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Regiochemistry of an ambident cyclic ketene-*N,O*-acetal nucleophile and its anion toward electrophiles

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ABSTRACT

The five-membered cyclic ketene-*N,O*-acetal, 2-oxazolidin-2-ylidene-1-phenylethanone **1**, and its anion **2**, formed on deprotonation, are ambident nucleophiles. Compound **1** was synthesized by benzoylation of 2-methyl-2-oxazoline to give a ring-opened N,C,O-trisbenzoylation product, **9**, followed by N,O-double debenzoylation using methanolic KOH. Compound **1** reacted with benzoyl chloride to give N,C,O-tris-benzoylated **9**, and reacted with phenyl chloroformate to give the similar ring-opened carbonic acid 3-[(2-chloro-ethyl)-phenoxycarbonyl-amino]-3-oxo-1-phenyl-propenyl ester phenyl ester, **13**. In contrast, ambident anion **2** reacted with benzoyl chloride to give the β,β-bisbenzoylated cyclic ketene-*N,O*-acetal, **16**, and reacted with phenyl chloroformate to give the novel heterocycle 3-(2-hydroxy-ethyl)-6-phenyl-[1,3]oxazine-2,4-dione, **17**.

2-Oxazolidin-2-ylidene-1-phenylethanone **1**, a five-membered cyclic ketene-*N,O*-acetal, and its deprotonated form, anion **2**, are both ambident nucleophiles (Fig. 1). The ring nitrogen, exocyclic β-carbon and carbonyl oxygen are nucleophilic in both **1** and **2**.

Compound **1** has been used in the syntheses of fused indole derivatives,[1] bicyclic pyridones,[2] 1,3-oxazoheterocycle-fused-[1,2-*b*]isoquino-lin-1(2H)-imines[3] and 5H-oxazolo[3,2-a]pyridine derivatives.[4] These reactions used **1** as an ambident nucleophile which reacted with ambident electrophiles to effect ring closures. The regiochemistry of **1** reacting with electrophiles having only one nucleophilic site has not been reported.

During studies of cyclic ketene-*N,O*-acetal chemistry with various electrophiles,[5] interest grew in the regiochemistry of **1** and **2** reacting with acid chlorides and aryl chloroformates. Preliminary results are reported here.

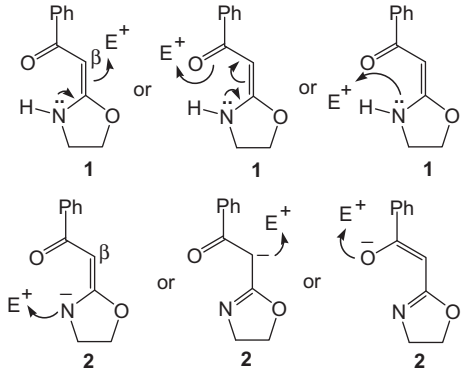
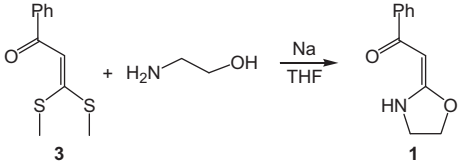


Figure 1. The five-membered cyclic ketene-*N,O*-acetal **1**, and its deprotonated form, anion **2**, are ambident nucleophiles.

Results

Benzoylation of 2-methyl-2-oxazoline and 2-methyl-2-oxazine

Compound **1** was previously made from ketene dithioacetal **3** and 2-aminoethanol[4] (Eq. 1). Starting material **3**, in turn, was prepared from acetophenone with NaH and CS_2, followed by methylation with methyl iodide. In contrast, cyclic ketene-*N,O*-acetal **4**, an analog of **1** with two methyl groups at C-4, was



(1)

synthesized via benzoylation of 2,4,4-trimethyl-2-oxazoline **5** to give the N,O-bisbenzoylated cyclic ketene-*N,O*-acetal **6**, followed by N-debenzoylation with KOH/methanol (Eq. 2).[6] Thus, an

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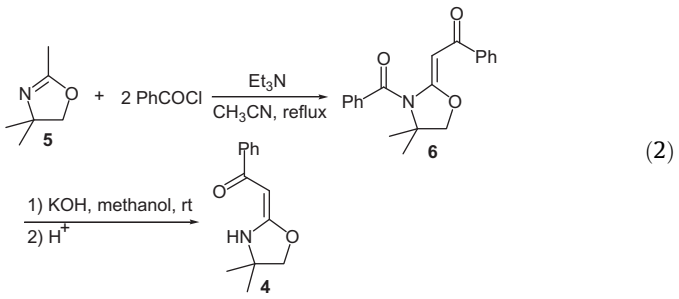
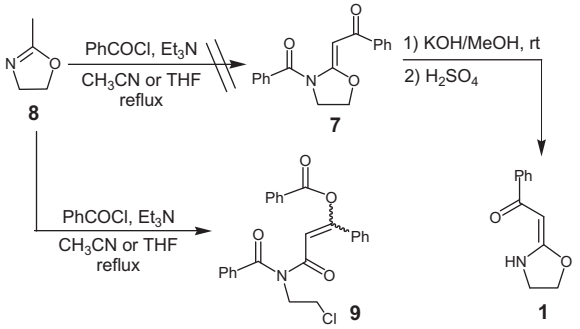


(2)

alternative route to 1 would be N-debenzoylation of the bisbenzoylated cyclic ketene-*N*,*O*-acetal 7 (Eq. 3), an analog of **6**. **7** might form by the N,O-bisbenzoylation of 2-methyl-2-oxazoline, **8**. However, repeated attempts to generate 7 by this route failed (Table 1). Surprisingly, N,O,C-trisbenzoylation of 2-methyl-2-oxazoline occurred instead, followed by ring-opening, giving only the vinyl ester imide, 9. Formation of 9 occurred employing only 2 equiv of benzoyl chloride in either CH_3CN or THF. This same reaction pattern was followed in benzoylation of 2-methyl-2-oxazine, 10, which produced only the analogous ring-opened vinyl ester imide 11 where the crystal structure showed the (Z) geometrical isomer was made (Eq. 4).



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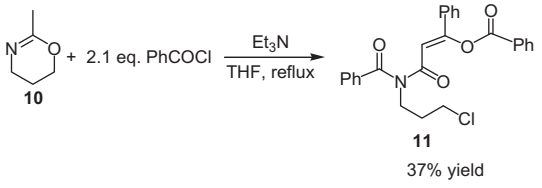
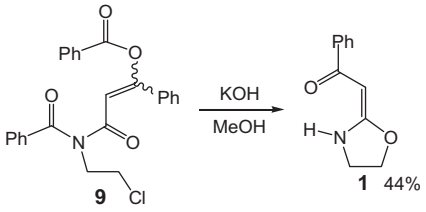


(4)

Preparation of cyclic ketene-*N*,*O*-acetal 1

Interestingly, **1** was prepared directly from **9**. Subjecting ring-opened **9** to methanolic KOH gave a 44% isolated yield of **1** (Eq. 5), the product originally sought through **7**. However, subjecting **11** to methanolic KOH gave an unidentified product (Eq. 6) rather than **12**, the six-membered ring analog of **1**.



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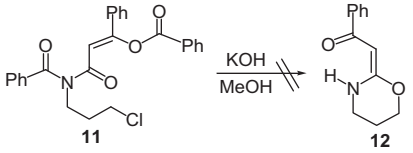
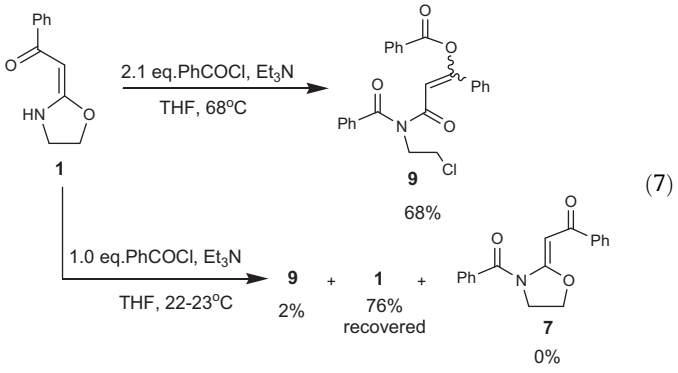


(6)

The combination of Eqs. 3 and 5 provides an easier and safer route to **1** than from ketene dithioacetal and 2-aminoethanol (Eq. 1). With **1** available, nucleophilic reactions of **1** and its deprotonated form, anion **2**, with the electrophiles, benzoyl chloride and phenyl chloroformate, were studied.

Benzoylation of 1

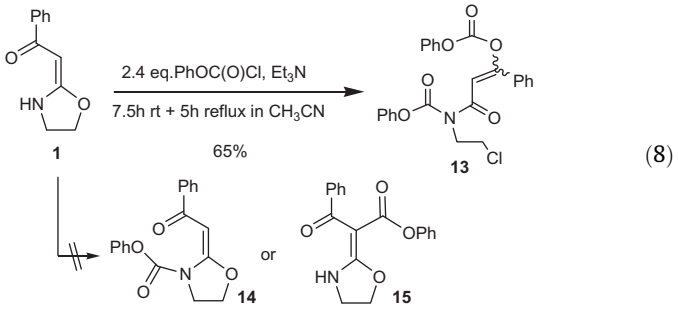
2-Oxazolidin-2-ylidene-1-phenylethanone **1** produced only trisbenzoylated ring-opened product **9** (Eq. 7) when reacted with benzoyl chloride in refluxing THF in the presence of Et_3N. Thus, 1 equiv of benzoyl chloride, diluted in THF, was added over 5 h to **1**/THF at 22–23 °C, in an attempt to generate N,C-bisbenzoylated **7** by kinetically favored *N*-benzoylation (Eq. 7) without further reaction occuring to produce **9**. However, **7** was still not formed. A 2% yield of **9** was obtained and most of the starting material **1** was recovered.



(7)

Reaction of 1 with phenyl chloroformate

Compound **1** did not react with phenyl chloroformate in CH_3CN/Et_3N after 7.5 h at 22–23 °C. No new products were detected by TLC analysis. After refluxing for 5 h, however, ring-opened carbonic acid 3-[(2-chloro-ethyl)-phenoxycarbonyl-amino]-3-oxo-1-phenyl-propenyl ester phenyl ester, **13**, was isolated and purified in 65% yield (Eq. 8). Two equivalents of phenyl chloroformate were consumed generating **13**, as was the case during bisbenzoylation of **1** to form **9** (Eq. 7) with the stronger benzoyl chloride electrophile. No N-phenoxycarbonylation product **14** or C-phenoxycarbonylation product **15** were detected.



(8)

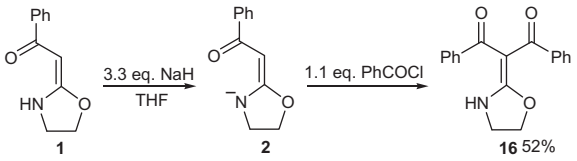
Benzoylation of ambident anion 2

Ambident anion **2**, obtained by deprotonation of **1** by sodium hydride in THF, was reacted with 1 equiv of benzoyl chloride to explore its regiochemistry. Mono-benzoylation occurred at the exocyclic β-carbon, giving the β,β-bisbenzoylated **16**, in a 52% isolated yield (Eq. 9).

Table 1
Benzoylation of 2-methyl-2-oxazoline **8** and 2-methyl-2-oxazine **10**[a]

Entry	Substrate	Equiv of PhCOCl	Solvent	Product	Yield[b] (%)
1	**8**	2.2	CH_3CN	**9**	60[c]
2	**8**	2.2	THF	**9**	56[c,d]
3	**8**	3.3	THF	**9**	60[e]
4[f]	**10**	2.1	THF	**11**	52[c]

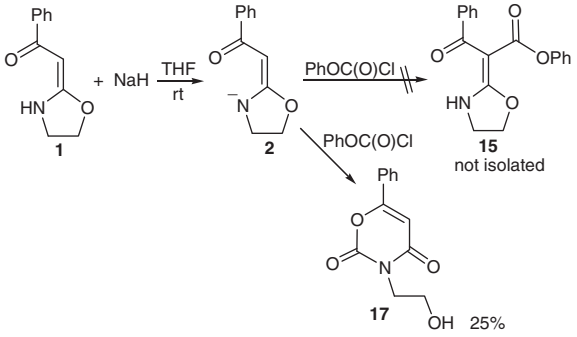
[a] Reactions were run in refluxing THF or CH_3CN for 5 h. Et_3N was used as the acid scavenger. Column chromatography was used for purification (stationary phase: silica gel, eluting solvent: acetone/hexanes or ethyl acetate/hexanes).
[b] Isolated/purified yield.
[c] Yield was based on PhCOCl (the limiting reagent).
[d] A 89% yield (based on PhCOCl, the limiting reagent) was obtained using 1.80 g of **8** and 2.3 equiv PhCOCl, freshly distilled from SOCl2, and flame-dried glassware.
[e] Yield was based on **8** (the limiting reagent).
[f] Reaction was run for 4.5 h.



(9)

Reaction of phenyl chloroformate with ambident anion 2

Compound **2** was also reacted with 1 equiv of the weaker electrophile, phenyl chloroformate in THF at room temperature (Eq. 10). Surprisingly, the expected C-alkoxycarbonylation adduct **15**, an analog of **16** (Eq. 9), was not isolated. Instead, the completely unforseen 3-(2-hydroxy-ethyl)-6-phenyl-[1,3]oxazine-2,4-dione, **17**, was formed in 25% yield. In addition, the starting material **1** was recovered in 12% yield.

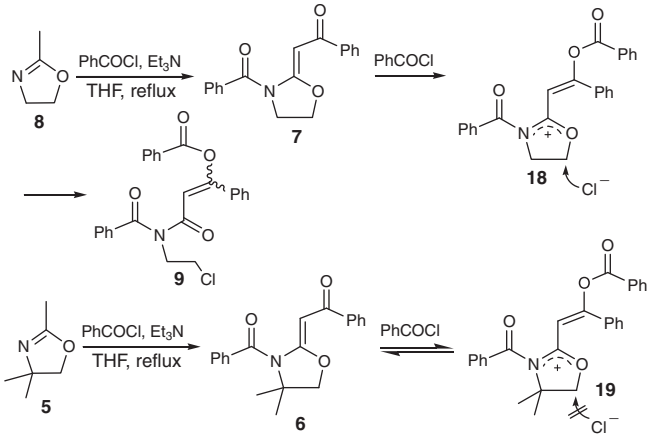


(10)

Discussion

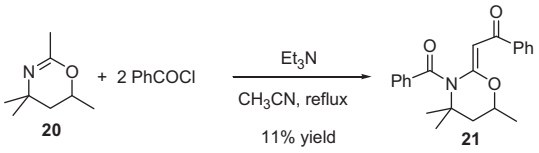
Benzoylation of 2-methyl-2-oxazoline to N,C,O-trisbenzoylated, ring-opened **9** presumably arises from N,C-bisbenzoylated compound **7** (Scheme 1). The ketone oxygen of **7** may subsequently have been O-benzoylated to form cation **18**, followed by chloride nucleophilic attack at C-5 to open the ring. O-Benzoylation would be promoted by strong electron donation in **7** from the ring oxygen and nitrogen atoms making this keto oxygen more negative and nucleophilic.

The contrasting benzoylation behavior of 2-methyl-2-oxazoline to **9** versus 2,4,4-trimethyl-2-oxazoline to **6** (Eq. 2 vs 3) highlights the importance of the C-4 methyl substituents on these reaction paths. These two methyl groups stop 2,4,4-trimethyl-2-oxazoline benzoylation at the N,C-bisbenzoylation stage. Even if a third benzoylation does occur at the ketone oxygen to form a 1,3-oxazolinium cation **19**, analogous to **18** (Scheme 1), the two C-4 methyl groups hinder the chloride attack at C-5, so ring opening cannot occur. Thus, O-benzoylation will be reversible and **6** is the isolated product.



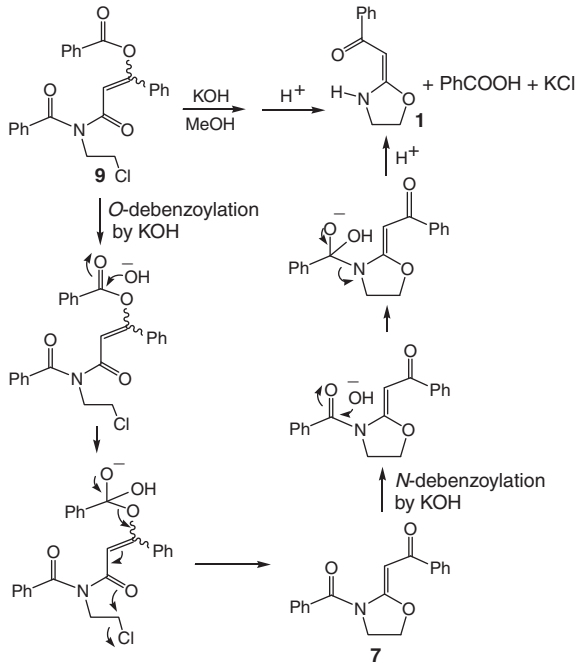
Scheme 1. A mechanism for benzoylation of 2-methyl-2-oxazoline to *N,C,O*-trisbenzoylated, ring-opened compound **9**.

Likewise, benzoylation of 2-methyl-2-oxazine **10** gave **11** (Eq. 4). In contrast, benzoylation of **20** gave ring-retained N,C-bisbenzoylation product **21** (Eq. 11).[6] This substituent effect has been observed elsewhere.[51]



(11)

The reaction of N,C,O-trisbenzoylated, ring-opened **9** with methanolic KOH reclosed the ring and formed cyclic ketene-*N,O*-acetal **1**. O-debenzoylation by hydroxide likely triggers a subsequent intramolecular S_N2 attack by an imide carbonyl oxygen on the methylene carbon bearing chlorine, giving rise to **7**[7] (Scheme 2). N-Debenzoylation then leads to cyclic ketene-*N,O*-acetal **1**. Alternatively, N-debenzoylation might occur prior to O-debenzoylation, similar to the preparation of 2-oxazolines by dehydrohalogenation of β-haloalkylamides with aqueous or alcoholic alkali.[8]



Scheme 2. A suggested route from **9** to **1**.

Benzoylation of **1** was slow at ambient temperature and formed only 2% of trisbenzoylated, ring-opened **9**. Most of **1** was recovered. N,C-Bisbenzoylated **7** may have formed as an intermediate which rapidly reacted with more benzoyl chloride to form **9** (Eq. 7).

Benzoylation of **2** is totally different than benzoylation of **1** (Scheme 3). The β-carbon site of **2** reacted with benzoyl chloride to give adduct **22**. Using excess NaH ensures removal of the acidic β-proton of **22** to form stable anion **23**. This is similar to the Claisen condensation where a stoichiometric amount of base drives the reaction to completion. Excess NaH also reduced the possibility of **22** being deprotonated by **2**, which would regenerate **1** (Scheme 3). Aqueous workup transforms **23** to **16**.

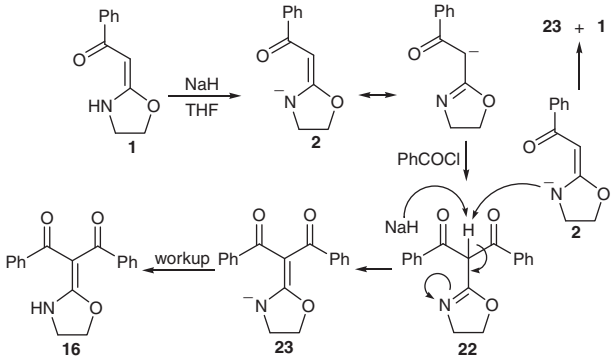
N,C-Dibenzoylation product **7** could have formed via *N*-benzoylation of **2** (Scheme 4). However, **7** could further react with **2** in two ways. The nitrogen of **2** could attack the amide carbonyl carbon of **7** (route **a** in Scheme 4), regenerating **7** and **2** with no net change. However, if the β-carbon of **2** attacks **7** (route **b**), β,β-dibenzoyl product, **22**, will form. Subsequent deprotonation of **22** by sodium hydride gives stable anion **23**, which gives **16** on workup. This accounts for why benzoylation of **2** appears to occur at the softer carbon site rather than the harder nitrogen site, despite the fact that benzoyl chloride is a harder electrophile than methyl iodide. For comparison, methyl iodide reacted with **4**, the C-4 dimethylated analog of **1**, on the β-carbon.[6]

Reaction of **1** with phenyl chloroformate gave ring-opened product **13** (Scheme 5). This route is similar to formation of **9** (Eq. 7). Nucleophilic attack by **1** on phenyl chloroformate probably occurs via the ring nitrogen, giving rise to intermediate **14** (similar to **7** in Eq. 7). Subsequent β-keto oxygen phenoxycarbonylation leads to cation **28**, which is ring-opened by chloride attack. This ring-opening finds analogy in Scheme 1.

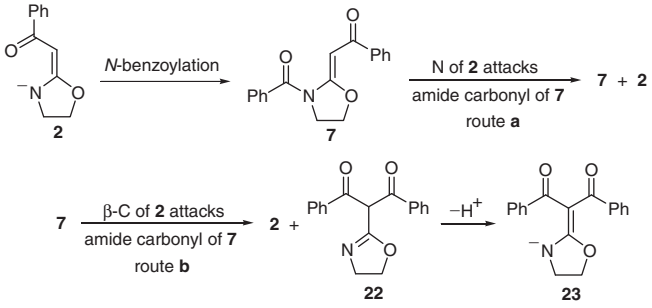
In contrast to the conversion of **1** to **9** (Eq. 7), **2** reacted with phenyl chloroformate generating the substituted [1,3]-oxazine-2,4-dione **17** (Scheme 6 and Eq. 10) instead of the expected β,β-disubstituted cyclic ketene-*N*,*O*-acetal **15** from C-phenoxycarbonylation. Phenyl chloroformate, a harder electrophile than iodomethane, reacted with anion **2** at its nitrogen, which is a harder nucleophilic site than its β-carbon. This produces **14**. Compound **14** is expected to undergo an intramolecular nucleophilic attack of the carbonyl oxygen on the carbamate carbonyl carbon to form intermediate **29**. Compound **29** loses phenoxide to generate the fused ring oxazolinium cation **30** rather than cleaving the bond to the ring nitrogen to generate the oxazoline **31**.[9] Hydrolysis of cation **30** provides ring-opened product **17**.

The differences when reacting **1** versus **2** with phenyl chloroformate may be due to differences in reaction conditions rather than intrinsic reactivity differences. Intermediate **14**, formed during reaction of **1** with phenyl chloroformate, in the presence of Et_3N (Scheme 5), might have undergone β-keto oxygen phenoxycarbonylation faster than intramolecular nucleophilic attack of the ketone's oxygen on the carbamate carbonyl carbon to form oxazolinium cation **29** (Scheme 6). Et_3N may have activated phenyl chloroformate for β-keto oxygen phenoxycarbonylation via nucleophilic catalysis.[10] Intermediate **14**, formed by reaction of **2** with phenyl chloroformate, in the absence of Et_3N, simply undergoes intramolecular nucleophilic attack to form **17**, since keto oxygen attack on unactivated phenyl chloroformate would be slower.

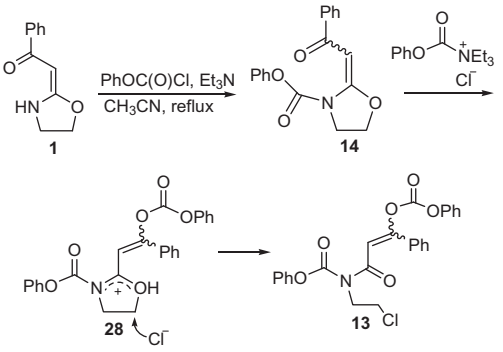
Similar [1,3]-oxazine-2,4-dione compounds have been synthesized from β-oxo-esters.[11] [1,3]-Oxazine derivatives oxazinomycin and minimycin are reported to have antibiotic activity.[11] Therefore, the preparation of [1,3]-oxazine-2,4-diones from



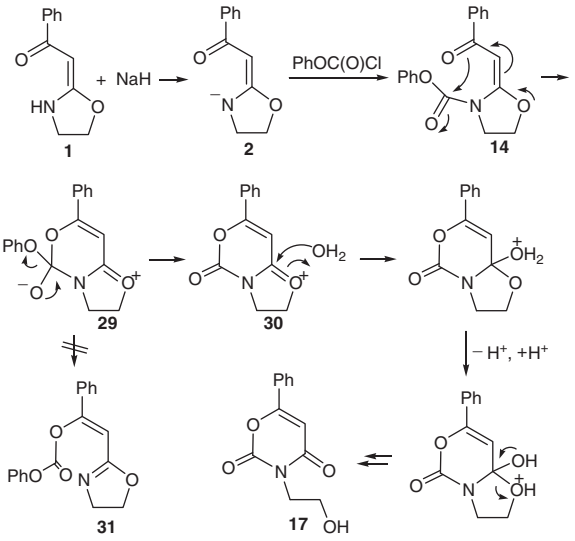
Scheme 3. Benzoylation of ambident anion **2** gave **16**.



Scheme 4. The reason why *N*,*C*-dibenzoylated **7** is not observed.



Scheme 5. A suggested route to **13**.



Scheme 6. A suggested route to **17**.

2-methyl-2-oxazoline via cyclic ketene-*N*,*O*-acetal chemistry may have synthetical potential.

Acknowledgments

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Supplementary data

Complete experimental synthetic descriptions and characterizations of all the compounds described here, including crystal structures of **1**, **11** and **17**, can be found in the online version, at doi:10.1016/j.tetlet.2011.06.023.

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