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Highly regioselective dipolar cycloadditions of nitrile oxides with α,β-acetylenic aldehydes

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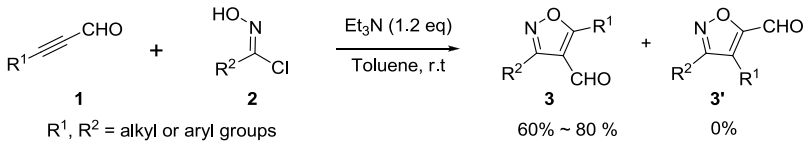
Graphic abstract



Keywords:

1,3-dipolar cycloaddition, nitrile oxide, α,β-acetylenic aldehydes, regioselectivity

Abstract

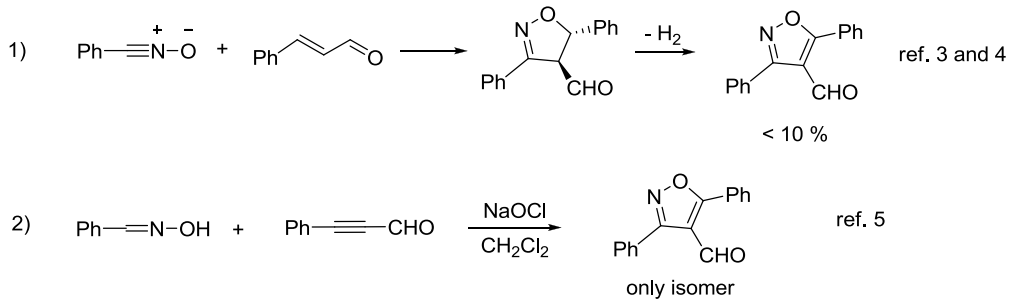
1,2-oxazol derivatives **3** were prepared by a highly regioselective 1,3-dipolar cycloaddition of nitrile oxides and α, β-acetylenicaldehydes **1** in good yields. Reactive nitrile oxides were generated in situ from stable chloro-oxime reagents **2** and triethyl amine. The cycloaddition reaction showed broad substrate scopes and good functional groups compatibility.

Introduction

Nitrile oxides have been extensively utilized in 1,3-dipolar cycloaddition reactions as dipoles to generate synthetically useful heterocyclic structures.[1] But to achieve the regioselective 1,3-dipolar cycloaddition of nitrile oxides has always been a challenge in organic synthesis.[2] Over the years, ketones and aldehydes have been thoroughly studied as dipolarphiles in the regioselective cycloadditions to nitrile oxides.[2] However, regioselective 1,3-dipolar cycloaddition of nitrile oxides with α, β-acetylenic aldehydes to afford isoxazole derivatives **3** have not been systematically investigated.

Isoxazole derivatives **3** are versatile structure motifs in organic synthesis.[3] Both Sarlo[4] and Caramella[5] reported a synthesis of

3,5-diphenylisoxazole-4-carbaldehyde from 1,3-dipolar cycloaddition of phenyl nitrile oxide and *trans*-cinnamaldehyde followed by dehydration. Unfortunately, the reaction yields of both cases were low, and thus their protocols were not synthetically applicable. Suzuki et al. described a regioselective preparation of 3,5-diphenylisoxazole-4-carbaldehyde, the precursor of a fluorescent 1,2-oxazole compound, from 1,3-dipolar cycloaddition of phenyl nitrile oxide and 3-phenylpropiolaldehyde.[6] However, the reaction conditions were not optimized and the substrate scopes and the limitations were not explored. Moreover, the nitrile oxide was generated from the unstable and explosive benzaldoxime under strong oxidative conditions.



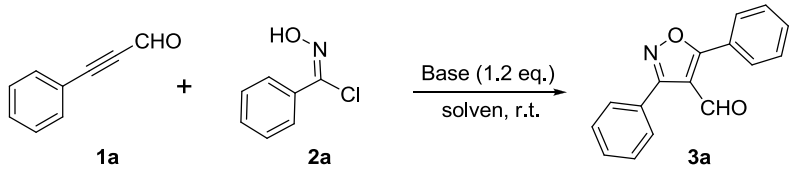
Scheme 1. Synthesis of 1,2-oxazole compounds from Sarlo, Caramella and Suzuki.

As part of our ongoing effort to develop efficient and regioselective methods in preparation of heterocyclic compounds, we have found a simple, efficient and regioselective synthesis of 1,2-oxazol derivatives from 1,3-dipolar cycloaddition of nitrile oxides with α, β-acetylenic aldehydes.

Results and Discussion

Since nitrile oxides are very reactive and unstable, we decided to use relatively stable reagents chloro-oximes to generate nitrile oxides in situ upon treatment with base. The reagents chloro-oximes could be easily prepared based on a known procedure.[7,8] We chose phenylpropiolaldehyde,[9] an α, β-acetylenic aldehyde, and α-chlorobenzaldoxime as model substrates to investigate the regioselectvity and determine the optimal reaction conditions. First different bases that were used to facilitate the oxime formation were tested. In terms of reaction yield and regioselectivity, the 1,3-dipolar cycloaddition proceeded well with many types of bases (Table 1). Generally, amine-type bases participated in the 1,3-dipolar cycloaddition with a better yield than inorganic bases. Trimethylamine (TEA) was found to afford the product **3a** as the single regioisomer in best yield (80%) at room temperature in 0.5 h

in toluene (entry 1). This high regioselectivity was consistent with Suzuki's report.[6] We then screened different solvents of this cycloaddition reaction. Toluene delivered higher regioselectivity (80% yield) than benzene, THF, CH_3CN, or C_2H_5OH (entries 1-8), whereas poor yields were observed in chlorinated solvents such as CH_2Cl_2 and $CHCl_3$ (~ 40%) even with longer reaction time and no reaction at all in H_2O. The single product 3a was obtained in all the above conditions with no other isomers detected. Therefore, TEA and Toluene as the base and solvent respectively at room temperature were identified as the optimal reaction conditions.



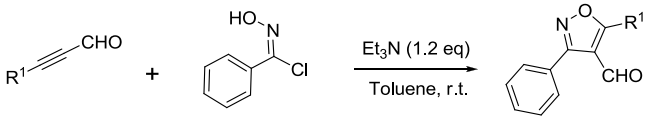
1a **2a** **3a**

Entry[a]	Base	Solvent	T (h)	Yield (%)[b]
1	TEA	Toluene	0.5	80
2	TEA	Benzene	0.5	75
3	TEA	THF	0.5	73
4	TEA	CH_3CN	0.5	65
5	TEA	C_2H_5OH	2	62
6	TEA	CH_2Cl_2	3	45
7	TEA	$CHCl_3$	3	43
8	TEA	H_2O	4	n.r
9	DCHA	Toluene	0.5	73
10	*n*-butylamine	Toluene	0.5	75
11	pyridine	Toluene	2	70
12	NaOH	Toluene	2	40
13	NaOAc	Toluene	2	65
14	$NaHCO_3$	Toluene	2	55
15	K_2HPO_4	Toluene	2	72

[a] Reaction conditions: a mixture of **1a** (1.0 mmol), **2a** (1.1 mmol), Base (1.2 mmol), in solvent (2 mL) were stirred at room temperature for a certain period of time. [b] Yield of isolated product.

Table 1. Optimization of reaction conditions

With the optimal conditions in hand, we next extended our attention to explore the substrate scopes and limitations of one reaction partner α, β-acetylenic aldehydes (Table 2). A wide scope of α, β-acetylenic aldehydes including aromatic, aliphatic and heterocyclic aromatic derivatives could participate well in the cycloadditon reaction regioselectively. Aryl α, β-acetylenic aldehydes all regioselectively provided the cycloaddition products in good to moderate yields (products 3a-3h). Electron withdrawing groups such as fluorine and bromine and electron donating groups such as methoxyl, methyl, and t-butyl groups on the aromatic ring did not affect the reaction yields. Heterocyclic aromatic ring such as thiophene also gave good yield (3g, 75%) of the corresponding product. Relatively lower yields (3i-3j) were observed when alkyl α, β-acetylenic aldehydes were used in this cycloaddition reaction.



1a-j **2a** **3a-3j**

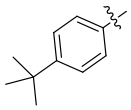
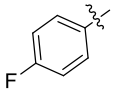
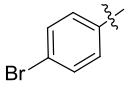
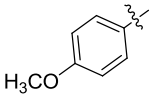
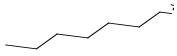
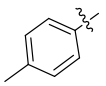
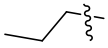
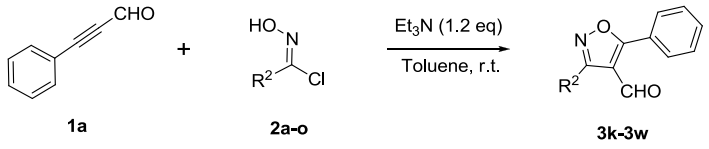
Product	R^1	Yield（%）	Product	R^1	Yield（%）
3a		**80**	**3f**		**70**
3b		**78**	**3g**		**75**
3c		**81**	**3h**		**70**
3d		**73**	**3i**		**65**
3e		**76**	**3j**		**67**

Table 2: Scope of propioaldehydes

We lastly investigated the substrate scopes and limitations of another reaction partner chloro-oximes (Table 3). Aryl chloro-oximes underwent the 1,3-dipolar cycloaddition with phenylpropiolaldehyde in good yields and showed excellent regioselectivity. The substitution of aryl chloro-oximes with electron-donating or withdrawing groups on different positions of the aromatic rings was all accommodated, furnishing the 1,2-oxazol derivatives regioselectively in good yields (3k-n, 3q, 3r, 3t). Similar as that of alkyl

aldehydes partner, alkyl or alkene substituted chloro-oximes gave relatively lower yields than that of aromatic counterparts.



1a 2a-o 3k-3w

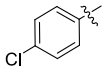
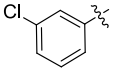
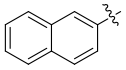
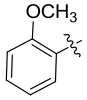
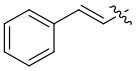
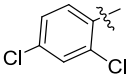
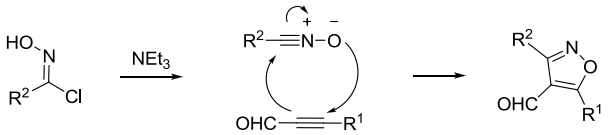
product	R^2	Yield (%)	product	R^2	Yield (%)
3k		**76**	**3p**		**65**
3l		**78**	**3q**		**82**
3m		**78**	**3r**		**83**
3n		**69**	**3s**		**65**
3o		**68**	**3t**		**76**

Table 3 Scope of chloro-oximes

This reaction is a typical 1,3-dipolar cycloaddition reaction. First, treatment of chloro-oximes with TEA generates the reactive 1,3-dipolar nitrile oxide in situ. Then the typical 1,3-dipolar cycloaddition of nitrile oxide with alkynes delivers the isoxazole derivatives. The excellent regioselectivity of this cycloaddition can be explained by the electronic effect of the α, β-acetylenic aldehyde, as shown in scheme 2, the nucleophilic oxygen of nitrile oxide would regioselectively add to the electron-deficient β-carbon of the aldehyde.



Scheme 2. Reaction mechanism

Conclusion

In summary, a highly regioselective 1,3-dipolar cycloaddition of nitrile oxides and α, β-acetylenic aldehydes was developed using nitrile oxides generated in situ from stable chloro-oximes reagents by base. The cycloaddition reaction afforded the 1,2-oxazol derivatives at room temperature in good yields under mild reaction conditions and in short time. Both chloro-oximes and α, β-acetylenic aldehydes reaction partners showed broad substrate scopes. To the best of our knowledge, this is the first systematic investigation of a regioselective 1,3-dipolar cycloaddition of nitrile oxides and α, β-acetylenic aldehydes to prepare 1,2-oxazol

derivatives. Further extension of this efficient synthetic strategy to the scope of α, β-acetylenic ketones and esters and continuing exploration of its application is under way in our laboratory and will be presented in due course.

Acknowledgement

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References

[1] a) Nitrile oxides, nitrones and nitronates in organic synthesis, Henry Feuer, Ed.; Wiley: New York, 2007. b) Heaney, F. *Eur. J. Org. Chem.* **2012**, 3043

[2] a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565; b) Huisgen, R. In 1,3-Dipolar Cycloaddition Chemistry; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 1.2. c) Huisgen, R. *J. Org. Chem*. **1968**, *33*, 2291.

[3] a) Lee, C. K. Y.; Easton. C. J.; Gebara-Coghlan, M.; Radom, L.; Scott, A. P.; Simpson, G. W.; Willis, A. C. *J. Chem. Soc. Perkin Trans. 2*., **2002**, *12*, 2031. b) Pae, A.; Lee, J. E.; Bo, H.; Cha, J. H.; Kim, H. Y.; Cho, Y. S.; Choi, K. I.; Koh, H. Y.; Lee, E.; Kim, J. H. *Tetrahedron* **2000**, *56*, 5657.

[4] Sarlo, F. D.; Guarna, A.; Brandi, A., *J. Heterocyclic. Chem*., **1983**, *20*, 1505

[5] Toma, L.; Quadrelli, P.; Perrini, G.; Gandolfi, R.; Valentin, C. D. Corsaro. A.; Caramella, P., *Tetrahedron*, **2000**, *56*, 4299

[6] Suzuki, K.; Ueno, K. *J. Photopolym. Sci. Technol.*, **2001**, *14*, 311.

[7] See the supporting information for the procedure for synthesis of chloro-oxime

[8] a) Liu, K. C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem*. **1980**, *45*, 3916. b) Lee, G. A. *Synthesis*, **1982**, *6*, 508

[9] Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, 39, 6427-6428.