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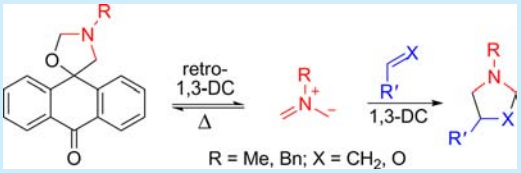
Reagents for Storage and Regeneration of Nonstabilized Azomethine Ylides: Spiroanthraceneoxazolidines

Evgeny M. Buev, Vladimir S. Moshkin,* and Vyacheslav Y. Sosnovskikh

Department of Chemistry, Institute of Natural Sciences, Ural Federal University, 620000 Ekaterinburg, Russian Federation

Supporting Information

ABSTRACT: Nonstabilized azomethine ylides are easily trapped by anthraquinone to form stable spiro-oxazolidines, which have an unusual ability to undergo a cycloreversion in the presence of other dipolarophiles at 120−150 °C. All tested recycloadditions with carbonyl compounds and electron-poor alkenes occurred in moderate to high yields (41−92%). Moreover, increasing the reaction temperature to 210 °C made it possible to obtain adducts with low reactive dipolarophiles.



Azomethine ylides of nonstabilized type are highly reactive intermediates, which possess significant synthetic utility in the preparation of various nitrogen compounds.[1] These dipoles bearing no ylide-stabilizing substituent are especially effective for introducing a nonfunctionalized alkylaminomethyl moiety in a molecule and were successfully used in the synthesis of a wide variety of natural compounds and drugs.[2] Due to high reactivity, azomethine ylides are generated in situ by such methods as desilylation of a methyliminium ion (H^+, Lewis acid, F^-, oxidant-mediated),[3] interaction of *N*-oxides with a strong base such as BuLi or LDA,[4] condensations of *α*-amino acids with carbonyl compounds,[5] and extrusion of CO_2 from oxazolidinones.[6] Many of these methods are difficult to apply, and most of the published works contain ylides derived from *N*-alkyl-*α*-amino acids with carbonyl compounds and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine with TFA (Figure 1). Thus, new and efficient methods for the generation of nonstabilized azomethine ylides are in high demand.

In previous research,[7] we paid attention to the unusual properties of 3′-methyl-10*H*-spiro[anthracene-9,5′-oxazolidin]-10-one (**1a**) obtained from anthraquinone, sarcosine, and formaldehyde. Our first attempts to realize any reactions with it, such as hydrolysis to amino alcohol, reduction with $NaBH_4$, or even purification by recrystallization from MeOH, resulted in a complicated mixture of products. However, the most unexpected circumstance was the formation of starting anthraquinone and dimethylamine (reaction product between azomethine ylide and water). This phenomenon is not typical for other 5-aryloxazolidines and prompted us to think about the reversibility of the cycloaddition and about the idea that anthraquinone could be a specific acceptor and then a donor of the nonstabilized azomethine ylide. To the best of our knowledge, only three specific methods for a generation of stabilized azomethine ylides from functionalized oxazolidines[8a−c] were previously known in the literature. Additionally, there is one work of a more synthetically usable generation of stabilized ylide by cyclodegradation of an oxazolidine preliminarily obtained from methyl prolinate and benzaldehyde.[8d] It is noteworthy that we could not find any examples of the generation of nonstabilized azomethine ylides for [3 + 2] cycloaddition from oxazolidines in the literature.

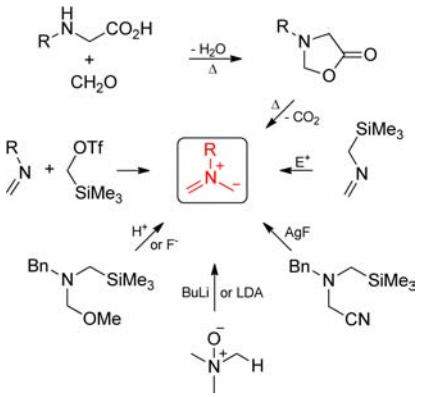


Figure 1. Methods for the generation of nonstabilized azomethine ylides.

Solid spiroanthraceneoxazolidine **1a** (mp 102−103 °C) was readily obtained from anthraquinone, sarcosine, and formaldehyde in quantitative yield (97% purity, insignificant traces of anthraquinone). In such a manner, adduct **1b**, bearing a benzyl substituent, was also prepared from anthraquinone, benzylglycine, and formaldehyde. Both crude solid oxazolidines were used in further experiments without any purification. To examine the sequence of retro-1,3-DC/1,3-DC, we chose an interaction between **1a** and benzaldehyde **3**. Indeed, reflux of the reagents in toluene for 45 min resulted in the formation of 5-phenyl-3-methyloxazolidine (**4a**) in 8% NMR yield. During subsequent experiments, we optimized conditions and achieved 95% transformation of spiro-oxazolidine **1a** to oxazolidine **4a** (*o*-xylene, 4.5 h, reflux, molar ratio 1:1) isolated in 73% yield (Table 1).

Note that the formation and the cycloreversion of oxazolidine **1** to ylide and anthraquinone is an unusual process. On the one

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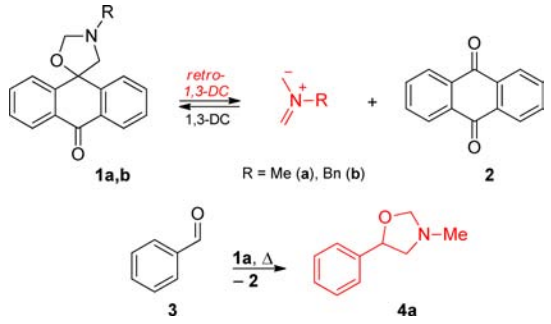
Table 1. Optimization of the Reaction Conditions



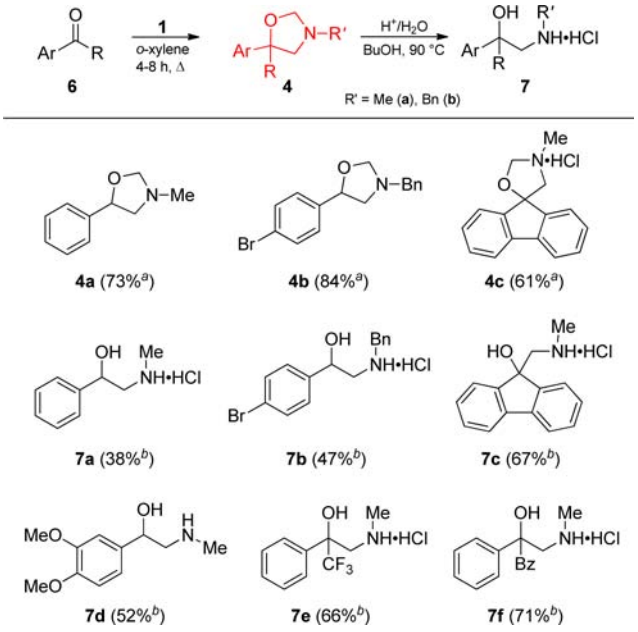
entry	conditions	yield (%)[a]
1	PhMe, reflux, 45 min	8
2	PhMe, MW, 160 °C, 20 min	72
3	*o*-xylene, reflux, 3.5 h	83
4	*o*-xylene, reflux, 4.5 h	95
5	*o*-xylene, reflux, 4.5 h, then isolation of **4a**	73[b]

[a]Yield was determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield.

hand, the extrusion of such a highly reactive electron-donating species as a nonstabilized azomethine ylide indicates that spiroanthraceneoxazolidine **1** is unstable and has high potential energy. On the other hand, the latter can be obtained and is easy to store at room temperature for a long time. Presumably, these two facts should limit a number of carbonyl compounds such as anthraquinone. It is important to outline a distinction between the observed phenomenon and the formation of stabilized azomethine ylides.[8] Some ylides of this type have been isolated.[9] Therefore, it should be easier to find a compound that could form an unstable adduct with a stabilized ylide, which could be deconstructed under more stringent conditions. For example, benzaldehyde acted as an acceptor and as a donor of a stabilized azomethine ylide,[8d] but at the same time, it acts only like an acceptor of the nonstabilized azomethine ylide in the reaction with oxazolidine **1a**. Such special properties of spiroanthraceneoxazolidines **1** are apparently connected to their geometry and strain due to the presence of the sp^3-hybridized spiro-carbon in a planar system of sp^2 carbons. On the other hand, the formation of these spiro-oxazolidines is possible due to the high electron-withdrawing characteristics of anthraquinone and to the high nucleophilicity of nonstabilized azomethine ylides.

With the found conditions for the generation of non-stabilized azomethine ylides in hand, we decided to examine the sequence of retro-1,3-DC/1,3-DC on other aldehydes and ketones. Taking into account that aromatic carbonyl compounds react smoothly with nonstabilized azomethine ylides generated by other early known methods, we chose substrates **6**. 4-Bromobenzaldehyde and 9-fluorenone reacted like benzaldehyde to give corresponding 5-aryloxazolidines **4b,c**, which were then isolated in good yields (Scheme 1). Reactions of spiro-oxazolidine **1a** with electron-rich veratraldehyde and with such electron-poor ketones as (trifluoromethyl)phenylketone and benzil were tolerant to substituents and resulted in corresponding adducts in high NMR yields. Additionally, all aryloxazolidines **4** were hydrolyzed to arylaminoethanols **7a–f** in moderate to good yields (38–71%). Such transformation is an example of a formal addition of the alkylaminomethyl anion to a carbonyl compound using new generator of azomethine ylides **1**. This sequence is easy for practical

Scheme 1. Reactions with Carbonyl Compounds

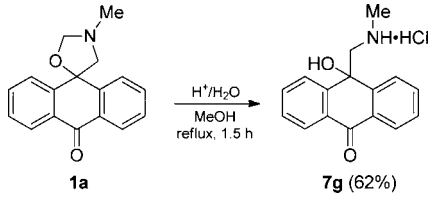


[a]Isolated yield. [b]Overall isolated yield after two steps.

implementation and does not require the usage of toxic benzene opposed to a previous technique[2e,7] for the preparation of biologically valuable halostachine **7a** and its derivatives **7b–f**. As a result, high to quantitative NMR detected yields and moderate to high isolated yields of all performed retro-1,3-DC/1,3-DC reactions with a number of aromatic carbonyl compounds confirmed that spiro-oxazolidines **1a,b** are special types of adducts and differ significantly from similar aryloxazolidines **4**.

As a side note, we also managed to carry out the hydrolysis of starting oxazolidine **1a** (Scheme 2) under mild conditions

Scheme 2. Mild Demethylenation of Oxazolidine 1a



(2 equiv of 12 M HCl, MeOH, reflux for 1.5 h) that resulted in the formation of hydrochloride of 2-amino-1-arylethanol **7g** in 62% yield (its heating above 80 °C leads to slow decomposition; the base is unstable).

In the next step of our work, to demonstrate the scope of spiroanthraceneoxazolidines **1** in the recycloaddition, we examined the reactions of alkenes bearing an electron-withdrawing substituent (Scheme 3). As expected, styrenes **8** smoothly reacted with oxazolidines **1a,b** to give corresponding substituted pyrrolidines **9a–l** (^{1}H NMR detected yields of 85–100%), and purified adducts were isolated in moderate to high yields (41–92%).

Upon inspection of the results, we were interested whether oxazolidine **1** is an outstanding compound or the ability to release nonstabilized azomethine ylide in the presence of more stringent dipolarophiles with respect to a starting carbonyl

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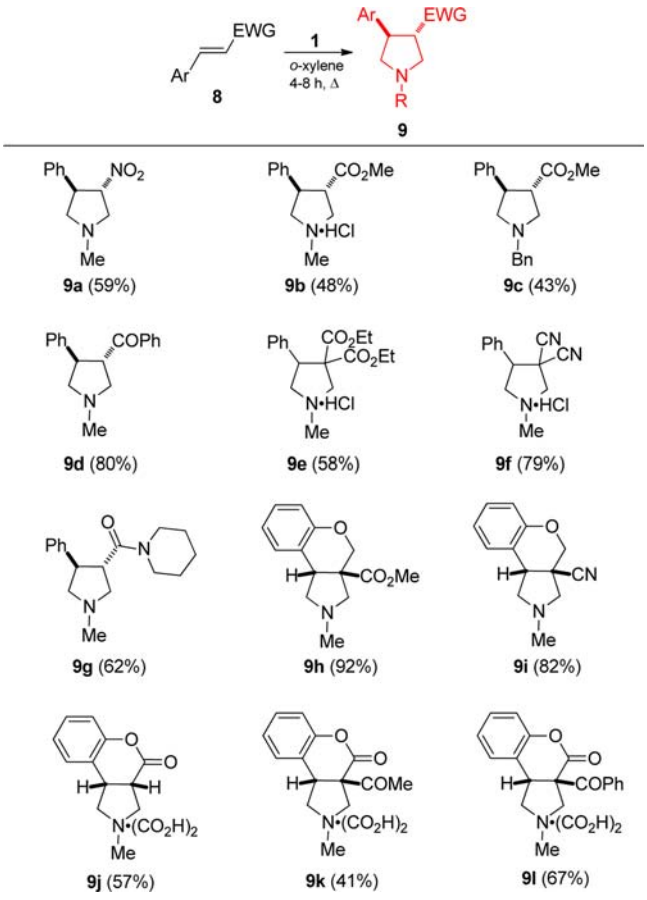
Scheme 3. Recycloadditions with Alkenes



compound is typical for other oxazolidines.[2e,7] To test the feasibility of this idea, we synthesized a simpler 5-(4-bromophenyl)-3-methyloxazolidine **4d** (Figure 2) from 4-bromobenzaldehyde,

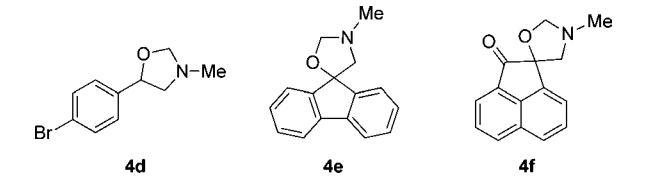


Figure 2. Possible analogues of spiroanthraceneoxazolidines **1**.

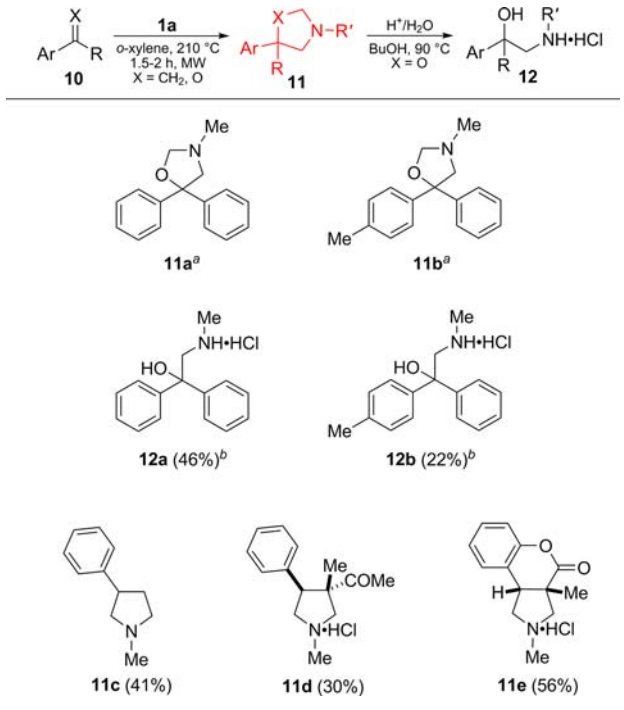
and it was heated in *o*-xylene at 210 °C with diethyl 2-benzylidenemalonate in a sealed vial in a microwave reactor for 1.5 h. This reaction resulted in a complicated mixture and the formation of only traces of the cycloadduct **9e** (molar ratio of starting dipolarophile and cycloadduct was 32:1 determined by ^{1}H NMR spectroscopy data). Further, we carried out the same reaction with spiro-oxazolidine **4e** obtained from fluoren-9-one and **4f** derived from acenaphthoquinone. It is notable that these oxazolidines are more similar in structure to oxazolidines **1**. However, we also obtained a complicated mixture (the molar ratio of the starting dipolarophile and the cycloadduct was 1:3 for **4e** and 5:1 for **4f**). Such results suggest that the ability of cycloreversion with the formation of a nonstabilized azomethine ylide is not unique to oxazolidine **1**; nevertheless, the latter reactions are of little synthetic importance.

We carried out the [3 + 2] cycloaddition of anthraquinone **2** with an asymmetrical nonstabilized azomethine ylide generated from proline and formaldehyde, which successfully resulted in the formation of corresponding spiro-oxazolidines. However, conditions for using them in the recycloaddition were not found. It is worth noting that cycloaddition of a stabilized azomethine ylide derived from isatin and sarcosine to anthraquinone failed.

On the other hand, the proposed method for the generation of the ylides from spiroanthraceneoxazolidines obtained from anthraquinone possesses a number of obvious advantages over the interaction between dipolarophiles with sarcosine and formaldehyde: an absence of formed water and of the necessity to remove it from the reaction medium; performing syntheses in *o*-xylene instead of toxic benzene (the best solvent for obtaining 5-aryloxazolidines by an azeotropic method); the possibility to obtain high concentration in a reaction mixture. Considering the features outlined above, this method of the generation of nonstabilized azomethine ylides has a prospective preparative value. Furthermore, another promising feature of oxazolidines **1** is to provide the opportunity to carry out the reactions at high temperature. While reflux in benzene or toluene is a suitable method for the [3 + 2] cycloaddition of azomethine ylide generated from sarcosine and formaldehyde, more high-boiling solvents do not increase the yield of the cycloadduct but, on the contrary, lead to side processes.

For instance, previously, we found that reaction of benzophenone resulted in only 23% NMR yield of crude 3-methyl-5,5-diphenyloxazolidine **11a** after reflux with a high excess of sarcosine and formaldehyde in benzene.[7] At the same time, the heating of oxazolidine **1a** with Ph_2CO in a sealed vial at 210 °C for 2 h in a microwave reactor leads to an increased NMR yield of up to 50%. The same reaction was carried out with 4-methylbenzophenone, and intermediate oxazolidines **11a,b** were successfully demethylenated to crystalline hydrochlorides of 2-methylamino-1,1-diarylethanols **12a,b** (Scheme 4). Under these conditions, we also examined the reaction of oxazolidine

Scheme 4. Reactions with Low Reactive Dipolarophiles



[a]Used as intermediates in the synthesis of **12a,b**. [b]Overall isolated yield after two steps.

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1a with alkenes, which have low reactivity toward sarcosine and formaldehyde, such as styrene, *E*-3-methyl-4-phenylbut-3-en-2-one, and 3-methylcoumarin.[10] This reaction allowed us to isolate cycloadducts **11c–e** in moderate yields (22–56%).

In summary, we have found the unusual properties of spiroanthraceneoxazolidines derived from easily accessible anthraquinone, N-substituted glycine, and formaldehyde. It was demonstrated that these stable at room temperature cycloadducts allow one to store and to regenerate nonstabilized azomethine ylides. The proposed method is a promising avenue, and it has already been used successfully in the [3 + 2] cycloaddition with low reactive dipolarophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00475.

General experimental procedures and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mvslc@mail.ru.

Notes

The authors declare no competing financial interest.

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