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Control of Regioselectivity in Nitrile Oxide Cycloadditions to Cinnamic Acid Derivatives

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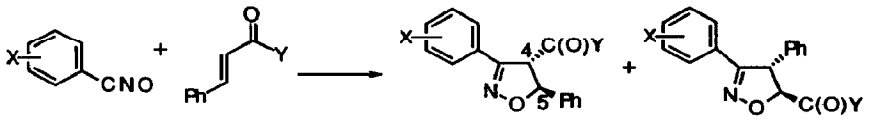
Abstract: Tertiary cinnamides undergo cycloaddition with benzonitrile oxides producing the 5-phenyl and 4-phenyl regioisomers **2b** and **3b** in a 25-30:75-70 ratio. This result is opposite to that obtained utilizing methyl cinnamate **1a** as the dipolarophile. A synthetically useful method for the preparation of the acid **3c**, derived from what is usually the minor regioisomer, has been developed by taking advantage of this reversal of regiochemistry.

Benzonitrile oxides, generated by dehydrohalogenation of hydroximinoyl chlorides (chlorooximes), undergo a 1,3-dipolar cycloaddition reaction with methyl cinnamate **1a** to yield the 5-phenyl and 4-phenyl regioisomeric dihydroisoxazoles **2a** and **3a** in an 80:20 ratio (Equation 1).[1] We have reported that use of tertiary cinnamides as the dipolarophile unexpectedly results in a reversal of regioselectivity (**2b**:**3b** = 25-30:75-70), while primary and non-aniline secondary cinnamides undergo cycloaddition with the same regioselectivity as methyl cinnamate.[2]



(Eq. 1)

1a Y=OMe
1b Y=NEt_2
1c Y=OH

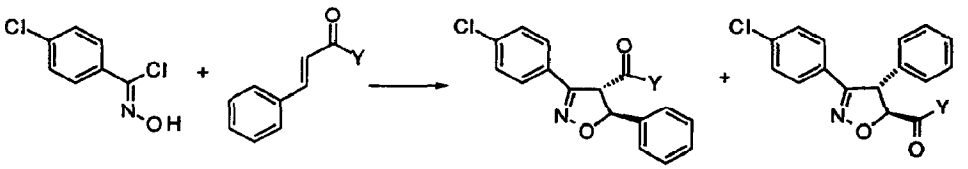
2a
2b
2c

3a
3b
3c

We sought to develop an improved method for the synthesis of 3,4-diarylisoxazole-5-carboxylic acid **3c**, normally obtained by hydrolysis of the minor ester **3a**, by utilization of this reversal of regioselectivity

for tertiary amides. Hydrolysis of tertiary amides can be accomplished under harsh conditions, but a method more tolerant of other functional groups was desired. Soai and Ookawa[3] have shown that amides derived from α-aminoacetates readily undergo hydrolysis to the corresponding acids in good yields, presumably as a result of neighboring group participation. Hence the cycloaddition of 4-chlorobenzonitrile oxide (generated *in situ* from the chlorooxime **4**[4]) and cinnamide **1d**,[5] derived from N-methyl glycine methyl ester, was investigated. The 5-phenyl and 4-phenyl regioisomers **2d** and **3d** were obtained in a 35:65 ratio, based on the integration of the H_4 and H_5 methine doublets in the ^1H NMR spectrum of the crude reaction mixture.[6] (Table 1, entry d.) The difference in chemical shifts of the H_4 and H_5 methine protons clearly distinguishes between the isomers.[1,2] For the 5-phenyl isomer **2**, the signals are *ca.* 1.4 ppm apart, but for the 4-phenyl isomer **3**, the difference is *ca.* 0.3 ppm. This distinction holds true whether the products are esters or amides. In further support of our assignment, only the 5-phenyl isomers **2** are capable of fragmenting with loss of benzaldehyde (MH^+-106) in the mass spectrum.[7]

Table 1. Ratios of Regioisomers of Dihydroisoxazoles **2** and **3**



4 **1** **2** **3**

Entry	Y	5-Phenyl isomer **2**	4-Phenyl isomer **3**	note
a	OMe	80	20	a
b	NEt_2	27	73	a
d	$N(Me)CH_2CO_2Me$	35	65	a
e	$N(Ph)CH_2CO_2Me$	32	68	a
f	L-proline Me ester	minor	major	a,c
g	$N(CH_2CO_2Et)_2$	33	67	a
g'	$N(CH_2CO_2Et)_2$	24	76	b

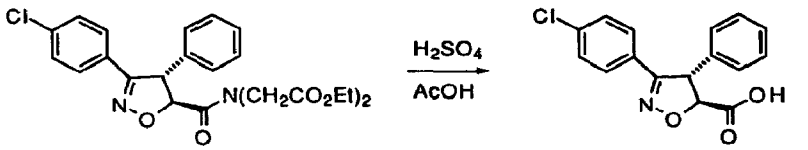
a. Ethyl acetate solvent
b. Diethyl ether solvent
c. Due to the presence of diastereomeric products, accurate integration of the crude NMR spectrum was difficult to achieve.

In an attempt to improve the ratio of products, the N-methyl substituent of the amide was replaced with the larger N-phenyl group (entry e). Surprisingly, only a slight increase in the amount of 4-phenyl isomer **3e** was realized. Since N,N-diethylcinnamide afforded a 27:73 ratio of cycloadducts (entry b), it appeared that two alkyl substituents larger than methyl provided superior regioselectivity. Thus N-cinnamoyl-L-proline methyl ester **1f**[8] (entry f) was utilized as the dipolarophile, but accurate interpretation

of the NMR spectrum of the crude product was extremely difficult even at 300 MHz. The isomers **2** and **3** were each obtained as a pair of diastereomeric products, and all four diastereomers existed in solution as rotamers around the amide bond. It was apparent, however, that the desired 4-phenylisomer **3f** was the major reaction product. The four products could not be separated using normal-phase chromatographic techniques.

The diethyl iminodiacetate amide **1g** (entry g) produced the two regioisomers in a 33:67 ratio and 86% yield. Switching the solvent from ethyl acetate to diethyl ether (entry g') improved the product ratio to 24:76. A similar solvent effect was observed in the N,N-diethylcinnamide case, where the 27:73 ratio in ethyl acetate improved to 20:80 in ether.[2]

Hydrolysis (Equation 2) of 4-phenyl amide **3g** occurs smoothly with H_2SO_4 in refluxing aqueous acetic acid to produce acid **3c** in 89% yield. The acid had spectral data and physical properties identical to those of the product previously[2] obtained from alkaline hydrolysis of ester **3a**.



3g **3c** (Eq. 2)

The control of regiochemistry provided by this method should be particularly applicable to the synthesis of beta-hydroxy ketones, which are conveniently prepared by reductive cleavage of isoxazolines[9].

General Procedure for the Cycloaddition Reactions: To 10 mmol of chlorooxime **4** and 8 mmol of cinnamide **1** in 100 mL EtOAc, was added dropwise 10 mmol of triethylamine in 25 mL of EtOAc over a period of 30-45 minutes. The reaction was stirred at room temperature overnight and then examined by TLC. Usually, TLC indicated the presence of starting cinnamide. An additional 10 mmol of chlorooxime was added, followed by the dropwise addition of 10 mmol of triethylamine in 25 mL of EtOAc. The reaction was stirred overnight, then washed with water (3 x 200 mL), dried ($MgSO_4$), filtered and evaporated. The ratio of cycloadducts was determined by integration of H_4 and H_5 protons of each product in the crude NMR spectrum. Most of the major isomer was isolated by fractional recrystallization from EtOAc/hexane or ether/hexane. The remaining mother liquor was chromatographed on silica gel using 10-15% EtOAc/hexane to yield additional quantities of the major and minor isomers.

***Trans* N,N-[Bis(carboethoxymethyl)] 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide 2g.** Isolated yield 68.8%, mp=104-106°C. ^1H NMR δ 7.67 (d, J=8.7 Hz, 2H), 7.38-7.66 (m, 5H), 7.34 (d, J=8.7 Hz, 2H), 5.70 (d, J=8.9 Hz, 1H), 4.65 (d, J=8.9 Hz, 1H), 4.33 (d, J=17.6 Hz, 1H), 4.16-4.24 (m, 2H), 4.09 (q, J=7.1 Hz, 2H), 4.03 (d, J=17.6 Hz, 1H), 3.88 (s, 2H), 1.25 (t, J=7.1 Hz, 3H), 1.18 (d,

J=7.1 Hz, 3H). IR 1748, 1734, 1669 cm^{-1}. MS m/z 473, 475 (MH+), 367, 369 (MH+-PhCHO). Anal. calcd. for $C_{24}H_{25}ClN_2O_6$: C, 60.95; H, 5.33; N, 5.92. Found: C, 60.82; H, 5.31; N, 6.05.

***Trans* N,N-[Bis(carboethoxymethyl)] 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide 3g.** Isolated yield 19.4%, mp=86-87°C. ^1H NMR δ 7.53 (d, J=8.6 Hz, 2H), 7.16-7.48 (m, 7H), 5.59 (d, J=4.7 Hz, 1H), 5.18 (d, J=4.7 Hz, 1H), 4.43 (d, J=17.5 Hz, 1H), 4.15-4.34 (m, 6H), 4.05 (d, J=17.5 Hz, 1H), 1.27 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H). IR 1748, 1669 cm^{-1}. MS m/z 473, 475 (MH^+). Anal. calcd for $C_{24}H_{25}ClN_2O_6$: C, 60.95; H, 5.33; N, 5.92. Found: C, 60.97; H, 5.13; N, 5.89.

General Procedure for the Amide Hydrolysis: Amide 3g (2.75 g), 30 mL 6M aq. H_2SO_4, and 15 mL HOAc were heated at reflux for 3 h. The mixture was cooled and poured into 250 mL water, and extracted with 250 mL EtOAc. The organic layer was washed with an additional 250 mL water, dried ($MgSO_4$), filtered and evaporated to afford acid 3c (89% yield) as a white solid, mp 188-190°C (EtOAc/hexane). ^1H NMR (DMSO-d_6) δ 13.40 (br s, 1H), 7.67 (d, J=8.7 Hz, 2H), 7.42 (d, J=8.7 Hz, 2H), 7.24-7.40 (m, 5H), 5.32 (d, J=4.3 Hz, 1H), 5.01 (d, J=4.3 Hz, 1H). IR 2800-3200 (br), 1737 cm^{-1}. MS m/z 302, 304 (MH^+).

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