Synthesis of Δ^2-1,3-Oxazolines and Δ^2-1,3-Oxazines Using Potassium Fluoride on Alumina

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Potassium fluoride (40%) on alumina was used as a basic reagent for the ring closure of *N*-(β- or γ-haloalkyl)amides to give Δ^2-1,3-oxazolines and Δ^2-1,3-oxazines, respectively. Various 2-alkyl and 2-aryl derivatives were synthesized in moderate to high yield under relatively mild conditions (KF/Al_2O_3, solvent, room temperature). The procedure also facilitated simple workup and purification of the products. New compounds synthesized by this method are: 5-bromomethyl-2-phenyl-Δ^2-1,3-oxazoline, 4,4-dimethyl-2-vinyl-Δ^2-1,3-oxazoline, and 5-methylene-2-phenyl-Δ^2-1,3-oxazine. The last compound represents the first authentic example of a 5-functionally substituted oxazine without substitution in the 4- or the 6-position.

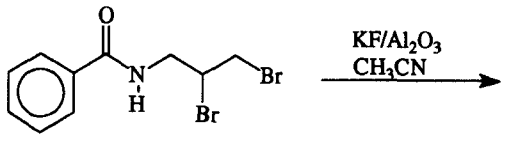
Δ^2-1,3-Oxazolines and Δ^2-1,3-oxazines have found use in a wide variety of procedures. Both classes of compounds are actively studied as monomers for cationic ring-opening polymerizations,[1] and are used as protecting groups for the carboxyl moiety in organic syntheses.[2] Furthermore, chiral oxazolines are also helpful for certain asymmetric syntheses.[3,4] Also, derivatives of these ring systems have various useful pharmacological activities. For example 2-amino-1,3-oxazolines show promise as sedatives,[5] for treatment of hypertension[6] and glaucoma.[7]

The syntheses of Δ^2-1,3-oxazolines and Δ^2-1,3-oxazines can be accomplished by several routes.[1,8] The reaction between amino alcohols and nitriles is a very convenient synthesis, but fails in some instances. Carboxylic acids can also be reacted with amino alcohols,[9,10] but this procedure can involve complicated reaction conditions and isolation. Dehydration of ω-hydroxy amides is also a very common technique, but harsh conditions and special experimental setup and procedures can limit the utility of this method. Other reagents such as thionyl chloride,[11] phosphorotriazolides,[12] and Mitsunobu conditions[13] have been used for this dehydration. However, these latter reagents have some problems associated with them. Thionyl chloride is a rather harsh reagent and the method is not general.[13] The phosphorotriazolide reagents are not commercially available and yields are mediocre. Mitsunobu conditions give moderate yields, usually require chromatographic separation, and the method is not general.[14] Also, the use of these reagents to prepare oxazines have not been investigated.

A third important method is ring closure of ω-halo amides under basic conditions. This procedure has limited synthetic use because it usually involves aqueous or alcoholic conditions with strong base in high concentration. However, Ando and co-workers[15,16] have shown that 40% potassium fluoride on neutral alumina is a convenient and efficient reagent for the *N*-alkylation of amides in organic solvents. Thus the reagent should also efficiently convert *N*-(ω-haloalkyl)amides to Δ^2-1,3-oxazines and Δ^2-1,3-oxazolines. The purpose of this report is to convey the use of these milder conditions which increase the utility of the ring closure of *N*-(ω-haloalkyl)amides to form Δ^2-1,3-oxazolines and Δ^2-1,3-oxazines.

Δ^2-1,3-Oxazines with functional group substitution in the 5-position would be an interesting class of new monomers which would give rise to new polymeric architectures. However, syntheses of 5-functionally substituted oxazines are rare because formation of oxazolines are favored. Treatment of *N*-(3-phenyl-2-propenyl)amides with an electrophilic halide leads to 5-halo-6-phenyl-Δ^2-1,3-oxazines,[17] but these compounds would probably polymerize poorly for steric reasons. There are only two reports of 5-functionally substituted Δ^2-1,3-oxazines which lack extraneous substitution in the 4- and 6-positions. The first was 5-hydroxy-2-phenyl-Δ^2-1,3-oxazine[18] which we have identified as 5-hydroxymethyl-2-phenyl-Δ^2-1,3-oxazoline (proton NMR of this compound in DMSO-d_6 treated with Na_2CO_3 shows the hydroxy proton as a triplet which proves the presence of the oxazoline rather than the oxazine). The second was 5-oxo-2-phenyl-Δ^2-1,3-oxazine[19] which was eventually identified as 2-phenyl-1,3-oxazolidinone.[20]

The ring closure of *N*-(2,3-dibromopropyl)benzamide was evaluated as a test for the formation of oxazines or oxazolines. The *N*-(2,3-dibromopropyl)benzamide was made by reacting 2,3-dibromopropylamine hydrobromide[21] with benzoyl chloride under Schotten–Baumann conditions. Attempts to ring close this compound using standard conditions (aqueous potassium hydroxide, or ethanolic sodium ethoxide) led to substantial formation of byproducts. However, using 40% potassium fluoride on alumina in acetonitrile afforded a 76% yield of product **2**. Interestingly, the product isolated was exclusively 5-bromomethyl-2-phenyl-1,3-oxazoline. The formation of oxazine was not observed using these conditions. The structure of compound **2** was confirmed by a DEPT spectra which clearly showed a CH_2Br at $\delta = 33.5$, CH_2N at 59.2, and CHO at 77.7.



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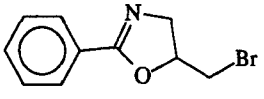

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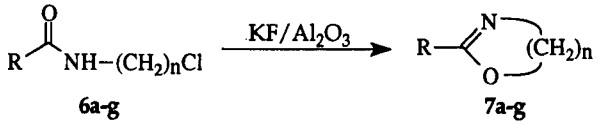
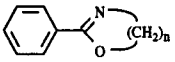
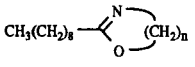
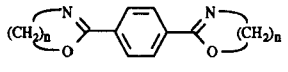
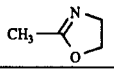
The utility of these conditions was examined for the synthesis of the various compounds listed in Scheme 1. The yields were excellent except for the 2-nonyl-Δ^2-1,3-oxazine (**7c**). Except for the 2-phenyl-Δ^2-1,3-oxazine (**7a**) and the 2-methyl-Δ^2-1,3-oxazoline (**7g**) conditions were not optimized. Compound **7g** was prepared by Procedure A, while all the other compounds in Scheme 1 were prepared by Procedure B.



6a-g 7a-g

Educt	n	Product	Structure	Reaction Time(hrs)	Yield(%)	Literature Yield(%)
6a	3	7a		24	93	75[22]
6b	2	7b		24	83	74[23]
6c	3	7c		72	31	
6d	2	7d		6	93	
6e	3	7e		24	78	68[24]
6f	2	7f		24	86	61[24]
6g		7g		2	75	75[23]

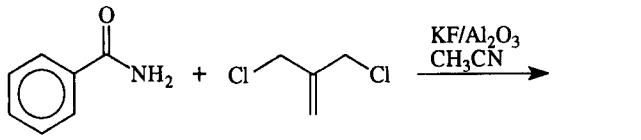
Scheme 1

Reaction of *N*-(chloro-*tert*-butyl)acrylamide (**3**) under Procedure A conditions afforded the desired 4,4-dimethyl-2-vinyl-Δ^2-1,3-oxazoline (**4**). By GCMS the reaction appears to go completely and cleanly to the vinyloxazoline, but the best isolated yield was 14%.

3 **4**

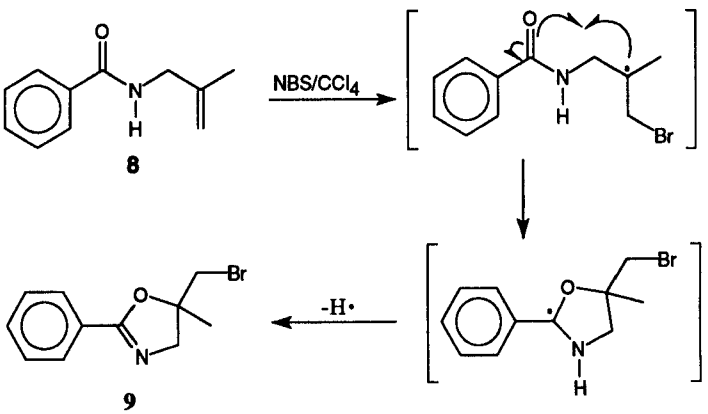
Attempts to directly transform an unsubstituted amide and a dihalopropane into Δ^2-1,3-oxazines were for the most part unsuccessful. Reaction of benzamide with 1,3-dibromopropane gave a low yield of the desired 2-phenyl-Δ^2-1,3-oxazine, but numerous byproducts were formed. Probably the major side reaction was elimination of HBr prior to *N*-alkylation of the amide. With this fact in mind, the same reaction was attempted with the ditosylate of 2,2-dimethylpropanediol. However, the ditosylate did not react at all, most likely due to steric considerations.

More successful results were achieved by the reaction of benzamide with 3-chloro-2-chloromethyl-1-propene. A 25% yield of 5-methylene-2-phenyl-Δ^2-1,3-oxazine (**5**) was obtained. To our knowledge, this represents the first 5-functionally substituted Δ^2-1,3-oxazine which does not possess extraneous substitution in the 4- or the 6-position. In the reaction, a large amount of the benzamide was left unreacted, leading to the conclusion that a large portion of the dichloro compound had undergone side reactions. Presumably a Favorskii type of reaction could be competing. Other conditions for the *N*-alkylation of amides did not work as well for the synthesis of this product. Compound **5** readily ring-open-polymerized in the presence of methyl triflate at 140 °C.



5

The stepwise synthesis of the 5-methyleneoxazine was attempted by free radical bromination of compound **8**. Interestingly, free radical bromination of the allylic position was not observed. It seems that the product of the bromine radical addition to the olefin is readily converted into 5-bromomethyl-5-methyl-2-phenyl-Δ^2-1,3-oxazoline (**9**) in good yield (Scheme 2). This appears to be the first synthesis of a 1,3-oxazoline by a radical addition, and may be a general reaction.



8 **9**

Scheme 2

The 40% KF on alumina was prepared by the method of Ando et al.[16] or purchased from Aldrich Chemical Co. Reagent grade solvents were used as received. *N*-(2-Chloroethyl)acetamide (**6g**) and

N-(2-chloroethyl)benzamide (**6b**) were used as received from Aldrich Chemical Co. Compounds **7a,b,e–g** have previously been reported and were all greater than 99% pure by GCMS. Amides were synthesized by various techniques: the Schotten–Baumann procedure (compounds **1**, **6a,c,d**, and **8**), by the action of Et_3N in $CHCl_3$ (compounds **6e,f**), or by the method of Ritter[25] (compound **3**). Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250, FTIR were recorded on a Nicolet 710, and GCMS were recorded on an HP 5890 GC/5971 MS. Compounds **2**, **4**, **7c,d**, and **9** gave C,H,N ± 0.3%.

Procedure A:
The amide (8 mmol) was mixed with 10 mL of tetramethylene sulfone. To this mixture 4 equiv (4.7 g) of 40% KF on alumina was slowly added. (The amount was calculated to give 4 equiv of KF.) When the reaction was complete by GCMS, the product was vacuum distilled. Water was liberated from the KF reagent during the course of the reaction. The product was separated from water which had codistilled and then dried (NaOH).

4,4-Dimethyl-2-vinyl-Δ^2-1,3-oxazoline (4):
Product steam distilled (46–54 °C at 300 mmHg) and was then dried as above.

FTIR (neat): ν = 2968, 1669, 1601, 1300, 1033, 985 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.23 (m, 1 H), 6.03 (d, 1 H), 5.66 (d, 1 H), 3.98 (s, 2 H), 1.31 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 161.24, 125.51, 125.32, 78.76, 28.28.

Procedure B:
The amide (8 mmol) was dissolved in 10 mL of MeCN. To this mixture 4 equiv (4.7 g) of 40% KF on alumina was slowly added. (The amount was calculated to give 4 equiv of KF.) This slurry was mechanically stirred until the reaction was complete. The reaction was followed by TLC (silica gel; EtOAc). The KF on alumina was filtered off with Celite, and the MeCN was evaporated from the filtrate (For the bisoxazoline and bisoxazine, the reaction mixture was poured into a thimble and Soxhlet extracted with MeCN for 2 d). The resulting product was vacuum distilled or recrystallized.

2-Nonyl-Δ^2-1,3-oxazoline (7d):
Bp = 63 °C at 0.06 mmHg.

FTIR (neat): ν = 2927, 2858, 1669, 985 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.21 (t, 2 H), 3.81 (t, 2 H), 2.26 (t, 2 H), *1.63 (m, 2 H), 1.27 (s, 12 H), 0.88 (t, 3 H).*

^{13}C NMR ($CDCl_3$): δ = 168.68, 67.13, 54.50, 31.94, 29.52, 29.35, 28.03, 26.06, 22.72, 14.11.

2-Nonyl-Δ^2-1,3-oxazine (7c):
Bp = 74 °C at 0.2 mmHg.

FTIR (neat): ν = 2927, 1676, 1238, 1088 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.13 (t, 2 H), 3.35 (s, 2 H), 2.08 (t, 2 H), 1.84 (t, 2 H), 1.55 (bs, 2 H), 1.26 (s, 12 H), 0.86 (t, 3 H).

^{13}C NMR ($CDCl_3$): δ = 160.54, 64.75, 42.22, 35.64, 31.94, 29.54, 29.44, 29.35, 29.30, 26.31, 22.75, 21.96, 14.11.

5-Bromomethyl-2-phenyl-Δ^2-1,3-oxazoline (2):
This compound was synthesized from *N*-(2,3-dibromopropyl)benzamide by Procedure B. The crude product was originally obtained as an oil. The compound was purified by dissolving in hexanes and decanting away from the insoluble impurities. The hexane solution was then slowly cooled to − 50 °C which gave a 76% yield of white crystalline product, mp = 31–32 °C.

FTIR (neat): ν = 3062, 2936, 2870, 1653, 1061, 694 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.95 (d, 2 H), 7.40 (m, 3 H), 4.90 (m, 1 H), 4.15 and 3.90 (m, 2 H), 3.5 (m, 2 H).

^{13}C NMR (DEPT, $CDCl_3$): δ = 163.4 (C=N), 131.3 (CH), 128.2 (CH), 128.0 (CH), 127 (C), 77.7 (CH), 59.2 (CH_2), 33.6 (CH_2).

5-Methylene-2-phenyl-Δ^2-1,3-oxazine (5):
The synthesis of this compound was the same as Procedure B. Benzamide (0.49 g, 4 mmol) was reacted with 3-chloro-2-chloromethyl-1-propene (0.5 g, 4 mmol) and KF on alumina (3.5 g, 24 mmol KF) in 10 mL of MeCN. The mixture was stirred at r.t. for 24 h. After filtration and evaporation of the MeCN an oil was obtained which was taken up in 10 mL of cyclohexane and filtered to separate the product from the unreacted benzamide. After evaporation of the cyclohexane, the product was purified by radial chromatography (silica gel; hexanes). The product obtained in 25% yield was 99.9% pure by GCMS.

FTIR (neat): 3060, 2930, 2869, 1653, 1325, 1115, 695 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.90 (m, 2 H), 7.37 (m, 3 H), 5.11 (s, 2 H), 4.70 (s, 2 H), 4.17 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 155.38, 137.63, 133.60, 130.31, 127.94, 127.05, 110.29, 68.88, 48.99.

5-Bromomethyl-5-methyl-2-phenyl-Δ^2-1,3-oxazoline (9):
N-Bromosuccinimide (2.03 g, 11.4 mmol) and *N*-(2-methyl-2-propenyl)benzamide (2 g, 1 equiv) were mixed in 25 mL of CCl_4 and refluxed while being irradiated with a 250 W lamp until the reaction was complete (7 h). The succinimide was filtered off and the CCl_4 evaporated. The product was purified by radial chromatography to give a 50% yield of a white solid (mp = 33–34 °C).

FTIR (neat): ν = 2932, 1651, 1350, 1061, 694 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.93 (d, 2 H), 7.43 (m, 3 H), 4.09 (d, 1 H), 3.81 (d, 1 H), 3.54 (m, 2 H), 1.63 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 163.04, 31.45, 128.35, 128.18, 127.67, 84.13, 64.62, 38.77, 24.47.

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