Studies On Isoxazole Formation from Alkyl Carboxylic Esters

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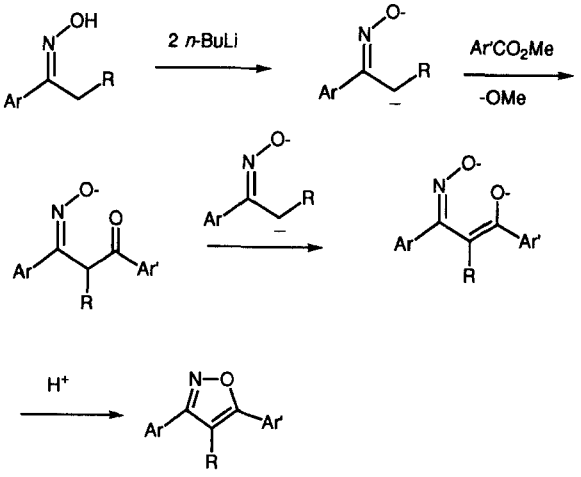
Alkylisoxazoles **1a–12a** were prepared in moderate to high yields (58–83%) by condensation of 1.5 equivalents of the appropriate ketone oximes with an alkyl ester, followed by a mineral acid induced cyclization–dehydration reaction.

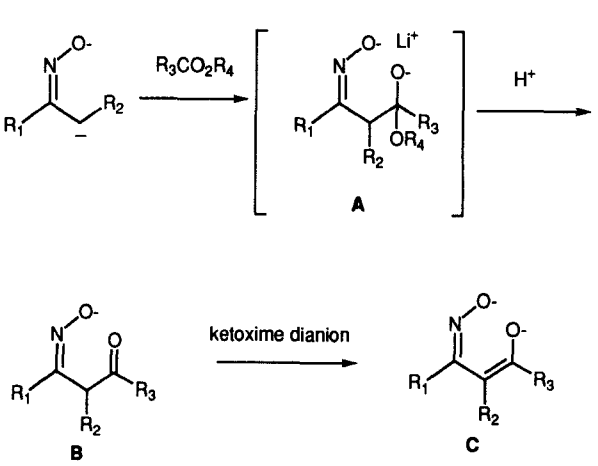
For a long time, isoxazoles and their derivatives have been recognized as highly useful components in medicinal chemistry. Among the available methods for the preparation of 3,5-dialkyl substituted isoxazoles, oximation of 1,3-dicarbonyl compounds[1] (mainly β-keto aldehydes and β-diketones) and cycloaddition of nitrile oxides[2] to unsaturated compounds are by far the most widely utilized. However, with non-symmetrical starting materials, neither of these methods is completely unequivocal with respect to control of site- and regioselectivities.[3] Only a few methods, such as treatment of an α,β-dihalo ketone with hydroxylamine in the presence of alkali,[4] oximation of chalcone epoxide,[5] cyclization of functionalized propargyloximes[6] or α,β-unsaturated oximes,[7] gold(III) catalyzed cycloaddition of nitric acid with alkyne,[8] condensation of carboxylic acid derivatives[9,10] or nitriles[11] with 1,4-dilithium oxime salts[12] afford 3,5-disubstituted isoxazoles in a regioselective fashion. Although it has been demonstrated that the latter methodology provides the isoxazole in moderate to high yield (40–100%) with aryl carboxylic esters, poor yields (26%) were observed when alkyl carboxylic acid derivatives were employed as starting materials.[13] Nevertheless, generalization of this methodology to encompass the use of alkyl carboxylic esters or other alkyl carboxylic acid derivatives as starting materials was considered worthy of further investigation, owing to the ready availability of a wide range of carboxylic esters and the simple one-pot experimental procedure.



Scheme 1

The reported reaction conditions[9] involves treatment of 1 equivalent of a methyl or ethyl ester with 2 equivalents of keto oxime dianion, generated by reaction of oxime with 2 equivalents of butyllithium, followed by addition of dilute aqueous acid and cyclization–dehydration in situ at reflux temperature. Our initial efforts to prepare 5-alkylisoxazoles from an alkyl carboxylic ester by employing the reported procedure confirmed that the reaction gave only poor to moderate yields of product. For instance, when ethyl adamantanecarboxylate was reacted with two equivalents of cyclohexanone oxime dianion, generated by reaction of cyclohexanone oxime with butyllithium in tetrahydrofuran/hexane, the corresponding isoxazole was produced in 41% yield based on the starting ester. Upon using 3 equivalents of lithium diisopropylamide[14] instead of butyllithium, the desired isoxazole was furnished in only 24% yield. No improvement in yield was obtained using the corresponding *N,O*-dimethylamide or imidazolide.

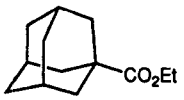
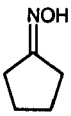
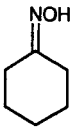
Ultimately it was found that the crucial factors for obtaining good yields were to reduce the excess of the keto oxime dianion used and to modify the cyclization–dehydration as described below. Thus, treatment of ethyl adamatanecarboxylate with 1.5 equivalents of acetone oxime dianion followed by addition of concentrated sulfuric acid and cyclization–dehydration at room temperature gave the corresponding isoxazole in 83% yield (see Table 2, entry 1). It was somewhat surprising that an improved yield resulted from using less than 2 equivalents of the keto oxime dianion, since the intermediate β-keto oxime, once fomed, possesses an acidic proton that would quench oxime dianion. We speculate that the intermediate A might be stabilized by chelation with the lithium cation and thus be stable in the basic reaction medium. If intermediate A does not fragment to keto oxime B until subsequent acid treatment, the excess dilithium oxime anion would not react with keto oxime B to generate enolate C. Thus, two moles of dilithium salt would not be required under this circumstance.



Scheme 2

In order to determine the usefulness and limitations of the oxime dianion reaction with alkyl esters, we extended our investigation to several oximes and a variety of car-

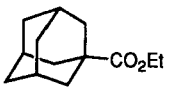
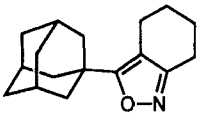
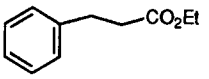
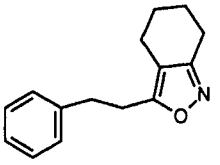
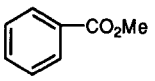
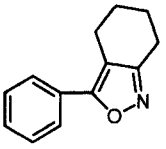
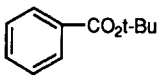
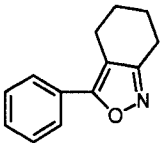
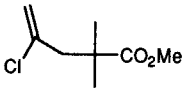
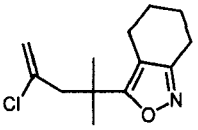
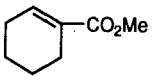
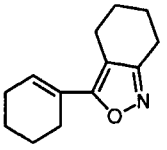
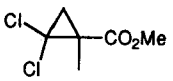
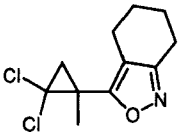
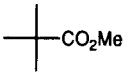
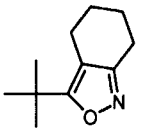
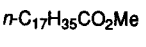
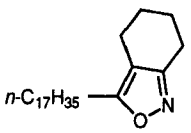
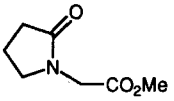
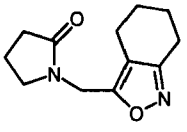
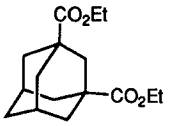
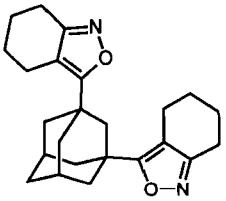
Table 1.

Substrate	Oxime	Time (h)	Yield (%)
		0.5	57
		1.0	58
		4.0	59
		1.0	66
		1.0	83

boxylic acid derivatives. Table 1 shows the results from the reaction of different oximes with adamantanecarboxylic ester and also an initial time course study employing acetone oxime. We first investigated the effect of reaction time on the yield. As indicated in Table 1, reaction times ranging from 0.5 to 4 h hour did not affect the reaction yield. Therefore, the 1 hour reaction time was employed throughout the remainder of this study. On the other hand, studies on the preparation of adamantane isoxazoles by the condensation of the 1,3-dianion of acetone, cyclopentanone and cyclohexanone oximes with ethyl adamantanecarboxylate indicate that the structure of the oxime dianion does affect the yield. As shown in Table 1, the reaction with cyclohexanone oxime gives the best result with ethyl adamantanecarboxylate under the modified standard conditions.

The synthetic potential of this method is demonstrated by the large number of esters which undergo condensation and cyclization to give the corresponding isoxazoles. Each ester **1**–**11** was converted into the corresponding isoxazole by reaction with the 1,3-dianion of cyclohexanone oxime, employing the procedure as described in the experimental section. The structures and reaction yields of isoxazole products are presented in Table 2, and physical data are shown in Table 3. Regular straight chain primary aliphatic esters such as ethyl hydrocinnamate (compound **2**) react cleanly to give the corresponding isoxazole in 66% yield. A methyl ester and a *tert*-butyl ester (cf. compound **3** vs. compound **4**) give comparable yields, suggesting that the reaction has little sensitivity to the structure of the alkoxycarbonyl moiety itself. Bulky tertiary esters (see compounds **1**, **7**, **8** and **11**) also react with cyclohexanone oxime dianion without any difficulty giving the desired isoxazoles in high yields (64–83%). The vinyl chloride group in **5** is stable under the strong acid cyclization conditions, since none of the corresponding ketone was detected in this reaction. In addition, an exclusive 1,2-condensation product was obtained when

Table 2.

	Starting Material		Product	Yield (%)
1		**3a**		83
2		**4a**		66
3		**5a**		81
4		**5a**		80
5		**6a**		60
6		**7a**		70
7		**8a**		67
8		**9a**		74
9		**10a**		55
10		**11a**		55
11		**12a**		64

α,β-unsaturated ester **6** was reacted with the keto oxime dianion. Although it has been demonstrated[10] that dimethylformamide can act as a better substrate than esters

for the condensation reaction, none of the ring-opening product was detected when lactam **10** was treated with cyclohexanone oxime dianion. It is also interesting to note that diisoxazole **12a** was obtained in 64% yield when diester **11** was employed as starting material.

The results of this work show that the Claisen condensation of esters with ketone oxime dianions followed by acid catalyzed cyclization is not confined to aromatic systems, but also can be advantageously carried out in moderate to high yields with aliphatic and cyclic deriva-

Table 3.

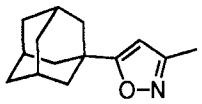
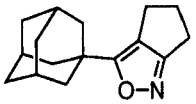
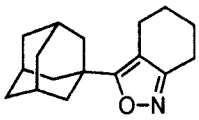
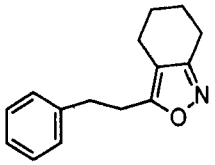
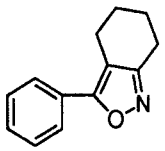
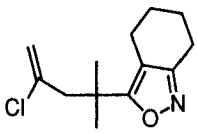
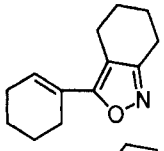
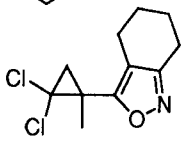
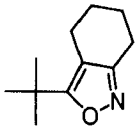
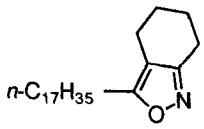
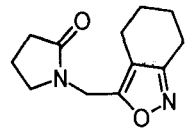
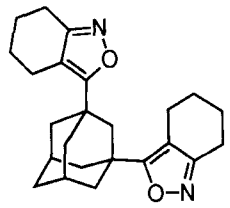
	Product[a]	Yield[b] (%)	mp (°C)[c]	^{1}H NMR ($CDCl_3$) δ, J (Hz)
1a		58	57–59	1.70–1.88 (m, 6H, $3CH_2$), 1.93–2.00 (m, 6H, $3CH_2$), 2.04–2.12 (m, 3H, 3CH), 2.27 (s, 3H, CH_3), 5.72 (s, 1H, ArH)
2a		66	183–185	1.70–1.85 (m, 6H, $3CH_2$), 1.95–2.04 (m, 6H, $3CH_2$), 2.00–2.10 (m, 3H, 3CH), 2.43 (tt, J = 6.6, 6.6 Hz, 2H, $ArCCH_2CAr$), 2.64 (t, J = 6.6 Hz, 2H, $ArCH_2$), 2.72 (t, J = 6.6, 2H, $ArCH_2$)
3a		83 73[d]	83–85	1.63–1.85 (m, 10H, $5CH_2$), 2.01–2.12 (m, 9H, $3CH_2$, 3CH), 2.63 (t, J = 6.6, 2H, $ArCH_2$), 2.69 (t, J = 6.6, 2H, $ArCH_2$)
4a		66	oil	1.55–1.77 (m, 4H, $2CH_2$), 2.17 (t, J = 6.3, $ArCH_2$), 2.69 (t, J = 6.3, $ArCH_2$), 2.96 (t, J = 3.9, 2H, $ArCH_2$), 2.97 (J = 3.9, 2H, $ArCH_2$), 7.10–7.31 (m, 5H, ArH)
5a		81	65–67	1.57–1.82 (m, 4H, $2CH_2$), 2.75–2.88 (m, 4H, $2ArCH_2$), 7.37–7.52 (3H, 3ArH), 7.74 (d, J = 7.5, 2H, 2ArH)
6a		60	oil	1.44 (s, 6H, $2CH_3$), 1.66–1.78 (m, 4H, $2CH_2$), 2.62 (t, J = 6.2, 2H, $ArCH_2$), 2.71 (s, 2H, $=CCH_2$), 2.72 (t, J = 6.2, 2H, $ArCH_2$), 4.94 (d, J = 2.0, 1H, =CHH), 5.22 (d, J = 2.0, 1H, =CHH)
7a		70	57–59	1.60–1.83 (m, 8H, $4CH_2$), 2.19–2.28 (m, 2H, $=CCH_2$), 2.40–2.47 (m, 2H, $=CCH_2$), 2.60 (t, J = 6.8, 2H, $ArCH_2$), 2.72 (t, J = 6.8, 2H, $ArCH_2$), 6.30 (m, 1H, =CH)
8a		67 63[d]	oil	1.61 (d, J = 7.5, 1H, CCl_2CHH), 1.68 (s, 3H, CH_3), 1.65–1.89 (m, 4H, $2CH_2$), 2.29 (d, J = 7.5, 1H, CCl_2CHH), 2.45–2.83 (m, 4H, $2CH_2$)
9a		74	oil	1.35 (s, 9H, $3CH_3$), 1.67–1.80 (m, 4H, $2CH_2$), 2.60 (t, J = 6.6, 2H, $ArCH_2$), 2.71 (t, J = 6.6, 2H, $ArCH_2$)
10a		55	47–49	0.88 (t, J = 6.9, 3H, CH_3), 1.20–1.36 (m, 28H, $14CH_2$), 1.58–1.82 (m, 6H, $3CH_2$), 2.63 (t, J = 6.6, 2H, $ArCH_2$), 2.64 (t, J = 6.9, 2H, $ArCH_2$), 2.72 (t, J = 6.9, 2H, $ArCH_2$)

Table 3 (continued).

Product[a]	Yield[b] (%)	mp (°C)[c]	^{1}H NMR ($CDCl_3$) δ, J (Hz)
11a 	55	oil	1.67–1.83 (m, 4H, $2CH_2$), 2.04 (tt, J = 7.2, 7.2, 2H, $NCCH_2$), 2.40 (t, J = 7.2, 2H, $COCH_2$), 2.51 (t, J = 6.6, 2H, $ArCH_2$), 2.73 (t, J = 6.6, 2H, $ArCH_2$), 3.44 (t, J = 7.2, 2H, NCH_2), 4.49 (s, 2H, NCH_2Ar)
12a 	64	158–159	1.66–1.83 (m, 10H, 2CH, $4CH_2$), 2.07 (d, J = 3.0, 8H, $4CCH_2$), 2.24 (t, J = 3.0, 2H, $2CCH_2C$), 2.29 (s, 2H, $ArCCH_2CAr$), 2.63 (t, J = 6.3, 4H, $2ArCH_2$), 2.70 (t, J = 6.3, 4H, $2ArCH_2$)

[a] Satisfactory microanalysis obtained: C ± 0.40, H ± 0.40, N ± 0.40%.
[b] Yield of isolated product based on 1.5 mmol of substrate; a fair amount of unreacted ester was isolated in some cases (e.g. **1a**, 29; **2a**, 24; **3a**, 17; **8a**, 30%).
[c] Uncorrected.
[d] Reaction was run on 15 mmol scale by gradual addition (50 min) of ester to oxime dianion solution. Unreacted esters recovered: **3a** (26), **8a** (34).

tives in the presence of a variety of functional groups. Extension of this methodology to chiral materials is being explored in our laboratory. The result of these studies will be reported in due course.

Isoxazoles Representative Procedure:
To cyclohexanone oxime (261 mg, 2.25 mmol) in THF (4 mL) at 0°C was added butyllithium (1.5 M in hexane/THF, 2.25 mL, 4.50 mmol). After stirring at r.t. for 0.5 h, ethyl 1-adamantanecarboxylate (312 mg, 1.50 mmol) in THF (2 mL) was added and the resultant solution allowed to stir until the ester was consumed (ca. 1 h), then concentrated sulfuric acid (1.25 mL) was added and stirring was continued for an additional 1 h. The organic layer was decanted and the yellow residue was washed with EtOAc (4 × 5 mL). The combined organic layers were dried and concentrated under reduced pressure. The oil was purified on a flash silica gel column (EtOAc/hexane, 1:5) to provide 320 mg (83%) of the desired isoxazole.

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