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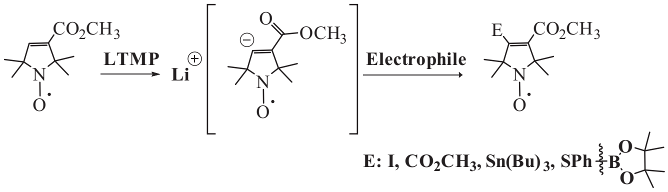
Facile syntheses of 3,4-disubstituted pyrroline nitroxides and their further synthetic applications **pp xxx–xxx**

Györgyi Úr, Tamás Kálai, Kálmán Hideg [*]



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Facile syntheses of 3,4-disubstituted pyrroline nitroxides and their further synthetic applications

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ABSTRACT

Lithiation of an α,β-unsaturated pyrroline nitroxide ester at the β-carbon with LTMP followed by treatment with electrophiles led to a new series of 3,4-disubstituted pyrroline nitroxides, which could be used as valuable paramagnetic building blocks. The new compounds were tested in Sonogashira and Stille cross coupling reactions, which offered methyl 1-oxyl-4-substituted-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-carboxylate radicals for new C–C bond formation in poor to moderate yields. The reaction of an α,β-unsaturated pyrroline nitroxide ester with methyl chloroformate generated diester **2b**; the partial hydrolysis product of this reaction was shown to be a key compound for the synthesis of paramagnetic uracil derivative **10**.

Introduction

Scientists have been intrigued by the chemistry of stable free radicals since their discovery in 1900.[1] Stable radicals have been utilized in a variety of fields[2] including spin labeling,[3] the construction of organic magnetic materials,[4] MRI contrast agents,[5] redox-active components of organic radical batteries,[6] co-oxidants,[7] and tools for controlled radical polymerization.[8] The best studied stable radicals are nitroxide free radicals, however, their chemistry faces challenges, including carbon–carbon bond formation in the presence of ambiphilic nitroxide moieties or the synthesis of hybrid molecules, for example, incorporating nitroxide moieties into biomolecules. Our laboratory has a long-standing interest in synthesizing pyrroline- and piperidine-based paramagnetic building blocks,[9–11] as well as discerning pertinent reactions in the presence of stable free radicals. Over the last two decades, the syntheses of 3,4-disubstituted pyrroline nitroxides including Pd-catalyzed cross-coupling reactions were reported by our laboratory.[12,13] However, many of these approaches demonstrate reactivity for a limited number of substrates, have low yields, and require multi-step reactions. In this paper we report a simple methodology for the synthesis of 3,4-disubstituted pyrroline nitroxides, by constructing new C–B, C–C, C–S, C–Sn, and C–I bonds starting from readily available methyl 1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-carboxylate radical (**1**).[14] Although directed lithiations of α,β-unsaturated esters have been extensively studied,[15] to the best of our knowledge this reaction has not been extended to the functionalization of nitroxides.

In this report we present our preliminary findings on this topic.

Results and discussion

To synthesize the 3,4-disubstituted pyrroline nitroxides, compound **1** was added dropwise to a lithium 2,2,6,6-tetramethylpiperidine (LTMP) solution at −78 °C in dry THF, followed by the addition of an equivalent amount of electrophile in THF (Table 1). Addition of an iodine solution to the Li-salt of **1** afforded 4-iodoester **2a,** while treatment of **1** with methyl chloroformate furnished diester **2b**. Palladium-catalyzed cross-coupling reactions have become invaluable tools for the formation of carbon–carbon bonds,[16] and the modification of carbocycles and heterocycles.[17] These reactions can also be conducted in the presence of nitroxide free radicals.[10,12,13] Thus, we hypothesized that halogenated vinyl-nitroxides, as well as paramagnetic boronic acids or trialkyl-stannanes could be partners in these cross-coupling reactions. Therefore we attempted C–Sn and C–B forming reactions (Table 1). Treatment of the Li-salt of **1** with tributyltin chloride or 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane furnished vinylstannane derivative **2c** in 38% yield and boronic acid pinacolate **2d** in 11% yield, respectively. The low yield of the latter reaction is presumably because of the bulkiness of the pinacolate ester

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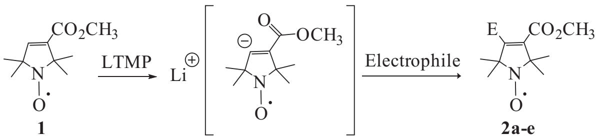
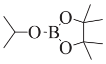
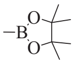
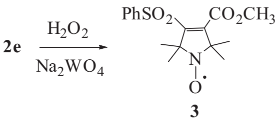
Table 1
Synthesis of 3,4-disubstituted pyrroline nitroxides



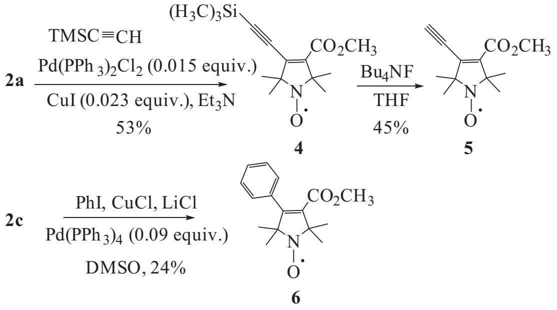
Compound	Electrophile	E	Yield %
2a	I_2	I	38
2b	$ClCO_2CH_3$	CO_2CH_3	33
2c	$ClSn(Bu)_3$	$Sn(Bu)_3$	38
2d			11
2e	PhSSPh	PhS	29[a]

[a] Estimated from compound **3** yield.

group that was introduced. The reaction of diphenyl disulfide with the Li-salt of **1** afforded the corresponding phenylsulfide derivative **2e**. However, we found that the product could not be separated from the remaining compound **1**. Fortunately, upon oxidation of the reaction mixture with H_2O_2 in the presence of Na_2WO_4 in MeOH, we were able to obtain phenylsulfone **3** (Scheme 1), which was more polar than compound **1** and could be easily separated by flash column chromatography. It is crucial to be able to carry out C–C bond forming reactions in the presence of ambiphilic nitroxide free radicals without compound degradation. The application of the Pd-catalyzed cross-coupling reactions such as the Suzuki,[10,12] Heck,[13] and Sonogashira[12] reactions has simplified this problem. However, we observed that paramagnetic vinylbromides exhibited limited reactivity in Sonogashira and Heck couplings. Gratifyingly the treatment of compound **2a** with trimethylsilyl acetylene in Et_3N and in the presence $Pd(Ph_3P)_2Cl_2$ and CuI generated compound **4** in 53% yield. Deprotection of compound **4** with tetrabutylammonium fluoride gave acetylene ester **5** in 45% yield. The reaction of compound **2c** with iodobenzene in DMSO with CuCl, LiCl, and $Pd(PPh_3)_4$ as a catalyst afforded phenyl ester **6** in 24% yield. To the best of our knowledge this is the first report of a Stille coupling reaction[18] using a paramagnetic stannous compound as a reactant.

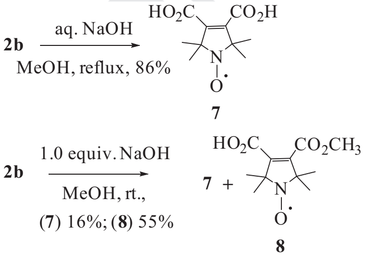


Scheme 1. Conversion of **2e** sulfide to sulfone **3**.



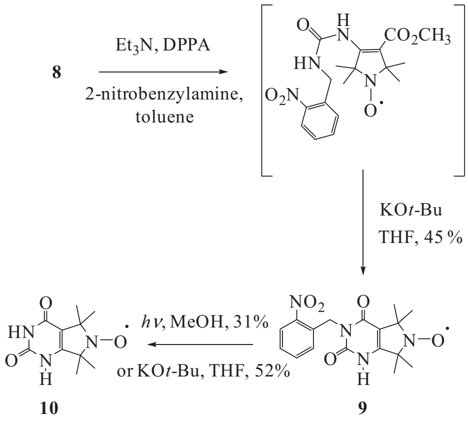
Scheme 2. Pd-catalyzed cross-coupling reactions of 3,4-disubstituted pyrroline nitroxides.

The low yield of the reaction was likely due to the introduction of a relatively bulky group to the densely substituted pyrroline compound (Scheme 2). Of the newly prepared 3,4-disubstituted pyrroline nitroxides, the most versatile compound was the symmetrical diester **2b**. Its hydrolysis with aqueous NaOH in methanol afforded the dicarboxylic acid **7**, which was previously reported from our laboratory[19] via an 11-step procedure starting from compound **1** (see ESI). It is interesting to note that partial hydrolysis could also be carried out in anhydrous MeOH with 1 equiv of NaOH[20] to generate compound **8**. This compound could be easily separated by adjusting the pH and using a CH_2Cl_2 extraction to separate the remaining compounds **1** and **7** (Scheme 3).



Scheme 3. Hydrolysis and partial hydrolysis of **2b** diester.

A paper published by DeCoen et al.[21] inspired us to attempt the synthesis of spin-labeled uracil from compound **8**, recognizing the increasing importance of spin-labeled nucleic acids.[3,22] This monomethyl ester could be converted to the acyl azide through treatment with diphenylphosphoryl azide (DPPA) and trimethylamine. Heating the reaction mixture in toluene initiated a Curtius rearrangement and afforded an intermediate isocyanate. Reacting this intermediate with photocleavable 2-nitrobenzylamine yielded the corresponding ureide in a one-pot reaction. We attempted to purify the ureide compound using silica gel chromatography prior to ring closure, but the pure product could not be obtained. The partially purified product was therefore used for the ring closure reaction. Treatment of the ureide with 1.1 equiv of KO*t*-Bu in anhydrous THF afforded 3-(2-nitrobenzyl)-protected SL-uracil **9** in 45% yield after flash column chromatography. Illumination of compound **9** in a quartz tube with an OSRAM HQL 250 W mercury lamp in degassed methanol for 4 h generated SL-uracil derivative **10** in 31% yield (Scheme 4).[23]



Scheme 4. Synthesis of **10** SL-uracil.

During the cyclization of ureide with KO*t*-Bu in THF, as monitored by TLC, we observed the appearance of a spot at R_f 0.61 ($CHCl_3$/MeOH 9/1) after acidic work-up. After isolation of this product, it proved to be identical with compound **10**. Therefore we attempted the treatment of isolated, pure compound **9** with

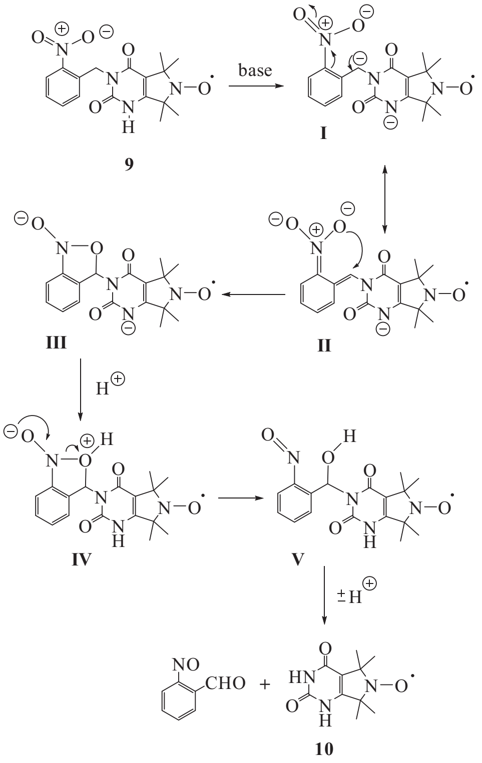


Figure 1. A proposed mechanism for the base promoted cleavage of the 2-nitrobenzyl group.

2.1 equiv KO*t*-Bu in THF and observed the unexpected formation of compound **10** in 52% yield. The possible mechanism of this base-promoted process can be initiated by deprotonation of the benzylic carbon followed by intramolecular cyclization to intermediate **III** which upon protonation and hydrolysis offers compound **10** (Fig. 1).

In summary, we have developed a new method to synthesize 3,4-disubstituted pyrroline nitroxides from a readily available pyrroline ester to access various paramagnetic building blocks. We demonstrated that these compounds could be used for Stille and Sonogashira cross-coupling reactions. The partial hydrolysis of the diester yielded a monomethylester, which was a key compound for the synthesis of SL-uracil. Further investigations to improve the yields of the cross-coupling reactions, to study the base promoted cleavage of the 2-nitrobenzyl protecting group and to extend the applications of Li-salt of compound **1** are still in progress.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, physical and spectroscopic data, a scheme illustrating an earlier procedure and copies of ^{1}H and ^{13}C NMR spectra of selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.012.

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