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Synthetic Studies of the Formation of Oxazoles and Isoxazoles from *N*-Acetoacetyl Derivatives: Scope and Limitations

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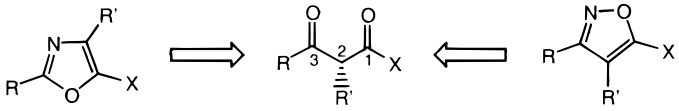
ABSTRACT



The preparation of two types of heterocycles, oxazoles and isoxazoles, were achieved in good yields in a rapid and simple way by using *N*-acetoacetyl derivatives. Steric and electronic effects caused by the nature of the substituents at C1, C2, and C3 were studied. The best results were obtained with a chiral oxazolidinone moiety on C1 derived from (1*R*,2*S*)-(−)-norephedrine.

The prevalence of oxazole and isoxazole cores in natural products and biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocycles.[1] A considerable number of methods to synthesize substituted oxazoles and isoxazoles have been published including approaches based on intermolecular cycloadditions,[2] condensations,[3] and intramolecular cyclizations of amino acids.[4] These methods sometimes suffer in their versatility, convenience, and yield.

Our goal was to prepare novel enantiomerically pure protected amino acids by a Beckmann or Schmidt rearrangement of a configurationally stable β-ketoimide.[5] Moreno-Mañas and co-workers[6] observed the formation of oxazoles and isoxazoles when *N*-acetoacetyl oxazolidinone derivatives were submitted to these conditions. The scope of the reaction was not well established, and in particular, the lack of data related to steric effects at C1, C2, and C3 as well as electronic effects at C1 and C3 prompted our studies. We prepared (1*R*,2*S*)-(−)-norephedrine-derived oxazolidinone β-ketoimides containing different aliphatic and aromatic R groups according to the methodology developed by Evans and co-workers[7] (Table 1, entries 1−7). Upon treatment with NH_2-OH·HCl, the corresponding isoxazoles were isolated in good yields when aliphatic R groups were present (entries 1−3 and 7). Substrates with aromatic substituents proved to be substantially less reactive (entries 4−6). The yields were lower, starting material was recovered, and in one case, epimerization at C2 was observed (entry 6). Two factors may be responsible for this outcome. The carbonyl group undergoing reaction (C3) may be less electrophilic due to conjugation with the aromatic ring. Second, the aromatic ring

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(4) Kondrat'eva, G. T.; Aitzhanova, M. A.; Bogdanov, V. S.; Ivanova, Z. N. *Bull. Acad. Sci. USSR Div. Chem. Sci*. **1978**, 27, 773−777.

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(6) (a) Gálvez, N.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A. *Tetrahedron* **1996**, *52*, 1609−1616. (b) Gálvez, N.; Moreno-Mañas, M.; Vallribera, A.; Molins, E.; Cabrero, A. *Tetrahedron Lett*. **1996**, 37, 6197−6200.

(7) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc*. **1984**, *106*, 1154−1156.

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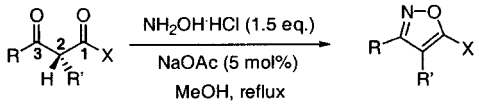
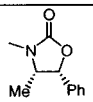
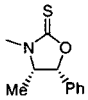
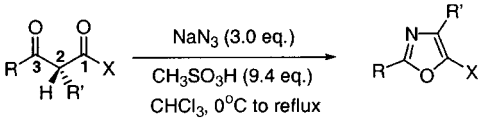
Table 1. Synthesis of Isoxazoles

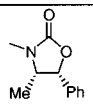
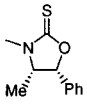
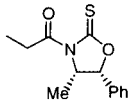
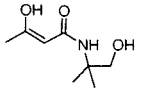


entry	R	R'	X	yield (%)
1	CH_3	CH_3		80
2	CH_3CH_2	CH_3	"	84
3	$PhCH_2CH_2$	CH_3	"	67
4	Ph	CH_3	"	45 (15)[a]
5	*p*-F-Ph	CH_3	"	30 (25)[a]
6	*p*-OMe-Ph	CH_3	"	6 (36)[a] (6)[b]
7	CH_3	H	"	82
8[c]	CH_3	CH_3	$N(CH_3)_2$	degradation
9[c]	CH_3	CH_3	$N(Et)_2$	degradation
10[c]	CH_3	CH_3	$N(i\text{-}Pr)_2$	60
11[c]	CH_3	CH_3		95
12[c]	CH_3CH_2	CH_3	"	72
13[c]	$PhCH_2CH_2$	CH_3	"	53
14[c]	CH_3	CH_3		85
15[c]	CH_3CH_2	CH_3	"	no reaction
16	CH_3CH_2	H	"	92
17	CH_3CH_2	CH_3		auxiliary recovered
18	CH_3	H		degradation

[a] Recovered starting material. [b] Epimerization at C2. [c] The racemates were used.

Table 2. Synthesis of Oxazoles

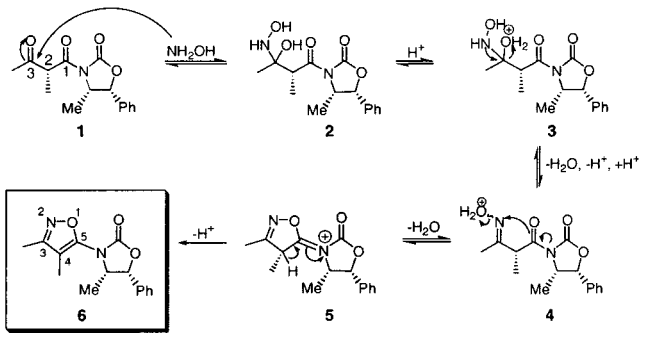


entry	R	R'	X	yield (%)
1	CH_3	CH_3		60
2	CH_3CH_2	CH_3	"	64
3	$PhCH_2CH_2$	CH_3	"	58
4	Ph	CH_3	"	(50)[a] (28)[b]
5	*p*-F-Ph	CH_3	"	(50)[a] (36)[b]
6	*p*-OMe-Ph	CH_3	"	degradation
7	CH_3	H	"	50
8[c]	Ph	CH_3	$N(CH_3)_2$	no reaction
9[c]	CH_3	CH_3	$N(CH_3)_2$	degradation
10[c]	CH_3		$N(Et)_2$	degradation
11[c]	CH_3	CH_3	$N(i\text{-}Pr)_2$	70% of isoxazole
12[c]	CH_3	CH_3		47
13[c]	CH_3CH_2	CH_3	"	complex mixture
14[c]	$PhCH_2CH_2$	CH_3	"	complex mixture
15[c]	CH_3	CH_3		80 % of isoxazole
16	CH_3CH_2	H	"	25
17	CH_3CH_2	CH_3	 	
18	CH_3	H	 	

[a] Recovered starting material. [b] Epimerization at C2. [c] The racemates were used.

may disfavor the trans oxime, which is necessary for the reaction to occur (Scheme 1). In an effort to form the α-amino acids, the same substrates were reacted with sodium azide in the presence of methanesulfonic acid in refluxing chloroform. Consistent with other observations,[6] oxazoles were obtained under these conditions (Table 2, entries 1−7).

Scheme 1. Proposed Mechanism for the Formation of Isoxazoles

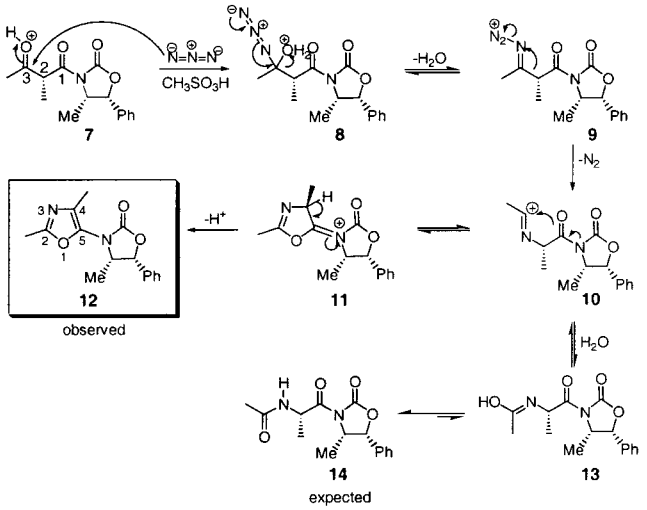


Again, the same trend was observed, i.e., substrates with aliphatic groups furnished the desired oxazoles, this time in moderate yields, whereas substrates with aromatic groups seem less reactive and more prone to epimerization at C2.

Since neither product retained the stereochemical information at C2, it seemed obvious to continue the investigation in the absence of the chiral oxazolidinone.

When acyclic amides were examined, decomposition or no reaction was observed (Table 1, entries 8 and 9, and Table 2, entries 8−10). In contrast, the desired isoxazole was obtained in 60% yield when the *N*,*N*-diisopropylamide derivative was reacted with $NH_2OH{\cdot}HCl$ (Table 1, entry 10), but when the same substrate was reacted with NaN_3, the isoxazole was also isolated (Table 2, entry 11). This result may arise because the nitrogen of the amide is sufficiently nucleophilic that the displacement of N_2 occurs before the migration can take place (Scheme 2). Thus, an electronic effect of the oxazolidinone seemed necessary to obtain the desired heterocycles. The simplest unsubstituted oxazolidone was then prepared and furnished the expected compounds in excellent or decent yields depending on the reaction conditions (Table 1, entries 11−13, and Table 2, entry 12).

Scheme 2. Proposed Mechanism for the Formation of Oxazoles



However, substrates with larger substituents at C3 reacted with NaN_3 to furnish complex mixtures containing amino acids, oxazoles, and additional products (Table 2, entries 13 and 14). A number of different conditions (solvent, temperature, azide source, Lewis acid) were tried to favor the formation of one product over the others but without success. Although this problem of obtaining complex mixtures was not observed with $NH_2OH{\cdot}HCl$, it seemed that steric hindrance on the auxiliary was important. The 4,4-dimethyloxazolidinone derivative was synthesized and tested (Table 1, entry 14, and Table 2, entry 15). The desired isoxazole was obtained in 85% yield with $NH_2OH{\cdot}HCl$, and to our surprise, the isoxazole was also formed in 80% yield with NaN_3. In this case, the presence of three methyl groups seemed to inhibit the formation of the oxazole. If the methyl group between the two carbonyls C_1 and C_3 was removed, the reactions with $NH_2OH{\cdot}HCl$ and NaN_3 proceeded quickly to give the isoxazole and oxazole in 92% and 25% yield, respectively.

Next, we studied the effect of the nature of the auxiliary carbonyl on the reactivity of the starting materials. The oxazolidinethione derivative gave the retro-Claisen product in 45% yield when reacted with NaN_3 (Table 2, entry 17), and the auxiliary was recovered when the substrate was reacted with $NH_2OH{\cdot}HCl$ (Table 1, entry 17). The 2,2,4,4-tetramethyloxazolidine derivative, which lacks the carbonyl group, was not stable to the reaction conditions. In one case, degradation was observed (Table 1, entry 18), and in the other the hydroxyketoamide corresponding to the starting material was recovered in 60% yield (Table 2, entry 18).

Two different mechanisms can be considered to explain the formation of isoxazoles and oxazoles. In the first case (Scheme 1), it seems that the participation of the nitrogen's lone pair to eliminate a molecule of H_2O is faster than the bond migration, which would give the Beckmann rearrangement product. It is also possible that the equilibration between the cis oxime, which is more stable because of hydrogen bonding, and the trans oxime, which is the reactive species, is very slow, and as soon as the trans oxime is formed water is eliminated to furnish the isoxazole. Oxazoles are formed upon loss of N_2 to form **10**, which is trapped by the carbonyl oxygen faster than an external nucleophile (Scheme 2). Subsequent loss of the α-proton provides the oxazole.

In conclusion, we have shown that two useful heterocycles, oxazoles and isozaxoles,[8] can be prepared in good yield in a rapid and simple manner. The best way to make these heterocycles is to use a chiral oxazolidinone derived from (1*R*,2*S*)-(−)-norephedrine. Finally, steric and electronic effects caused by the nature of the auxiliary have a significant influence on the reactivity of the substrate.

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Supporting Information Available: Detailed experimental as well as ^1H and ^{13}C NMR spectra for compounds **6** and **12** is provided. This material is free of charge via the Internet at http://pubs.acs.org.

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(8) Although the isoxazoles and oxazoles have very similar spectroscopic data, they can be differentiated by ^{13}C NMR. C4 of the isoxazoles shows a peak at around 100 ppm, whereas the oxazoles show signals for C4 between 120 and 130 ppm. The structure of isoxazole **6** was confirmed by X-ray crystallography.