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Synthesis of the Antimalarial Drug FR900098 Utilizing the Nitroso-Ene Reaction

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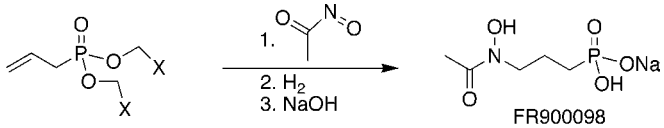
ABSTRACT



X = Me, 4 steps, 64% or X = Ph, 3 steps, 50%

The antimalarial drug FR900098 was prepared from diethyl allylphosphonate involving the nitroso–ene reaction with nitrosocarbonyl methane as the key step followed by hydrogenation and dealkylation. The utilization of dibenzyl allylphosphonate as the starting compound allows one-step hydrogenation with dealkylation, which simplifies the preparative scheme further.

The most deadly malaria parasite *plasmodium falciparum* has already developed resistance to the major classes of antimalarial drugs. A possible solution to the problem lays in the development of drugs with new mechanisms of action.[1,2] FR900098 (**1**) was first found in nature as a phosphonic acid antibiotic[3] but its antimalarial activity was discovered only in 1999;[4] the clinical studies of **1** are currently underway. This drug inhibits the mevalonate-independent pathway of isoprenoid biosynthesis in *plasmodium falciparum* that includes 1-deoxy-D-xylulose-5-phosphate[5] as the key metabolite.

A critical step in the known synthesis of compound **1** involves incorporation of the acetyl hydroxamate function that is introduced by acetylation of the respective hydroxylamines (**2**, Scheme 1) with Ac_2O.[6] The starting compounds **2**, however, are difficult to prepare through the reaction of organic bromides with hydroxyl amine, especially if additional functional groups X are present. The reaction of (3-bromopropyl)diethyl phosphonate {**3**, X = $CH_2P(O)(OEt)_2$} with hydroxylamine[7] for the synthesis of **1** gives only moderate yields of the substituted hydroxylamine derivative (Scheme 1, pathway A); protection of the oxime (e.g., with the benzylic group) increases the yields substantially. Selected alternative routes for the preparation of functionalized hydroxylamines **2** in the presence of strong bases (usually NaH) are shown in Scheme 1. These involve the

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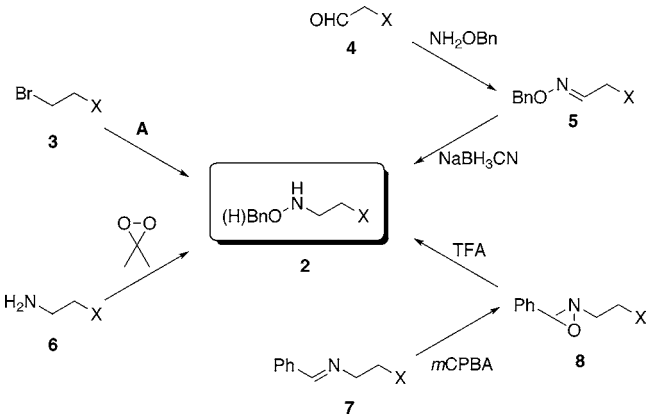
Scheme 1. Existing Synthetic Approaches to Functionalized Hydroxylamines Potentially Applicable for the Preparation of FR900098

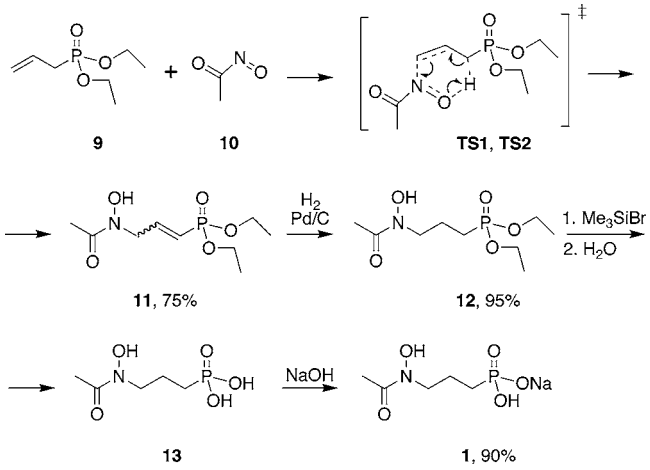


reaction of protected hydroxyl amines BnONHBoc and HN(Ts)OBn with esters {**3**, X = $CH_2C(O)OBn$[8] and X = CH_2COOEt},[9] $BnONH_2$ with amino acid derivatives {**3**, X = $(CH_2)_nCH_2CH(NHAc)COOt$-Bu}[10] and amines {**3**, X = $(CH_2)_3NHBoc$},[11] or BocONHBoc with phosphites {**3**, X = $CH_2P(O)(OAr)_2$},[12] as well as some others.[13−15] The hydroxylamines **2** were also prepared from substituted aldehydes **4** {X = $CH(R)P(O)(OEt)_2$} via imination with NH_2OBn and further reduction of the intermediate imines **5** with $NaBH_3CN$.[16] This approach was developed for the preparation of the imino derivatives **5** {X = $(CH_2)_2NHBoc$}[17] and phosphonic esters **2** {X = $CH_2P(O)(OEt)_2$}[16,18−20] and **5** {X = $CH(Ar)P(O)(OEt)_2$}.[21]

Difficulties arise from the fact that the transformations of protected hydroxylamines require the reagents, e.g., strong bases, which are difficult for large-scale synthesis. Alternatively, the oxidation of functionalized amines **6** {X = $(CH_2)_2$-$CH(NHCBn)CO_2Me$} with dimethyldioxirane[22−24] or imines **7** with peracids {X = $(CH_2)_3COOH$},[25] followed by reaction with TFA, led to unprotected *N*-substituted hydroxyl amines (Scheme 1).

The nitroso−ene reaction[26] represents a convenient method for the preparation of hydroxylamine derivatives through the addition of nitroso-reagents to olefins. Herein we present a new approach to **1** involving the nitroso−ene reaction of commercially available diethyl allylphosphonate **9** with in situ prepared nitrosocarbonyl methane (**10**) as the key step. This leads to the unsaturated derivative **11**, whose hydrogenation gives diethyl phosphonic ester **12**. Upon hydrolysis to acid **13** and partial neutralization, **1** was isolated in 64% overall preparative yield over four steps (Scheme 2).

Scheme 2. Preparation of FR900098 (**1**) from Diethyl Allylphosphonate via the Nitroso−Ene Reaction



Nitrosocarbonyl methane[27] is among the most powerful enophiles[28] and it is highly reactive toward many nucleophilic functional groups. This is the main reason why the nitroso−ene additions of **10** were previously studied only for unfunctionalized alkanes.[29−33] Owing to its instability, **10** is usually generated in situ via thermolysis of its 9,10-dimethylanthracene adduct[34] and we have chosen this method for the preparation of **11** (Scheme 2). Alternative less

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convenient methods for the generation of **10** are based on the oxidation of hydroxamic acids with iodosobenzene[32,34,35] or through the reactions of nitrile oxides with *N*-methylmorpholine *N*-oxide.[30,36]

As the reactivities of unactivated olefins are generally low, we used a ca. 1.2 molar excess of the complex of **10** to achieve satisfactory conversions of **9**. Remarkably, the phosphoryl group remains untouched in **11**. This is the first example of the nitroso−ene reaction of nitrosocarbonyl methane with a functionalized olefin.

Previous experimental and computational mechanistic studies[37−40] revealed that the nitroso−ene reaction proceeds stepwise through biradical intermediates.[40] Although we were not able to identify biradical minima at the MP2 level of theory,[41] the hydrogen shift transition structures are strongly spin-contaminated (up to $\langle S^2 \rangle = 0.96$ for a broken spin symmetry MP2 wave function). We found that the barriers for hydrogen shift via conformationally related transition structures **TS1** and **TS2** (Figure 1 and Scheme 2) for the formation of *E*- and *Z*-isomers, respectively, are comparable in energies at both the MP2/6-31G* and DFT (B3PW91/6-31+G**) levels of theory, as well as with correlation consistent basis sets (cc-pVDZ).

This agrees well with our experimental result for the stereochemistry of the reaction of **9** with **10** that gives a mixture of *E*- and *Z*-**11** in ca. 1:1 ratio. This is also in line with the known stereochemistry of the reaction of 1-octene with **10**.[29,31] We separated the diastereomers of **11** by column chromatography and characterized them individually. The structural assignments were based on the analysis of the ^{13}C NMR spectra of the allylic fragments for which the larger ^3J-values (24 vs 9 Hz) of the $^{13}C-^{31}P$ coupling are characteristic for the *E*-isomer of **11**.

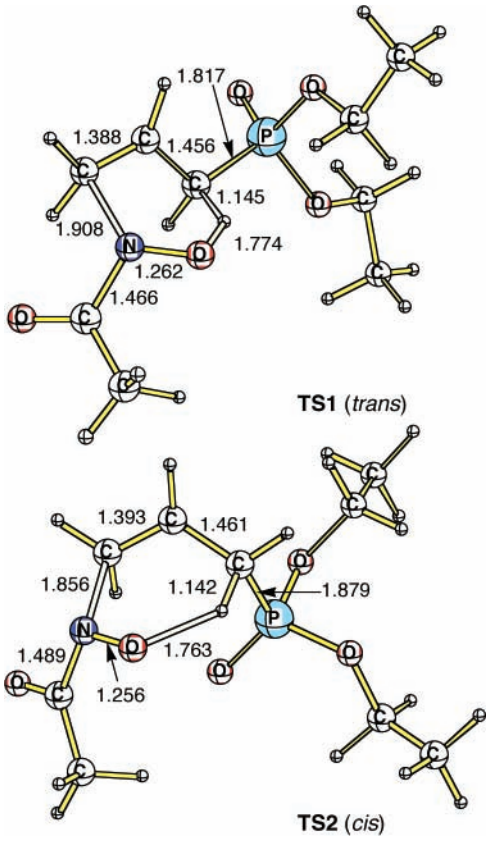

Figure 1. The B3PW91/6-31+G** optimized geometries of the conformeric transition structures for the nitroso−ene reaction of diethyl allylphosphonate with nitrosocarbonyl methane (critical bond distances in Å).

Further transformation of adduct **11** involved the hydrogenation on PtO_2 or Pd/C at atmospheric pressure that gives diester **12** in 95% yield. Since the acetylhydroxamate function is sensitive toward hydrolysis in acidic media, traditional treatment with HCl/H_2O is not viable for the dealkylation of **12** to acid **13**. We employed McKenna's[42] mild protocol, based on a treatment with trimethylbromosilane and in situ hydrolysis of the thus formed trimethylsilyl triester. This procedure gave acid **13** in 90% yield with complete conservation of the acetylhydroxamic function. Compound **1** derived after partial neutralization of **13** with NaOH was identical with an authentic sample of FR900098 obtained independently.

Thus, we developed a simple methodology for the preparation of **1** from commercially available **9** in 64% total yield. The main drawback of the scheme arises from the hydrolytic step, which utilizes trimethylbromosilane. To avoid the use of this reagent and to simplify the procedure further, we also developed another pathway (Scheme 3) to **1** utilizing the nitroso−ene reaction of allylbenzyl phosphonate (**14**). Hovewer, the literature procedure for the synthesis of **14** was not satisfactory for us because it is, again, based

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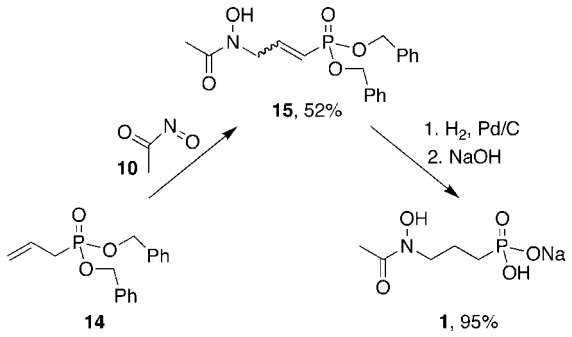
Scheme 3. An Alternative Route to FR900098 (**1**) Utilizing the Nitroso−Ene Reaction and Dibenzyl Allylphosphonate



on the Me_3SiBr-promoted hydrolysis of diethyl allylphosphonate (**9**).[43]

Hence, we developed an alternative method for the preparation of **14** utilizing the Michaelis−Becker reaction[44] of lithium dibenzyl phosphite with allyl bromide in dry ether (see experimental details in the Supporting Information). The use of the benzyl protecting group avoids the Me_3SiBr-assisted hydrolytic step since the benzyl function may be simply removed by catalytic hydrogenation with the extrusion of toluene. As expected, the diastereoselectivity of the nitroso−ene reaction of dibenzyl allylphosphonate (**14**) does not change relative to the respective diethyl derivative (**9**). A mixture of *E*/*Z*-diastereomers, which forms in 52% preparative yield (not optimized), was separated by column chromatography and the diastereomeric phosohonates **15** were isolated and characterized individually. After the hydrogenation of the diastereomeric mixture of phosphonates (**15**) in methanol at 1 atm followed by partial neutralization, **1** was obtained in 50% overall preparative yield with NMR spectra identical with those for the authenic sample of FR900098.

We conclude that the nitroso−ene reaction of allyl phosphonates is highly effective for the preparation of antimalarial drug FR900098. The addition of nitrosocarbonyl methane to the olefin moiety of allylphosphonic esters gives mixtures of unsaturated diastereomeric acetylhydroxamic derivatives. Since the acetylhydroxamic function is quite sensitive toward hydrolysis, milder hydrolytic reaction conditions were employed for deprotection. Whereas the removal of the ethyl groups in the product of the nitroso−ene reaction requires dealkylation in the presence of Me_3SiBr, this can be circumvented in the case of benzylic esters for which deprotection occurs simultaneously with hydrogenation. Incorporation of the acetylhydroxamate function for the synthesis of FR900098 seems quite promising in view of the previously developed approaches to acetylhydroxamates outlined in Scheme 1.

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Supporting Information Available: The experimental procedures, spectral data for compounds **11e**, **11z**, **12**, and **15**, as well as *XYZ*-coordinates of computed species. This material is available free of charge via the Internet at http://pubs.acs.org.

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