A Mild and Convenient Synthesis of 4-Tosyl-4,5-dihydrooxazoles

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Received October 23, 2008: Revised March 04, 2009: Accepted March 04, 2009

Abstract: A facile and mild synthesis of 4-tosyl-4,5-dihydrooxazoles is described. The reaction between tosyl methyl isocyanide (TosMIC) and cinnamic or aromatic aldehydes is catalyzed by triethylamine, affording *trans*-5-styryl- or 5-aryl-4-tosyl-4,5-dihydrooxazoles in quantitative yields without further purification. The mild reaction conditions allowed for the first time the use of cinnamaldehyde derivatives with excellent results.

Keywords: TosMIC, Catalytic reaction, α,β-Unsaturated aldehydes, Oxazolines, 4,5-Dihydrooxazoles.

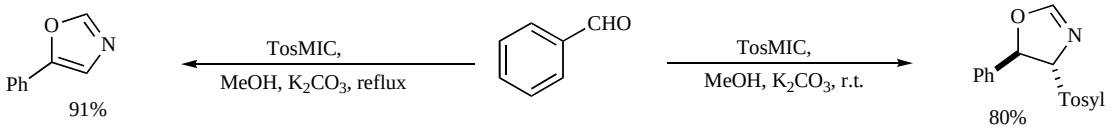
The discovery of new reaction protocols that allow us to build complex molecular scaffolds in an efficient way from readily available starting materials and in mild conditions remains a challenging goal in chemical synthesis. The aldol-type condensation of aldehydes and isocyanides containing an electron-withdrawing group at the α-carbon atom provides an important method for the preparation of synthetically useful 4,5-disubstituted-4,5-dihydrooxazoles. The chemistry of tosyl methyl isocyanide (TosMIC) [1] has been extensively elaborated by the Dutch chemist A. M. van Leusen and his school. TosMIC constitutes by far the most versatile synthon derived from methyl isocyanide and exhibits a multifaceted chemistry that is of great utility in organic synthesis [2].

Since the pioneering discovery of A. M. van Leusen [3] of the reaction between aldehydes and TosMIC mediated by alkali metal bases in 1972, few other methods for the synthesis of 4-tosyl-4,5-dihydrooxazoles have been reported. In organometallic chemistry there are several examples such as the silver catalyzed reaction developed by Ito and coworkers [4]. In 2002, Motoyama and coworkers disclosed a very elegant synthesis of 4-tosyl-4,5-dihydrooxazoles using metal catalysts such as Ag, Au or Pt [5]. However, to the best of our knowledge there are no methods that allow us to build 4-tosyl-4,5-dihydrooxazoles without the use of metals or in mild conditions.

In the van Leusen original paper [3], the reaction furnished the elimination product (a 5-substituted oxazoline) in good yields; however, when less drastic conditions were used the precursor 4-tosyl-4,5-dihydrooxazoles were obtained only in moderate yields (Scheme **1**).

When we attempted to apply van Leusen's procedure (TosMIC, K_2CO_3, refluxing methanol) to an α,β-unsaturated aldehyde (cinnamaldehyde), the oxazole product was obtained in much lower yield, and chromatographic purification was necessary to isolate the desired compound from a complex reaction mixture. On the other hand, when the reaction was performed at room temperature, the conversion after 24 h, monitored by NMR, was very low, and the formation of numerous side-products was again apparent (Scheme **2**).

With this chemo-information in mind, we decided to develop a new, organocatalytic approach to the synthesis of 4-tosyl-4,5-dihydrooxazoles that could be safely applied to α,β-unsaturated aldehydes. In initial experiments we screened different reaction conditions for the reaction of TosMIC **1** with cinnamic aldehyde **2a** (Table **1**). The reaction did not proceed in the absence of base (entries 1-3), and very low yields were achieved in chloroform solution when one molar equivalent of triethylamine was added to the reaction mixture (entry 4). To our delight, when methanol was used as a solvent at room temperature in the presence of either a stoichiometric (entry 5) or of a catalytic amount of triethylamine (entry 6), the reaction furnished the desired 4-tosyl-5-styryl-4,5-dihydrooxazole **3a** in quantitative yield and, as expected, with very high *trans*-diastereoselectivity (only one isomer was detected by NMR). Moreover, since both the solvent and triethylamine are volatile, the work-up of the reaction is a simple evaporation of the solvent from the reaction mixture that affords the compound **3a** in essentially pure form.



Scheme 1. Van Leusen synthesis of 4,5-dihydrooxazoles (2-oxazolines) and of oxazoles.

Next, we decided to screen different α,β-unsaturated aldehydes in order to study the scope of this convenient

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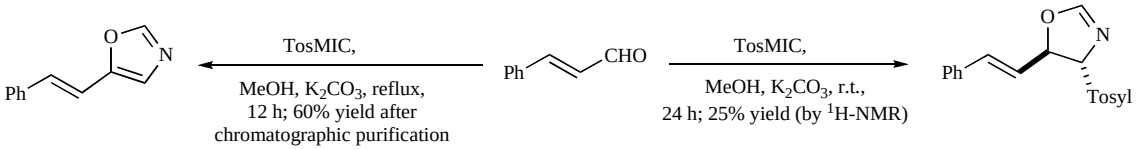
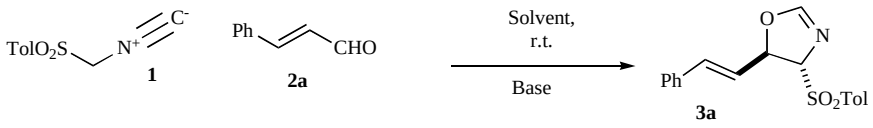


Scheme 2. Application of the van Leusen procedure to cinnamaldehyde.

Table 1. Optimized Conditions for the Synthesis of (*E*)-4-Tosyl-5-styryl-4,5-dihydrooxazole 3a[a]

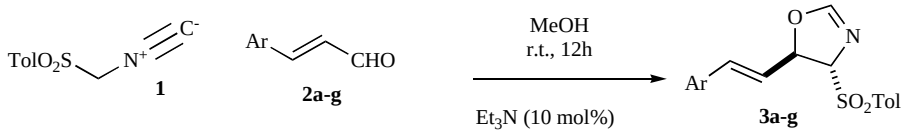


1 **2a** **3a**

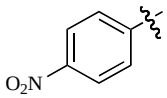
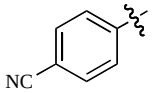
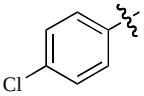
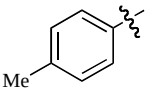
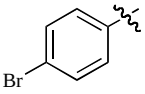
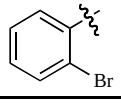
Entry	Solvent	Base	Yield (%)[b]	Dr[c]
1	$CDCl_3$	-	0	-
2	MeOH	-	0	-
3	Toluene	-	0	-
4	$CDCl_3$	Et_3N (1equiv.)	10	>25:1
5	MeOH	Et_3N (1equiv.)	100	>25:1
6	MeOH	Et_3N (10 mol%)	100	>25:1

[a]Experimental conditions: A mixture of cinnamaldehyde **2a** (0.25 mmol), base, and tosyl methyl isocyanide **1** (0.25 mmol) in the solvent indicated (1mL) was stirred at room temperature overnight. The product **3a** was isolated after evaporation of the reaction mixture.
[b]Isolated yield.
[c]Determined by ^{1}H-NMR analysis of crude reactions.

Table 2. Cinnamic Aldehyde Scope[a]

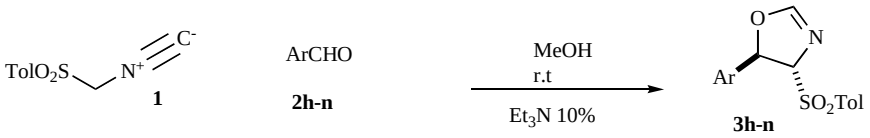


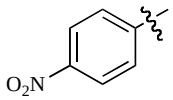
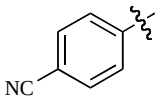
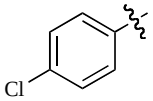
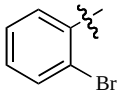
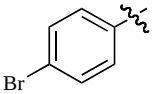
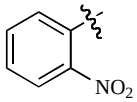
1 **2a-g** **3a-g**

Entry	Product	Ar	Yield (%)[b]	Dr[c]
1	**3a**	Ph	100	>25:1
2	**3b**		100	>25:1
3	**3c**		100	>25:1
4	**3d**		100	>25:1
5	**3e**		100	>25:1
6	**3f**		100	>25:1
7	**3g**		100	>25:1

[a]Experimental conditions: A mixture of aldehyde **2a-g** (0.25 mmol), Et_3N (10%, 0.025 mmol), and tosyl methyl isocyanide **1** (0.25 mmol) in MeOH (1mL) was stirred at room temperature overnight. The pure products **3a-g** were isolated after evaporation of the solvent.
[b]Isolated yield.
[c]Determined by ^{1}H-NMR analysis of the crude reaction mixtures.

Table 3. Aromatic Aldehyde Scope[a]



Entry	Product	Ar	Yield (%)[b]	Dr[c]
1	**3h**	Ph	100	>25:1
2	**3i**		100	>25:1
3	**3j**		100	>25:1
4	**3k**		100	>25:1
5	**3l**		100	>25:1
6	**3m**		100	>25:1
7	**3n**		100	>25:1

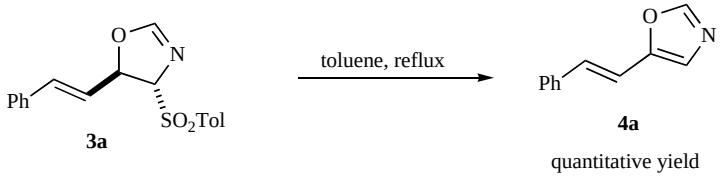
[a]Experimental conditions: A mixture of aldehyde **2h-n** (0.25 mmol), Et_3N (10%, 0.025 mmol), **1** (0.25 mmol) in MeOH (1mL) was stirred at room temperature overnight. Products **3h-n** were isolated after evaporation of the solvent.
[b]Isolated yield.
[c]Determined by ^{1}H-NMR analysis of the crude reaction mixture.

methodology. Remarkably, we obtained the final compounds **3** in quantitative yields in all of the examples investigated (Table **2**). There are no differences for different substitution of the phenyl ring in cinnamic aldehydes. In all the examples we observe an extremely high (>25:1 d.r.) diastereoselectivity, probably arising from the greater thermodynamic stability of the *trans* isomer and from the ready epimerization of the C4 stereogenic center.

In order to expand the scope of the process, we applied the previously optimized reaction conditions to several aryl aldehydes. To our delight, in all the examples the products were obtained in quantitative yield and with essentially complete diastereoselectivity (Table **3**) [6].

These 4-tosyl-4,5-dihydrooxazoles **3** can be easily transformed to the corresponding 5-substituted oxazoles **4** by simply heating in toluene as exemplified in Scheme **3** for (*E*)-5-styryl-1,3-oxazole **4a**.

In summary, we have developed a mild and convenient methodology to synthesize 5-substituted-4-tosyl-4,5-dihydrooxazoles from aromatic or α,β-unsaturated aldehydes and TosMIC, that takes place in quantitative yields and with very high *trans*-diastereoselectivities. Moreover, the work-up of the reaction is a simple evaporation of the solvent that gives the desired products in essentially pure form without any further purification.



Scheme 3. Synthesis of oxazoles.

EXPERIMENTAL SECTION

Representative Procedure for the Synthesis of 4-Tosyl-4,5-dihydrooxazoles: Synthesis of *trans*-(*E*)-5-(4-Nitrostyryl)-4-tosyl-4,5-dihydrooxazole 3b

In a small vial, 49 mg of TosMIC **1** (0.25 mmol, 1 equiv), 44 mg of 3-(4-nitrophenyl)-2-propenal **2b** (0.25 mmol, 1 equiv), and 2.5 mg (0.025 mmol) of Et_3N were dissolved in 1 mL of MeOH. The reaction was stirred at room temperature overnight. Next, the solvent and triethylamine were removed at reduced pressure to afford the pure compound **3b** (93 mg) in quantitative yield.

^{1}H NMR ($CDCl_3$, 400 MHz): 8.21 (d, *J* = 9.0 Hz, 2H), 7.86 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.10 (s, 1H), 6.84 (d, *J* = 15.8 Hz, 1H), 6.32 (dd, *J* = 6.9 Hz, *J'* = 15.8 Hz, 1H), 5.72 (t, *J* = 6.9 Hz, 1H), 4.99 (d, *J* = 6.2 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz): 159.4, 146.1, 141.6, 133.2, 132.0, 130.2, 129.7, 128.9, 127.7, 127.5, 124.3, 90.6, 78.6, 22.0.

HRMS (ESI): Calcd. for $C_{18}H_{17}N_2O_5S$ $[(M+H)^+]$, 373.0853; found, 373.0864; calcd. for $C_{18}H_{17}N_2NaO_5S$ $[(M+Na)^+]$, 395.0672; found, 395.0679.

Representative Procedure for the Synthesis of 5-Substituted Oxazoles: Synthesis of (*E*)-5-Styryloxazole 4a

In a round-bottomed flask, a solution of compound **3a** (82 mg, 0.25 mmol) in toluene (4 mL) was heated at reflux for 3 h. Next, the crude was directly purified by column chromatography on silica gel (hexanes-ethyl acetate) to afford compound **4a** (43 mg, quantitative yield).

^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ (ppm) = 7.84 (s, 1H), 7.50-7.28 (m, 5H), 7.11 (d, J=10.2 Hz, 1H), 7.07 (s, 1H), 6.91 (d, J=10.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 150.5, 150.4, 136.4, 130.5, 129.0, 128.6, 126.8, 124.3, 113.1.

HRMS (ESI): Calcd. for $C_{11}H_{10}NO$ $[(M+H)^+]$, 172.0762; found, 172.0757.

ACKNOWLEDGEMENT

We thank the Spanish Ministry of Science and Innovation for financial support (Project AYA2006-15648-C02-01).

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