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Alkylation of Oxazolones and Related Heterocycles through an S_N1 Reaction

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Dedicated to the memory of Prof. Rafel Suau

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The alkylation of oxazolones through an S_N1 reaction by using stabilized carbocations is reported. The reaction (catalyzed by Brønsted acids, such as TFA or thioureas) affords the final compounds in excellent yields. Reaction with other heterocycles has also been studied, rendering pyrazolone or oxindole derivatives in good yields.

Introduction

Oxazol-5-(4*H*)-ones are common starting materials, due to their importance in the synthesis of chiral amino acids.[1] They have a dual behavior, presenting both nucleophilic and electrophilic nature. As shown in Figure 1, there are three different nucleophilic sites and one electrophilic site. This makes the reactivity of oxazolones rich and interesting.

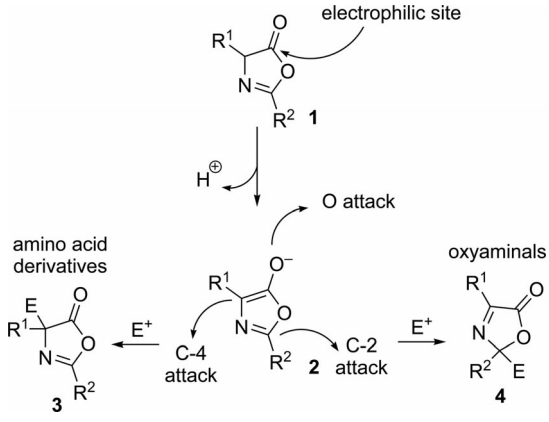

Figure 1. Reactive sites of oxazolones.

The use of oxazolones as suitable nucleophile starting materials for the synthesis of quaternary amino acids or oxyaminals has attracted much attention in organocatalysis.[2] Recently, Jørgensen's research group and ours have developed several methodologies for the synthesis of quaternary amino acids. Concretely, Jørgensen and co-workers have reported the use of 5-oxazolones (azlactones) in the asymmetric organocatalytic Michael addition[3] to α,β-unsaturated aldehydes,[4] nitroalkenes,[5] and unsaturated acyl phosphonates,[6] On the other hand, our research group has developed the addition of oxazolones to maleimides,[7] 1,1-(bisphenylsulfonyl)ethene,[8] and 1,2-(bisphenylsulfonyl)ethene.[9] Terada and co-workers have described efficient access to β-hydroxy-α-amino acid derivatives having a quaternary stereocenter at the α-carbon atom by an aldol reaction between oxazolones and aldehydes.[10] All these methodologies afforded the desired oxazolone precursors in excellent yields and enantioselectivities.

However, one of the characteristics of those methodologies is the increase in molecular complexity, as several functional groups are present in the final compound. An important drawback of all these procedures remains in the difficult synthesis of very bulky disubstituted oxazolones due the Michael nature of all these methodologies. Interestingly, bulky quaternary α-amino acids (in the case of C-4 addition) included in the amino end of a peptide sequence can induce a determined structural conformation and increase the enzymatic stability of the peptide.[11] With this information in mind, and interested in the synthesis of bulkily substituted quaternary oxazolones, we turned our attention to S_N1 reactions that overcome the previously discussed limitations. Very recently, Cozzi and co-workers reported the use of highly stabilized carbocations in the α-alkylation of aldehydes catalyzed by secondary amines.[12] Based on those previous reports, in conjunction with our experience in organocatalysis[13] and the fascinating studies of Mayr about the stability of carbocations,[14] we envisioned easy

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entry to bulky quaternary amino acids taking advantage of our previous experience in the use of oxazolones and related heterocycles.

As is well known, benzylic, propargylic, and allylic alcohols can form, in the presence of acids, carbocations that are found on the electrophilicity scale of Mayr. Strong electron-donating substituents enhance the stability of the carbocations. For this reason, we choose compound **5a** (with strong electron-donating groups: *p*-dimethylamino) to study the reaction.

Results and Discussion

First of all, we were concerned about the nature of the addition. When enals or vinyl sulfones are used as nucleophiles, the addition takes place at C-4. On the other hand, acylphosphonates, nitrostyrenes, and maleimides make the nature of the addition strongly dependent of the structures of both the nucleophile and the electrophile. Because highly reactive electrophiles – such as enals (in their iminium form) or vinyl sulfones – react exclusively at C-4, we expected, accordingly, similar behavior when stabilized carbocations were used. As a study reaction, we chose the addition of oxazolone **1a** to alcohol **5a**. This alcohol has been chosen based on the previous work of Cozzi and the parameters of Mayr.

To our delight, when azlactone **1a** was treated with alcohol **5a** the final product was obtained after 14 h under TFA catalysis. The regiochemistry was determined by X-ray diffraction of compound **6a**. As expected, the regiochemistry of **6a** corresponds to addition at C-4 (Figure 2). Next, we tried different catalysts, including bases (Table 1, Entry 2) and thioureas (Table 1, Entries 3–7). Remarkably, when base was used, no reaction was observed, probably because it is impossible to generate the carbocation. A different set of thioureas was used, revealing that the thiourea moiety is able to promote carbocation formation. However, although the inclusion of a chiral moiety in the thiourea and a new functionality (a base) increased the rate of the reaction, it negatively affected the enantioselectivity (Table 1, Entries 5 and 7). Surprisingly, when a phosphoric acid derivative was used, no reaction was observed.

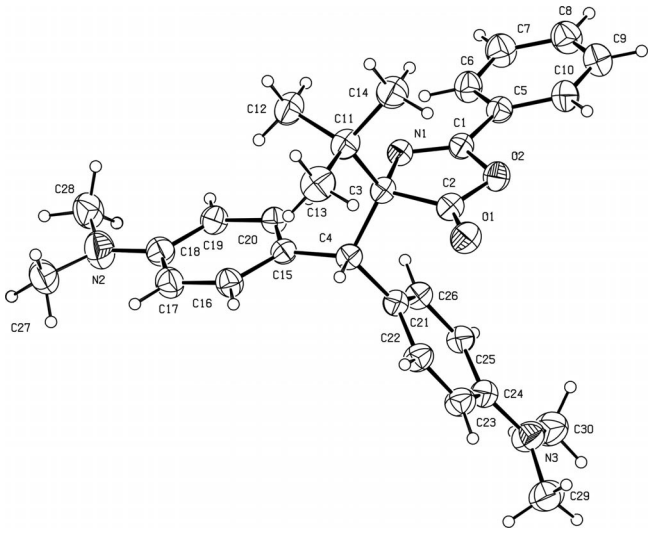
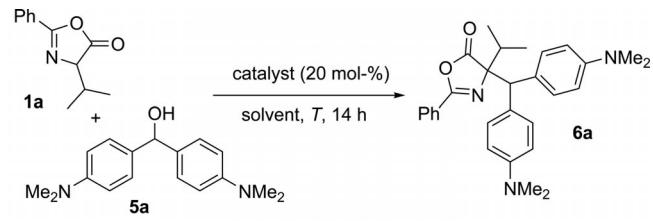
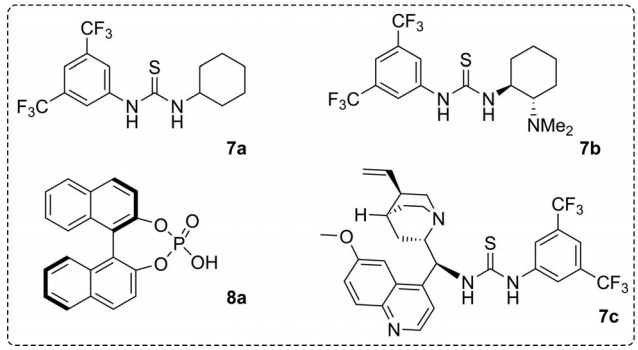


Figure 2. X-ray analysis of **6a**.[15]

Table 1. Screening of the reaction conditions.[a]





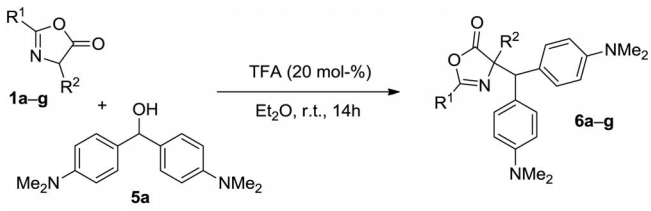
Entry	Catalyst	*T* [°C]	Solvent	Conversion [%][b]
1	TFA	r.t.	Et_2O	100
2	TEA	r.t.	Et_2O	0
3	**7a**	r.t.	Et_2O	100
4[c]	**7b**	r.t.	Et_2O	100
5	**7b**	r.t.	toluene	100
6	**7b**	4	Et_2O	0
7	**7c**	r.t.	Et_2O	33
8[d]	**8a**	r.t.	Et_2O	0

[a] In a small vial, oxazolone **1a** (0.225 mmol) and alcohol **5a** (0.15 mmol) were stirred in the presence of the desired catalyst (20 mol-%, 0.03 mmol) at room temperature overnight. [b] Determined by ^1H NMR spectroscopic analysis of the crude mixture. [c] *ee* = 13% (determined by chiral HPLC analysis). [d] 50% conversion was obtained at 60 °C in toluene.

Once suitable reaction conditions for the reaction had been found (TFA as catalyst, Et_2O at room temperature), we explored the scope of the reaction in terms of the oxazolone substitution pattern. To our delight, final products **6a**–**f** were obtained in good yields (Table 2, Entries 1–6), and only when a very bulky oxazolone, such as **1g** (with two *tert*-butyl moieties), was used did the reaction not occur.

Next, we explored the scope of the electrophile. Oxazolone **1a** was treated with different electrophiles (based on Mayr's parameters). The term *E* of alcohol **5a** was calculated to be –7.0. We then chose different alcohols with a Mayr parameter between –7.0 and 0 (Scheme 1). Benzylic carbocations are of moderate stability and high reactivity (for this reason, we decided to include compound **5c**, although its *E* value does not belong to the initially proposed range of *E* parameters), and ferrocenyl compounds are well known for their capacity to stabilize a carbocation. Because of the low ability of the alkynyl group to stabilize a positive charge, reactions of propargyl cations are quite limited;

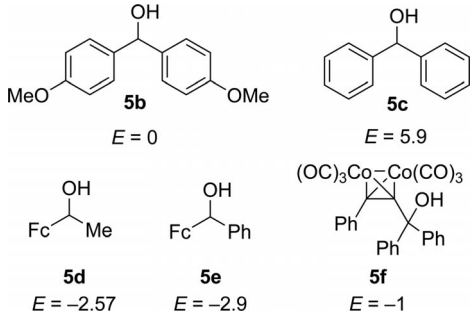
Table 2. Oxazolone scope.[a]



Entry	R^1	R^2	Product	Yield [%][b]
1	Ph	*i*Pr	**6a**	55
2	*m*-FC_6H_4	*t*Bu	**6b**	67
3	Ph		**6c**	84[c]
4	Ph	*t*Bu	**6d**	77
5	*t*Bu	Ph	**6e**	70
6	2,4-$F_2C_6H_3$	*i*Bu	**6f**	78
7	*t*Bu	*t*Bu	**6g**	n.r.
8	Ph	H	**6h**	33[d]

[a] In a small vial, oxazolone **1a**–**g** (0.225 mmol) and alcohol **5a** (0.15 mmol) were stirred in the presence of trifluoroacetic acid (20 mol-%, 0.03 mmol) at room temperature overnight. [b] Isolated yield after column chromatography. [c] 1.4:1 *dr* (determined by ^1H NMR spectroscopic analysis of the crude mixture). [d] Compound **6h** is the double addition product.

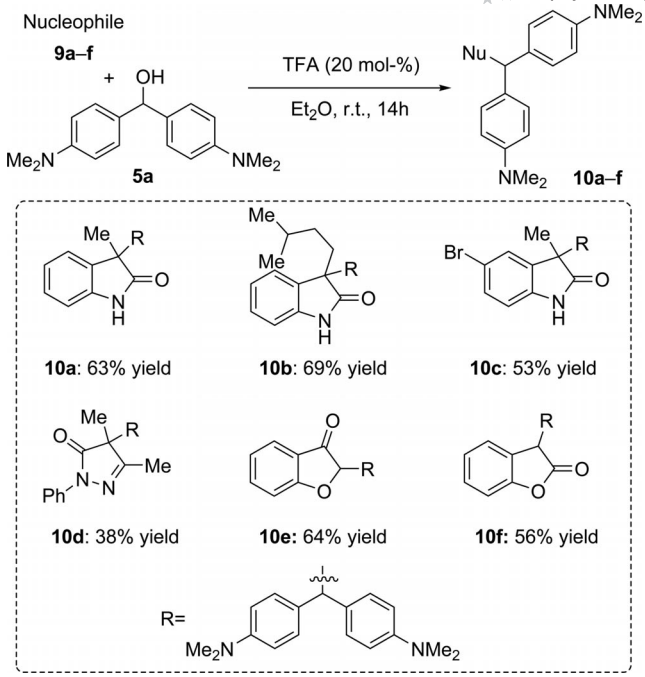
however, the complexation of an alkyne with $Co(CO)_8$ reduces the electrophilicity of the carbocation generated, stabilizing it (Nicholas reaction).



Scheme 1. Different studied alcohols and the expected or calculated *E* parameter of the corresponding carbocations.

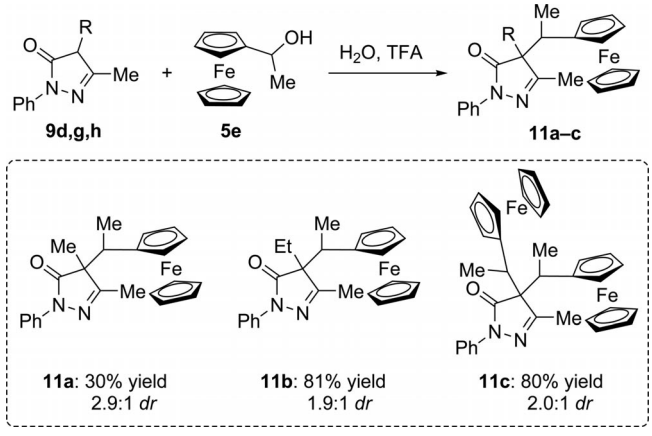
Unfortunately, under our reaction conditions, none of the selected substrates reacted with oxazolone **1a**, probably due to the difficult formation of the corresponding carbocation under the optimized reaction conditions. One important limitation of the use of oxazolones is the need to avoid water as solvent, due to their inherent reactivity in water (formation of the opened *N*-substituted amino acid).

Encouraged by the results obtained when testing oxazolones in this reaction, we decided to expand this methodology by using different nucleophiles, such as oxindole,[16] pyrazolones,[17] and benzofuranones[18] (Scheme 2), which could be interesting targets in medicinal chemistry. In all the examples, we obtained the desired final products in good yields, showing that this methodology can be useful for the synthesis of bulky quaternary centers.



Scheme 2. S_N1 reactions performed with different heterocycles.

Next, we decided to use these substrates with different carbocations. Unfortunately, we did not observe any reaction with ferrocenyl or dibenzyl alcohols. To overcome this limitation, we run the reaction in water this time (a strategy that could not be employed with azlactones due to their inherent instability in water). To our delight, the reaction afforded, under these conditions, the corresponding alkylated compounds in good yields when pyrazolones were employed (Scheme 3).



Scheme 3. Reactions between pyrazolones and ferrocenes in water.

Conclusions

In conclusion, we have developed a new methodology for the alkylation of azlactones through the formation of stable carbocations. This methodology allows the construction of bulky amino acid derivatives that cannot be built with other methodologies. The reaction renders the final bulky disub-

stituted oxazolones in good yields, albeit with low enantioselectivities when then Takemoto catalyst was employed (Table 1, footnote). We studied the scope of the reaction by using different stabilized carbocations. However, the reaction did not render the final products. We expanded the reaction scope by employing other interesting scaffolds such as pyrazolones or oxindoles, affording the final alkylated products in excellent yields.[19]

Experimental Section

General Procedure: Bis[4-(dimethylamino)phenyl]methanol (41 mg, 0.15 mmol, 1 equiv.), the desired oxazol-5(4*H*)-one (0.225 mmol, 1.5 equiv.), and trifluoroacetic acid (3 mg, 0.03 mmol, 0.2 equiv.) were added to a vial containing diethyl ether (2 mL). The reaction mixture was stirred at room temperature overnight. The crude reaction mixture was directly subjected to flash chromatography [silica gel/triethylamine 10:1 (v/v) as stationary phase and hexane/ethyl acetate of increasing polarity as mobile phase].

Supporting Information (see footnote on the first page of this article): Experimental data for all compounds and crystallographic data.

Acknowledgments

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