

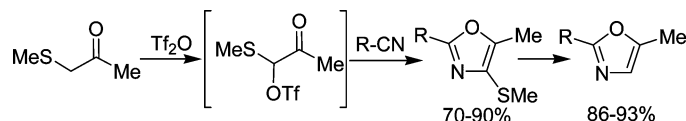
New Easy Approach to the Synthesis of 2,5-Disubstituted and 2,4,5-Trisubstituted 1,3-Oxazoles. The Reaction of 1-(Methylthio)acetone with Nitriles

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The reaction of 1-(methylthio)acetone with different nitriles in the presence of triflic anhydride led to the one-pot formation of 2-substituted 5-methyl-4-methylthio-1,3-oxazoles in good yield. 1,2- and 1,4-Bisoxazolyl-substituted benzenes were obtained when the reaction was carried out using aromatic dinitriles. The methylthio group at the C4 position of the oxazole ring was easily removed with Raney nickel to form 2-substituted 5-methyl-1,3-oxazoles in good yields. 4-Methylsulfonyl derivatives were prepared by the oxidation of the MeS group with *m*-CPBA. The proposed mechanism for the formation of oxazoles involves an unstable 1-(methylthio)-2-oxopropyl triflate, which was detected from the low-temperature NMR spectra.

Introduction

1,3-Oxazole (Chart 1), also known simply as oxazole, is not found in nature in the free state, but the ring is usually encountered as a 2,4-disubstituted oxazole within the structures of complex natural products. A large number of oxazole-containing natural products have been isolated from marine invertebrates and microorganisms, many of which exhibit potent biological activities.^{1–3} The synthesis of natural products with the common biogenic 2,4-disubstituted oxazole moiety has attracted the attention of several chemists.^{4–6} The 2,4-disubstituted oxazoles are formally biosynthesized from acylserine

CHART 1. The 1,3-Oxazole Ring and Its Numbering System



precursors by enzyme-catalyzed cyclodehydration-oxidation.⁷ Synthetic procedures for the preparation of the target oxazoles are based on biomimetic variations of the latter sequence. To date, there is no general synthesis of oxazoles that is satisfactory for the preparation of all substituted analogues.⁸ The most general and widely used method is still the procedure developed by Cornforth and Cornforth⁹ and improved by Yokohama et al.¹⁰ Common methods for the preparation of 2,5- and 2,4,5-substituted oxazoles include dehydration of α -acylaminocarbo-

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nyl compounds,¹¹ catalytic decomposition of α -diazocarbonyl compounds in nitriles,¹² photolysis and pyrolysis of *N*-acyl-isoozalones,¹³ improved and modified Robison–Gabriel reactions,¹⁴ and various rhodium-,¹⁵ ruthenium-,¹⁶ and gold-catalyzed¹⁷ reactions.

The synthetic procedures for the conversion of ketones to oxazoles reported to date involve multistep reactions^{8,18} that suffer one or more drawbacks including reactive starting materials, long reaction times, low yields, and harsh reaction conditions. In contrast, the direct conversion of ketones to substituted oxazoles has received little attention. The reaction of aromatic ketones with thallium(III) acetate¹⁹ or iodobenzene diacetate²⁰ in the presence of TfOH with nitriles affords 2-alkyl-5-aryl disubstituted oxazoles. Aromatic ketones and benzonitrile react in the presence of mercury(II) tosylate under microwave irradiation to form 4-aryl-2-phenyloxazoles.²¹ The treatment of aromatic ketones with [hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene and amides under solvent-free conditions and microwave irradiation gives multisubstituted oxazoles.²² Either strong acidic conditions or hypervalent iodine(III) sulfonates that are not directly available are the principal drawbacks of these procedures. Moreover, a limited class of ketones and nitriles must be used, and the mechanism remains unclear. Therefore, a development of a more convenient and efficient method is needed for the direct preparation of substituted oxazoles from ketones together with an explanation of their formation.

We report here a novel and direct synthesis of oxazoles. The reaction of 1-(methylthio)acetone with various nitriles in the presence of triflic anhydride under mild conditions affords a variety of 2-substituted 5-methyl-4-methylthio-1,3-oxazoles. The MeS group at the C4 position can be easily removed by reductive displacement to form substituted oxazoles with the C4 position free. The methylthio group can also be transformed by oxidation to yield the corresponding 4-methylsulfonyl derivatives. The use of aromatic dinitriles and control of the reaction stoichiometry permits the preparation of mono- and bisoxazolyl derivatives. In addition, we propose a reaction mechanism on the basis of the reactive intermediates observed from low-temperature NMR experiments.

Results and Discussion

The reaction of ketones **1** with nitriles in the presence of triflic anhydride affords substituted pyrimidines **4**.²³ Substituted

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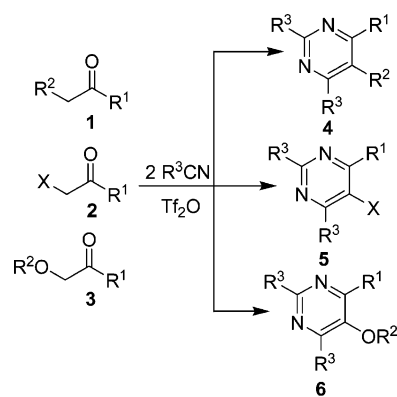
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SCHEME 1. Reaction of α -Substituted Ketones with Nitriles



SCHEME 2. Reaction of 1-(Methylthio)acetone **7** with Nitriles

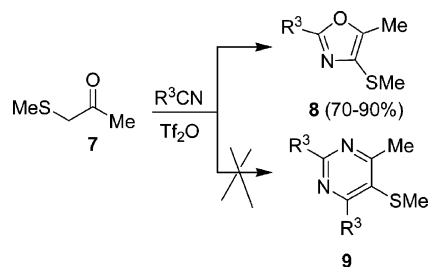


TABLE 1. Preparation of 2,4,5-Trisubstituted 1,3-Oxazoles **8**

nitrile R ³ CN	compound	yield ^a (%)
R ³ = Me	8a	88
R ³ = Et	8b	80
R ³ = MeS	8c	70
R ³ = C ₆ H ₅	8d	92
R ³ = 4-MeC ₆ H ₄	8e	89
R ³ = 4-ClC ₆ H ₄	8f	90
R ³ = 4-MeOC ₆ H ₄	8g	86
R ³ = 4-MeC ₆ H ₄ CH ₂	8h	76
R ³ = 4-ClC ₆ H ₄ CH ₂	8i	75
R ³ = 4-NO ₂ C ₆ H ₄ CH ₂	8j	72

^a Yield of isolated product.

ketones such as α -haloketones **2** undergo the same process giving substituted 5-halopyrimidines **5**.²⁴ Similarly, α -alkoxyketones **3** form the corresponding substituted 5-alkoxy-pyrimidines **6**²⁵ (Scheme 1).

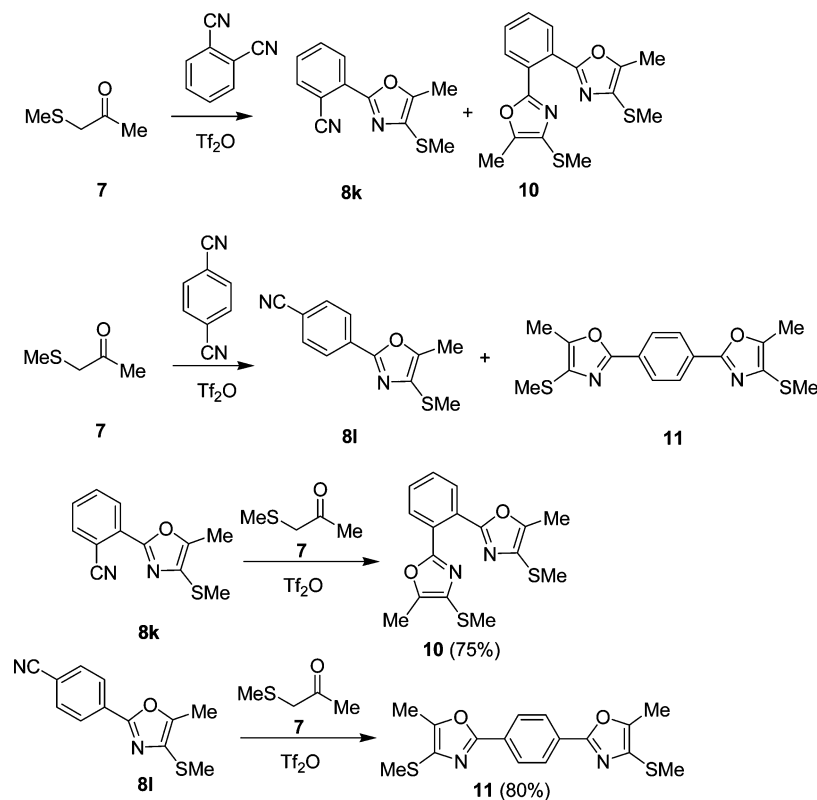
We have extended this synthetic study by examining the reaction of 1-(methylthio)acetone **7** with nitriles in the presence of Tf₂O. In contrast to the previous results, trisubstituted 1,3-oxazoles **8** were formed in good yields, while the expected 5-methylthiopyrimidines **9** were not detected (Scheme 2).

The reaction was carried out under mild conditions (0 °C, 36 h) with a variety of nitriles (Table 1). Higher temperatures considerably reduce the yields. The structure of the nitrile seems to have no influence on the observed yields. The structural elucidation was accomplished by means of one-dimensional

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SCHEME 3. Reaction of Methylthioacetone **7** with Dinitriles to Form Mono- and Bisoxazolyl Derivatives

(1D) and two-dimensional (2D) NMR spectra. These spectra revealed that only one molecule of nitrile is involved in the reaction. The same spectra also showed the formation of three new sp^2 carbon atoms that resonate around 160, 130, and 150 ppm; these signals are almost invariant with respect to substitution.⁸ These signals were assigned to C2, C4, and C5 positions, respectively, on the oxazole ring. In addition, electron impact mass spectra show the characteristic fission of the C2–C3 and C5–O bonds to form the corresponding R^3CO^+ ion, which is frequently the base peak of the spectra.²⁶

We also investigated the reaction of aromatic dinitriles with methylthioacetone **7** and obtained mono- and bisoxazolyl benzene derivatives. Thus, **7** reacts with phthalonitrile in the presence of triflic anhydride to form two new 1,3-oxazoles **8k** and **10**. Similarly, terephthalonitrile gave the new compounds **8l** and **11** (Scheme 3).

Monooxazolyl derivatives **8k** and **8l** are the predominant products if stoichiometric amounts of starting materials are reacted at low temperature. The formation of **10** and **11** was not enhanced by using higher amounts of the starting ketone and a higher temperature (Table 2). Instead, bisoxazolyl derivatives **8k** and **8l** were isolated and then treated again with **7** in the presence of triflic anhydride to afford **10** and **11** in good yields (Scheme 3).

The versatility of the MeS group was used to advantage by its ability to undergo reductive displacement to form oxazoles without substitution at C4. Subsequent deprotonation at this position followed by electrophilic addition can give the corresponding 4-substituted derivatives.²⁷ Reductive desulfuration of

TABLE 2. Temperature and Stoichiometry Dependence of the Product Ratios in the Reaction of Methylthioacetone **7** and Dinitriles

dinitrile	ratio ketone/dinitrile	temp (°C)	product and yield ^a (%)
phthalonitrile	1/1	0	8k (52) + 10 (12)
phthalonitrile	2/1	0	8k (41) + 10 (18)
phthalonitrile	2/1	40	8k (7) + 10 (48)
terephthalonitrile	1/1	0	8l (46) + 11 (22)
terephthalonitrile	2/1	0	8l (36) + 11 (5)
terephthalonitrile	2/1	40	8l (25) + 11 (23)

^a Yield of isolated product.

TABLE 3. Reductive Desulfuration of **8** to 2-substituted 5-Methyl-1,3-oxazoles **12**

starting material	product	yield ^a (%)
8d	12d	86
8g	12g	93

^a Yield of isolated product.

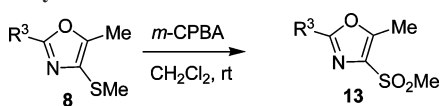
oxazoles **8** was achieved with Raney nickel in ethanol at room temperature.²⁸ Illustrative examples are collected in Table 3. Raney nickel was prepared prior to use, because this commercially available reagent was unable to perform the reaction.

The hydrogen atom at the C4 position of the oxazole ring in compounds **12** was easily observed from the ¹H NMR spectra as it appears as a quartet with a ³J = 1.1 Hz. Signals for methyl groups at C5 which are singlets for compounds **8** become doublets for compounds **12**.

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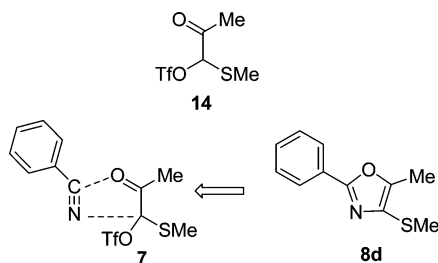
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TABLE 4. Oxidation of Oxazoles **8** To Form 4-Methylsulfonyloxazoles **13**


starting material	product	yield ^a (%)
8c	13c	91
8d	13d	93
8f	13f	97
8j	13j	97

^a Yield of isolated product.

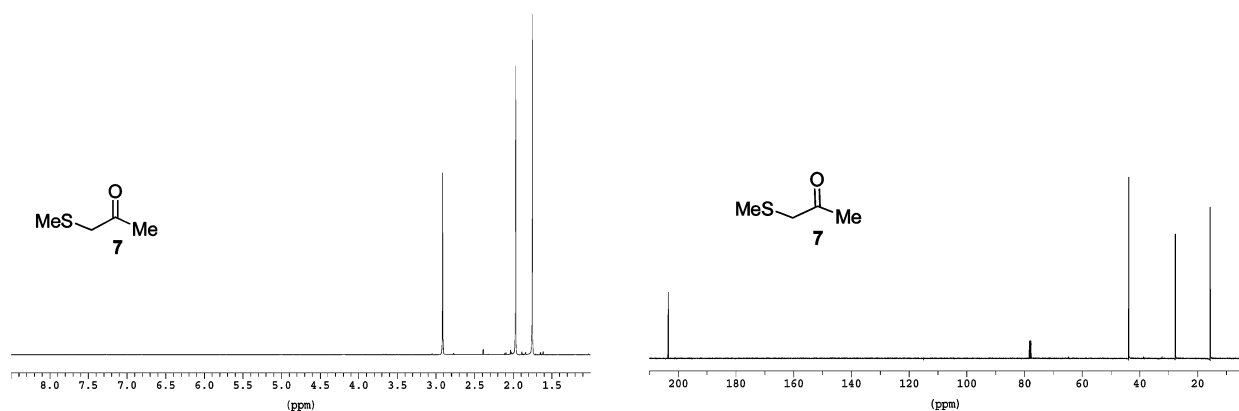
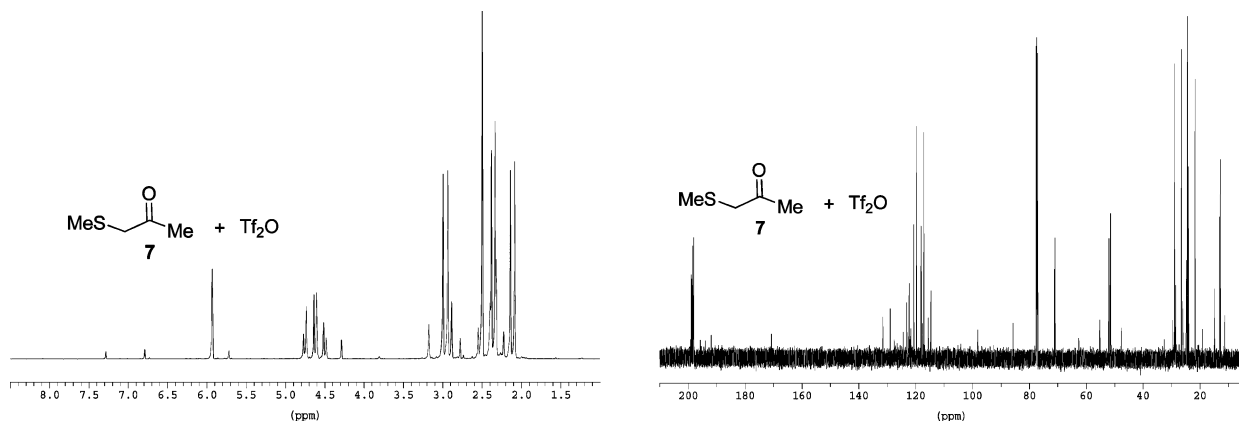
SCHEME 4

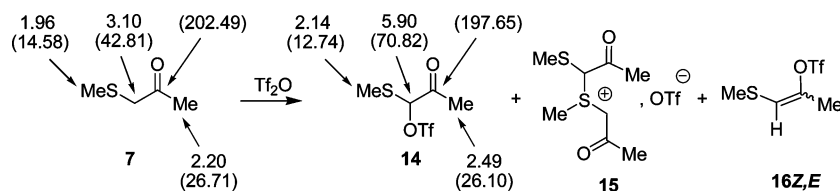
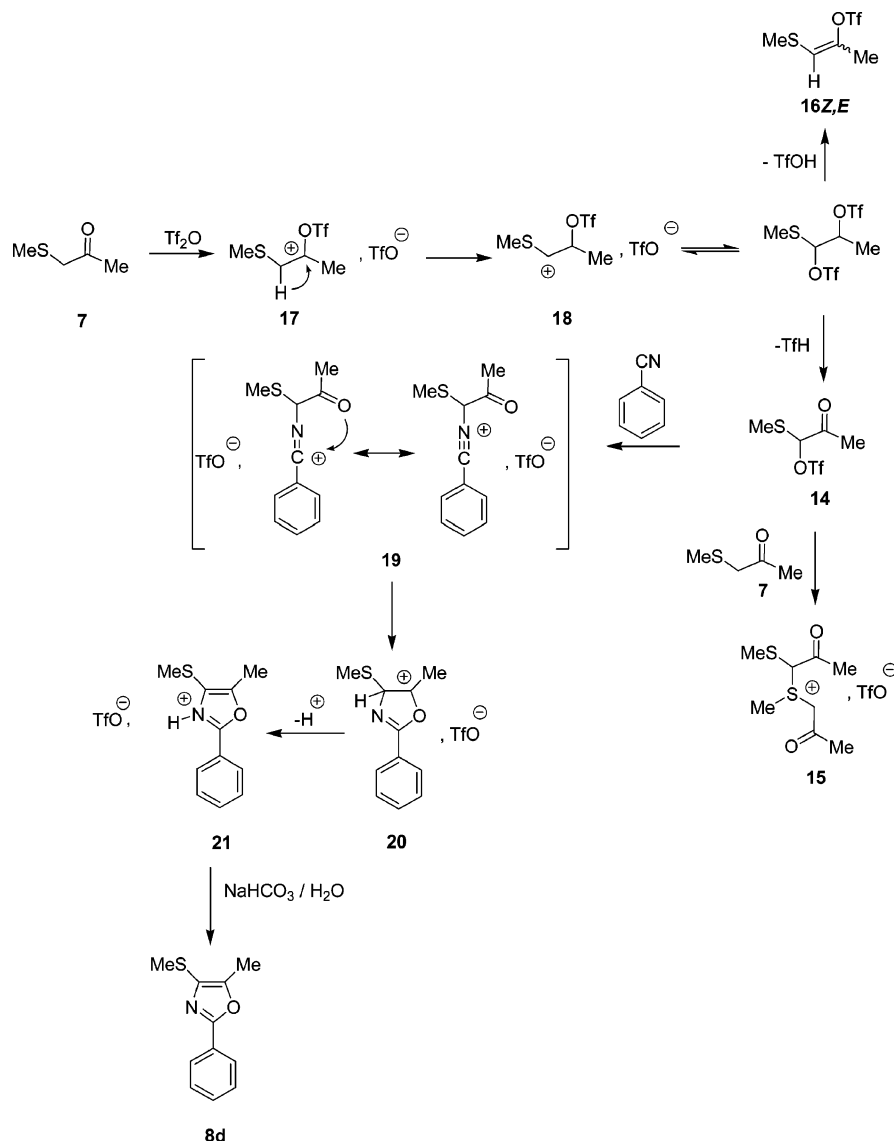
Nucleophilic displacement of the MeS group normally requires very harsh conditions, but these can be avoided if the MeS is oxidized to the methylsulfonyl, a more reactive leaving group. Thus, oxidation of the methylthio group of oxazoles **8** with *m*-CPBA leads to the formation of 4-methylsulfonyl derivatives, **13**. Table 4 gives some illustrative examples.

Studies of nucleophilic substitutions in substituted oxazole rings show that the C2 position is more reactive than the C4 position, with C5 being the least reactive position.²⁹ We carried out the reaction of sulfones **13** with ammonia and with sodium methoxide. In both cases, no reaction products were found, although attempts were carried out with ammonia under atmospheric pressure for 2 days and with sodium methoxide in methanol under reflux for 2 days.

In regard to the mechanism of the formation of the oxazoles, two findings, the participation of only one nitrile molecule and the C–O bond formation (between the carbon of the cyano group and the carbonyl oxygen, Scheme 4), are incompatible with a reaction path involving the intermediate triflioxycarbenium ion that explained prior results.²³ The structure of **8** suggests a nucleophilic attack of the nitrogen atom of the nitrile to the methylene group of thioacetone **7**. For this, the CH₂ group (α to the carbonyl group) needs to be activated by a powerful leaving group triflate, as in the intermediate **14**.

To support this hypothesis, we studied the role of Tf₂O, finding that catalytic amounts of triflic anhydride did not produce a significant reaction of the starting materials. The same results were obtained using a catalytic amount of triflic acid. This indicated that Tf₂O plays an important role in the rate-determining step, probably forming a reactive intermediate. To identify the possible reaction intermediates and to propose a mechanism, we have investigated the reaction at low temperature (5 °C) by means of NMR spectroscopy. ¹H and ¹³C NMR spectra (500 and 125 MHz) of the methylthioacetone **7** are collected in Figure 1. The addition of an equimolar amount of

**FIGURE 1.** ¹H (500 MHz) and ¹³C NMR spectra (125 MHz) of methylthioacetone **7** at 5 °C.**FIGURE 2.** ¹H (500 MHz) and ¹³C NMR spectra (125 MHz) of the reaction mixture after 1 h at 5 °C.

SCHEME 5. Proposed Intermediates and Their Observed ^1H Chemical Shifts (^{13}C Data Are Enclosed in Brackets) in ppmSCHEME 6. Proposed Mechanism for the Formation of Oxazole 8d from Methylthioacetone 7 and Benzonitrile in the Presence of Tf_2O 

Tf_2O produces a significant increase in the number of signals as a result of the formation of several intermediates. The reaction mixture was allowed to stand at this temperature for 1 h (Figure 2). A detailed study of the 1D and 2D spectra (Supporting Information) permits the identification of some reaction intermediates. Among these was the main species detected, 1-(methylthio)-2-oxopropyl triflate **14** (Schemes 4 and 5). Other observed intermediates include compound **15**, which can be considered as the dimer of the starting ketone **7** and vinyl triflate

16, albeit in low concentrations. The integration of the NMR signals has permitted a determination of the intermediate ratio as **14** (40%), **15** (40%), **16Z** (10%), and **16E** (10%). Observed chemical shifts (Supporting Information) were in agreement with the corresponding calculated values.³⁰ The reaction mixture slowly decomposes, and the spectra revealed that any of the above-reported intermediates cannot be detected from the mixture after 15 h at 5 °C (Supporting Information).

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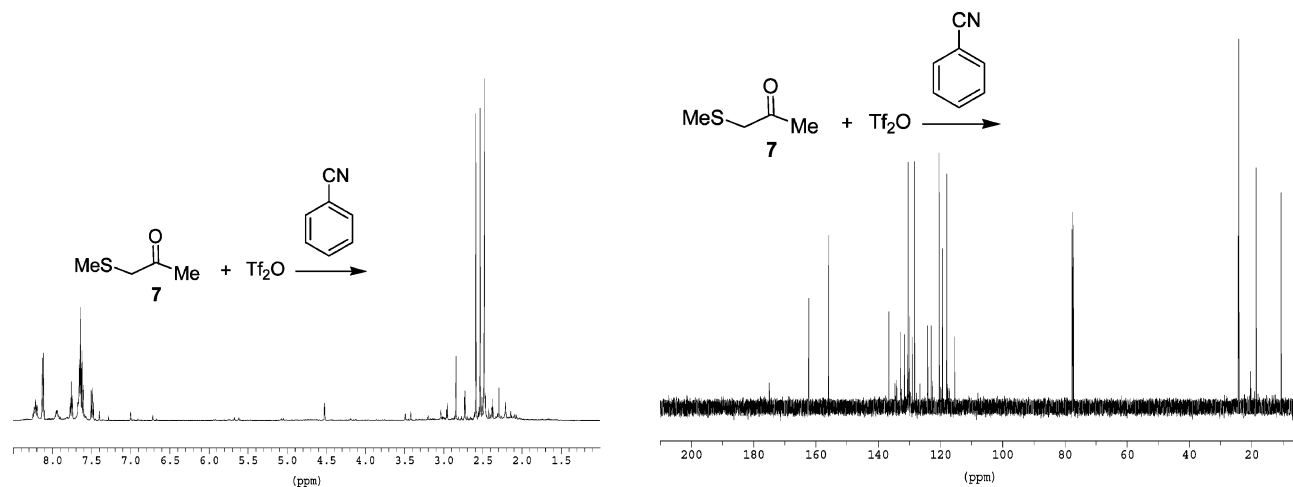


FIGURE 3. NMR spectra of the reaction mixture at 5 °C and 15 h after the benzonitrile addition.

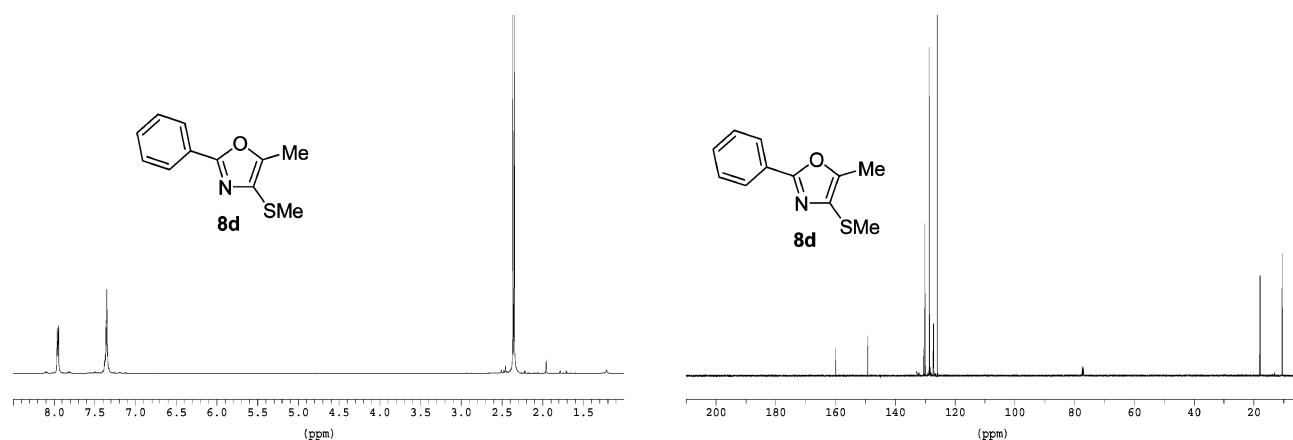


FIGURE 4. ^1H and ^{13}C NMR spectra of compound **8d**.

An addition of an equimolar amount of benzonitrile after 1 h to the reaction mixture produced the slow disappearance of the signals from intermediate **14** and the emergence of new ones that were attributed to the protonated oxazole **20** (Scheme 6). Figure 3 shows the spectra of the reaction mixture after 15 h. Finally, after a 24 h reaction time, the conversion was almost complete. Figure 4 shows the spectra of the final product **8d**, obtained after basic hydrolysis of the reaction mixture.

From the results of the NMR experiments, we propose a mechanism on the basis of the observed intermediates **14** and **15** (Scheme 6). The first step is the formation of a triflioxycarbenium ion **17** that, after a hydride shift, leads to cation **18**, which is stabilized directly by the methylthio group. Subsequent elimination of trifluoromethanesulfonic acid forms the α -keto-triflate **14**. The nucleophilic displacement of the triflate by the nitrogen of the cyano group of nitrile afforded the intermediate **19**. A further cyclization process forms **20**, which leads to a more stable substituted oxazol-3-ium triflate, **21**. Finally, the basic hydrolysis leads to the corresponding oxazole **8d**. The formation of **14** from **7** seems to be the rate-determining step of the reaction. To confirm this, we carried out the competitive reaction of **7** and Tf_2O with two different nitriles in equal amounts (Supporting Information). The ratio products (nearly 1/1) clearly indicated that the reaction pathway is determined by the formation of the intermediate ketotriflate **14**.

To explain the side products **15** and **16**, we propose that **16** is the product of elimination of TfOH from the intermediate **18**, but it is well-known that a vinyl triflate like **16** cannot react with benzonitrile at low temperature.³¹ The formation of the dimer species **15** can be explained from **14** as a result of a nucleophilic displacement of the triflate by methylthio ketone **7**. Hence, due to the formation of dimer **15**, yields of the obtained oxazoles decreased when equimolar amounts of ketone and nitrile were used. Higher amounts of ketone **7** improved notably the yields of oxazoles **8**.

Unstable intermediates such as **14** have been postulated to explain the reaction mechanism of oxazole formation from aryl ketones and thallium(III) acetate or iodobenzene diacetate with TfOH .^{19,20} Neither chemical nor spectroscopic proof was offered to support this hypothesis. The above-reported results represent the first spectroscopic observation of an intermediate α -keto-triflate. Attempts to trap **14** by the addition to the reaction mixture of nucleophiles other than nitriles were unsuccessful. To isolate **14**, we carried out the reaction of **7** with Tf_2O under

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classical conditions to obtain triflates from ketones.³² The instability of **14** did not allow its isolation.

In summary, we reported a new and simple procedure to prepare 2,4,5-trisubstituted 1,3-oxazoles. The easy desulfuration with Raney nickel of the methylthio group at the C4 position allows the synthesis of 2,5-disubstituted 1,3-oxazoles. The oxidation of the methylthio group with *m*-CPBA permits the preparation of 4-methylsulfonyl derivatives. A NMR study of the reaction at low temperature revealed species that were incorporated in a proposed mechanism for the reaction.

Experimental Section

General Procedure for the Synthesis of 2-Substituted 5-Methyl-4-(methylthio)-1,3-oxazoles, 8. To a solution of 1-(methylthio)acetone **7** (2.00 g, 19.2 mmol) in dry CH₂Cl₂ (25 mL) was added triflic anhydride (5.34 g, 19.2 mmol) in CH₂Cl₂ (20 mL) dropwise at 0 °C. The mixture was stirred for 1 h at this temperature, and then a solution of the corresponding nitrile (9.6 mmol) in CH₂Cl₂ (20 mL) was added. The mixture was stirred and allowed to stand at 0 °C for 3 days. The progress of the reaction was monitored by TLC. The reaction mixture was hydrolyzed by the careful addition of saturated NaHCO₃. The organic layer was separated, washed with brine, and dried over MgSO₄. The solvent was evaporated in vacuo, and the residue was purified by distillation or recrystallization after column chromatography (eluent, EtOAc/hexanes = 5/95).

2-Phenyl-5-methyl-4-(methylthio)-1,3-oxazole (8d): yellow oil; yield 92%; bp 125 °C/0.4 Torr (kugelrohr); IR (film) ν 2924, 1591, 1487, 1109, 714 cm⁻¹; ¹H NMR δ 2.35 (s, 3H, CH₃), 2.37 (s, 3H, CH₃S), 7.35 (m, 3H, Ar-H), 7.95 (m, 2H, Ar-H); ¹³C NMR δ 10.3 (CH₃-C5), 17.7 (CH₃S), 125.8, 127.0, 128.41, 128.9 (aromatic), 130.4 (C5), 148.9 (C4), 159.7 (C2); MS (EI) *m/z* (% B) 205 (M⁺, 43), 172 (M - SH, 38), 105 (C₆H₅CO⁺, 100), 77 (C₆H₅⁺, 54); Anal. Calcd for C₁₁H₁₁NOS: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.13; H, 5.22; N, 6.69; S, 15.49.

Bisoxazolyl derivatives **10** and **11** were prepared using the general procedure from methylthioacetone **7** and nitriles **8k** and **8l**.

5-Methyl-2-[4-[5-methyl-4-(methylthio)-1,3-oxazol-2-yl]phenyl]-4-(methylthio)-1,3-oxazole (11): pale yellow solid (from EtOH); yield 80%, mp 142–143 °C; this compound presents in solution an intense greenish fluorescence; IR (KBr) ν 1589, 1418, 1063, 719 cm⁻¹; ¹H NMR δ 2.47 (s, 6H, 2CH₃), 2.48 (s, 6H, 2CH₃S), 8.17 (s, 4H, Ar-H); ¹³C NMR δ 10.6 (CH₃-C5), 18.0 (CH₃S), 126.5, 128.37 (aromatic), 131.0 (C5), 149.8 (C4), 159.4 (C2); MS (EI) *m/z* (% B) 332 (M⁺, 100), 317 (M - CH₃, 5), 299 (M - SH, 50), 232 ([C₅H₆NOS]C₆H₅CO⁺, 14); Anal. Calcd. for C₁₆H₁₆N₂O₂S₂: C, 57.81; H, 4.85; N, 8.43; S, 19.29. Found: C, 57.70; H, 4.69; N, 8.32; S, 19.14.

General Procedure for the Synthesis of 2-Substituted 5-Methyl-1,3-oxazoles, 12. Compound **8** (3 mmol) was dissolved in EtOH and added to a suspension of recently prepared Raney nickel³² in 20 mL EtOH. The reaction mixture was refluxed for 48 h and then

filtered through Celite, which was washed with EtOH (100 mL). The solvent was removed in vacuo, and the residue was purified by distillation or recrystallization after column chromatography (eluent, EtOAc/hexanes = 5/95).

5-Methyl-2-(4-methoxyphenyl)-1,3-oxazole (12g): white needles (from MeOH); yield 93%; mp 60–61 °C; IR (KBr) ν 1616, 1501, 1254, 1173, 837 cm⁻¹; ¹H NMR (CD₃OD) δ 2.39 (d, *J* = 1.1 Hz, 3H, CH₃), 3.85 (s, 3H, CH₃O), 6.85 (q, *J* = 1.1 Hz, 1H, H4), 7.02 (m, 2H, Ar-H), 7.88 (m, 2H, Ar-H); ¹³C NMR (CD₃OD) δ 10.77 (CH₃-C5), 55.9 (CH₃O), 121.0, 124.1 (aromatic), 128.6 (C5), 150.3 (C4), 162.3 (C2), 162.9 (aromatic); MS (EI) *m/z* (% B) 189 (M⁺, 100), 174 (M - CH₃, 16), 146 (M - CH₃CO, 44); Anal. Calcd. for C₁₁H₁₁NO₂: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.73; N, 7.33.

General Procedure for the Synthesis of 2-Substituted 5-Methyl-4-(methylsulfonyl)-1,3-oxazoles, 13. To a solution of the corresponding oxazole **8** (3 mmol) in 25 mL dry CH₂Cl₂ was added dropwise a solution of *m*-CPBA (7 mmol, 12 mmol for **8c**) in 25 mL of dry CH₂Cl₂. The reaction mixture was stirred at room temperature for 12 h. The reaction was hydrolyzed by the addition of 20 mL of 5% sodium thiosulfate. The organic layer was washed with saturated NaHCO₃ and brine and dried over MgSO₄. The solvent was removed in vacuo, and the residue was purified by distillation or recrystallization after column chromatography (eluent, EtOAc/hexanes = 5/95).

2-Phenyl-5-methyl-4-(methylsulfonyl)-1,3-oxazole (13d): white crystals (from MeOH); yield 93%; mp 130–131 °C; IR (KBr) ν 1595, 1313, 1153, 785, 714 cm⁻¹; ¹H NMR δ 2.71 (s, 3H, CH₃), 3.22 (s, 3H, CH₃SO₂), 7.48 (m, 3H, Ar-H), 8.03 (m, 2H, Ar-H); ¹³C NMR δ 11.4 (CH₃-C5), 42.7 (CH₃SO₂), 125.8, 126.6, 128.8, 131.2 (aromatic), 135.7 (C5), 153.0 (C4), 160.2 (C2); MS (EI) *m/z* (% B) 237 (M⁺, 19), 105 (C₆H₅CO⁺, 100), 77 (C₆H₅⁺, 39); Anal. Calcd. for C₁₁H₁₁NO₃S: C, 55.68; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.55; H, 4.56; N, 5.80; S, 13.43.

Low-Temperature NMR Spectra. To a solution of 0.0104 g (0.10 mmol) of **7** in 0.8 mL of CDCl₃ at 5 °C contained in a NMR tube was added 0.0282 g (0.10 mmol) of Tf₂O. The tube was sealed with a septum, introduced in the spectrometer, and spun. The spectra were recorded at 30 min intervals. After the appropriate time, benzonitrile (0.0103 g, 0.10 mmol) was added, and the spectra were recorded at the same time intervals.

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Supporting Information Available: General experimental methods and characterization data of compounds **8a–c**, **8e–l**, **10**, **12d**, **13c**, **13f**, and **13j**; ¹H, ¹³C, and DEPT (135) NMR spectra of compounds **8a–l**, **10**, **11**, **12d**, **12g**, **13c**, **13d**, **13f**, and **13j**; 2D NMR (HMOC and HMBC) spectra of compound **8d**; fluorescence spectra of **11**; ¹H, ¹³C, and 2D NMR spectra of the reaction mixture at low temperature (5 °C); and ¹H and ¹³C chemical shifts of intermediates **14**, **15**, and **16**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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