Facile Synthesis of 2,4,5-Trisubstituted Oxazole Derivatives from Deoxybenzoins

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Numerous methods for synthesizing the oxazole ring system have been reported to date.[1] Interest in oxazoles has been renewed recently in view of their utility in synthetic chemistry as a masked carbonyl group[2] and also their various pharmacological activities.[3]

Synthesis of oxazoles is usually accomplished through the oxidized forms of ketones at the α-position such as α-halo ketones,[1i] α-acylamino ketones,[1a] α-diazo ketones,[1j,1l] or α-azido ketones[1c,1k] as precursors. Although there were many methods reported for the preparation of oxazoles, little has been known for direct synthesis of oxazoles from ketones.[1g,1h,1i] Synthesis of oxazoles directly from ketones must include one oxidation step by using an oxidant such as $Tl(OTf)_3$[1h] or $Cu(OTf)_2$.[1i] To our knowledge, there was no report using sulfuric acid as an oxidizing reagent for the preparation of oxazoles.

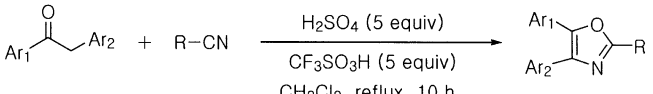
In the course of our program on the studies of the Ritter type reaction of deoxybenzoins with acetonitrile in the presence of various acid catalysts, we have found unexpected oxazole formation when we use TfOH-H_2SO_4 system as the acid catalyst. Thus, we examined the reaction, and report herein the results for the preparation of 2,4,5-trisubstituted oxazoles.

To find the best conditions, we examined the reaction by using deoxybenzoin and acetonitrile as a model system in CH_2Cl_2. Trifluoromethanesulfonic acid or sulfuric acid alone did not give the corresponding 2-methyl-4,5-diphenyloxazole (**2a**). Fuming sulfuric acid (5 equiv) gave trace amounts of the oxazole (8% of **2a**). We could obtain **2a** in 93% isolated yield, the best results in our trials, with 5 equivalents of H_2SO_4 and triflic acid respectively.[4] As shown in Table 1, the reaction of some deoxybenzoin derivatives **1** and various nitriles gave oxazoles **2a-j** in low to good yields depending upon the substrates.[4]

General procedure is as follows: To a stirred solution of deoxybenzoins (1 mmol) and appropriate nitrile (0.5 g, 4.8-12 mmol) in CH_2Cl_2 (10 mL) was added H_2SO_4 (5 mmol) and TfOH (5 mmol). The reaction mixtures were heated to reflux for 10 h. After the usual workup column chromatographic purification gave the oxazoles in 10-93% isolated yields.

We tentatively propose the reaction mechanism as follows as shown in Scheme 1: (1) acid catalyzed addition of sulfuric acid to the carbonyl group of **1** to give the intermediate **I**, (2) elimination of water to give **II**, (3) acid catalyzed simultaneous attack of nitrile and elimination of water and sulfur dioxide afforded **III** (oxidation occurrs in this step),[5] and finally (4) cyclization[6] of **III** gave oxazole derivatives **2**.

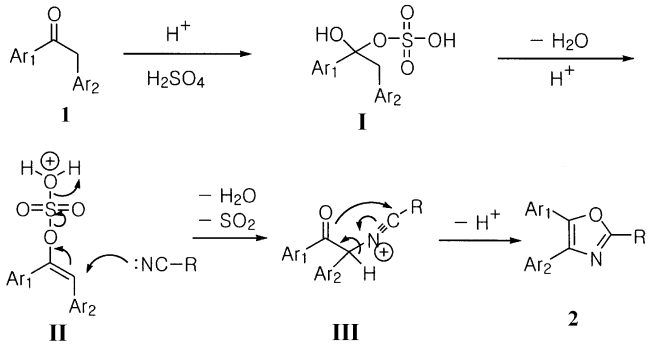
Table 1. Synthesis of 2,4,5-trisubstituted oxazoles



1 (1 mmol) (0.5 g) **2**

entry	Ar_1	Ar_2	R	yield (%)[a]
a	C_6H_5-	C_6H_5-	CH_3-	93
b	C_6H_5-	C_6H_5-	CH_3CH_2-	76
c	C_6H_5-	C_6H_5-	$ClCH_2$-	63
d	C_6H_5-	C_6H_5-	$NCCH_2$-	71
e	C_6H_5-	C_6H_5-	C_6H_5-	68
f	4-$CH_3OC_6H_4$-	4-$CH_3OC_6H_4$-	CH_3-	26[b]
g	4-$CH_3OC_6H_4$-	4-$CH_3OC_6H_4$-	CH_3CH_2-	10[b]
h[c]	2,5-$Me_2C_6H_3$-	C_6H_5-	CH_3-	88
i[c]	2,5-$Me_2C_6H_3$-	C_6H_5-	C_6H_5-	49
j[c]	2,4,6-$Me_3C_6H_2$-	C_6H_5-	CH_3-	20

[a]The products were identified by their mp and/or ^1H and ^{13}C NMR spectra.[7] [b]H_2SO_4 (3 equiv)+TfOH (3 equiv).[4] [c]Starting materials were prepared from phenylacetyl chloride.



Scheme 1

The products were identified with their ^1H and ^{13}C NMR spectral data and/or their mp and IR.[7] For deoxybenzoin (entries a-e) the corresponding oxazoles **2a-e** were obtained in 63-93% isolated yields. Desoxyanisoin (entry f and entry g) afforded low yields of products **2f** and **2g** by using 3 equivalents of TfOH/H_2SO_4. Excess use of acid catalyst (eg, 5 equiv) deteriorates the yields, which might be due to the basic nature of the methoxy group. Unsymmetrically substituted deoxybenzoin derivatives (entries h-j) gave the oxazoles **2h-j** in variable yields (20-88%). The possibility of regioisomeric oxazole (2-R, 4-Ar_1, 5-Ar_2) formation can be excluded, **2h** as the representative example, by the comparison of the ^1H and ^{13}C NMR data of the authentic sample (**2h**, 20% yield) which was made by the known method using $Cu(OTf)_2$.[1i]

Unfortunately, however, the reaction did not afford the corresponding oxazoles when we use alkyl-substituted ketones such as acetophenone, propiophenone, or 2-butanone. Further experiments for the alkyl-substituted ketones and the studies on the reaction mechanism are underway.

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4. The best condition in terms of yields was found to be as follows: nitriles (excess amounts), TfOH (5 equiv), H_2SO_4 (5 equiv) in refluxing CH_2Cl_2 for 10 h. The use of lesser amounts of acids diminishs the yields of products. In the cases of desoxyanisoin (entries f and g) 3 equivalents of TfOH-H_2SO_4 gave the corresponding oxazoles in low yields. By using 5 equivalents in these cases, only trace amounts of products were observed.
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7. Some selected spectroscopic data of **2a-j** are as follows.
2a: oil[1g]; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 7.30-7.65 (m, 10H); ^{13}C NMR ($CDCl_3$) 14.00, 126.41, 127.83, 128.00, 128.36, 128.55, 128.63, 129.07, 132.52, 135.12, 145.29, 160.21.
2b: oil[1e]; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.5 Hz, 3H), 2.87 (q, J = 7.5 Hz, 2H), 7.26-7.66 (m, 10H); ^{13}C NMR ($CDCl_3$) 11.33, 21.75, 126.42, 127.94, 127.99, 128.31, 128.53, 128.60, 129.14, 132.54, 134.91, 145.08, 164.56.
2c: mp 40-41 °C; ^{1}H NMR ($CDCl_3$) δ 4.69 (s, 2H), 7.33-7.66 (m, 10H); ^{13}C NMR ($CDCl_3$) 35.99, 126.75, 127.90, 128.11, 128.37, 128.60, 128.70, 129.00, 131.82, 135.84, 146.99, 157.59.
2d: mp 85-86 °C (lit[3e] oil); ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 2H), 7.34-7.64 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 18.29, 113.41, 126.73, 127.85, 128.04, 128.55, 128.69, 128.80, 129.19, 131.48, 135.90, 147.32, 151.69; IR ($CHCl_3$) 3431, 2954, 2943, 2914, 2260 (CN), 1603, 1593 cm^{-1}.
2e: mp 114-116 °C (lit[1e] 114-115 °C); ^{1}H NMR ($CDCl_3$) δ 7.27-8.09 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 125.42, 125.51, 126.33, 127.12, 127.21, 127.52, 127.60, 127.66, 127.74, 127.94, 129.33, 131.54, 135.74, 144.51, 159.11.
2f: oil; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 3.83 (s, 6H), 6.89 (d, J = 8.4 Hz, 4H), 7.49 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.92, 55.25, 55.28, 113.95, 114.09, 121.86, 125.07, 127.91, 128.95, 133.63, 144.61, 159.26, 159.55, 159.57.
2g: oil; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.7 Hz, 3H), 2.87 (q, J = 7.7 Hz, 2H), 3.83 (s, 6H), 6.87 (d, J = 1.7 Hz, 2H), 6.90 (d, J = 1.7 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.42, 21.76, 55.28, 55.31, 113.95, 114.07, 121.92, 125.12, 127.89, 129.06, 133.41, 144.38, 159.24, 159.50, 163.99.
2h: oil; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.32 (s, 3H), 2.54 (s, 3H), 7.15-7.54 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 13.95, 19.36, 20.77, 126.27, 127.37, 128.36, 128.80, 130.34, 130.55, 130.88, 132.12, 134.69, 135.38, 135.52, 145.20, 160.28.
2i: mp 122-124 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.27 (s, 3H), 7.14-8.09 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 21.57, 22.83, 128.35, 128.55, 129.53, 129.61, 130.42, 130.66, 130.72, 132.23, 132.50, 132.66, 132.96, 134.11, 136.80, 137.60, 138.88, 147.51, 162.38.
2j: oil; ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 6H), 2.36 (s, 3H), 2.56 (s, 3H), 6.97 (s, 2H), 7.19-7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.01, 19.86, 21.27, 125.39, 125.82, 127.20, 128.46, 128.57, 132.05, 135.59, 138.77, 139.61, 144.02, 160.58.