Department of Organic Chemistry, Kiev Polytechnic Institute, pr. Pobedy 37, 03056 Kiev, Ukraine, Universitätsklinikum Giessen und Marburg, Institut für Klinische Chemie und Pathobiochemie, Gaffkystrasse 11, 35392 Giessen, Germany, and Institut für Organische Chemie, Justus-Liebig University, Heinrich-Buff-Ring 58, D-35392 Giessen, Germany

Synthesis of the Antimalarial Drug

FR900098 Utilizing the Nitroso-Ene

Andrey A. Fokin,*," Alexander G. Yurchenko," Vladimir N. Rodionov," Pavel A. Gunchenko," Raisa I. Yurchenko," Armin Reichenberg,[‡]

Jochen Wiesner,[‡] Martin Hintz,[‡] Hassan Jomaa,[‡] and Peter R. Schreiner^{*,§}

aaf@xtf.ntu-kpi.kiev.ua; prs@org.chemie.uni-giessen.de

Received August 27, 2007

Reaction

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 antibiotic³ but its antimalarial activity was discovered only in 1999;⁴ the clinical studies of 1 are currently underway. This drug inhibits the mevalonateindependent pathway of isoprenoid biosynthesis in plasmodium falciparum that includes 1-deoxy-D-xylulose-5-phosphate⁵ as the key metabolite.

(1) Thayer, A. M. Chem. Eng. News 2005, 83, 69-82.

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 (3bromopropyl)diethyl phosphonate { $3, X = CH_2P(O)(OEt)_2$ } with hydroxylamine⁷ 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

ORGANIC LETTERS 2007

Vol. 9, No. 21 4379-4382

[&]quot;Kiev Polytechnic Institute.

[‡] Institut für Klinische Chemie und Pathobiochemie.

[§] Justus-Liebig University.

⁽²⁾ Ridley, R. G. Nature 2002, 415, 686-693.

⁽³⁾ Kamiya, T.; Hemmi, K.; Takeno, H.; Hashimoto, M. Tetrahedron Lett. 1980, 21, 95-98.

⁽⁴⁾ Jomaa, H.; Wiesner, J.; Sanderbrand, S.; Altincicek, B.; Weidemeyer, C.; Hintz, M.; Türbachova, I.; Eberl, M.; Zeidler, J.; Lichtenthaler, H. K.; Soldati, D.; Beck, E. Science 1999, 285, 1573-1576.

⁽⁵⁾ Proteau, P. J. Bioorg. Chem. 2004, 32, 483-493.

⁽⁶⁾ Fadeev, E. A.; Luo, M.; Groves, J. T. J. Am. Chem. Soc. 2004, 126, 12065 - 12075.

⁽⁷⁾ Suita, T. K.; Takaruzuka, M. H.; Kyoto, K. H.; Nara, H. T. Hydroxyaminohydrocarbonphosphonic acids. US Patent 4206156, 1980.





reaction of protected hydroxyl amines BnONHBoc and HN(Ts)OBn with esters {**3**, $X = CH_2C(O)OBn^8$ and $X = CH_2COOEt$ },⁹ BnONH₂ 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 NH₂OBn and further reduction of the intermediate imines **5** with NaBH₃CN.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. Alterna-

- (10) Nishino, N.; Yoshikawa, D.; Watanabe, L. A.; Kato, T.; Jose, B.; Komatsu, Y.; Sumida, Y.; Yoshidab, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2427–2431.
- (11) Wu, T. Y. H.; Hassig, C.; Wu, Y.; Ding, S.; Schultz, P. G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 449–453.

(12) Reichenberg, A.; Wiesner, J.; Weidemeyer, C.; Dreiseidler, E.; Sanderbrand, S.; Altincicek, B.; Beck, E.; Schlitzer, M.; Jomaa, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 833–835.

(13) Ramurthy, S.; Miller, M. J. J. Org. Chem. 1996, 61, 4120–4124.
 (14) Devreux, V.; Wiesner, J.; Goeman, J. L.; Van der Eycken, J.; Jomaa, H.; Van Calenbergh, S. J. Med. Chem. 2006, 49, 2656–2660.

(15) Hamer, R. R. L.; Tegeler, J. J.; Kurtz, E. S.; Allen, R. C.; Bailey, S. C.; Elliott, M. E.; Hellyer, L.; Helsley, G. C.; Przekop, P.; Freed, B. S.;

White, J.; Martin, L. L. J. Med. Chem. 1996, 39, 246–252. (16) Kurz, T.; Schlüter, K.; Kaula, U.; Bergmann, B.; Walter, R. D.;

Geffken, D. Bioorg. Med. Chem. 2006, 14, 5121-5135. (17) Chaubet, F.; Nguen Van Duong, M.; Gref, A.; Courtieu, J.;

(17) Chaddel, F., Nguch Van Duois, M., Old, A., Souriel, J.,
 (18) Ortmann, R.; Wiesner, J.; Reichenberg, A.; Henschker, D.; Beck,

E.; Jomaa, H.; Schlitzer, M. Arch. Pharm. 2005, 338, 305-314.

(19) Kurz, T.; Geffken, D.; Wackendorff, C. Z. Naturforsch. 2003, 58b, 106–110.

(20) Ortmann, R.; Wiesner, J.; Reichenberg, A.; Henschker, D.; Beck, E.; Jomaa, H.; Schlitzer, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2163–2166.

(21) Haemers, T.; Wiesner, J.; Busson, R.; Jomaa, H.; Van Calenbergh, S. *Eur. J. Org. Chem.* **2006**, 3856–3863.

tively, the oxidation of functionalized amines **6** { $X = (CH_2)_2$ -CH(NHCBn)CO₂Me} with dimethyldioxirane^{22–24} or imines **7** with peracids { $X = (CH_2)_3$ COOH},²⁵ followed by reaction with TFA, led to unprotected *N*-substituted hydroxyl amines (Scheme 1).

The nitroso-ene reaction²⁶ 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).



Nitrosocarbonyl methane²⁷ is among the most powerful enophiles²⁸ 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 adduct³⁴ and we have chosen this method for the preparation of **11** (Scheme 2). Alternative less

(22) Hu, J.; Miller, M. J. J. Org. Chem. 1994, 59, 4858-4861.

(23) Hu, J.; Miller, M. J. Tetrahedron Lett. 1995, 36, 6379-6382

- (24) Hu, J.; Miller, M. J. J. Am. Chem. Soc. 1997, 119, 3462-3468.
- (25) Lin, Y.-M.; Miller, M. J. J. Org. Chem. **1999**, 64, 7451–7458.
- (26) Adam, W.; Krebs, O. Chem. Rev. 2003, 103, 4131-4146.
 (27) Sklarz, B.; al-Sayyab, A. F. J. Chem. Soc. 1964, 1318.
- (27) SKialz, B., al-Sayyab, A. F. J. Chem. Soc. 1904 (28) Kirby, G. W. Chem. Soc. Rev. 1977, 6, 1–24.
- (28) Kirby, G. W. Chem. Soc. Rev. **19**77, 6, 1–24. (29) Keck, G. E.; Yates, J. B. *Tetrahedron Lett.* **1979**, 48, 4627–4630.
- (29) Keck, G. E.; Fales, J. B. *Tetrahedron Lett.* **1919**, 48, 4627–4650. (30) Quadrelli, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1998**, *39*,
- (30) Quadrelli, F., Weila, M., Caraniena, F. Terranetrow Lett. 1996, 59 3233–3236.
- (31) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007–4016.
- (32) Adam, W.; Bottke, N.; Krebs, O.; Saha-Möller, C. R. Eur. J. Org. Chem. 1999, 1963–1965.
- (33) Keck, G. E.; Webb, R. R. J. Am. Chem. Soc. 1981, 103, 3173-3177.
- (34) Kirby, G. W.; Sweeny, J. C. J. Chem. Soc., Chem. Commun. 1973, 19, 704–705.

⁽⁸⁾ Kurz, T.; Geffken, D.; Wackendorff, C. Z. Naturforsch. 2003, 58b, 457–461.

⁽⁹⁾ Woo, Y.-H.; Fernandes, R. P. M.; Proteau, P. J. Bioorg. Med. Chem. 2006, 14, 2375–2385.

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 studies³⁷⁻⁴⁰ 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 ¹³C NMR spectra of the allylic fragments for which the larger ³*J*-values (24 vs 9 Hz) of the ¹³C–³¹P 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 PtO₂ 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/H₂O is not viable for the dealkylation of **12** to acid **13**. We employed McKenna's⁴² 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

⁽³⁵⁾ Keck, G. E. Tetrahedron Lett. 1978, 48, 4767-4770.

⁽³⁶⁾ Quadrelli, P.; Mella, M.; Invernizzi, A. G.; Caramella, P. *Tetrahedron* **1999**, *55*, 10497–10510.

⁽³⁷⁾ Adam, W.; Bottke, N.; Engels, B.; Krebs, O. J. Am. Chem. Soc. 2001, 123, 5542–5548.

⁽³⁸⁾ Leach, A. G.; Houk, K. N. Chem. Commun. 2002, 1243–1255.
(39) Lu, X. Org. Lett. 2004, 6, 2813–2815.

⁽⁴⁰⁾ Leach, A. G.; Houk, K. N. J. Am. Chem. Soc. 2002, 124, 14820-14821.

⁽⁴¹⁾ All computations were performed with the GAUSSIAN03 program suite (Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision D.02; Gaussian, Inc.: Wallingford CT, 2004) utilizing analytical first and second energy derivatives. Harmonic vibrational frequencies were computed to ascertain the nature of the stationary points. We used 6-31+G** basis sets for DFT and correlation-consistent cc-pVDZ for MP2 computations. The B3PW91 functional was chosen because it is more trustworthy for large molecules than other popular DFT methods (see, for instance: Schreiner, P. R.; Fokin, A. A.; Pascal, R. A.; de Meijere, A. Org. Lett. 2006, 8, 3635-3638).

⁽⁴²⁾ McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. Tetrahedron Lett. 1977, 155-158.





on the Me₃SiBr-promoted hydrolysis of diethyl allylphosphonate (9).⁴³

Hence, we developed an alternative method for the preparation of **14** utilizing the Michaelis–Becker reaction⁴⁴ 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 Me₃SiBr-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 Me₃SiBr, 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.

Acknowledgment. This work was supported by the European Commission AntiMal FP6 Malaria Drug Initiative Framework Program (project LSHP-CT-2005-018834). We thank Prof. Dr. Martin Schlitzer (University of Marburg) for fruitful discussions and for the procedure for the experimental details for the preparation of dibenzyl phosphite.

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.

OL702082K

⁽⁴³⁾ Yamagishi, T.; Fujii, K.; Shibuya, S.; Yokomatsu, T. *Tetrahedron* **2006**, *62*, 54–65.

⁽⁴⁴⁾ Engel, R. Synthesis of Carbon-Phosphorous Bonds; CRC Press: Boca Raton, FL, 1988; p 7.