Unusual Regioselectivity of the Dipolar Cycloaddition Reactions of Nitrile Oxides and Tertiary Cinnamides and Crotonamides[1]

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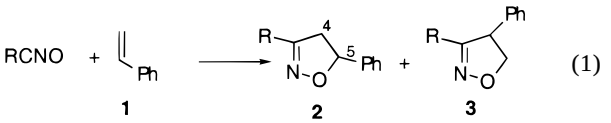
Benzonitrile oxides undergo 1,3-dipolar cycloaddition reactions with methyl cinnamate to produce the 5-phenyl and 4-phenyl regioisomers in approximately an 80:20 ratio. However, use of *N*,*N*-diethylcinnamide as the dipolarophile unexpectedly resulted in the formation of the 5-phenyl and 4-phenyl regioisomers in a 23:77 ratio. Studies have shown that this phenomena occurs only for tertiary cinnamides. In addition, it has been demonstrated that the phenyl group of tertiary cinnamides is not essential for the reversal of regioselectivity since crotonamides produce the same results and trends as the cinnamides. However, since acrylates and acrylamides both produce the 5-carbonyl regioisomers, it can be concluded that the β-substituent is playing a key role for the unexpected results by possibly increasing steric interactions between the dipole and dipolarophile in the transition state. Transition state energies were calculated for the regioisomeric cycloadduct pairs derived from several crotonamides as well as methyl crotonate. These calculations indicate that steric factors are indeed responsible for the reversal of regioselectivity.

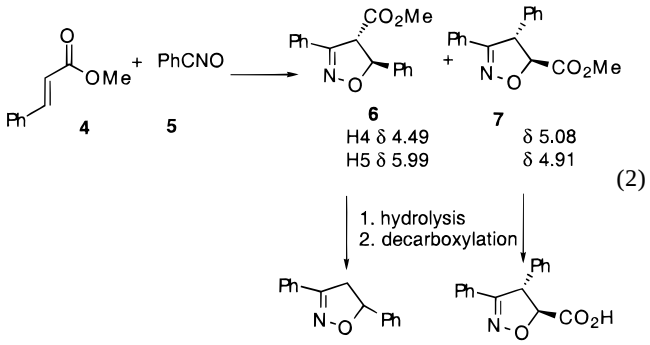
Introduction

Nitrile oxides, generated by dehydrohalogenation of hydroximinoyl acid chlorides (chloro oximes), undergo 1,3-dipolar cycloaddition reactions with a wide variety of olefins to produce 4,5-dihydroisoxazoles in a stereospecific manner.[3] Cycloadditions with monosubstituted olefins proceed rapidly and regioselectively to yield the 5-substituted dihydroisoxazole (eq 1). For example, the use of styrene (**1**) as the dipolarophile results in the formation of the 5-phenyl isomer **2** and the 4-phenyl isomer **3** in a 99:1 ratio.[3]



1 2 3 (1)

On the other hand, reaction of nitrile oxides with 1,2-disubstituted olefins tends to be slower and have reduced regioselectivity. For example, trans methyl cinnamate (**4**) undergoes cycloaddition with phenyl nitrile oxide (**5**) to form the 5- and 4-phenyl trans substituted isomers **6** and **7** in an 80:20 ratio, respectively (eq 2).[4,5] Monforte[5] distinguished between the regioisomers by subjecting each isomer to hydrolysis/decarboxylation conditions. In recent years, the regioisomers **6** and **7** have been characterized by spectral properties. Huisgen and Christl[4] have reported that the differences in chemical shifts between the H_4 and H_5 methine protons clearly distinguishes between the two regioisomers. In addition, DeSarlo and co-workers[6] have shown for the cycloadducts derived from cinnamaldehyde that the 5-phenyl isomer exhibits a large $MH^+ - 106$ peak in the mass spectrum corresponding to loss of benzaldehyde.



(2)

During the course of our studies, it was desired to replace the ester functionality of each regioisomer **6** and **7** with various amide moieties.[7] Instead of preparing both amides via the corresponding acids, the cycloaddition reaction was accomplished using the appropriate cinnamide **9** as the dipolarophile to produce the desired compounds **10** and **11** directly in one step (eq 3). This route was very attractive since large quantities of chloro oximes **8** and cinnamides **9** with diverse substitution patterns could be easily prepared and, therefore, numerous permutations of **8** and **9** in the cycloaddition reaction would rapidly produce the corresponding two isomers **10** and **11** required for biological testing.

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(1) This work was presented in part at the ACS National Meeting in Chicago, IL, in August 1995.

(2) Department of Process Chemistry.

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(4) (a) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3275. (b) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3345.

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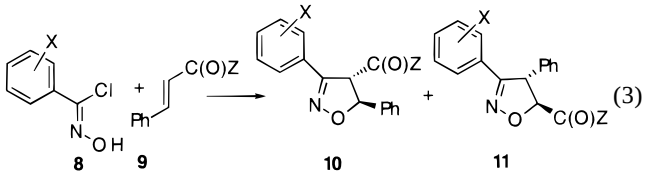
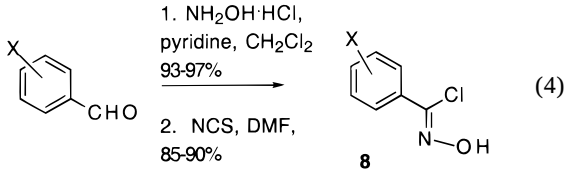


Results

The chloro oximes **8** were synthesized in two steps from the corresponding benzaldehyde (eq 4). The intermediate oximes were chlorinated with *N*-chlorosuccinimide in DMF.[8] The resulting chloro oximes **8** were not contaminated with ring chlorinated products, require no purification, and may be stored for several months without any decomposition. The nitrile oxides were generated in situ, by dehydrohalogenation of the chloro oxime with triethylamine.[4]



Reaction of nitrile oxide **8e** (X = 4-Cl) and *N*,*N*-diethylcinnamide (**9e**) (eq 3 and Table 1, entry e) unexpectedly led to a reversal of regioselectivity to yield the 5-phenyl **10e** and the 4-phenyl **11e** cycloadducts in a 23:77 ratio as determined by the integration of the C-4 and C-5 isoxazoline methine protons in the NMR of the crude reaction mixture. The structures were initially assigned on the basis of the relative chemical shifts and coupling constants of the C-4 and C-5 methine doublets. Major isomer **11e** exhibits two closely spaced doublets (δ 5.12 and 5.64) similar to that found for the 4-phenyl-5-carbomethoxy adduct **11b** (δ 4.97 and 5.02), while minor isomer **10e** exhibits two largely spaced doublets (δ 4.64 and 5.73), similar to that for the corresponding ester **10b** (δ 4.43 and 6.00). The H_4-H_5 coupling constants for the pair of isomers of **10e** and **11e** are 9.3 and 5.7 Hz, respectively, indicating a trans relationship[9] in the cycloadducts (cis coupling ~11−12 Hz). These values are similar to the reported values[4] for **10a** and **11a** (6.2 and 4.1 Hz). More importantly, the mass spectrum of amide **10e** exhibits a peak corresponding to the loss of benzaldehyde ($MH^+ - 106$), thus indicating that the phenyl group is attached to the 5-position of the dihydroisoxazole ring. This same regiochemistry was observed when piperidinyl amide **9i** was used as the dipolarophile in the reaction.

Confirmation of the structural assignments was achieved by independent synthesis of several adducts from the ester intermediates **10b** or **11b** (Scheme 1) via acid **12** or acid **13**, respectively.

As is evident from Table 1, the regioselectivity of the reaction using either an ester (entries a−d) or an amide (entries e−h) dipolarophile is independent of the electronic nature of the substituents on the phenyl ring of the benzonitrile oxide. (4-Nitrobenzonitrile oxide was not used since it dimerizes to the furoxane faster than it undergoes cycloaddition with cinnamates.)

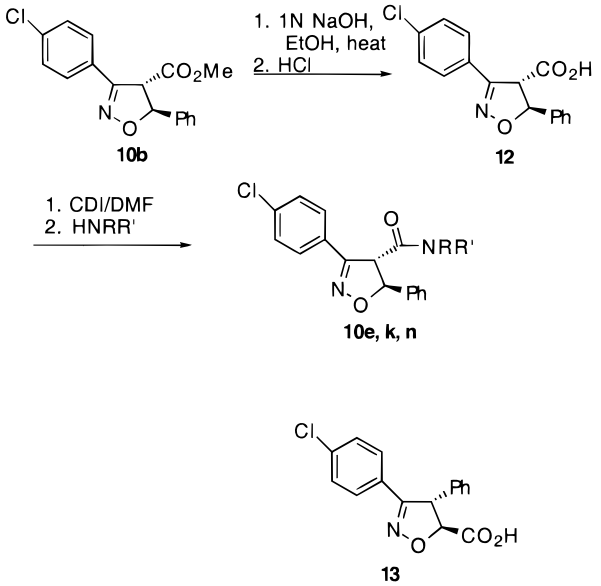
(8) Liu, K.; Shelton, B.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.
(9) Sustmann, R.; Huisgen, R.; Huber, H. *Chem. Ber.* **1967**, *100*, 1802.

Table 1. Regioisomeric Ratios of Dihydroisoxazoles 10 and 11[a]

entry	X of nitrile oxide **8**	Z of dipolarophile **9**	5-phenyl isomer **10**	4-phenyl isomer **11**	yield (%) of cycloadducts
a	H	OMe	80	20	84
b	4-Cl	OMe	78	22	85
c	4-MeO	OMe	81	19	64
d	3-NO_2	OMe	82	18	70 (88)[b]
e	4-Cl	NEt_2	23	77	95
f	H	NEt_2	28	72	83
g	4-MeO	NEt_2	25	75	40
h	3-NO_2	NEt_2	29	71	63
i	4-Cl	piperidinyl	18	82	85
j	4-Cl	NHPh	51	49	54 (71)[b]
k	4-Cl	NHPh(4-OMe)	45	55	88
l	H	NHPh(4-OMe)	52	48	88
m	4-Cl	NHPh(4-NO_2)	47	53	66
n	4-Cl	NMe(Ph)	35	65	54
o	4-Cl	NH(c-C_5H_9)	73	27	79
p	H	NH(c-C_5H_9)	74	26	76
q	4-Cl	NH_2	78	22	80
r	4-Cl	NMe_2	31	69	85

[a] Determined by integration of the C4 and C5 methines in the NMR of the crude reaction mixture. [b] Yield based on recovered starting material in parentheses.

Scheme 1



We initially proposed that the difference in electronics between an ester carbonyl and an amide carbonyl may be responsible for altering the dipolarophilic nature of the olefin leading to a reversal of selectivity. To this end, the aniline amides **9j**−**m** were prepared. These cycloaddition reactions were found to be nonregioselective with the products being formed in approximately equal amounts. However, when the tertiary aniline amide **9n** was the dipolarophile, the ratio of cycloadducts was similar to that of the other tertiary cinnamides, thus ruling out electronic effects due to the difference in the type of carbonyl.

With the cinnamides studied to this point, reversal of regiochemistry occurred with the tertiary amides, thus hinting that steric factors may be playing an important role. Less bulky amides such as cyclopentyl amide **9o** and cinnamide (**9q**) were investigated. Interestingly, both cases afford the 5-phenyl **10o** or **10q** and the 4-phenyl **11o** or **11q** cycloadducts in approximately the same ratio as for methyl cinnamate! Since cinnamide

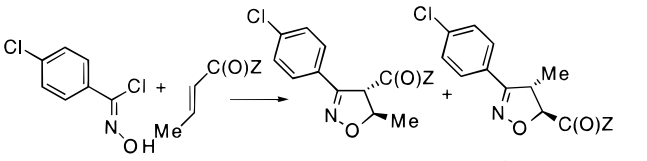
Table 2. Regiosomeric Ratios of Dihydroisoxazoles 15 and 16[a]

entry	X of nitrile oxide **8**	Z of dipolarophile **14**	5-methyl isomer **15**	4-methyl isomer **16**	yield (%) of cycloadducts
a	4-Cl	OMe	66	34	65
b	4-Cl	NEt_2	16	84	86
c	4-Cl	piperidinyl	23	77	83
d	4-Cl	NH_2	59	41	65
e	4-Cl	NH(c-C_5H_9)	60	40	69
f	4-Cl	TMP[b]	3	97	74

[a] Determined by integration of the C4 and C5 methines in the NMR of the crude reaction mixture. [b] TMP = 2,2,6,6-tetramethylpiperidinyl.

(**9q**) did not result in a reversal of regioselectivity and *N*,*N*-diethylcinnamide (**9e**) did, the smallest tertiary cinnamide, *N*,*N*-dimethylcinnamide (**9r**), was subjected to the cycloaddition reaction. This dipolarophile did reverse the regioselectivity of the reaction, producing the isomeric isoxazolines **10r** and **11r** in a 31:69 ratio.

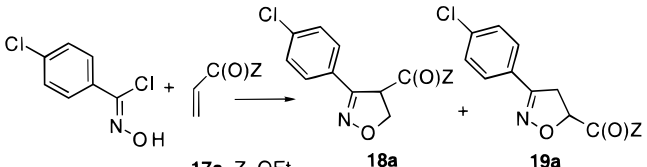
The effect of the β-substituent of the dipolarophile was next investigated (eq 5, Table 2). The first dipolarophile



8 **14** **15** **16** (5)

examined was where the β-substituent was a methyl group, thus eliminating the possibility of any electronic effects, due to conjugation, between the phenyl ring and the olefinic ester (or amide) portions of the molecule. The crotonate/crotonamide series of compounds produced the same results and trends as those for cinnamides. The extremely bulky *N*-2,2,6,6-tetramethylpiperidinyl crotonamide (**14f**) furnished the 4-methyl isomer **16f** with excellent regioselectivity. These results also indicate that sterics of the amide moiety could be responsible for this unusual regiochemistry. Examination of the coupling patterns for the C-4 and C-5 methines in the proton NMR and the fragmentation pattern in the mass spectrum differentiated between the two regioisomers for the ester and the amide pairs.

The third dipolarophile examined was the unsubstituted example where the β-substituent was a hydrogen (eq 6). Ethyl acrylate (**17a**) produced the 5-carboethoxydihydroisoxazole **19a** along with only trace amounts of the 4-carboethoxy isomer **18a**.[3] *N*,*N*-Diethylacrylamide (**17b**) exclusively forms the 5-carboxamide adduct **19b** with no trace of isomer **18b** being observed in the crude NMR. Interestingly, there is no reversal in the regioselectivity with this dipolarophile. These results indicate that the β-substituent of the dipolarophile is also playing an important role along with the amide moiety in determining the regiochemistry of the reaction.



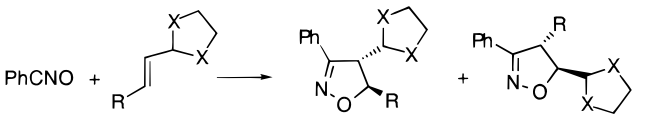
8 (X=Cl) **17a** Z=OEt **17b** Z=NEt_2 **18a** **18b** **19a** **19b** (6)

Discussion

From these studies, we have shown that primary and secondary cinnamides and crotonamides produce the cycloadducts with the opposite regiochemistry as the analogous tertiary amides. One difference between these types of amides is the presence or absence of the amide hydrogen which can function as a hydrogen bond donor which may lead to a templating effect and, hence, affect the regiochemistry of the reaction. Curran has reported that allylic secondary amides can alter the regio- and diastereoselectivity of nitrile oxide cycloadditions.[10] The authors proposed that the amide hydrogen forms a hydrogen bond with the oxygen of the nitrile oxide, thus leading to a preponderance (90:10 ratio) of the 5-substituted cycloadduct. However, when this model is applied to the secondary cinnamides/crotonamides, one would predict that the major adduct would be the 5-carboxamide product **11** or **16**. Since this is not the case, then this type of templating effect is miminal in the cinnamide/crotonamide system.

Fronter molecular orbital (FMO) theory has enjoyed considerable success in rationalizing the regiochemistry of Diels–Alder reactions.[11] In many cases, FMO theory is inadequate for the treatment of 1,3-dipolar cycloadditions. This is due to, in simple FMO theory, the disregard of steric and electrostatic effects as well as the effects of interactions of other high-energy filled orbitals with low-energy unfilled orbitals. Often in dipolar cycloadditions it is difficult to determine if the reaction is dipole HOMO or LUMO controlled in cases where the HOMO–LUMO gaps are of similar energy.

Kamimura and Hori reported that the choice of carbonyl protecting group reverses the regioselectivity in the nitrile oxide cycloadditions to cinnamaldehyde and crotonaldehyde derivatives **20**.[12] Acetals provide a majority of the C-4 acetal cycloadducts **21** whereas the dithioacetal affords mainly the C-5 dithioacetal adduct **22** (eq 7). The



20 **21** **22**

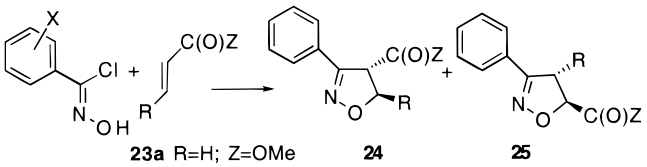
R=Me, X=O	68	32
R=Me, X=S	17	83
R=Ph, X=O	91	9
R=Ph, X=S	27	73

(7)

authors invoke FMO theory to rationalize the regiochemical outcome of the cycloaddition with acetals and steric factors to rationalize the opposite outcome with the dithioacetals. MNDO calculations indicated that the steric interaction between the C-3 phenyl group and the 1,3-dithiolane ring at C-4 raises the energy of the adduct **21** by 4.2 kcal/mol, thus leading to a majority of **22** being preferentially formed. However, these calculations failed to correctly predict the regioselectivity of the acetal derivatives, even though the authors note that the steric biases of the acetal and thioacetal groups are similar. Likewise, the FMO theory failed to correctly predict the regioselectivity for the dithioacetals.

(10) Curran, D. P.; Choi, S.-M.; Gothe, S. A.; Lin, F.-T. *J. Org. Chem.* **1990**, *55*, 3710.
(11) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.
(12) Kamimura, A.; Hori, K. *Tetrahedron* **1994**, *50*, 7969.

We applied FMO theory to the cycloaddition of benzonitrile oxide with *N*,*N*-dimethylcrotonamide (**23h**) (eq 8). The geometry optimization of each was performed



(8)

at the RHF/3-21G and AM1[13] levels of theory. Using the ab initio eigenvalues it was determined that the reaction was dipole LUMO controlled and this orbital interacts with the (HOMO-1) of the dipolarophile, which is centered on the olefinic carbon atoms. The LUMO dipole−(HOMO-1) dipolarophile gap is 12.04 eV. The HOMO dipole−LUMO dipolarophile gap is 12.86 eV. The larger LUMO coefficient of benzonitrile oxide is on the carbon of the dipole and the larger (HOMO-1) coefficient of the dipolarophile is on the carbon bearing the amide (both inner and outer coefficients for each). This leads to the prediction that 5-methyl-4-carboxamide isomer **24h** would be the preferred regioisomer. This is contrary to the experimental results. Using the AM1 calculated eigenvalues, the HOMO dipole−LUMO dipolarophile gap was nearly the same as the LUMO dipole−(HOMO-1) dipolarophile gap, and therefore, no clear regiochemical preference is apparent.

The failure of FMO theory to correctly predict the regiochemical course of the nitrile oxide cycloaddition with *N*,*N*-dimethylcrotonamide (**23h**) led us to apply semiempirical (AM1),[13] ab initio, and density functional theory (DFT) methods to examine the regioisomeric transition structures, thus allowing for a quantitative comparison of ΔE and ΔH for these reactions. Because of the large size of the systems under study, geometry optimizations were performed at the AM1 and RHF/3-21G levels of theory. Since the regiochemical outcome of these cycloadditions is independent of the substituent on the phenyl ring of the benzonitrile oxide (vide supra), only benzonitrile oxide was examined as the dipole for the theoretical studies.

Figure 1 shows the RHF/3-21G and AM1 transition structures (TS) for the cycloaddition of benzonitrile oxide with *N*,*N*-dimethylcrotonamide (**23h**). Table 3 shows the lengths of the forming bonds in the cycloadditions of benzonitrile oxide with methyl acrylate (**23a**), methyl crotonate (**23b**), the acrylamides **23c**−**e** and the crotonamides **23f**−**i** calculated at the RHF/3-21G and AM1 levels.

The most striking feature derived from these calculations is the asynchronicity in the RHF/3-21G transition structures leading to the 4-carbonyl regioisomer **24** with the C−O bond being shorter than the C−C bond by 0.53 Å on average. The RHF/3-21G calculated C−O and C−C bond lengths for the transition structures for the cycloaddition of formonitrile oxide with *N*,*N*-dimethylcrotonamide (**23h**) leading to the 4-carbonyl 5-methyl regioisomer are 2.073 and 2.330 Å, respectively, a difference of only 0.26 Å. The AM1 transition structures leading to the 4-carbonyl regioisomer **24** are much more synchronous with the C−O bond being shorter than the C−C bond by only 0.08 Å on average. The AM1 calculated C−O and C−C bond lengths for the transition structures for the cycloaddition of formonitrile oxide with *N*,*N*-dimethylcrotonamide (**23h**) leading to the 4-carbonyl-5-methyl regioisomer are 2.186 and 2.080 Å, respectively. In this case the C−O bond is longer than the C−C bond by 0.11 Å.

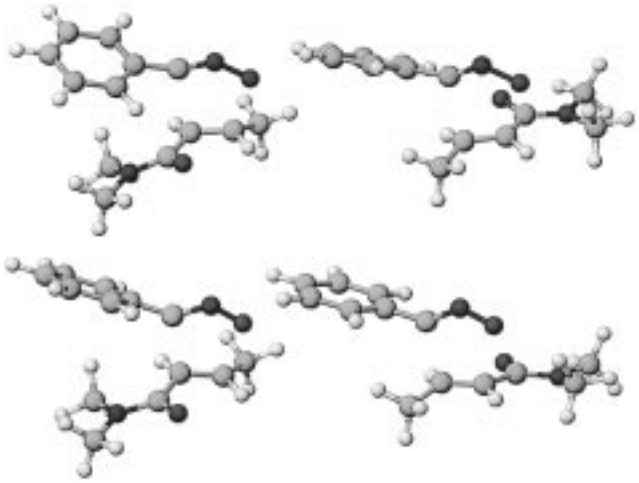


Figure 1. Transition structures (RHF/3-21G top; AM1 bottom) for the cycloaddition of benzonitrile oxide with *N*,*N*-dimethylcrotonamide (**23h**) leading to the 5- and 4-methylisoxazolines **24** (left) and **25** (right).

The RHF/3-21G transition structures leading to the 5-carbonyl regioisomers **25** are more synchronous than those leading to the 4-carbonyl regioisomers **24**. The C−O bond is shorter than the C−C bond by 0.13 Å on average while for the AM1 transition structures, the C−O bond is *longer* than the C−C bond by 0.07 Å on average. Houk[14] reported that in the RHF/3-21G transition structure for the reaction of formonitrile oxide with ethylene, the forming bonds are nearly the same length; the C−O bond is 2.281 Å and the C−C bond is 2.265 Å. We obtained similar results for the cycloaddition of formonitrile oxide with *N*,*N*-dimethylcrotonamide (**23h**) leading to the 5-carbonyl-4-methyl regioisomer. In this case, the RHF/3-21G transition structure is nearly synchronous. The C−O bond length is 2.197 Å, and the C−C bond length is 2.192 Å. The bond lengths for the AM1 transitions structure are 2.205 Å for the C−O bond and 2.032 Å for the C−C bond.

These results suggest that there are unfavorable steric (and possibly electrostatic) repulsions between the phenyl ring of the nitrile oxide and the ester or amide functionalities of the dipolarophiles in the transition structures of the 4-carbonyl regioisomers **24**. These interactions can be partially overcome by the asynchronicity of the transition structures with the forming C−O bond being shorter than the forming C−C bond. The bulkier the amide portion is, the more unfavorable steric interactions are in the transition structure, therefore favoring the 4-

(13) Dewar, M. J. S.; Zoenison, E. G.; Healy, E. F. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(14) Brown, F. K.; Singh, U. C.; Kollman, P. A.; Raimondi, L.; Houk, K. N.; Bock, C. W. *J. Org. Chem.* **1992**, *57*, 4862.

Table 3. RHF/3-21G and AM1 Bond Lengths for the Forming Bonds in the Transition Structures Leading to Regioisomers 24 and 25

	RHF/3-21G for isomer **24**		AM1 for isomer **24**		RHF/3-21G for isomer **25**		AM1 for isomer **25**	
dipolarophile **23**	R_{C-C}	R_{C-O}	R_{C-C}	R_{C-O}	R_{C-C}	R_{C-O}	R_{C-C}	R_{C-O}
a	2.439	1.891	2.193	2.020	2.207	2.087	2.049	2.144
b	2.438	1.899	2.152	2.070	2.200	2.073	2.078	2.087
c	2.433	1.894	2.169	2.067	2.215	2.071	2.047	2.173
d	2.426	1.906	2.167	2.064	2.215	2.072	2.049	2.164
e	2.428	1.902	2.181	2.038	2.214	2.082	2.050	2.166
f	2.433	1.902	2.122	2.122	2.206	2.074	2.073	2.112
g	2.427	1.914	2.123	2.123	2.207	2.075	2.074	2.106
h	2.426	1.913	2.133	2.086	2.205	2.086	2.075	2.106
i	2.427	1.924	2.136	2.084	2.198	2.087	2.075	2.105

Table 4. Calculated Activation Energies and Activation Enthalpies (kcal/mol) for the Cycloaddition of Benzonitrile Oxide with Dipolarophiles and Differences in the Activation Energies and Activation Enthalpies for the Formation of the Regioisomers 24 and 25

product	$E^{\ddagger}$ [a]	$\Delta E^{\ddagger}$ [e]	$E^{\ddagger}$ [b]	$\Delta E^{\ddagger}$ [e]	$\Delta H^{\ddagger}$ [c]	$\Delta\Delta H^{\ddagger}$ [e]	$E^{\ddagger}$ [d]	$\Delta E^{\ddagger}$ [e]
24a	19.57		16.86		16.67		15.47	
25a	24.27	−4.70	15.24	1.62	17.31	−0.64	13.18	2.29
24b	20.49		18.97		13.30		15.80	
25b	27.46	−6.97	19.61	−0.64	15.02	−1.72	18.12	−2.32
24c	19.57		17.22		16.83		15.91	
25c	23.34	−3.77	16.29	0.93	15.10	1.73	12.62	3.29
24d	19.69		17.36		16.95		16.21	
25d	23.35	−3.66	16.36	1.00	16.38	0.57	15.79	0.42
24e	19.52		17.20		17.28		15.67	
25e	22.26	−2.74	15.80	1.40	16.08	1.20	11.44	4.23
24f	20.47		19.21		12.88		16.91	
25f	25.87	−5.40	18.85	0.36[f]	12.88	0.00	16.99	−0.08
24g	20.59		19.30		19.47		17.16	
25g	25.85	−5.26	18.94	0.36[g]	20.66	−1.19	20.23	−3.07
24h	20.45		19.25		13.31		17.17	
25h	24.74	−4.29	18.33	0.92	13.60	−0.29	16.25	0.92
24i	26.08		19.24		23.54		24.06	
25i	29.17	−3.09	17.79	1.45	21.48	2.06	18.17	5.89

[a] RHF/3-21G//RHF/3-21G+ZPE (scaled by 0.8929). [b] B3LYP/6-31G(d)//RHF/3-21G+ZPE (scaled by 0.8929). [c] AM1//AM1 (no ZPE). [d] B3LYP/6-31G(d)//AM1 (no ZPE). [e] $\Delta E^{\ddagger} = (E_{\text{transition structure}} - E_{\text{separated reactants}})$; $\Delta\Delta H^{\ddagger} = (\Delta H_{\text{transition structure}} - \Delta H_{\text{separated reactants}})$; a negative value for $\Delta E^{\ddagger}$ or $\Delta\Delta H^{\ddagger}$ means that the 4-regioisomer is preferred. [f] B3LYP/6-311+G(2d,p)//RHF/3-21G; $\Delta E^{\ddagger} = -0.24$. [g] B3LYP/6-311+G(2d,p)//RHF/3-21G; $\Delta E^{\ddagger} = 0.17$.

methyl regioisomer **25** since the steric interaction of the methyl groups of methyl crotonate and the tertiary crotonamides with the phenyl ring of the nitrile oxide should be smaller. For esters and less bulky amides, the steric interaction for the carbonyl moiety and the phenyl ring of the nitrile oxide is less than that between the β-substituent and the phenyl ring yielding the 5-methyl adduct **24** as the major product. However, for the acrylate/acrylamide series, the ester/amide is always oriented toward the oxygen of the nitrile oxide and the β-hydrogen is close to the phenyl ring of the nitrile oxide so as to miminize steric interactions leading to almost exclusive formation of the 5-substituted isomers **25a** and **25c**−**e**.

The calculated activation energies (ab initio and DFT) and enthalpies of activation (AM1) for the cycloaddition of benzonitrile oxide to methyl acrylate (**23a**), methyl crotonate (**23b**), the acrylamides **23c**−**e**, and crotonamides **23f**−**i** are given in Table 4 as well as the $\Delta E^{\ddagger}$ (ab initio and DFT) and $\Delta\Delta H^{\ddagger}$ (AM1) for the formation of the 4-carbonyl regioisomer **24** and 5-carbonyl regioisomers **25** ($\Delta E^{\ddagger} = E^{\ddagger}$(**24**) − $E^{\ddagger}$(**25**); $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}$(**24**) − $\Delta H^{\ddagger}$(**25**); i.e., when $\Delta E^{\ddagger}$ (or $\Delta\Delta H^{\ddagger}$) < 0 kcal/mol, regioisomer **24** is favored). The RHF/3-21G activation energies are in each case higher than the B3LYP/6-31G(d)//RHF/3-21G activation energies as well as the AM1 activation enthalpies. This is generally the case for Hartree−Fock calculated activation energies for cycloadditions since Coulomb correlation effects are neglected.[15] Correlation effects are partially included in semiempirical methods in the experimental parameters. Solely on the basis of the calculated $\Delta E^{\ddagger}$, RHF/3-21G predicts that only the 4-carbonyl regioisomer **24** will be formed exclusively in these reactions.[16,17] This is contrary with the experimental results. The $\Delta E^{\ddagger}$s calculated by the B3LYP/6-31G(d)//RHF/3-21G and the B3LYP/6-31G(d)//AM1 procedures and the AM1 calculated $\Delta\Delta H^{\ddagger}$s are much smaller and predict that mixtures of regioisomers should arise from these cycloadditions. The B3LYP/6-31G(d)//RHF/3-21G method even predicts the predominant regioisomer in all but two cases, i.e., the cycloaddition of benzonitrile oxide with crotonamide **23f** and *N*-methylcrotonamide **23g**. However, use of a larger basis set in the calculation (B3LYP/6-311+G(2d,p)//RHF/3-21G) correctly predicts that regioisomer **24f** will predominate in the cycloaddition with crotonamide **23f**. It should be mentioned that for each of these two cases the experimental results indicate a small preference for the 5-methyl cycloadducts **24**, thereby making the theoretical predictions more

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(16) The calculated (RHF/3-21G and AM1) $\Delta\Delta S^{\ddagger}$ for the 4- and 5-regioisomers are <2 eu.

(17) RHF/6-31G(d)//RHF/3-21G single-point calculated energies give only slightly better results than the RHF/3-21G calculations with the 4-regioisomer predominating in each case while MP2/6-31G(d)//RHF/3-21G single-point calculations predict that the 5-regioisomers predominate in each case.

Table 5. Calculated Energies and Enthalpies of Reaction (kcal/mol) for the Cycloaddition of Benzonitrile Oxide with Dipolarophiles of the Regioisomers 24 and 25

product	E_r[a]	E_r[b]	ΔH_r[c]	E_r[d]
24a	−46.69	−36.89	−36.02	−33.61
25a	−46.48	−38.98	−35.31	−34.95
24b	−47.53	−35.72	−30.84	−32.74
25b	−44.04	−33.53	−29.35	−28.93
24c	−45.31	−36.75	−38.20	−33.86
25c	−54.63	−44.47	−39.71	−39.51
24d	−45.64	−36.89	−38.15	−33.61
25d	−54.88	−44.80	−39.83	−34.95
24e	−45.20	−36.41	−35.59	−31.12
25e	−52.59	−42.91	−38.67	−38.77
24f	−48.13	−37.26	−32.98	−33.24
25f	−52.81	−39.74	−33.72	−34.37
24g	−46.47	−36.30	−32.94	−32.74
25g	−53.09	−40.21	−33.78	−34.45
24h	−45.89	−35.62	−30.52	−30.13
25h	−50.36	−37.62	−32.73	−33.11
24i	−39.35	−33.55	−27.86	−25.31
25i	−46.55	−37.30	−29.93	−30.83

[a] RHF/3-21G//RHF/3-21G+ZPE (scaled by 0.8929). [b] B3LYP/6-31G(d)//RHF/3-21G+ZPE (scaled by 0.8929). [c] AM1//AM1 (no ZPE). [d] B3LYP/6-31G(d)//AM1 (no ZPE). $E_r = E_{products} - E_{separated\ reactants}$; $\Delta H_r = \Delta H_{products} - \Delta H_{separated\ reactants}$.

difficult since the corresponding differences in energies is smaller than for the tertiary crotonamides which exhibit a large preference for the 4-methyl isomer **25**.

Table 5 gives the energies (ab initio and DFT) and enthalpies of reaction for the cycloadditions. As expected the reactions are very exothermic with the RHF/3-21G giving higher E_rs than the DFT and AM1 values.

Recently, Houk and co-workers published several reports of the successful application of DFT, especially the hybrid HF-DFT gradient corrected methods, to the study of pericyclic reactions.[18] On the basis of our experimental results, we have shown that the B3LYP energies with a moderately sized basis set using the RHF/3-21G optimized geometries gives excellent estimates of the ratios of regioisomers in the cycloaddition of benzonitrile oxide with methyl acrylate (**23a**), methyl crotonate (**23b**), and various acrylamides and crotonamides. Interestingly, the semiempirical AM1 method gives significantly better results than the ab initio RHF/3-21G method.

Conclusions

Methyl cinnamate (**9a**) and methyl crotonate (**14a**) undergo a [3 + 2] cycloaddition reaction with phenyl nitrile oxides to predominantly afford the 5-phenyl or the 5-methyl isoxazoline **10** or **15**, respectively. However, utilization of tertiary cinnamides or tertiary crotonamides as the dipolarophile unexpectedly resulted in a reversal of regioselectivity such that the 4-phenyl or 4-methyl isoxazoline **11** or **16** is the major cycloadduct. The primary or secondary cinnamides and crotonamides produce the regioisomeric adducts with the same selectivity as the parent ester, except for the secondary anilides amides that yield approximately 1:1 ratios. Interestingly, all acrylamides exhibit the same selectivity as ethyl acrylate (**17a**), yielding the 5-substituted isoxazolines **19**. These experimental results indicate that the β-substitutent of the dipolarophile as well as the amide functionality is responsible for the regioselectivities observed.

Semiempirical (AM1) and ab initio calculations were performed on a series of crotonate/crotonamide and acrylate/acrylamide dipolarophiles. These results indicate that the RHF/3-21G transition structures of the 4-carbonyl isomers **24** are highly asynchronous such that the C−C bond is approximately 0.5 Å longer than the C−O bond. However, the RHF/3-21G transition structures of the 5-carbonyl isomers **25** are more synchronous. This is most likely due to steric interactions between the phenyl group of the nitrile oxide and the ester or amide portion of the molecule. The larger tertiary amide directs the formation of **25** while the more sterically congested transition state leads to **24**.

In addition, ab initio and DFT activation energies were calculated. The $\Delta E^{\ddagger}$s calculated by the B3LYP/6-31G (d)//RHF/3-21G method correctly predicts the predominate regioisomer in all cases but one.

Experimental Section

Melting points are uncorrected. Proton NMR spectra were recorded at 300 MHz using tetramethylsilane as an internal standard. Carbon NMR were recorded at 75 MHz using either chloroform-*d* or dimethyl sulfoxide-d_6 as an internal standard. Carbon multiplicities were assigned by either DEPT experiments or HETCORR experiments. Reported NMR data were obtained in chloroform-*d* unless otherwise noted.

Chloro oximes **8** were prepared according to the literature procedure[8] from the corresponding oximes and NCS in DMF at 0−20 °C for activated rings and at ∼45 °C for deactivated rings and had physical properties identical to those reported. The corresponding nitrile oxides were generated in situ by dehydrohalogenation with triethylamine.

General Procedure for the Preparation of Cinnamides 9, Crotonamides 14, or Acrylamides 17. To cinnamoyl chloride, crotonyl chloride, or acryoyl chloride (15 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added the appropriate amine (30 mmol) in CH_2Cl_2 (50 mL) over 30 min. After being stirred at room temperature for 2 h, the reaction mixture was poured into 1 N HCl (50 mL) and extracted. The organic layer was washed with water (50 mL), dried ($MgSO_4$), filtered, and evaporated. If necessary, the amides were purified by recrystallization or column chromatography generally using ethyl acetate/hexanes.

***N,N*-Diethylcinnamide (9e):** mp = 66.5−67.5 °C (white needles from ether/hexanes) (lit.[19] mp = 68−69 °C).

Piperidinylcinnamide (9i): mp = 114−116 °C (white needles from ether/hexanes) (lit.[19] mp = 119−120 °C).

***N*-Phenylcinnamide (9j):** mp = 168−172 °C (lit.[20] mp = 174 °C).

***N*-(4-Methoxyphenyl)cinnamide (9k):** mp = 165−167 °C (gray solid from EtOAc/hexanes) (lit.[20] mp = 185 °C).

***N*-(4-Nitrophenyl)cinnamide (9m):** mp = 216−219 °C (yellow solid from EtOAc) (lit.[21] mp = 208 °C).

***N*-Methyl-*N*-phenylcinnamide (9n):** mp = 68−70 °C (lit.[22] mp = 71.5−72.5 °C).

***N*-Cyclopentylcinnamide (9o):** mp = 142−143 °C (lit.[23] mp = 145−146 °C).

***N,N*-Dimethylcinnamide (9r):** mp = 91−93 °C (lit.[24] mp = 94−95 °C).

***N,N*-Diethylcrotonamide (14b):** oil, ref 25.

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***N*-Piperidinylcrotonamide (14c):** oil, ref 26.

***N*-Cyclopentylcrotonamide (14e):** mp = 107−108 °C (white solid from ether/hexanes); ^{1}H NMR δ 6.82 (dq, J = 15.0, 6.8 Hz, 1H), 5.76 (dq, J = 15.0, 1.5 Hz, 1H), 5.41 (br s, 1H), 4.23−4.33 (m, 1H), 1.97−2.04 (m, 2H), 1.84 (dd, J = 6.8, 1.5 Hz, 3H), 1.56−1.74 (m, 4H), 1.35−1.42 (m, 2H); IR 3265, 1623 cm^{-1}; MS m/z 154 (MH$^+$). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.18; H, 9.48; N, 8.97.

2,2,6,6-Tetramethylpiperidinylcrotonamide (14f): white, waxy solid, mp = 39−40 °C; ^{1}H NMR δ 6.65 (dq, J = 15.0, 6.8 Hz, 1H), 6.22 (dq, J = 15.0, 1.5 Hz, 1H), 1.85 (dd, J = 6.8, 1.5 Hz, 3H), 1.76 (s, 6H), 1.40−1.50 (br m, 12H); IR 1623 cm^{-1}; MS m/z 210 (MH$^+$). Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.49; H, 10.97; N, 6.62.

***N*,*N*-Diethylacrylamide (17b):** oil, ref 27.

General Procedure for the Cycloaddition Reactions. To hydroximinoyl acid chloride **8** (10 mmol) and dipolarophile **9**, **14**, or **17** (8 mmol) in EtOAc (100 mL) was added triethylamine (10 mmol) in EtOAc (25 mL) dropwise over a period of 30−45 min. The reaction was stirred at room temperature overnight and then examined by TLC. Usually, for reactions with cinnamides and crotonamides, the TLC indicated the presence of starting olefin. An additional amount of hydroximinoyl acid chloride **8** (10 mmol) was added, followed by the dropwise addition of triethylamine (10 mmol) in EtOAc (25 mL). After being stirred overnight, the reaction mixture was washed with water (3 × 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. Most of the major isomer was isolated by fractional recrystallization from EtOAc/hexanes or ether/hexanes. The remaining mother liquor was chromatographed using 10−15% EtOAc/hexanes to yield an additional amount of the major isomer and the minor isomer.

***trans*-Methyl 3,5-diphenyl-4,5-dihydroisoxazole-4-carboxylate (10a)** (84% yield both isomers): mp = 83−85 °C (lit.[4a] mp = 83−84 °C); ^{1}H NMR δ 7.70−7.73 (m, 2H), 7.33−7.41 (m, 8H), 5.98 (d, J = 6.2 Hz, 1H), 4.46 (d, J = 6.2 Hz, 1H), 3.77 (s, 3H); IR 3031, 2952, 1733 cm^{-1}; MS m/z 282 (MH$^+$), 176 (MH$^+$ − PhCHO). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.61; H, 5.39; N, 5.03.

***trans*-Methyl 3,4-diphenyl-4,5-dihydroisoxazole-5-carboxylate (11a):** mp = 106−109 °C (lit.[4a] mp = 108−110 °C); ^{1}H NMR δ 7.60−7.63 (m, 2H), 7.27−7.42 (m, 8H), 5.05 (d, J = 4.1 Hz, 1H), 4.97 (d, J = 4.1 Hz, 1H), 3.84 (s, 3H); IR 2965, 1752 cm^{-1}; MS m/z 282 (MH$^+$). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.61; H, 5.50; N, 5.15.

***trans*-Methyl 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxylate (10b)** (85% yield both isomers): mp = 87−88 °C; ^{1}H NMR δ 7.65 (d, J = 8.7 Hz, 2H), 7.34−7.42 (m, 7H), 6.00 (d, J = 6.2 Hz, 1H), 4.43 (d, J = 6.2 Hz, 1H), 3.78 (s, 3H); IR 2985, 1732 cm^{-1}; MS m/z 316, 318 (MH$^+$), 210, 212 (MH$^+$ − PhCHO). Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.71; H, 4.67; N, 4.45.

***trans*-Methyl 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxylate (11b):** mp = 80−82 °C; ^{1}H NMR δ 7.54 (d, J = 8.7 Hz, 2H) 7.24−7.36 (m, 7H), 5.02 (d, J = 4.3 Hz, 1H), 4.97 (d, J = 4.3 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR δ 170.1, 157.2, 137.5, 136.3, 129.5 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 127.5 (CH), 126.5, 86.8 (CH), 58.0 (CH), 52.8 (CH_3); IR 2991, 1761 cm^{-1}; MS m/z 316, 318 (MH$^+$). Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.61; H, 4.43; N, 4.46.

***trans*-Methyl 3-(4-methoxyphenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxylate (10c)** (64% yield both isomers): mp = 80−81 °C; ^{1}H NMR δ 7.65 (d, J = 8.8 Hz, 2H), 7.32−7.38 (m, 5H), 6.91 (d, J = 8.8 Hz, 2H), 5.95 (d, J = 6.0 Hz, 1H), 4.43 (d, J = 6.0 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H); IR 1733 cm^{-1}; MS m/z 312 (MH$^+$), 206 (MH$^+$ − PhCHO). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.38; H, 5.43; N, 4.59.

***trans*-Methyl 3-(4-Methoxyphenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxylate (11c).** This was isolated as a mixture of **10c** and **11c**: ^{1}H NMR δ 7.67 (d, J = 8.7 Hz, 2H), 7.30−7.38 (m, 5H), 6.80 (d, J = 8.7 Hz, 2H), 5.01 (d, J = 4.0 Hz, 1H), 4.94 (d, J = 4.0 Hz, 1H), 3.93 (s, 3H), 3.79 (s, 3H).

***trans*-Methyl 3-(3-nitrophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxylate (10d)** (70% yield both isomers; 88% yield based on recovered starting material): mp = 88−90.5 °C; ^{1}H NMR δ 8.55 (t, J = 2.1 Hz, 1H), 8.27 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 8.11 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.61 (t, J = 8.1 Hz, 1H), 7.34−7.44 (m, 5H), 6.10 (d, J = 6.3 Hz, 1H), 4.51 (d, J = 6.3 Hz, 1H), 3.81 (s, 3H); IR 1735 cm^{-1}; MS m/z 327 (MH$^+$), 221 (MH$^+$ − PhCHO). Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.58; H, 4.32; N, 8.58. Found: C, 62.55; H, 4.29; N, 8.97.

***trans*-Methyl 3-(3-nitrophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxylate (11d):** mp = 123−124 °C; ^{1}H NMR δ 8.42 (t, J = 2.2 Hz, 1H), 8.18 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 7.99 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.28−7.41 (m, 5H), 5.09 (d, J = 4.4 Hz, 1H), 5.06 (d, J = 4.4 Hz, 1H), 3.87 (s, 3H); IR 1743 cm^{-1}; MS m/z 327 (MH$^+$). Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.58; H, 4.32; N, 8.58. Found: C, 62.77; H, 4.38; N, 8.62.

***trans*-*N*,*N*-Diethyl 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10e)** (95% yield both isomers): mp = 123−124.5 °C; ^{1}H NMR δ 7.54 (d, J = 8.7 Hz, 2H), 7.33−7.52 (m, 7H), 5.73 (d, J = 9.3 Hz, 1H), 4.64 (d, J = 9.3 Hz, 1H), 3.13−3.50 (3m, 4H), 1.14 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 167.7, 154.8, 138.6, 135.9, 129.1 (CH), 129.0 (CH), 128.9 (CH), 127.8 (CH), 127.5, 126.2 (CH), 89.0 (CH), 59.9 (CH), 42.3 (CH_2), 40.9 (CH_2), 14.5 (CH_3), 12.6 (CH_3); IR 2975, 1638, 1598 cm^{-1}; MS m/z 357, 359 (MH$^+$), 251, 253 (MH$^+$ − PhCHO). Anal. Calcd for $C_{20}H_{21}ClN_2O_2$: C, 67.32; H, 5.93; N, 7.85. Found: C, 67.47; H, 5.91; N, 7.96.

***trans*-*N*,*N*-Diethyl 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11e):** mp = 116−118 °C; ^{1}H NMR δ 7.53 (d, J = 8.7 Hz, 2H), 7.25−7.35 (m, 7H), 5.64 (d, J = 5.7 Hz, 1H), 5.12 (d, J = 5.7 Hz, 1H), 3.38−3.50 (2m, 4H), 1.23 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 166.2, 158.1, 138.2, 135.8, 129.3 (CH), 128.7 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.6, 87.3 (CH), 55.7 (CH), 41.9 (CH_2), 40.6 (CH_2), 14.2 (CH_3), 12.5 (CH_3); IR 2975, 1645, 1598 cm^{-1}; MS m/z 357, 359 (MH$^+$). Anal. Calcd for $C_{20}H_{21}ClN_2O_2$: C, 67.32; H, 5.93; N, 7.85. Found: C, 67.12; H, 5.80; N, 7.61.

***trans*-*N*,*N*-Diethyl 3,5-diphenyl-4,5-dihydroisoxazole-4-carboxamide (10f)** (83% yield both isomers): mp = 94−96 °C; ^{1}H NMR δ 7.58−7.63 (m, 2H), 7.33−7.43 (m, 8H), 5.74 (d, J = 9.2 Hz, 1H), 4.68 (d, J = 9.2 Hz, 1H), 3.10−3.54 (4m, 4H), 1.13 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); IR 2976, 1626 cm^{-1}; MS m/z 323 (MH$^+$), 217 (MH$^+$ − PhCHO). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.29; H, 6.82; N, 8.67.

***trans*-*N*,*N*-Diethyl 3,4-diphenyl-4,5-dihydroisoxazole-5-carboxamide (11f):** mp = 118−119 °C; ^{1}H NMR δ 7.60−7.64 (m, 2H), 7.23−7.35 (m, 8H), 5.67 (d, J = 5.6 Hz, 1H), 5.11 (d, J = 5.6 Hz, 1H), 3.67 (q, J = 7.1 Hz, 2H), 3.42 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); IR 2969, 1644 cm^{-1}; MS m/z 323 (MH$^+$). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.56; H, 6.88; N, 8.58.

***trans*-*N*,*N*-Diethyl 3-(4-methoxyphenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10g)** (40% yield both isomers): mp = 107−108 °C; ^{1}H NMR δ 7.54 (d, J = 8.8 Hz, 2H), 7.35−7.41 (m, 5H), 6.88 (d, J = 8.8 Hz, 2H), 5.72 (d, J = 9.2 Hz, 1H), 4.64 (d, J = 9.2 Hz, 1H), 3.82 (s, 3H), 3.10−3.53 (4m, 4H), 1.14 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H); IR 2970, 1632 cm^{-1}; MS m/z 353 (MH$^+$), 247 (MH$^+$ − PhCHO). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.94. Found: C, 71.22; H, 6.72; N, 7.76.

***trans*-*N*,*N*-Diethyl 3-(4-methoxyphenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11g):** mp = 85−86 °C; ^{1}H NMR δ 7.55 (d, J = 8.9 Hz, 2H), 7.25−7.32 (m, 5H), 6.78 (d, J = 8.9 Hz, 2H), 5.64 (d, J = 5.6 Hz, 1H), 5.07 (d, J = 5.6 Hz,

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1H), 3.76 (s, 3H), 3.47 (q, J = 7.1 Hz, 2H), 3.42 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); IR 2973, 1645 cm^{-1}; MS m/z 353 (MH^+). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.60; H, 6.92; N, 7.99.

***trans*-*N*,*N*-Diethyl 3-(3-nitrophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10h)** (63% yield both isomers): mp = 124−125 °C; ^1H NMR δ 8.18−8.28 (m, 3H), 7.60 (t, J = 7.9 Hz, 1H), 7.40−7.45 (m, 5H), 5.80 (d, J = 9.6 Jz, 1H), 4.74 (d, J = 9.6 Hz, 1H), 3.19−3.60 (3m, 4H), 1.16 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H); IR 1638 cm^{-1}; MS m/z 368 (MH^+), 262 (MH^+ − PhCHO). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.33; H, 5.71; N, 11.80.

***trans*-*N*,*N*-Diethyl 3-(3-nitrophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11h):** mp = 85−87 °C; ^1H NMR δ 8.48 (t, J = 1.9 Hz, 1H), 8.15 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 7.91 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.28−7.42 (m, 5H), 5.68 (d, J = 5.4 Hz, 1H), 5.20 (d, J = 5.4 Hz, 1H), 3.48 (q, J = 7.1 Hz, 2H), 3.43 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); IR 1645 cm^{-1}; MS m/z 368 (MH^+). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 64.99; H, 5.75; N, 11.50.

***trans*-1-[3-(4-Chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carbonyl]piperidine (10i)** (85% yield both isomers): mp = 128−130 °C; ^1H NMR δ 7.55 (d, J = 8.7 Hz, 2H), 7.34−7.42 (m, 7H), 5.70 (d, J = 8.3 Hz, 1H), 4.75 (d, J = 8.3 Hz, 1H), 3.65−3.80 (m, 1H), 3.45−3.55 (m, 1H), 3.32 (t, J = 5.5 Hz, 2H), 1.23−1.70 (m, 6H); IR 2968, 1628 cm^{-1}; MS m/z 369, 371 (MH^+), 263, 265 (MH^+ − PhCHO). Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; N, 7.59. Found: C, 68.50; H, 5.51; N, 7.33.

***trans*-1-[3-(4-Chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carbonyl]piperidine (11i):** mp = 163−165.5 °C; ^1H NMR δ 7.54 (d, J = 8.7 Hz, 2H), 7.22−7.36 (m, 7H), 5.66 (d, J = 5.6 Hz, 1H), 5.15 (d, J = 5.6 Hz, 1H), 3.61−3.80 (m, 2H), 3.39−3.47 (m, 2H), 1.58−1.75 (m, 6H); IR 2948, 1647 cm^{-1}; MS m/z 369, 371 (MH^+). Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; N, 7.59. Found: C, 68.56; H, 5.86; N, 7.51.

***trans*-*N*-Phenyl 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10j)** (54% yield both isomers; 71% based on recovered starting material): mp = 244−245 °C; ^1H NMR (DMSO-d_6) δ 10.62 (br s, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.29−7.57 (m, 11H), 7.09−7.12 (m, 1H), 5.92 (d, J = 7.0 Hz, 1H), 4.82 (d, J = 7.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.9, 152.9, 138.8, 137.1, 134.5, 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 126.3, 124.8 (CH), 123.1 (CH), 118.6 (CH), 87.0 (CH), 62.1 (CH); IR 3340, 1654 cm^{-1}; MS m/z 377, 379 (MH^+), 271, 273 (MH^+ − PhCHO). Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 69.96; H, 4.44; N, 7.33.

***trans*-*N*-Phenyl 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11j):** mp = 163−165 °C; ^1H NMR δ 8.53 (br s, 1H), 7.55−7.62 (m, 4H), 7.27−7.39 (m, 9H), 7.15−7.17 (m, 1H), 5.19 (d, J = 3.4 Hz, 1H), 5.01 (d, J = 3.4 Hz, 1H); ^{13}C NMR δ 168.2, 158.9, 137.4, 136.8, 136.7, 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 127.4 (CH), 125.9, 125.0 (CH), 119.8 (CH), 87.4 (CH), 58.3 (CH); IR 3354, 1683 cm^{-1}; MS m/z 377, 379 (MH^+), 256, 258 (MH^+ − C(O)NHPh). Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.02; H, 4.43; N, 7.38.

***trans*-*N*-(4-Methoxyphenyl) 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10k)** (88% yield both isomers): mp = 222−224 °C; ^1H NMR δ 7.72 (d, J = 8.7 Hz, 2H), 7.25−7.40 (m, 10H), 6.84 (d, J = 9.0 Hz, 2H), 6.02 (d, J = 5.0 Hz, 1H), 4.36 (d, J = 5.0 Hz, 1H), 3.78 (s, 3H); IR 3269, 1653, 1513 cm^{-1}; MS m/z 407, 409 (MH^+), 301, 303 (MH^+ − PhCHO). Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89. Found: C, 67.52; H, 4.81; N, 6.85.

***trans*-*N*-(4-Methoxyphenyl) 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11k):** mp = 155−157 °C; ^1H NMR δ 8.43 (br s, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 7.27−7.39 (m, 7H), 6.87 (d, J = 9.0 Hz, 2H), 5.19 (d, J = 3.4 Hz, 1H), 5.00 (d, J = 3.4 Hz, 1H), 3.79 (s, 3H); IR 3369, 1678, 1528 cm^{-1}; MS m/z 407, 409 (MH^+). Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89. Found: C, 67.46; H, 4.81; N, 6.96.

***trans*-*N*-(4-Methoxyphenyl) 3,5-diphenyl-4,5-dihydroisoxazole-4-carboxamide (10l)** (88% yield both isomers): mp = 166−167.5 °C; ^1H NMR δ 7.77−7.82 (m, 2H), 7.30−7.47 (m, 11H), 6.83 (d, J = 9.0 Hz, 2H), 6.02 (d, J = 4.8 Hz, 1H), 4.40 (d, J = 4.8 Hz, 1H), 3.77 (s, 3H); IR 3271, 1650 cm^{-1}; MS m/z 373 (MH^+), 267 (MH^+ − PhCHO). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.94; H, 5.31; N, 7.43.

***trans*-*N*-(4-Methoxyphenyl) 3,4-diphenyl-4,5-dihydroisoxazole-5-carboxamide (11l):** mp = 183−184 °C; ^1H NMR δ 8.46 (br s, 1H), 7.62−7.66 (m, 2H), 7.51 (d, J = 9.1 Hz, 2H), 7.28−7.40 (m, 8H), 6.87 (d, J = 9.1 Hz, 2H), 5.21 (d, J = 3.3 Hz, 1H), 4.98 (d, J = 3.3 Hz, 1H), 3.79 (s, 3H); IR 3352, 1677, 1513 cm^{-1}; MS m/z 373 (MH^+). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.04; H, 5.32; N, 7.51.

***trans*-*N*-(4-Nitrophenyl) 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10m)** (66% yield both isomers): mp = 188−190 °C; ^1H NMR δ 8.21 (d, J = 9.2 Hz, 2H), 7.85 (br s, 1H), 7.66−7.74 (m, 5H), 7.36−7.44 (m, 6H), 6.04 (d, J = 4.4 Hz, 1H), 4.44 (d, J = 4.4 Hz, 1H); IR 3356, 1677 cm^{-1}; MS m/z 422, 424 (MH^+), 316, 318 (MH^+ − PhCHO).

***trans*-*N*-(4-Nitrophenyl) 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11m):** mp = 169−170.5 °C; ^1H NMR δ 8.83 (br s, 1H), 8.25 (d, J = 9.1 Hz, 2H), 7.81 (d, J = 9.1 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.28−7.41 (m, 7H), 5.19 (d, J = 3.3 Hz, 1H), 5.04 (d, J = 3.3 Hz, 1H); ^{13}C NMR δ 168.9, 159.0, 144.0, 142.2, 136.9, 136.8, 129.5 (CH), 129.1 (CH), 128.8 (CH), 128.4 (CH), 127.2 (CH), 125.5, 125.0 (CH), 119.4 (CH), 87.1 (CH), 58.2 (CH); IR 3359, 1694 cm^{-1}; MS m/z 422, 424 (MH^+). Anal. Calcd for $C_{22}H_{16}ClN_3O_4$ (was performed on a mixture of both isomers): C, 62.64; H, 3.82; N, 9.96. Found: C, 62.68; H, 3.77; N, 10.01.

***trans*-*N*-Methyl-*N*-phenyl 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10n)** (54% yield both isomers): mp = 178−179 °C; ^1H NMR δ 7.50 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.16−7.36 (m, 8H), 6.80 (br s, 2H), 5.81 (d, J = 9.3 Hz, 1H), 4.46 (d, J = 9.3 Hz, 1H), 3.31 (s, 3H); ^{13}C NMR δ 168.6, 154.8, 142.1, 137.7, 135.9, 129.8 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.3, 126.8 (CH), 126.7 (CH), 89.2 (CH), 59.8 (CH), 38.0 (CH_3); IR 1653 cm^{-1}; MS m/z 391, 393 (MH^+), 285, 287 (MH^+ − PhCHO). Anal. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17. Found: C, 70.53; H, 4.83; N, 7.13.

***trans*-*N*-Methyl-*N*-phenyl 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11n):** mp = 144−145.5 °C; ^1H NMR δ 7.48 (d, J = 8.6 Hz, 2H), 7.08−7.37 (m, 12H), 5.36 (d, J = 5.7 Hz, 1H), 4.84 (d, J = 5.7 Hz, 1H), 3.34 (s, 3H); ^{13}C NMR δ 167.7, 157.5, 142.1, 137.5, 135.7, 129.6 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.6, 85.7 (CH), 56.9 (CH), 38.2 (CH_3); IR 1661 cm^{-1}; MS m/z 391, 393 (MH^+). Anal. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17. Found: C, 70.51; H, 4.75; N, 7.12.

***trans*-*N*-Cyclopentyl 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10o)** (79% yield both isomers): mp = 220−221 °C; ^1H NMR δ 7.65 (d, J = 8.5 Hz, 2H), 7.32−7.64 (m, 7H), 5.86 (d, J = 5.4 Hz, 1H), 5.56 (br d, J = 7.0 Hz, 1H), 4.15−4.24 (m, 1H), 4.20 (d, J = 5.4 Hz, 1H), 1.87−2.02 (m, 2H), 1.51−1.62 (m, 4H), 1.17−1.39 (2m, 2H); ^{13}C NMR δ 167.5, 154.4, 139.2, 136.7, 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 126.5, 125.1 (CH), 87.7 (CH), 64.1 (CH), 51.7 (CH), 32.7 (CH_2), 23.4 (CH_2); IR 3290, 2961, 1638 cm^{-1}; MS m/z 369, 371 (MH^+), 263, 265 (MH^+ − PhCHO). Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; N, 7.59. Found: C, 68.42; H, 5.79; N, 7.55.

***trans*-*N*-Cyclopentyl 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11o):** mp = 137.5−140 °C; ^1H NMR δ 7.55 (d, J = 8.7 Hz, 2H), 7.27−7.36 (m, 7H), 6.72 (br d, J = 7.5 Hz, 1H), 5.10 (d, J = 3.5 Hz, 1H), 4.85 (d, J = 3.5 Hz, 1H), 4.20 (sextet, J = 7.5 Hz, 1H), 1.95−2.05 (m, 2H), 1.58−1.70 (m, 4H), 1.35−1.44 (m, 2H); IR 3306, 2962, 1667

cm^{-1}; MS *m*/*z* 369, 371 (MH$^+$). Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; N, 7.59. Found: C, 68.14; H, 5.77; N, 7.40.

***trans*-*N*-Cyclopentyl 3,5-diphenyl-4,5-dihydroisoxazole-4-carboxamide (10p)** (76% yield both isomers): mp = 195−197 °C; ^{1}H NMR δ 7.71−7.75 (m, 2H), 7.29−7.47 (m, 8H), 5.88 (d, *J* = 5.2 Hz, 1H), 5.58 (br d, *J* = 6.9 Hz, 1H), 4.25 (d, *J* = 5.2 Hz, 1H), 4.16−4.23 (m, 1H), 1.84−2.04 (m, 2H), 1.45−1.62 (m, 4H), 1.17−1.38 (2m, 2H); IR 3263, 3076, 1641 cm^{-1}; MS *m*/*z* 335 (MH$^+$), 229 (MH$^+$ − PhCHO). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.17; H, 6.61; N, 8.26.

***trans*-*N*-Cyclopentyl 3,4-diphenyl-4,5-dihydroisoxazole-5-carboxamide (11p):** mp = 123−125 °C; ^{1}H NMR δ 7.61−7.64 (m, 2H), 7.27−7.35 (m, 8H), 6.75 (br d, *J* = 6.0 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 4.84 (d, *J* = 3.4 Hz, 1H), 4.20 (sextet, *J* = 6.0 Hz, 1H), 1.95−2.06 (m, 2H), 1.55−1.68 (m, 4H), 1.32−1.50 (m, 2H); IR 3359, 2964, 1667 cm^{-1}; MS *m*/*z* 335 (MH$^+$). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.08; H, 6.68; N, 8.46.

***trans*-3-(4-Chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10q)** (80% yield both isomers): mp = 245−246 °C; ^{1}H NMR (DMSO-d_6) δ 7.99 (br s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.48 (br s, 1H), 7.37−7.46 (m, 5H), 5.77 (d, *J* = 7.4 Hz, 1H), 4.58 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 171.7, 156.0, 141.4, 136.5, 130.7 (CH), 130.5 (CH), 130.3 (CH), 130.1 (CH), 129.3, 127.9 (CH), 89.3 (CH), 62.9 (CH); IR 3420, 3179, 1656 cm^{-1}; MS *m*/*z* 301, 303 (MH$^+$), 195, 197 (MH$^+$ − PhCHO). Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.59; H, 4.30; N, 9.24.

***trans*-3-(4-Chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11q):** mp = 163−165 °C; ^{1}H NMR (DMSO-d_6) δ 7.71 (br s, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.53 (br s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.27−7.40 (m, 5H), 5.24 (d, *J* = 4.2 Hz, 1H), 4.89 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 172.9, 159.3, 140.3, 136.7, 130.9 (CH), 130.8 (CH), 130.7 (CH), 129.5 (CH), 129.2 (CH), 128.4, 89.0 (CH), 58.2 (CH); IR 3453, 1678 cm^{-1}; MS *m*/*z* 301, 303 (MH$^+$). Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.86; H, 4.38; N, 9.21.

***trans*-*N*,*N*-Dimethyl 3-(4-chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxamide (10r)** (85% yield both isomers): mp = 221−223 °C; ^{1}H NMR δ 7.52 (d, *J* = 8.6 Hz, 2H), 7.38−7.41 (m, 5H), 7.35 (d, *J* = 8.6 Hz, 2H), 5.73 (d, *J* = 8.4 Hz, 1H), 4.75 (d, *J* = 8.4 Hz, 1H), 3.02 (s, 3H), 2.93 (s, 3H); ^{13}C NMR δ 168.5, 154.6, 139.1, 136.1, 129.1 (CH), 129.0 (CH), 128.9 (CH), 127.9 (CH), 127.4, 126.0 (CH), 88.2 (CH), 60.3 (CH), 37.6 (CH$_3$), 36.4 (CH$_3$); IR 1646 cm^{-1}; MS *m*/*z* 329, 331 (MH$^+$). Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.78; H, 5.21; N, 8.52. Found: C, 65.38; H, 5.11; N, 8.43.

***trans*-*N*,*N*-Dimethyl 3-(4-chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxamide (11r):** mp = 127−129 °C; ^{1}H NMR δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.22−7.35 (m, 7H), 5.63 (d, *J* = 5.6 Hz, 1H), 5.17 (d, *J* = 5.6 Hz, 1H), 3.16 (s, 3H), 3.01 (s, 3H); ^{13}C NMR δ 167.0, 158.2, 138.2, 136.0, 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 126.7, 87.3 (CH), 55.6 (CH), 37.3 (CH$_3$), 36.2 (CH$_3$); IR 1652 cm^{-1}; MS *m*/*z* 329, 331 (MH$^+$). Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.78; H, 5.21; N, 8.52. Found: C, 65.47; H, 5.24; N, 8.43.

***trans*-Methyl 3-(4-chlorophenyl)-4,5-dihydro-5-methylisoxazole-4-carboxylate (15a)** (65% yield both isomers): clear oil; ^{1}H NMR δ 7.62 (d, *J* = 6.5 Hz, 2H), 7.36 (d, *J* = 6.5 Hz, 2H), 5.10 (quintet, *J* = 6.3 Hz, 1H), 4.05 (d, *J* = 6.3 Hz, 1H), 3.64 (s, 3H), 1.46 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR δ 169.6, 152.8, 136.2, 129.1 (CH), 128.0 (CH), 127.3, 82.5 (CH), 59.8 (CH$_3$), 53.0 (CH), 20.8 (CH$_3$); IR 1740 cm^{-1}; MS *m*/*z* 254, 256 (MH$^+$), 210, 212 (MH$^+$ − CH$_3$CHO). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.57; H, 4.80; N, 5.61.

***trans*-Methyl 3-(4-chlorophenyl)-4,5-dihydro-4-methylisoxazole-5-carboxylate (16a):** mp = 66.5−68 °C (white solid from EtOAc/hexanes); ^{1}H NMR δ 7.62 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 4.80 (d, *J* = 4.1 Hz, 1H), 3.95 (dq, *J* = 4.1, 7.1 Hz, 1H), 3.80 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 170.7, 159.5, 136.4, 129.2 (CH), 128.5 (CH), 126.2, 85.1 (CH), 52.8 (CH$_3$), 46.7 (CH), 18.0 (CH$_3$); IR 1740 cm^{-1}; MS *m*/*z* 254, 256 (MH$^+$). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.68; H, 4.84; N, 5.48.

***trans*-*N*,*N*-Diethyl 3-(chlorophenyl)-4,5-dihydro-5-methylisoxazole-4-carboxamide (15b)** (86% yield both isomers): mp = 105−107 °C (white crystals from EtOAc/hexane); ^{1}H NMR δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 4.91 (dq, *J* = 7.4, 6.3 Hz, 1H), 4.27 (d, *J* = 7.4 Hz, 1H), 3.30−3.55 (m, 4H), 1.53 (d, *J* = 6.3 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.8, 154.8, 135.9, 129.0 (CH), 127.8 (CH), 126.0, 83.0 (CH), 58.7 (CH), 42.2 (CH$_2$), 40.9 (CH$_2$), 20.7 (CH$_3$), 14.9 (CH$_3$), 12.7 (CH$_3$); IR 1633 cm^{-1}; MS *m*/*z* 295, 297 (MH$^+$), 251, 253 (MH$^+$ − MeCHO). Anal. Calcd for $C_{15}H_{19}ClN_2O_2$: C, 61.12; H, 6.50; N, 9.50. Found: C, 60.87; H, 6.22; N, 9.36.

***trans*-*N*,*N*-Diethyl 3-(4-chlorophenyl)-4,5-dihydro-4-methylisoxazole-5-carboxamide (16b):** pale yellow oil; ^{1}H NMR δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 4.92 (d, *J* = 5.3 Hz, 1H), 4.52 (dq, *J* = 5.3, 7.3 Hz, 1H), 3.46−3.59 (m, 2H), 3.40 (q, *J* = 7.1 Hz, 2H), 1.33 (d, *J* = 7.3 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 166.8, 160.9, 136.1, 129.1 (CH), 128.6 (CH), 126.8, 85.9 (CH), 44.1 (CH), 42.0 (CH$_2$), 40.7 (CH$_2$), 17.3 (CH$_3$), 14.4 (CH$_3$), 12.7 (CH$_3$); IR 1645 cm^{-1}; MS *m*/*z* 295, 297 (MH$^+$). Anal. Calcd for $C_{15}H_{19}ClN_2O_2$: C, 61.12; H, 6.50; N, 9.50. Found: C, 61.03; H, 6.54; N, 9.11.

***trans*-*N*-[3-(4-Chlorophenyl)-4,5-dihydro-5-methylisoxazole-4-carbonyl]piperidine (15c)** (83% yield both isomers): mp = 123−125 °C (off-white solid); ^{1}H NMR δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 4.90 (dq, *J* = 7.1, 6.2 Hz, 1H), 4.35 (d, *J* = 7.1 Hz, 1H), 3.45−3.66 (m, 4H), 1.45−1.67 (m, 9H with a 3H doublet (*J* = 6.2 Hz) at δ 1.52); ^{13}C NMR δ 166.8, 154.8, 136.0, 129.1 (CH), 127.8 (CH), 127.7, 82.6 (CH), 59.4 (CH), 46.9 (CH$_2$), 43.8 (CH$_2$), 26.6 (CH$_2$), 25.5 (CH$_2$), 24.3 (CH$_2$), 20.9 (CH$_3$); IR 1637 cm^{-1}; MS *m*/*z* 307, 309 (MH$^+$). Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.36; H, 6.29; N, 9.00.

***trans*-*N*-[3-(4-Chlorophenyl)-4,5-dihydro-4-methylisoxazole-5-carbonyl]piperidine (16c):** clear oil; ^{1}H NMR δ 7.64 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 4.95 (d, *J* = 5.3 Hz, 1H), 4.55 (dq, *J* = 5.3, 7.3 Hz, 1H), 3.70−3.77 (m, 2H), 3.33−3.53 (m, 2H), 1.57−1.72 (m, 6H), 1.33 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 165.7, 160.9, 136.1, 129.1 (CH), 128.5 (CH), 126.7, 85.8 (CH), 47.0 (CH$_2$), 43.8 (CH$_2$), 43.7 (CH), 26.5 (CH$_2$), 25.5 (CH$_2$), 24.5 (CH$_2$), 17.3 (CH$_3$); IR 1645 cm^{-1}; MS *m*/*z* 307, 309 (MH$^+$). Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.57; H, 6.24; N, 9.13.

***trans*-3-(4-Chlorophenyl)-4,5-dihydro-5-methylisoxazole-4-carboxamide (15d)** (65% yield of both isomers): mp = 212−214 °C (white solid from EtOAC/hexanes); ^{1}H NMR (DMSO-d_6) δ 7.96 (br s, 1H), 7.78 (br s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 4.83 (dq, *J* = 7.0, 6.4 Hz, 1H), 4.19 (d, *J* = 7.0 Hz, 1H), 1.38 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 170.3, 154.3, 134.4, 128.8 (CH), 128.1, 128.0 (CH), 82.8 (CH), 60.0 (CH), 20.4 (CH$_3$); IR 3395, 3171, 1666 cm^{-1}; MS *m*/*z* 239, 241 (MH$^+$), 197, 197 (MH$^+$ − MeCHO). Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.41; H, 4.64; N, 11.46.

***trans*-3-(4-Chlorophenyl)-4,5-dihydro-4-methylisoxazole-5-carboxamide (16d):** mp = 174−176 °C (white solid from EtOAc/hexanes); ^{1}H NMR (DMSO-d_6) δ 7.74 (d, *J* = 8.6 Hz, 2H), 7.59 (br s, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.42 (br s, 1H), 4.69 (d, *J* = 4.4 Hz, 2H), 4.00 (dq, *J* = 4.4, 7.2 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.9, 159.6, 134.9, 129.1 (CH), 128.8 (CH), 126.6, 85.7 (CH), 45.7 (CH), 17.9 (CH$_3$); IR 3437, 3175, 1688 cm^{-1}; MS *m*/*z* 239, 241 (MH$^+$). Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.55; H, 4.75; N, 11.43.

***trans*-*N*-Cyclopentyl 3-(4-chlorophenyl)-4,5-dihydro-5-methylisoxazole-4-carboxamide (15e)** (69% yield of both isomers): mp = 198−200 °C (white solid); ^{1}H NMR δ 7.68 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 5.46−5.48 (br m, 1H), 4.99 (dq, *J* = 4.3, 6.5 Hz, 1H), 4.10−4.19 (m, 1H), 3.86 (d, *J* = 4.3 Hz, 1H), 1.81−1.98 (m, 2H), 1.51−1.59 (m, 4H),

1.41 (d, J = 6.5 Hz, 3H), 1.26−1.34 (m, 1H), 1.13−1.18 (m, 1H); IR 3333, 1640 cm^{-1}; MS m/z 307, 309 (MH^+), 263 ($MH^+ - CH_3CHO$). Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.24; H, 6.19; N, 8.91.

***trans*-*N*-Cyclopentyl 3-(4-chlorophenyl)-4,5-dihydro-4-methylisoxazole-5-carboxamide (16e):** mp = 135−136 °C (light beige solid); ^1H NMR δ 7.62 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.67 (br d, J = 6.9 Hz, 1H), 4.67 (d, J = 3.4 Hz, 1H), 4.15−4.17 (m, 1H), 4.01 (dq, J = 3.4, 7.3 Hz, 1H), 1.89−2.03 (m, 2H), 1.55−1.68 (m, 4H), 1.40 (d, J = 7.3 Hz, 3H), 1.25−1.40 (m, 2H); IR 3330, 1643 cm^{-1}; MS m/z 307, 309 (MH^+). Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.28; H, 6.10; N, 8.97.

***trans*-*N*-[3-(4-Chlorophenyl)-4,5-dihydro-4-methylisoxazole-5-carbonyl]-2,2,6,6-tetramethylpiperidine (16f)** (74% yield): mp = 114−117 °C (white solid from EtOAc/hexanes); ^1H NMR δ 7.61 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 5.08 (d, J = 6.0 Hz, 1H), 4.07 (dq, J = 6.0, 7.3 Hz, 1H), 1.76−1.88 (m, 6H), 1.53 (s, 6H), 1.50 (s, 6H), 1.36 (d, J = 7.3 Hz, 3H); IR 1637 cm^{-1}; MS m/z 363, 365 (MH^+). Anal. Calcd for $C_{20}H_{27}ClN_2O_2$: C, 66.19; H, 7.50; N, 7.72. Found: C, 66.18; H, 7.48; N, 7.51.

Ethyl 3-(4-chlorophenyl)-4,5-dihydroisoxazole-5-carboxylate (19a) (95% yield): mp = 64−65.5 °C; ^1H NMR δ 7.61 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 5.18 (dd, J = 10.7, 7.7 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.58−3.65 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H); IR 1753 cm^{-1}; MS m/z 254, 256 (MH^+). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.84; H, 4.54; N, 5.34.

***N*,*N*-Diethyl 3-(4-chlorophenyl)-4,5-dihydroisoxazole-5-carboxamide (19b)** (83% yield): mp = 110−112 °C; ^1H NMR δ 7.65 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 5.35 (dd, J = 11.2, 7.9 Hz, 1H), 4.18 (dd, J = 16.8, 7.9 Hz, 1H), 3.40−3.63 (2m, 4H), 3.34 (dd, J = 16.8, 11.2 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); IR 1637 cm^{-1}; MS m/z 281, 283 (MH^+). Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.51; H, 6.05; N, 9.84.

***trans*-3-(4-Chlorophenyl)-4,5-dihydro-5-phenylisoxazole-4-carboxylic Acid (12).** 5-Phenyl ester **10b** (11.76 g; 37.23 mmol) and NaOH (1N, 75 mL) in ethanol (100 mL) were heated at reflux for 6 h (prolonged heating results in decarboxylation). After cooling, the ethanol was evaporated. The residue was diluted with water (200 mL), cooled to 0 °C, and acidified to pH = 1 with concentrated HCl. A yellowish gum formed, and the mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were washed with water (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to a pale yellow powder (11.14 g, 99% yield): mp = 124−125 °C; ^1H NMR (DMSO-d_6) δ 13.50 (br s, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.36−7.43 (m, 5H), 5.97 (d, J = 6.1 Hz, 1H), 4.82 (d, J = 6.1 Hz, 1H); IR 2800−3200 (br), 1698 cm^{-1}; MS m/z 302, 304 (MH^+), 258, 260 ($MH^+ - CO_2H$), 196, 198 (MH^+ − PhCHO). Anal. Calcd for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; N, 4.64. Found: C, 63.81; H, 3.82; N, 4.60.

***trans*-3-(4-Chlorophenyl)-4,5-dihydro-4-phenylisoxazole-5-carboxylic acid (13)** was prepared as above using ester **11b** (snow-white crystals, 79% yield) for acid **12**. **13:** mp = 188−190 °C (EtOAc/hexanes); ^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^+). Anal. Calcd for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; N, 4.64. Found: C, 63.58; H, 3.98; N, 4.53.

General Procedure for Conversion of Acid 12 (or 13) into Amide 10 (or 11). Acid **12** (or **13**) (~0.50 mmol) and carbonyldiimidazole (~100 mg; 0.6 mmol) in anhydrous DMF (3 mL) were stirred at room temperature for 2 h under a nitrogen atmosphere. Either piperidine, *p*-methoxyaniline, or cyclopentylamine (2−3 equiv) was added and the reaction stirred at room temperature overnight. The reaction was poured into water (30 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with water (3 × 25 mL), dried ($MgSO_4$), filtered, and evaporated. The crude amides **10** (or **11**) were purified by recrystallization. All spectral data and physical properties were identical to those of the amides prepared in the cycloaddition reaction.

Computational Details

The programs GAUSSIAN-94 and SPARTAN 4.1 were used for the ab initio and DFT calculations.[28,29] The CAChe (v. 3.8) worksystem[30] was used for the AM1 calculations. Optimized geometries were obtained at the AM1 and RHF/3-21G levels of theory. All stationary points (minima and transition structures) were characterized by calculation of their harmonic vibrational frequencies at the corresponding level (AM1 or RHF/3-21G). All minima had no negative eigenvalues of the Hessian and no imaginary frequencies. All first-order saddle points (transition structures) had one negative eigenvalue of the Hessian and one imaginary frequency. Single-point energies were calculated using the Becke three-parameter hybrid Hartree−Fock−DFT method[31] with a 6-31G(d) basis set (unless noted otherwise). ZPE corrections scaled by 0.8929 were applied to the RHF/3-21G calculated energies. RHF/3-21G ZPE corrections (scaled by 0.8929) were also applied to the B3LYP/6-31G(d)//RHF3-21G calculated energies. No ZPE corrections were made to the AM1 calculated enthalpies of formation.

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Supporting Information Available: The Cartesian coordinates for starting materials, transition structures, and product geometries as well as the corresponding energies (90 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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