6	$FeCl_2$ (1.0)	NaOH (2.0)	1,4-Dioxane	Reflux	2	62
7	$FeCl_2$ (1.0)	NEt_3 (2.0)	1,4-Dioxane	Reflux	24	Trace
8	$FeCl_2$ (1.0)	DBU (2.0)	1,4-Dioxane	Reflux	2	0
9	**$FeCl_2$ (0.5)**	**Na_2CO_3 (2.0)**	**1,4-Dioxane**	**Reflux**	**5**	**83**
10	$FeCl_2$ (0.2)	Na_2CO_3 (2.0)	1,4-Dioxane	Reflux	8	43
11	$FeCl_2$ (0.5)	Na_2CO_3 (1.0)	1,4-Dioxane	Reflux	6	71
12	—	Na_2CO_3 (2.0)	1,4-dioXane	Reflux	24	Trace

[a] General conditions: (1) enamine (1.0 mmol), PIDA (1.2 mmol) in solvent (5 mL) 0.2 h; (2) $FeCl_2$ added after the reaction mixture was cooled to rt.
[b] Reaction time for the second step.
[c] Isolated yields.

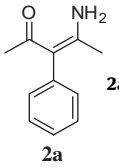
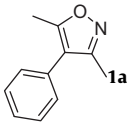
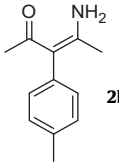
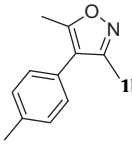
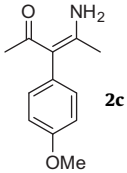
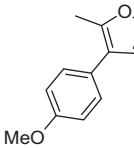
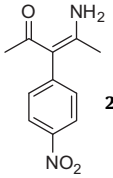
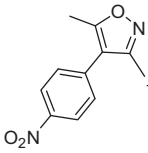
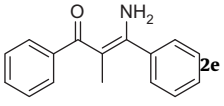
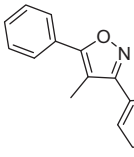
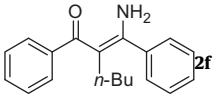
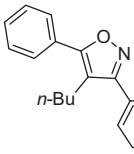
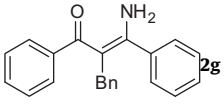
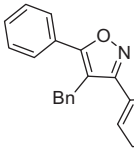
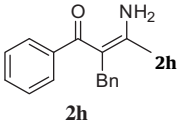
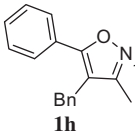
improved the product yield, possibly because the acetic acid released by $PhI(OAc)_2$during the first reaction got neutralized (Table 1, entries 5 and 6). However, the replacement of inorganic bases with NEt_3 or DBU led to a complex mixture of unidentified byproducts in each case (Table 1, entries 7 and 8). The best result was obtained when enaminone **2a** was subjected to the $PhI(OAc)_2$-mediated azirination in the presence of 2.0 equiv of sodium carbonate, followed by addition of 0.5 equiv of $FeCl_2$ to mediate the ring opening of the generated 2*H*-azirines, with both steps occurring in 1,4-dioxane as the solvent and at the reflux temperature (Table 1, entry 9). Reducing the dosage of either $FeCl_2$ or Na_2CO_3 afforded lower yields of isoxazole (Table 1, entries 10 and 11). It is worth noting that when no $FeCl_2$ was applied, the reaction only provided trace amount of its corresponding isoxazole product (Table 1, entry 12), which was probably due to the thermal rearrangements of the generated 2*H*-azirine intermediate. This result clearly implies that $FeCl_2$ plays an indispensable role in the rearrangement of 2*H*-azirine intermediate into isoxazole **1a**.

With the optimized reaction conditions obtained, the generality and substituent scope of this one-pot synthesis of isoxazoles was investigated. The results are summarized in Table 2. The analogous enaminone derivatives **2b–c**, both bearing electron-donating

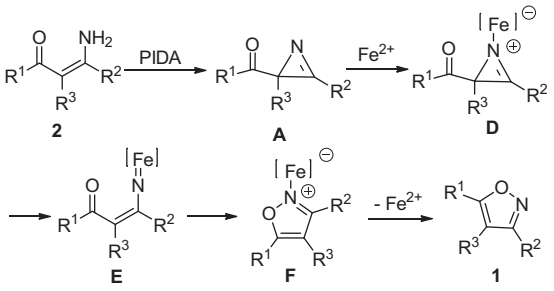
Table 2
One-pot synthesis of isoxazoles 1 from enaminones **2** mediated by PIDA and Fe(II)[a]



2 **1**

Entry	Enamine **2**	Isoxazole **1**	Time (h)	Yield[b] (%)
1	 **2a**	 **1a**	0.2/5	83
2	 **2b**	 **1b**	0.2/5	80
3	 **2c**	 **1c**	0.2/5	82
4	 **2d**	 **1d**	0.2/16	60[c]
5	 **2e**	 **1e**	0.3/10	46[d]
6	 **2f**	 **1f**	0.3/8	60
7	 **2g**	 **1g**	0.3/24	63[c]
8	 **2h**	 **1h**	0.3/8	81

[a] General conditions: (1) enamine (1.0 mmol), PIDA (1.2 mmol), Na_2CO_3 (2.0 mmol) in 1,4-dioxane (5 mL) under reflux; (2) $FeCl_2$ (0.5 mmol), stirred under reflux, under N_2 unless otherwise stated.
[b] Isolated yields.
[c] Another portion of $FeCl_2$ (0.5 mmol) was added after 8 h.
[d] 1.0 mmol of $FeCl_2$ was used.



Scheme 6. Proposed mechanistic pathways.

substituents on the benzene ring, can be converted into their corresponding isoxazoles **1b–c** in very good yields. However, with the nitro group as the substituent in **2d**, the yield of the desired isoxazole **1d** was drastically lowered, due to the formation of some unidentified byproducts during the rearrangement process. But to our delight, this one-pot protocol was also found to be applicable to the enaminones bearing α-alkyl substituents, such as methyl, *n*-butyl, and benzyl groups, which extends this method to the synthesis of 4-alky isoxazoles **1e–h**. However, these isoxazoles were obtained in comparably low yields due to the formation of more unidentified byproducts in both the azirination and rearrangement process.

Based on the mechanism Zheng described for the $FeCl_2$-catalyzed ring opening of 2*H*-azirines, we propose a plausible mechanistic pathway for the above one-pot synthesis of isoxazole **1** (Scheme 6). Initially, the starting enaminone **2** was conveniently converted into 2*H*-azirine **A** via the $PhI(OAc)_2$-mediated azirination.[10] Then the coordination of Fe(II) to the nitrogen atom of 2*H*-azirine **A** produced the iron-azirine complex **D**,[11] which was converted into iron vinyl nitrene complex **E**. Subsequent 6π-electron electrocyclization[12] of **E** afforded isoxazole **1** through the intermediate **F**. Due to the presence of an adjacent carbonyl group in the substrate, the five-centered 6π electrocyclization preferentially occurred between the vinyl nitrene moiety and the C=O bond, the result of which furnished the oxazole products, rather than the indole products in Zheng's work.[11]

In summary, we have described here an alternative synthetic methodology to form the biologically important isoxazoles from their corresponding enaminone compounds, based on our discovery of a $FeCl_2$-mediated rearrangement of 2*H*-azirines into isoxazoles. Other than the importance of the product, the convenience of the one-pot procedure, the specificity of the reaction, and the low cost of the environmentally benign Fe(II) catalyst are among the highlighted characteristics of the method herein reported.

Acknowledgments

Y.D. acknowledges the National Natural Science Foundation of China (#21072148), Foundation (B) for Peiyang Scholar–Young Core Faculty of Tianjin University (2013XR-0144), and the Innovation Foundation of Tianjin University (2013XJ-0005) for financial support.

Supplementary data

Supplementary data (list of new compounds along with their yield and copies of ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.079. These data include MOL files and InChiKeys of the most important compounds described in this article.

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