Preparation of Substituted Oxazoles by Ritter Reactions of α-Oxo Tosylates

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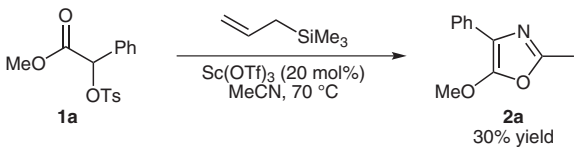
Abstract: The Lewis acid catalyzed Ritter reaction of α-oxo tosylates with nitriles forms the basis of an efficient synthesis of oxazoles. Oxazoles with various substituents can be readily prepared from inexpensive starting materials.

Key words: heterocycles, cyclizations, nitriles, carbocations, oxazoles, Ritter reaction

The oxazole ring is widely found in medicinal agents, biologically active natural products, and organic materials.[1] Much effort has been devoted towards devising methods for the synthesis of substituted oxazoles. Although venerable protocols such as the Robinson–Gabriel dehydration of 2-acylamino ketones[2] and the Cornforth method[3] remain in widespread use, metal-catalyzed reactions are growing rapidly in popularity and frequency of application.[4] Here, we report a general protocol for the synthesis of oxazoles by means of the Ritter reaction of α-oxo carbocations.[5] This approach permits the construction of a range of trisubstituted oxazoles from two readily available classes of organic feedstocks: nitriles and α-hydroxy carbonyl compounds.

In the course of developing carbon–carbon bond-forming reactions of α-carbonyl carbocations as 'reversed polarity' variants of the enolate alkylation reactivity pattern,[6] we explored the reaction of the methyl mandelate-derived tosylate **1a** with allyl(trimethyl)silane catalyzed by scandium trifluoromethanesulfonate in acetonitrile (Scheme 1). The expected allylation product was not observed; instead, oxazole **2a** was obtained, presumably through a Ritter reaction with the solvent, followed by ring closure of the resulting nitrilium ion and loss of a proton.



Scheme 1 Unexpected formation of oxazole **2a** from methyl mandelate-derived tosylate **1a**

We were surprised to find, upon surveying the literature, that this mode of reactivity is underexploited as a method for the synthesis of oxazoles. Although Lora-Tamayo and coworkers described the tin (IV) chloride-mediated Ritter reaction of α-halo ketones more than 40 years ago,[7] the need for stoichiometric quantities of tin-based reagents together with the rather limited availability of α-halo ketones appear to have discouraged the use of this method.[8] A related transformation is the reaction of nitriles with reactive unsubstituted α-oxo triflates generated in situ by oxidation of methyl ketones with reagents based on thallium(III),[8] mercury(II),[9] iodine(III),[10] iron(III),[11] or copper(II).[12] These methods provide moderate-to-good yields of 2,4-disubstituted oxazoles, and they are useful in situations where the requisite α-hydroxy or α-sulfonyloxy carbonyl compound is not readily available. However, they are limited in terms of the range of nitriles that can be used, and they require the use of toxic and/or expensive oxidants. In an example that is particularly relevant to the work described here, trifluoromethanesulfonic anhydride was used to oxidize 1-(methylsulfanyl)acetone to the corresponding triflate, which underwent Ritter reaction via a sulfur-stabilized carbocation to generate the corresponding methylsulfanyl-substituted oxazoles.[13]

Another relevant precedent is the metal- or Lewis acid promoted decomposition of α-diazocarbonyl compounds in nitrile solvents; this is a useful method, but one that requires the preparation and/or handling of potentially hazardous diazo compounds.[14] We felt that the ability to access oxazoles from nitriles and α-hydroxycarbonyl compounds, many of which are readily available and inexpensive, could represent a valuable addition to the set of reactions available for the preparation of this important class of heterocycle.[15]

Our experiments aimed at optimizing the lead result shown in Scheme 1 are summarized in Table 1. Whereas scandium triflate was not an adequate catalyst in the absence of allyl(trimethyl)silane (entry 1), other Lewis acids promoted the desired transformation (entries 2–5). Variations in the stoichiometry of trimethylsilyl triflate (TMSOTf), the promoter of choice, revealed that 2.5 equivalents of this reagent were required to obtain high yields (entries 6–8). We examined several solvents with the aim of avoiding the use of the nitrile component as the reaction medium (entries 9–14). The use of 12 equivalents of acetonitrile in 1,2-dichloroethane (DCE) was found to be optimal.

The optimized conditions proved to be applicable to the synthesis of a wide range of trisubstituted oxazoles (Table 2). Variations in the acyl substituent (R^1), the cat-

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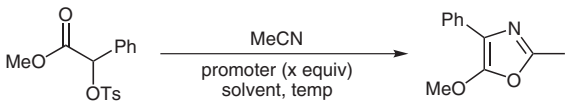
Table 1 Optimization of Reaction Conditions for the Synthesis of Oxazoles

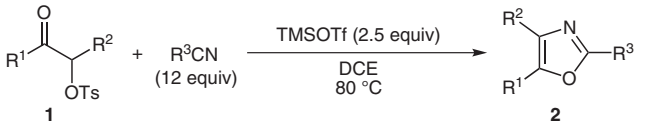


1a **2a**

Entry	Promoter (equiv)	Solvent	MeCN (equiv)	Temp (°C)	Yield (%)[a]
1	$Sc(OTf)_3$ (0.2)	MeCN	–	70	<5
2	BF_3-OEt_2 (2.5)	MeCN	–	70	95
3	$AlCl_3$ (2.5)	MeCN	–	70	30
4	TsOH (2.5)	MeCN	–	70	<5
5	$TiCl_4$ (2.5)	MeCN	–	70	<5
6	TMSOTf (2.5)	MeCN	–	70	>95
7	TMSOTf (1.5)	MeCN	–	70	35
8	TMSOTf (1.0)	MeCN	–	70	22
9	TMSOTf (2.5)	toluene	5	70	<5
10	TMSOTf (2.5)	THF	5	70	<5
11	TMSOTf (2.5)	DME	5	70	<5
12	TMSOTf (2.5)	DCE	5	80	60
13	TMSOTf (2.5)	DCE	10	80	80
14	TMSOTf (2.5)	DCE	12	80	>95

[a] Yield (0.2 mmol scale) determined by GC/MS using dodecane as a quantitative internal standard.

Table 2 Preparation of Substituted Oxazoles by the Ritter Reaction



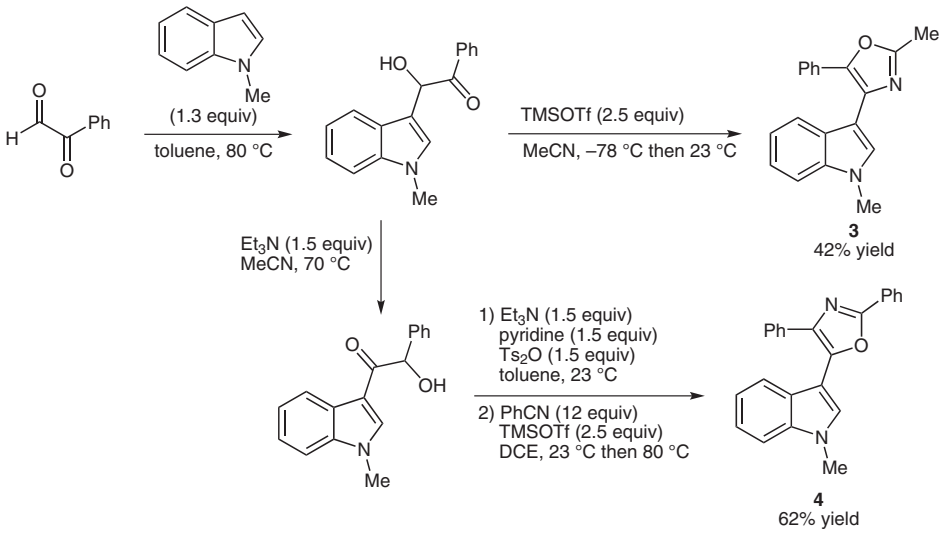
1 **2**

Entry	R^1	R^2	R^3	Product	Yield (%)[a]
1	OMe	Ph	Me	**2a**	99
2	OMe	Ph	Ph	**2b**	65
3	OEt	Ph	Ph	**2c**	82
4	O*i*-Pr	Ph	Ph	**2d**	55
5	piperidin-1-yl	Ph	Ph	**2e**	75[b]
6	Ph	Ph	Ph	**2f**	84
7	OEt	4-BrC_6H_4	Ph	**2g**	77
8	OEt	4-$MeOC_6H_4$	Ph	**2h**	89[b]
9	OEt	3,4-$(OCH_2O)C_6H_3$	Ph	**2i**	65[b]
10	Ph	Ph	Me	**2j**	92
11	Ph	Ph	Et	**2k**	76
12	Ph	Ph	hexyl	**2l**	90
13	Ph	Ph	*t*-Bu	**2m**	97
14	Ph	Ph	vinyl	**2n**	82

[a] Isolated yield after recrystallization or column chromatography. See experimental section and Supporting Information for details.
[b] Trifluoroacetate was used as the leaving group instead of tosylate.

ion-stabilizing substituent (R^2), and the nitrile substituent (R^3) were well tolerated. When cation-stabilizing 4-methoxyphenyl or 3,4-(methylenedioxy)phenyl groups were used, the preparation of the requisite α-oxo tosylates was challenging. In these cases, the trifluoroacetate leaving group proved to be a suitable replacement. The intrinsic yields of these reactions are generally high; problems associated with the isolation of electron-rich oxazoles by chromatography are responsible for some low yields (entries 2, 5, and 9).

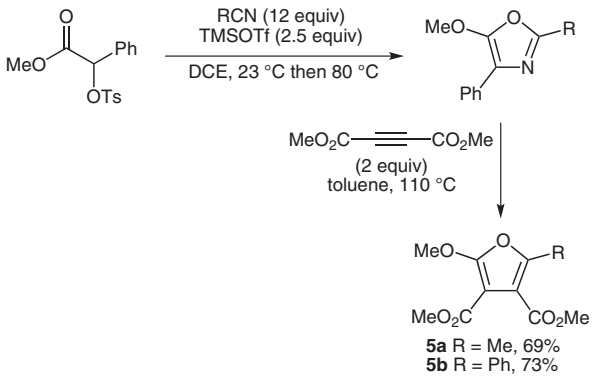
Heteroarene-substituted oxazoles are a class of targets that are well suited to this method (Scheme 2). The



Scheme 2 Preparation of indole-substituted oxazoles

Friedel–Crafts reaction of 1-methyl-1*H*-indole with oxo(phenyl)acetaledehyde (phenylglyoxal) gave an adduct that was sufficiently ionizable to undergo the Ritter reaction below room temperature without prior O-sulfonylation to give the oxazole **3**, bearing an indolyl substituent in the 4-position. Alternatively, base-catalyzed isomerization of the Friedel–Crafts adduct followed by O-sulfonylation and Ritter reaction generated oxazole **4**, bearing an indolyl substituent at the 5-position. As described above, the modest yields of these reactions reflect the moderate stabilities of these electron-rich oxazoles to column chromatography.

Electron-rich alkoxy- and amino-substituted oxazoles, which are obtained in high yields by this method (Table 2, entries 1–5 and 7–9), are useful partners in cycloaddition reactions with alkynes to give furans after expulsion of a nitrile by a retro-[4 + 2] cycloaddition (Scheme 3).[16] Furans **5a** and **5b** were obtained in good yields from **1a** in a two-step process without purification of the intermediate oxazole.



Scheme 3 Cycloaddition of electron-rich oxazoles

In conclusion, the Ritter reaction of α-carbonyl carbocations represents a useful strategy for the preparation of trisubstituted oxazoles. The yields are generally high, and the α-hydroxycarbonyl compounds and nitriles required as starting materials are inexpensive and readily available. Carbocations bearing a carbonyl or carboxyl group in the α-position are an interesting class of reactive intermediates that have not been extensively exploited in synthesis. Efforts to explore their application in other processes are underway in our laboratories.

All reactions were carried out in oven-dried round-bottomed flasks or Schlenk tubes. The flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of N_2 unless otherwise noted. Stainless-steel syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was carried out using neutral silica gel (Silicycle) or basic activated alumina gel (Sigma-Aldrich). HPLC-grade DCE was purchased from Sigma-Aldrich Chemical and dried over oven-activated MS. All other solvents were dried under argon with a solvent-purification system equipped with columns of activated alumina (Innovative Technology, Inc.). Commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, or Lancaster, and used as received. Starting materials were prepared by literature procedures (see Supporting Information). ^{1}H and ^{13}C NMR were recorded by using Varian Mercury 300- and 400-MHz spectrometers. Chemical shifts are reported in ppm relative to TMS, and referenced to residual protium in the solvent ($CHCl_3$: δ = 7.25) or the carbon resonances of the solvent ($CDCl_3$ δ = 77.0). IR spectra were recorded on a Perkin-Elmer Spectrum 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory (intensity, s: strong, m: medium, w: weak). HRMS were recorded on a VS 70-250S (double-focusing) mass spectrometer at 70 eV.

2,4,5-Trisubstituted Oxazoles; General Procedure

DCE (2.5 mL), the nitrile (6 mmol), and TMSOTf (0.23 mL, 1.25 mmol) were added sequentially to a dry flask containing an alkyl 2-aryl-2-(tosyloxy)acetate or 2-oxo-1,2-diphenylethyl tosylate (0.5 mmol, 1 equiv) at 23 °C. The resulting solution was stirred and heated at 80 °C for 20 h, then cooled to 23 °C and diluted with EtOAc (10 mL). The mixture was partitioned between EtOAc and H_2O. The organic phase was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (silica gel or basic activated alumina, 10% or 5% EtOAc–pentane).

5-Methoxy-2-methyl-4-phenyl-1,3-oxazole (2a)

The general procedure was carried out on 0.5 mmol scale using MeCN (0.31 mL, 6 mmol, 12 equiv) and methyl 2-phenyl-2-(tosyloxy)acetate (160 mg, 0.5 mmol). After 20 h at 80 °C, the mixture was worked up as described above. The residue was purified by precipitation from 10% EtOAc–pentane to give a colorless solid; yield: 94 mg (99%).

IR (solid): 3059 (m), 2983 (m), 1739 (w), 1629 (s), 1489 (s), 1381 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 2 H), 7.47 (m, 2 H), 7.40 (m, 1 H), 4.23 (s, 3 H), 2.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 154.2, 129.7, 129.6, 125.5, 123.5, 110.6, 62.2, 13.5.

HRMS (EI): *m/z* calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0790.

1-(2,4-diphenyl-1,3-oxazol-5-yl)piperidine (2e)

The general procedure was carried out on 0.5 mmol scale using benzonitrile (0.62 mL, 6 mmol, 12 equiv) and 2-oxo-1-phenyl-2-piperidin-1-ylethyl 2,2,2-trifluoroacetate **1e** (158 mg, 0.5 mmol). After 20 h at 80 °C, the mixture was worked up as described above. The residue was purified by flash chromatography (basic activated alumina, 5% EtOAc–pentane) to give a colorless solid; yield: 114 mg (75%).

IR (solid): 3056 (w), 2939 (m), 2849 (m), 1607 (s), 1596 (s), 1447 (s), 1382 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (m, 4 H), 7.44 (m, 5 H), 7.23 (m, 1 H), 3.13 (m, 4 H), 1.75 (m, 4 H), 1.63 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 152.8, 132.7, 129.8, 128.8, 128.5, 128.3, 126.8, 126.2, 126.0, 124.1, 51.6, 26.2, 24.2.

HRMS (EI): calcd for $C_{20}H_{20}N_2O$: 304.1576; found: 304.1569.

1-Methyl-3-(2-methyl-5-phenyl-1,3-oxazol-4-yl)-1*H*-indole (3)

MeCN (2.5 mL) and TMSOTf (0.23 mL, 1.25 mmol) were added sequentially to a dry flask containing 2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)-1-phenylethanone (133 mg, 0.5 mmol) at –78 °C. The resulting solution was allowed to warm slowly to 23 °C and stirred at this temperature for 20 h. The solution was then diluted with EtOAc (10 mL) and concentrated in vacuo. Purification of the residue by flash chromatography (basic activated alumina, 10% EtOAc–pentane) gave a yellow solid; yield: 61 mg (42%).

IR (solid): 3043 (w), 2921 (s), 2850 (m), 1584 (s), 1466 (s), 1336 (m), 1265 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (m, 2 H), 7.39 (m, 7 H), 7.05 (t, *J* = 8.4 Hz, 1 H), 3.84 (s, 3 H), 2.57 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 137.0, 129.4, 128.5, 128.4, 128.4, 127.5, 125.9, 125.7, 121.8, 119.7, 109.3, 107.3, 33.0, 14.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1327.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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