Pergamon

Tetrahedron 54 (1998) 12445–12456

TETRAHEDRON

A Novel Double Addition of Isocyanoacetamide to *N*-Sulfonylimines for the Synthesis of Trisubstituted Oxazoles ‡

Xiao-Ti Zhou, Ying-Rui Lin*, Li-Xin Dai, and Jie Sun

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Received 13 February 1998; revised 18 May 1998; accepted 28 July 1998

Abstract: The reaction of isocyanoacetamide with *N*-sulfonylimine gives a novel double addition product in the absence of acid, base and catalyst to form 2, 4-disubstituted-5-amino-1, 3-oxazole. A possible mechanism of this reaction is discussed.

Introduction

Heterocycles are ubiquitous structural constituents in biologically active molecules, and consequently, the synthesis of heterocyclic compounds has attracted considerable attention.[1] Isocyanides, possessing an active methylene group and isonitrile divalent carbon, may be involved in many novel synthetic approaches to construct a wide variety of nitrogen-containing heterocycles. Available methods for the synthesis of five-memerbed heterocycles using isocyanides as starting materials, such as 2-oxazolines,[2] 2-imidazolines,[3] have been extensively investigated. Recently, we have reported a Ru-catalyzed aldol reaction of methyl isocyanoacetate with *N*-sulfonylimines forming *trans*-2-imidazolines in high yields and high stereoselectivity, which can readily be hydrolyzed to *N*-sulfonyl-2, 3-diamino acids.[4] Since five-membered heterocycles containing nitrogen atoms have extensive applications in the synthesis of biologically active compounds, our continuing interest in catalytic aldol reaction has led us to extend the catalytic reaction of isocyanoacetate to isocyanoacetamide. However, we unexpectedly found another heterocycles, oxazoles, in the reaction of isocyanoacetamide with *N*-sulfonylimine which was carried out as a control experiment in the absence of acid, base and catalyst. On the other hand, the corresponding ester, methyl isocyanoacetate, gave no sign of any reaction under exactly the same conditions. The different reactivity of isocyanoacetamide and isocyanoacetate in their reaction to *N*-sulfonylimine attracted our great attention. Here, we disclose our detailed investigations of this reaction.

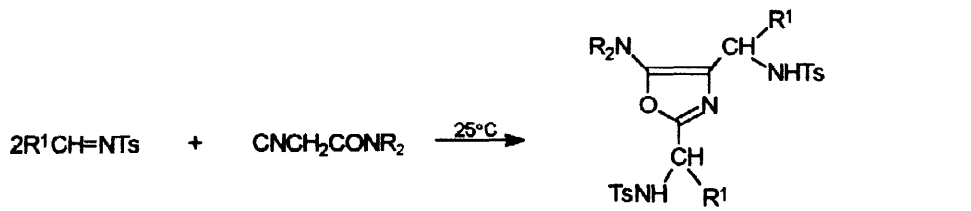
‡ This paper is respectfully dedicated to Professor Wang Yu in memory of his guidance and his enormous contribution to organic chemistry

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00726-1

Results and Discussion

Double Addition Reaction Before runing the Ru-catalyzed aldol reaction of isocyanoacetamide, a control experiment was carried out in CH_2Cl_2 at 25°C between isocyanoacetamide(**2a**) and *N*-tosyl-*p*-nitrobenzaldimine(**1b**) (1:1). Surprisingly, a yellow solid product was isolated in high yield, which was not the expected 2-imidazoline as indicated by ^1H NMR analysis. In this reaction, plenty of isocyanoacetamide(**2a**) remained unreacted even though *N*-tosyl-*p*-nitrobenzaldimine(**1b**) had disappeared completely.The same product was also obtained in 92 % yield when the amount of isocyanoacetamide(**2a**) was reduced to one half equivalent of that of *N*-sulfonylimine. ^1H NMR, elemental analysis and FAB-MS data showed that it was an addition product of one equivalent isocyanoacetamide with two equivalent *N*-sulfonylimines. Similarly, the reaction of **2b** with **1b** also gave a double addition product in 94 % yield. The result of ^1H NMR / D_2O exchange experiment of **3b** indicated two active hydrogens in the addition product which was assigned as two NH groups. I.R spectra showed no sign of the presence of isocyano group in 2100 - 2200 cm^{-1} and no strong absorbtion of amide carbonyl in 1600 - 1700 cm^{-1} , indicating the ring closure of amide carbonyl on the isocyanide carbon. Thus, the structure of the addition product was identified as 2, 4-disubstituted-5-amino-1,3-oxazole as shown in Scheme 1 and confirmed by X-ray crystallographic analysis of **3a**.[5]

Scheme 1



1a R¹=*p*-chloropheny l
1b R¹=*p*-nitropheny l
1c R¹=pheny l
1d R¹=α-naphthy l
1e R¹=2,6-dichloropheny l
1f R¹=*p*-methox ylpheny l

2a R₂=piperidiny l
2b R=Me

3a R¹=*p*-chloropheny l R₂=piperidiny l
3b R¹=*p*-nitropheny l R₂=piperidiny l
3c R¹=pheny l R₂=piperidiny l
3d R¹=α-naphthy l R₂=piperidiny l
3e R¹=2,6-dichloropheny l R₂=piperidiny l
3f R¹=*p*-methox ylpheny l R₂=piperidiny l
3g R¹=*p*-chloropheny l R=Me
3h R¹=*p*-nitropheny l R=Me

It is well known that active methylenes in the isocyanoacetamide condense with aldehydes, ketons or imines to give the aldol addition products in the presence of base or metal compounds. Recently, Au and Ru catalyzed aldol addition to form 2-imidazoline from isocyanoacetate and *N*-sulfonylimine have been reported.[3d,4] It has been also reported that α-metalated isocyanide, produced by the action of n-BuLi or potassium carbonate, reacted with acyl chlorides, carboxylic esters or amides to form oxazole derivatives.[6] In the presence of potassium carbonate, the tosylmethyl isocyanide reacted with aldehyde to yield oxazole with the elimination of tosyl group.[7] However, as presented above, the reaction of isocyanoacetamide with *N*-sulfonylimine under

neutral conditions forming oxazole and introducing two substituted group on the 2, 4-position of oxazole ring has not been described in the literature.[8]

We examined the effect of solvents on this addition reaction. When *N*-tosyl-benzaldimine(1c) was reacted with 2a in CH_2Cl_2, 60 % of oxazole was produced. Using CH_3CN, DMF, MeOH, and MeOH/CH_2Cl_2 (1:1) as solvent, the yield increased to 78, 76, 74 and 70% respectively. The results indicated that the polar solvents were preferred for this reaction. In the next, we examined the reaction of other *N*-sulfonylimines with isocyanoacetamide at 25°C. As shown in Table 1, the reaction of *N*-piperidinyl or *N*, *N*-dimethyl-α-isocyanoacetamide with *N*-sulfonylimines could proceed without the need of acid, base or catalyst and in moderate to high yields.

Table 1. Reaction of *N*-sulfonylimine (1) with Isocyanoacetamide (2) [a]

entry	R^1	R_2	Solvents	time	products (3) yield % [b]
1	*p*-chlorophenyl	piperidinyl	CH_2Cl_2	24 h	81 (3a)
2	*p*-nitrophenyl	piperidinyl	CH_2Cl_2	15 h	92 (3b)
3	phenyl	piperidinyl	CH_3CN	48 h	78 (3c)
4	α-naphthyl	piperidinyl	CH_3CN	48 h	71 (3d)
5	1,6-dichlorophenyl	piperidinyl	CH_3CN	48 h	81 (3e)
6	*p*-methoxylphenyl	piperidinyl	CH_3CN	48 h	60 (3f)
7	*p*-chlorophenyl	Me	CH_2Cl_2	24 h	78 (3g)
8	*p*-nitrophenyl	Me	CH_2Cl_2	15 h	94 (3h)

[a] The reaction was carried out at 25°C, 1/2=2.1/1. [b] Isolated yields based on 2.

For the ruthenium-catalyzed aldol reaction of methyl isocyanoacetate with *N*-sulfonylimines, *trans*-2-imidazolines were obtained in high yields and high stereoselectivity,[4] and no oxazole was observed. When 1a was treated with isocyanoacetamide(2a) in the presence of 1 % mol $RuH_2(PPh_3)_4$ in CH_2Cl_2 at 25°C for 24h, *trans*-2-imidazoline could be obtained in 46 % yield and oxazole could also be isolated in 34 % yield. On increasing the amount of catalyst to 20 % mol, the yield of 2-imidazoline increased to 77 % and the formation of oxazole was almost entirely suppressed. While using 20% of AgOTf as catalyst, only a trace of 2-imidazoline but 65 % of oxazole was isolated. This is also different from Ag-catalyzed reaction of isocyanoacetate with *N*-sulfonylimine to give *cis*-2-imidazoline reported by Hayashi.[3d] Moreover, 2-imidazoline was obtained in high yield on using NaH as base (Table 2 and Scheme 2), and oxazole was not observed in this reaction.

Scheme 2

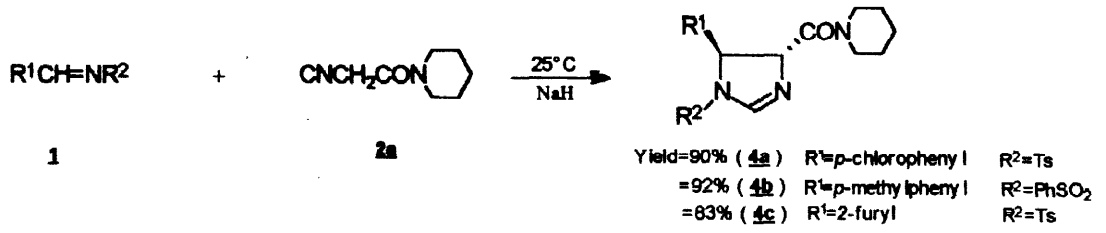


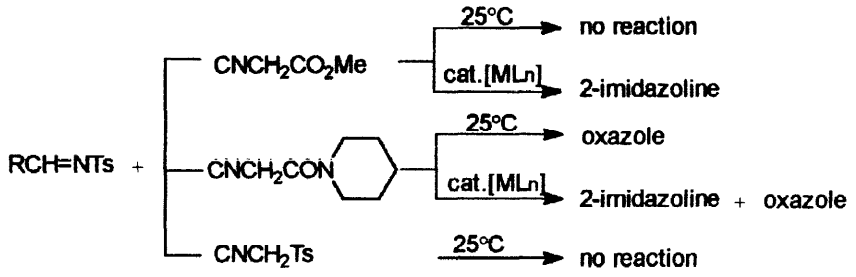
Table 2 Reaction of 1a with isocyanoacetamide(2a) catalyzed by transition metal or in the presence of NaH [a]

entry	Catalyst or base	time	temp	4a : 3a (Yield %)[b]
1	1 % mol $RuH_2(PPh_3)_4$	24 h	25°C	46 : 34
2	5 % mol $RuH_2(PPh_3)_4$	24 h	25°C	63 : 17
3	10 % mol $RuH_2(PPh_3)_4$	24 h	25°C	70 : 5
4	20 % mol $RuH_2(PPh_3)_4$	24 h	25°C	77 : trace
5	20 % mol AgOTf	24 h	reflux	trace : 65
6	1 equiv NaH	1 h	25°C	90 : 0

[a] The reaction was carried out in CH_2Cl_2, 1a/2a=1/1. [b] isolated yields based on 1a.

It appeared that there are two competing reaction in the solution containing *N*-sulfonylimine and isocyanoacetamide in the presence of $RuH_2(PPh_3)_4$. Obviously, 2-imidazoline was formed by the reaction of imine with resulting carbanion species or Ru-enolate intermediate originated from α-activated methylene. On the other hand, oxazole was presumably formed by ring closure of the amide carbonyl on the isocyanide carbon. So we deduced that this reaction of *N*-sulfonylimine with isocyanoacetamide may be triggered by isonitrile carbon, instead of α-activated methylene. In contrast, isocyanoacetate remains inert to cyclization in the presence of reactive *N*-sulfonylimine under neutral conditions. The different behaviour of isocyanoacetamide and methyl isocyanoacetate toward *N*-sulfonylimine was a reason to consider the reactivity of other isocyanide with stronger electron-withdrawing group than the ester group (Scheme 3).

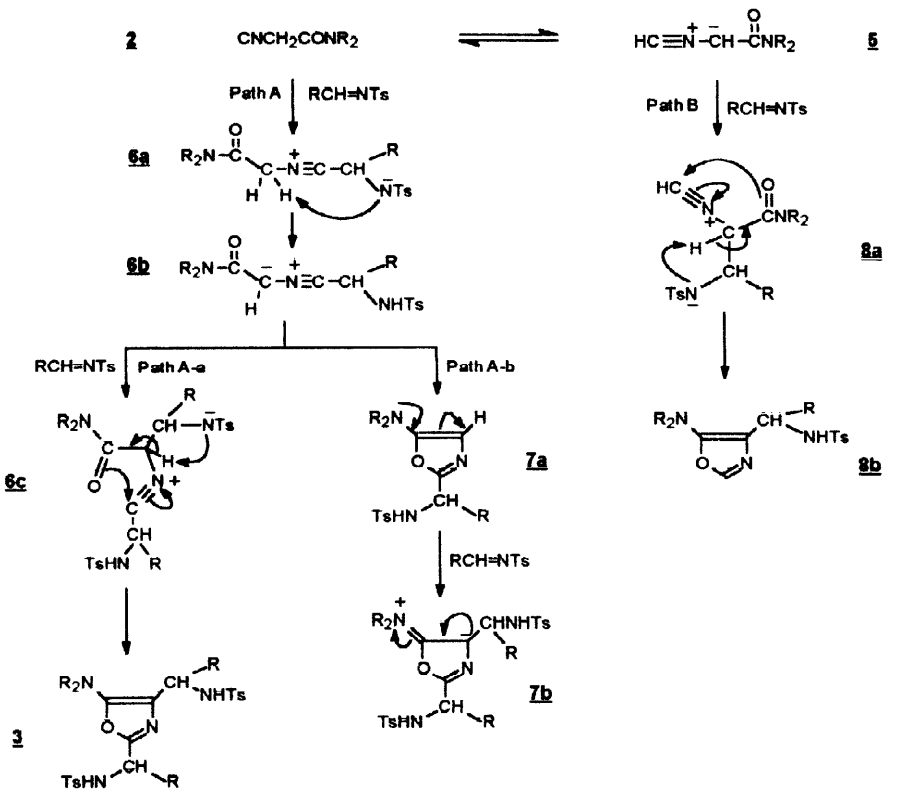
Scheme 3



When tosylmethyl isocyanide was used to replace isocyanoacetamide, no reaction took place under the same conditions. These results may be attributed to the reduced nucleophilicity of isonitrile carbon due to the electron-withdrawing group. Compared with the tosylmethyl isocyanide and isocyanoacetate, the less electron-withdrawing group of isocyanoacetamide may affect the nucleophilic sensitivity of isocyanide carbon and the facility of the cyclization. Therefore, an appropriate nucleophilicity of the isocyanide carbon and a reactive α-CH are necessary for this reaction. The activity of the electrophilic reagents, the reaction partner also play an important role in this reaction. In comparison with the *N*-sulfonylimine, 4-chlorobenzaldehyde failed to give any products under present conditions.[9]

Discussion of the Mechanism Isocyanoacetamide **2** may tautomerize to the nitrilium intermediate **5** as postulated in Scheme 4.

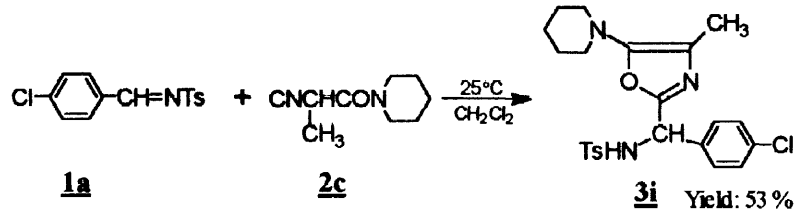
Scheme 4



Under neutral conditions, the possible pathway for our reaction may be triggered from nucleophilic attack of the isocyanide carbon (Path A) or proceed by nucleophilic attack on the carbanion of nitrile ylide **5** (Path B). If **5** is the intermediate of this reaction, cyclization initiated by a proton transfer from carbon to nitrogen, and subsequent reaction of the enolate oxygen with the nitrilium group, may produce product **8b**. In fact, 4-substituted oxazole **8b** was never identified. To support our explanation, an α-substituted isocyanoacetamide **2c**

(Scheme 5) was synthesized and tested in this reaction. If the reaction of α-methyl isocyanoacetamide **2c** with *N*-sulfonylimine proceed on the basis of Path B, the cyclization product will not obtained after the nucleophilic addition of the carbanion to *N*-sulfonylimine. However, when the reaction of **2c** with imine **1a** was carried out in the similar conditions, 2,4-disubstituted oxazole **3i** was isolated in 53 % yield. This result make Path B highly unlikely.

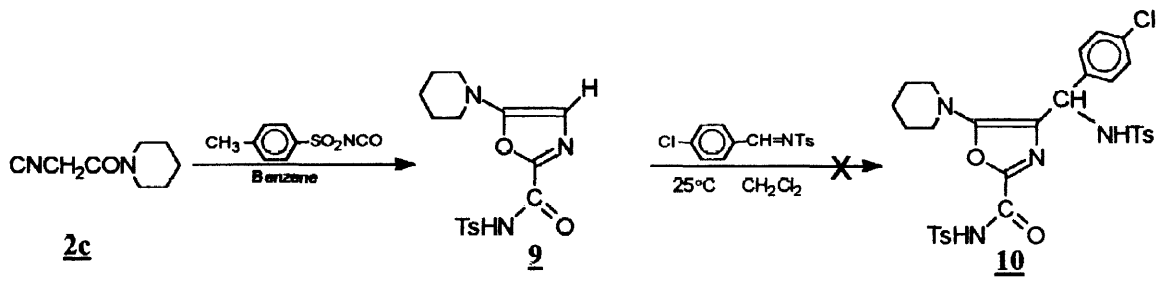
Scheme 5



1a **2c** **3i** Yield: 53 %

Therefore, we suggest that nucleophilic isonitrile carbon could attack polar C=N double bond of *N*-sulfonylimine to generate intermediate **6a** according to Path A. The nitrogen anion formed in situ behaved as a base to attract a proton of α-methylene so that intermediate **6b** was produced in the form of nitrile ylide. Intermediate **6b** may undergo direct cyclization by a intramolecular reaction of the enolate oxygen with the nitrilium moiety to give 2-substituted oxazole **7a**. Alternatively species **6b** can react with a second molecule of *N*-sulfonylimine to prduce intermediate **6c**. The direct cyclization to **7a** was not observed. In principle, reaction of enamine 7a with another molecule of imine can be envisaged which then leads to **3**. To test this possibility, 2-substituted oxazole **9** [10] was prepared from the reaction of isocyanoacetamide **2a** with *p*-toluenesulfonyl isocyanate as shown in Scheme 6. When 2-substituted oxazole **9** was treated with *N*-sulfonylimine, the desired product **10** was not observed with ^{1}H NMR spectra.

Scheme 6



2c **9** **10**

Chupp once reported that some isocyanoacetamide may undergo cyclization to give 2, 4-unsubstituted oxazole, which could react with isocyanates to afford 2-substituted oxazole or 4-substituted oxazole.[10] In the case of our expriments, however, no 2, 4-unsubstituted oxazole was observed when isocyanoacetamide was heated at 130°C in the absence of solvent or refluxed in CH_3CN. Thus, the pathway from the reaction of 2, 4-unsubstituted oxazole with *N*-sulfonylimine to give 2, 4-disubstituted oxazole could be precluded. So, the possible pathway of the present reaction is considered to proceed via Path A-a.[11] The adduct **6c** can undergo an

intramolecular cyclization involving the amide carbonyl group which is initiated by a proton transfer from carbon to nitrogen to afford the double addition products **3**.

Oxazoles have attracted considerable interest as starting materials and important building block for the synthesis of more complex molecules and macrocyclic antibiotics.[12] The reaction of *N*-sulfonylimine with isocyanoacetamide reported herein provide a facial and efficient method for the construction of trisubstituted oxazole with the same or different 2, 4-disubstituted groups. Moreover, the trisubstituted oxazole can be easily converted into the corresponding polyamines,[13] dipeptide and useful building block for the synthesis of the biologically active compounds.[14]

Experimental Section

Materials and General Procedure. All *N*-sulfonylimines **1**[15]and isocyanoacetamide **2**[16]were prepared according to literature methods. CH_2Cl_2 was distilled immediately prior to use from CaH_2 under nitrogen. The other solvents were treated according to the standard methods.

General Procedure for Double Addition Reaction of *N*-Sulfonylimine with Isocyanoacetamide. A mixture of *N*-sulfonylimine (**1,** 0.46 mmol), and isocyanoacetamide (**2,** 0.23 mmol) was stirred in CH_2Cl_2 or CH_3CN at 25 °C for 15-48 h under nitrogen. After removal of the solvent, the residue was isolated by preparative TLC eluting with a mixture of petroleum ether (60-90 °C) and ethyl acetate (2:1) to give double addition products (**3**) in 60-94% yields.

2,4-Di(1-*p*-chlorophenyl-*N*-tosyl-aminomethyl)-5-piperidinyl-1,3-oxazole (3a) ^{1}H NMR ($CDCl_3$/TMS): δ 1.50 (br, 6H), 2.33 (m, 6H), 2.62 (br, 4H), 5.45 (m, 2H), 5.76 (m, 1H), 6.03 (m, 1H), 7.15 (m, 12H), 7.53 (m, 4H). Mp: 78 - 80°C. IR: 3359, 1702, 1627cm^{-1}. FAB-MS *m/z* 739 (M^+), 569 (M^+-170), 155 (M^+-584), 91 (M^+-648). Anal. Calcd for $C_{36}H_{36}Cl_2N_4O_5S_2$: C, 58.45; H, 4.90; N, 7.57. Found: C, 58.43; H, 4.84; N, 7.28.

2,4-Di(1-*p*-nitrophenyl-*N*-tosyl-aminomethyl)-5-piperidinyl-1,3-oxazole (3b) ^{1}H NMR ($CDCl_3$/TMS): δ 1.51 (br, 6H), 2.33 (m, 6H), 2.62 (br, 4H), 5.57 (m, 2H), 6.26 (m, 1H), 6.34 (m, 1H), 7.15 (m, 4H), 7.35 (m, 4H). 7.51 (m, 4H), 8.01 (m, 4H). Mp: 98 - 100°C. IR: 3268, 1599, 1523cm^{-1}. FAB-MS *m/z* 760 (M^+), 590 (M^+-170), 155 (M^+-605), 91 (M^+-669). Anal. Calcd for $C_{36}H_{36}N_6O_9S_2$: C, 56.83; H, 5.03; N, 11.04. Found: C, 56.60; H, 4.78; N, 10.74.

2,4-Di(1-phenyl-*N*-tosyl-aminomethyl)-5-piperidinyl-1,3-oxazole (3c) ^{1}H NMR ($CDCl_3$/TMS): δ 1.50 (br, 6H), 2.33 (m, 6H), 2.62 (br, 4H), 5.45-5.63 (m, 3H), 6.01 (m, 1H), 7.00 (m, 4H), 7.26 (m, 10H). 7.53 (

m, 4H). Mp: 72 - 74°C. IR: 3264, 1653, 1629cm^{-1}. FAB-MS *m/z* 671 (M^++ 1), 500 (M^+-170), 155 (M^+-515), 91 (M^+-579). Anal. Calcd for $C_{36}H_{38}N_4O_5S_2$: C, 64.45; H, 5.71; N, 8.35. Found: C, 64.16; H, 5.76; N, 8.50.

2,4-Di(1-α-naphthyl-*N*-tosyl-aminomethyl)-5-piperidinyl-1,3-oxazole (3d) ^{1}H NMR ($CDCl_3$/TMS): δ 1.44 (br, 6H), 2.04-2.27 (m, 6H), 2.50 (br, 4H), 5.55-6.01 (m, 2H), 6.21 (m, 2H), 6.66 (m, 2H), 6.79-6.88 (m, 2H), 7.10 (m, 1H), 7.41 (m, 12H), 7.81 (m, 4H), 8.33-8.36 (m, 1H). Mp: 82 - 84°C. IR: 3265, 1687, 1639cm^{-1}. FAB-MS *m/z* 771 (M^++ 1), 600 (M^+-170), 155 (M^+-615), 91 (M^+-679). Anal. Calcd for $C_{44}H_{42}N_4O_5S_2$: C, 68.54; H, 5.49; N, 7.27. Found: C, 68.29; H, 5.61; N, 7.50.

2,4-Di(1-2,6-dichlorophenyl-*N*-tosyl-aminomethyl)-5-piperidinyl-1,3-oxazole (3e) ^{1}H NMR ($CDCl_3$/TMS): δ 1.31 (br, 6H), 2.36 (m, 6H), 2.50 (br, 2H), 2.61 (br, 2H), 6.00-6.65 (m, 4H), 7.08-7.27 (m, 10H), 7.45-7.75 (m, 4H). Mp: 100 - 102°C. IR: 3300, 1654, 1598cm^{-1}. FAB-MS *m/z* 808 (M^+), 638 (M^+-170), 155 (M^+-635), 91 (M^+-717). Anal. Calcd for $C_{36}H_{34}Cl_4N_4O_5S_2$: C, 53.47; H, 4.24; N, 6.93. Found: C, 53.60; H, 4.16; N, 7.08.

2,4-Di(1-*p*-methoxylphenyl-*N*-tosyl-aminomethyl)-5-piperidinyl-1,3-oxazole (3f) ^{1}H NMR ($CDCl_3$/TMS): δ 1.56 (br, 6H), 2.35 (m, 6H), 2.60 (br, 4H), 3.76 (s, 6H), 5.40 (m, 2H), 5.75-6.15 (m, 2H), 6.76 (m, 4H), 7.10 (m, 8H), 7.50 (m, 4H). Mp: 66 - 68°C. IR: 3268, 1611cm^{-1} FAB-MS *m/z* 730 (M^+), 560 (M^+-170), 155 (M^+-575), 91 (M^+-639). Anal. Calcd for $C_{38}H_{42}N_4O_6S_2$: C, 62.44; H, 5.79; N, 7.36. Found: C, 62.12; H, 5.85; N, 7.70.

2,4-Di(1-*p*-chlorophenyl-*N*-tosyl-aminomethyl)-5-*N*,*N*-dimethyl-1,3-oxazole (3g) ^{1}H NMR ($CDCl_3$/TMS): δ 2.35 (m, 6H), 2.49 (s, 3H), 2.51 (s, 3H), 5.45 (m, 2H), 5.85 (m, 2H), 7.1-7.5 (m, 16H). Mp: 102 - 104°C. IR: 3301, 1658, 1599cm^{-1}. FAB-MS *m/z* 699 (M^+ + 1), 155 (M^+-544), 91 (M^+-608). Anal. Calcd for $C_{33}H_{32}Cl_2N_4O_5S_2$: C, 56.65; H, 4.60; N, 8.00. Found: C, 56.50; H, 4.52; N, 7.98.

2,4-Di(1-*p*-nitrophenyl-*N*-tosyl-aminomethyl)-5-*N*,*N*-dimethyl-1,3-oxazole (3h) ^{1}H NMR ($CDCl_3$/TMS): δ 2.35 (m, 6H), 2.55 (s, 3H), 2.56 (s, 3H), 5.54 (m, 2H), 6.24-6.44 (m, 2H), 6.98-7.08 (m, 4H), 7.35 (m, 4H), 7.55 (m, 4H), 8.00 (m, 4H). Mp: 94 - 96°C. IR: 3264, 1699, 1620cm^{-1}. FAB-MS *m/z* 720 (M^+ + 1), 155 (M^+-565), 91 (M^+-629). Anal. Calcd for $C_{33}H_{32}N_6O_9S_2$: C, 54.99; H, 4.47; N, 11.66. Found: C, 55.01; H, 4.72; N, 11.14.

The Procedure for *N*-Sulfonylimine (1a) with Isocyanoacetamide (2c). A mixture of *N*-sulfonylimine (**1a,** 0.70 mmol), and α-methyl isocyanoacetamide (**2c,** 0.70 mmol) was stirred in 2 ml CH_2Cl_2 at 25 °C for 36 h under nitrogen. After removal of the solvent, the residue was isolated by preperative TLC eluting with a mixture of petroleum ether (60-90 °C) and ethyl acetate (2:1) to give **3i** in 53 % yield.

2-(1-*p*-chlorophenyl-*N*-tosyl-aminomethyl)-4-methyl-5-piperidinyl-1,3-oxazole (3i) ^{1}H NMR ($CDCl_3$/TMS): δ 1.53 (m, 6H), 1.91 (s, 3H), 2.35 (s, 3H), 2.80 (m, 4H), 5.48 (d, J = 7.86 Hz, 1H), 5.96 (d, J = 7.86 Hz, 1H), 7.20 (m, 6H), 7.60 (d, J = 12.6 Hz, 2H). Mp: 114 - 116°C. IR: 3351, 1672, 1601cm^{-1}. MS *m/z* 459 (M^+ , 47), 304 (46), 289 (100), 155 (26), 91 (49). Anal. Calcd for $C_{23}H_{26}N_3SO_3Cl$: C, 60.05; H, 5.69; N, 9.13. Found: C, 59.87; H, 5.50; N, 8.85.

Typical Procedure for Reaction of *N*-Sulfonylimine with Isocyanoacetamide Using NaH as Base To a stirred suspension containing 22mg (0.5 mmol) of NaH (ca. 55 % in mineral oil) in 2ml of CH_2Cl_2 was added a mixture of *N*-sulfonylimine (**1**, 0.46 mmol) and isocyanoacetamide (**2a**, 0.5 mmol) dissolved in 2ml of CH_2Cl_2 at 0°C under N_2. After the addition had been completed, the reaction mixture was stirred for 1 h at rt. 4 ml of water was added and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), concentrated, and purified by preperative TLC to give imidazoline (**5**).

***trans*-4-(piperidinyl)carboxamide-5-(*p*-chlorophenyl)-1-*N*-tosy-2-imidazoline(4a)** ^{1}H NMR ($CDCl_3$/TMS): δ 1.60 (m, 6H), 2.42 (s, 3H), 3.40 (m, 2H), 3.57 (m, 2H), 4.69 (d, J = 7.51 Hz, 1H), 5.50 (d, J = 7.51, 1H), 7.16 (d, J = 8.35 Hz, 2H), 7.26 (m, 5H), 7.55 (d, J = 7.90 Hz, 2H). IR: 3300, 1640cm^{-1}. MS *m/z* 446(M^++1, 0.8), 333(14), 290(17), 155(29), 112(100), 91(41). Anal. Calcd for $C_{22}H_{24}ClN_3SO_3$: C, 59.25; H, 5.42; N, 9.42. Found: C, 59.00; H, 5.31; N, 9.06.

***trans*-4-(piperidinyl)carboxamide-5-(*p*-methylphenyl)-1-*N*-benzenesulfonyl-2-imidazoline(4b)** ^{1}H NMR ($CDCl_3$/TMS): δ 1.52 (m, 6H), 2.27 (s, 3H), 3.40 (m, 2H), 3.60 (m, 2H), 4.77 (d, J = 7.22 Hz, 1H), 5.49 (d, J = 7.22, 1H), 7.02 (m, 3H), 7.45 (m, 2H), 7.59 (m, 2H), 7.67 (d, J = 7.59, 2H). IR: 3300, 1650cm^{-1}. MS *m/z* 412(M^++1, 19), 299(16), 270(34), 141(29), 112(100), 84(21). Anal. Calcd for $C_{22}H_{24}N_3SO_3$: C, 64.21; H, 6.12; N, 10.21. Found: C, 63.98; H, 6.14; N, 9.94.

***trans*-4-(piperidinyl)carboxamide-5-furyl-1-*N*-tosyl-2-imidazoline(4c)** ^{1}H NMR ($CDCl_3$/TMS): δ 1.52 (m, 6H), 2.41 (s, 3H), 3.37 - 3.57 (m, 4H), 5.05 (dd, J = 7.59, 2.25 Hz, 1H), 5.70 (d, J = 7.59 Hz, 1H), 6.26 (d, J = 3.19 Hz, 1H), 6.38 (d, J = 3.19 Hz, 1H), 7.25 (m, 3H), 7.47 (d, J = 2.25 Hz, 1H), 7.57 (d, J = 8.27

Hz, 2H). IR: 3300, 1640cm^{-1}. MS *m/z* 402(M^++1, 1), 289(5), 246(28), 155(16), 112(100), 91(28), 84(12). HRMS Calcd for ($C_{13}H_{16}N_3O_2$, M^+-Ts): 246.1242, Found: 246.1226.

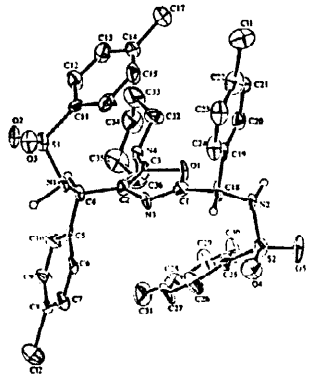
The procedure for the preparation of 9. Isocyanoacetamide **2a** (302 mg, 1.98 mmol) was dissoved in 2 ml benzene and 391 mg (1.98 mmol) *p*-toluenesulfonyl isocyanate was added at room temperature. After one hour, the benzene was removed and the residue was washed with ether for three times (3 x1ml). Recrystallization from isopropanol gave white crystals in 75 % yield.

***N*-(4-Toluenesulfonyl)-5-piperidinyl-2-oxazolecarboxamide (9)** ^{1}H NMR ($CDCl_3$/TMS): δ 1.62 (br, 6H), 2.42 (s, 3H), 3.25 (br, 4H), 6.04 (s, 1H), 7.32 (d, J = 8.27 Hz, 2H), 8.01 (d, J = 8.27 Hz, 2H), 9.32 (br, 1H). Mp: 128 - 130°C. IR: 1702, 1597cm^{-1}. MS *m/z* 349(M^+, 33), 242(100), 155(26), 112(8), 91(70), 84(14). HRMS Calcd for ($C_{16}H_{19}N_3O_4S$): 349.1096, Found: 349.1097.

References and Notes:

1. Potts, K. T. in *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 1.
2. For the synthesis of 2-oxazoline using isocyanide as synthon: (a) Hoppe, D.; Schöllkopf, U. *Liebigs. Ann. Chem.* **1972**, *763*, 1. (b) Matsumoto, K.; Ozaki, Y.; Suzuki, M.; Miyoshi, M. *Agric. Biol. Chem.* **1976**, *40*, 2045. (c) *Catalytic Asymmetric Synthesis* Ojima, I. Ed.: VCH Publishers, New York, 1993. (d) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (e) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 5935. (f) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649. (g) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073. (h) Sawamura, M.; Nakayama, Y.; Kato, T. Ito, Y. *J. Org. Chem.* **1995**, *60*, 1727. (i) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 4370.
3. For the synthesis of 2-imidazoline using isocyanide as synthon: (a) Meyer, R.; Schöllkopf, U.; Böhme, P. *Liebigs. Ann. Chem.* **1977**, 1183. (b) Van Leusen, A. M.; Wildeman, J; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153. (C) Schöllkopf, U. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339. (d) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969.
4. Lin, Y.-R.; Zhou, X.-T.; Dai, L-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799.

5. X-ray crystallographic of **3a**:



6. (a) Schöllkopf, U. *Pure. Appl. Chem.* **1979**, *51*, 1347. (b) Van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 2369.
7. Van Leusen, A. M. *Lect. Heterocyl. Chem.* **1980**, *5*, 11. (Supplementary issue *J. Heterocycl. Chem.* **1980**, 17.
8. For general method for the synthesis of oxazoles: (a) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99. (b) Turchi, I. J.; Dewar, M.J.S. *Chem. Rev.* **1975**, *75*, 389. (c) Potts, K. T. in *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 6. p 177. (d) Shinkai, I. in *Comprehensive Heterocyclic Chemistry II*; Katritzky, A., Rees, C. W., Scriven, E. V.; Eds.; Elsevier Science: Oxford, 1996; Vol. 3. p 261.
9. Note: the order of electrophilicity could be qualitatively considered as PhCH=NTs > PhCHO. Li, A. -H.; Dai, L. -X.; Hou, X. -L.; Chen, M. -B. *J. Org. Chem.* **1996**, *61*, 4641.
10. Chupp, J. P.; Leschinsky, K. L. *J. Heterocyclic. Chem.* **1980**, *17*, 711.
11. For the formation of oxazoles through intramolecular 1,5-cyclization of nitrile ylide intermediates: (a) Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181. (b) Connell, R.; Scavo, F.; Helquist, P.; Akermark, B. *Tetrahedron Lett* **1986**, *27*, 5559. (c) Ibata, T.; Fukushima, K. *Chem. Lett.* **1992**, 2197.
12. (a) Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35(2)*, 1441. (b) Iddon, B. *Heterocycles.* **1994**, *37(2)*, 1321. (c) Levin, J. I.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 4325. (d) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111. (e) Wasserman, H. H.; McCarthy, K. E.; Prowes, K. S. *Chem. Rev.* **1986**, *86*, 845. (f) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1987**, *52*, 3413. (g) Pridgen, L. N.; Shilcrat, S. C. *Synthesis.* **1984**, 1048. (h) Whitney, S. E.; Winters, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 929.
13. Fleming, I. *in Comprehensive Organic Sythesis*, Trost, B. M.; Fleming, I., Eds,; Pergamon Press: Oxford, 1991, Vol. 8, p. 650.

14. (a) Evans, D. A.; Dinsmore, C. J.; Ratz, A. M.; Evrard, D. A.; Barrow, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 3417. (b) Evans, D. A.; Barrow, J. C.; Watson, P. S.; Ratz, A. M.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. E.; Ellman, J. A.; Rychnovsky, S. D.; Lacour, J. *J. Am. Chem. Soc.* **1997**, *119*, 3419. (c) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T.-Y.; Brase, H. L. S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421. (d) Boger, D. L.; Zhou, J.-C.; Borzilleri, R. M.; Nukui, S.; Castle, S. L. *J. Org. Chem.* **1997**, *62*, 2054.

15. Love, B. E.; Raje, P. S.; Williams, T. C. *Synlett.* **1994**, 493.

16. (a) Matsumoto, K.; Suzuki, M.; Yoneda, N.; Miyoshi, M. *Synthesis.* **1977**, 249. (b) Ozaki, Y.; Matsumoto, K.; Miyoshi. *Agric. Biol. Chem.* **1978**, *42*, 1565.

Acknowledgment. Financial supports from National Natural Science Foundation of China (project number 29772046) and Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry are gratefully acknowledged.