ORGANIC LETTERS

2000
Vol. 2, No. 3
353−355

Dipolar Cycloaddition of Rhodium-Generated Carbonyl Ylides with *p*-Quinones

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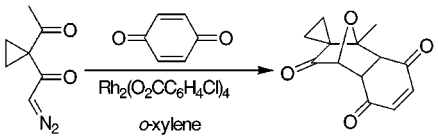
Received December 1, 1999

ABSTRACT



The dipolar cycloaddition of carbonyl ylides generated by the rhodium-catalyzed decomposition of δ- and ϵ-carbonyl-α-diazoketones with *p*-quinones leads to both C═O and C═C addition products. The product ratio is solvent- and catalyst-dependent and has been optimized to favor formation of either product. The C═C addition products of naphthoquinones are used in the assembly of structures hybridizing the illudin and anthraquinone anticancer agents.

Two illudane natural products, ptaquilosin and illudin M, show potent biological activity in cancer, believed to be related to their ability to serve as alkylating agents through the spirocyclopropyl group and/or other electrophilic sites (Figure 1).[1] Anticancer agents such as anthraquinones are activated by reduction to the hydroquinone in the relatively reducing environment of hypoxic tumor cells, facilitating quinone methide formation (through loss of benzylic substituents) and alkylation.[2] With these precedents, we have designed hybrid structures **2** in an effort to combine the potent electrophilicity of a spirocyclopropyl group[3] with the reductive activation characteristics of anthraquinones. It is expected that such materials would undergo reduction to **3**, permitting the formation of bis-quinonemethide **4** by cleavage of the strained oxabicyclo[2.2.1]heptane ring system and eventually leading to anthraquinone alkylation products such as **5** (Scheme 1). Adding appeal to this strategy was the brief and convergent synthesis of illudin M via intermediates such as **6** completed by Kinder,[4] which exploits a rhodium-generated carbonyl ylide as developed by Padwa.[5] This route

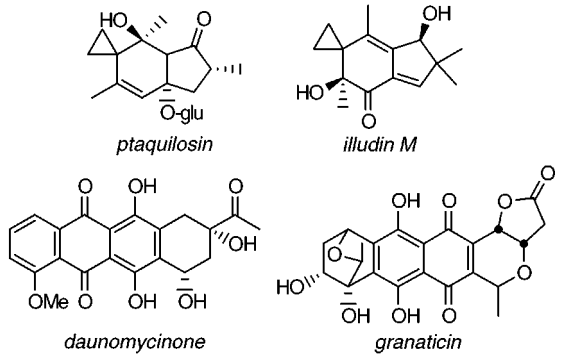


Figure 1. Illudin and anthraquinone anticancer agents.

(1) McMorris T. C. Discovery and development of sesquiterpenoid-derived hydroxymethylacylfulvene: a new anticancer drug. *Bioorg. Med. Chem.* **1999**, *7*, 881−6.

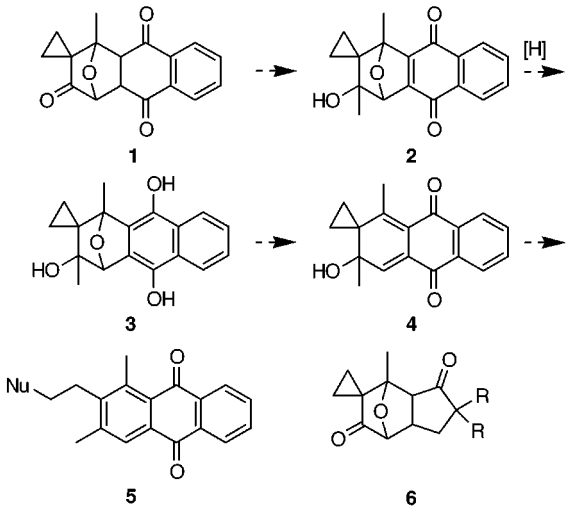
(2) Moore, H. W.; Karlsson, J. O. Naturally occurring quinones as bioreductive alkylating agents. *Recent Adv. Phytochem.* **1986**, *20*, 263−85. Moore, H. W.; Czerniak, R.; Hamdan, A. Natural quinones as quinonemethide precursors − ideas in rational drug design. *Drugs Exp. Clin. Res.* **1986**, *12*, 475−94. Moore, H. W.; Czerniak, R. Naturally occurring quinones as potential bioreductive alkylating agents. *Med. Res. Rev.* **1981**, *1*, 249−80.

(3) Danishefsky, S. Electrophilic cyclopropanes in organic synthesis. *Acc. Chem. Res.* **1979**, *12*, 66−72.

(4) Kinder, F. R.; Bair, K. W. Total synthesis of (±)-illudin M. *J. Org. Chem.* **1994**, *59*, 6965−7.

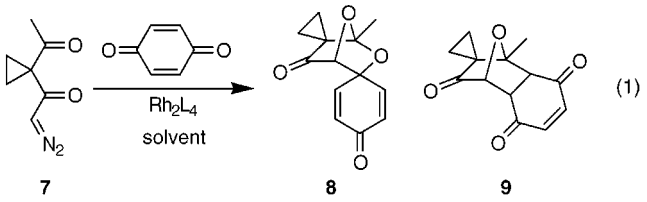
10.1021/ol991300s CCC: $19.00
Published on Web 01/11/2000

Scheme 1



seemed readily adaptable to the preparation of compounds **1** and holds potential for application of library synthesis methods. Adding further interest to this plan was the absence of earlier reports on the dipolar cycloaddition of carbonyl ylides with quinones. Only one report of the addition of azomethine ylides to quinones has been made.[6]

The prototype reaction used to develop this methodology is shown in eq 1. Initial experiments used dirhodium acetate



(1)

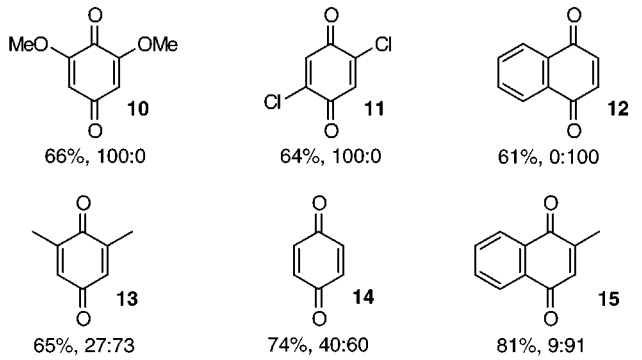
as catalyst (1 mol %) in CH_2Cl_2 at room temperature (0.05−0.2 M, 6−36 h) and produced a 1:1.7 mixture of **8** and **9** in 41% yield after chromatography. While it was initially surprising that dipolar cycloaddition of the carbonyl ylide to the *p*-quinone carbonyl was competitive with cycloaddition to the electron deficient alkene, in fact, parallel observations had earlier been made in the biased *o*-quinone system.[7] The exo stereochemistry was assigned to **9** on the basis of a lack of coupling between the bridgehead hydrogens. Varying ratios of **8** and **9** observed over different reaction times in different experiments suggested that reversion of the cycloadduct(s) might be occurring, allowing equilibration. To test this, **8** was submitted to reaction conditions with rhodium catalysts and to thermolysis, but no conversion to **9** was observed. Preliminary studies of solvent effects using the more soluble but less selective dirhodium octanoate (1:1 in CH_2Cl_2) showed that the production of **9** at the expense of **8** is enhanced in benzene.

Over 20 dirhodium catalysts for reaction 1 were examined in benzene using an internal NMR standard, leading to **8** and **9** in combined yields of 42−99% and product ratios ranging from 57:43 to 38:62 (see Supporting Information). The optimum catalyst from this survey was identified as dirhodium tetrakis(*m*-chlorobenzoate), which provides a 40:60 mixture of **8** and **9** in essentially quantitative yield. The variation of outcome with catalyst supports the idea that the role of the metal complex does not end with the generation of the carbonyl ylide. Rather, the metal must still be at least partially associated with the ylide as the cycloaddition occurs. A few additional metal catalysts for this reaction were examined. $Cu(acac)_2$ provided an enhanced product ratio of 35:65, at the expense of a reduction in yield (62%).

Over 30 solvents for reaction 1 were examined using rhodium octanoate as catalyst, leading to **8** and **9** in combined yields of 47−97% and product ratios from 77:23 to 41:59 (see Supporting Information). The best ratio favoring **9** was obtained in acetonitrile, while the best overall combination of yield and product ratio was obtained in *o*-xylene, which provides a 48:52 mixture of **8** and **9** in 92% yield. Several of these solvents, such as acetonitrile,[8] are good axial ligands for rhodium, can inhibit diazo decomposition, and tend to be among the more **9**-selective.

The so-far optimum combination of *o*-xylene and dirhodium tetrakis(*m*-chlorobenzoate) was then used to examine reaction scope with several symmetrical quinones (Table 1).

Table 1. Yield and Selectivity for Dipolar Cycloaddition of **7** to Quinones. Ratio of Type **8** Cycloadducts to Type **9** Cycloadducts



Chromatographed, isolated total yields and the ratio of the carbonyl adduct to the olefin adduct are given below each reactant. In general, the exo stereochemistry was observed for all of the olefin adducts. For quinones **13** and **15**,

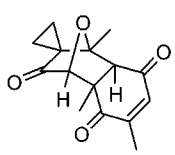
(5) Padwa, A.; Sandanayake, V. P.; Curtis, E. A. Synthetic studies toward illudins and ptaquilosin. A highly convergent approach via the dipolar cycloaddition of carbonyl ylides. *J. Am. Chem. Soc.* **1994**, *116*, 2667−8.

(6) Padwa, A.; Dean, D. C.; Osterhout, M. H.; Precedo, L.; Semones, M. A. Synthesis of functionalized azomethine ylides via the Rh(II)-catalyzed cyclization of α-diazocarbonyls onto imino π-bonds. *J. Org. Chem.* **1994**, *59*, 5347−5357.

(7) Nair, V.; Sheela, K. C.; Radhakrishnan, K. V.; Rath, N. P. Novel 1,3-dipolar cycloaddition reaction of carbonyl ylide with *o*-quinones. *Tetrahedron Lett.* **1998**, *39*, 5627−5630.

(8) Pirrung M. C.; Morehead, A. T., Jr. Saturation kinetics in dirhodium(II) carboxylate-catalyzed decompositions of diazocompounds. *J. Am. Chem. Soc.* **1996**, *118*, 8162−3.

regiochemical issues arise. For each case, only a single isomer was obtained whose structure was assigned as **16** and **17**, respectively, on the basis of NOEs between the endo angular methyl group and the bridgehead hydrogens.



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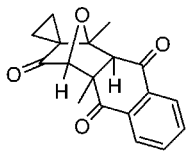

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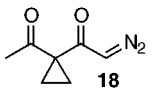
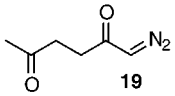
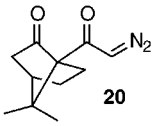
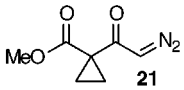
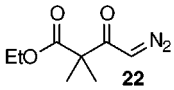
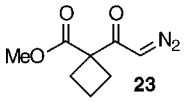
The scope of the reaction with respect to the diazo compound was investigated under standard reaction conditions with dirhodium tetrakis(*m*-chlorobenzoate), benzoquinone, and several known and novel carbonyl-substituted diazoketones (Table 2) in *o*-xylene. Chromatographed, isolated total yields and the ratio of the carbonyl adduct to the olefin adduct are given below each reactant. Reactions with **21**−**23** require brief (3 h) heating to 80 °C.

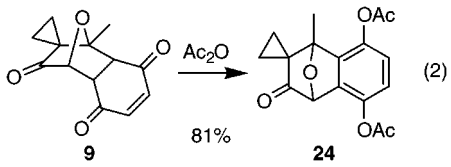
Table 2. Yield and Selectivity for Dipolar Cycloaddition of Diazoketones to Benzoquinone. Ratio of Type **8** Cycloadducts to Type **9** Cycloadducts

 **18**	 **19**	 **20**
74%, 40:60	48%, 100:0	58%, 76:24
 **21**	 **22**	 **23**
76%, 100:0	74%, 100:0	76%, 100:0

isolated total yields and the ratio of the carbonyl adduct to the olefin adduct are given below each reactant. Reactions with **21**−**23** require brief (3 h) heating to 80 °C.

As either acetals or ortho esters, carbonyl adducts such as **8** are acid-labile. Isolation of the products of cycloaddition with **21**−**23** is best accomplished by direct crystallization, as they are not stable to chromatography. Isolation of the pure olefin adducts **9** from reaction mixtures can be significantly simplified by stirring with Dowex 50-H^+ in methanol, which converts **8** to a much more polar substance, presumably quinol, readily removed by silica gel filtration.

The conversion of the cycloaddition products to the desired target systems was investigated (eq 2). Treatment with acetic anhydride efficiently aromatizes **9** (81%).



9 81% **24** (2)

The dipolar cycloaddition reaction of rhodium-generated carbonyl ylides with *p*-quinones provides ready access to complex functionalized carbon networks in a single step from readily available starting materials. Recently discovered rhodium catalysts that produce high enantiomeric excesses in the dipolar cycloaddition of carbonyl ylides[9] will be attractive to investigate for this reaction, as it desymmetrizes two highly symmetric educts and results in a large increase in molecular complexity. It should thus have value in the rapid assembly of families of natural product-like structures.

Acknowledgment. Financial support was provided by NIH GM-AI42151. We thank Hao Liu for providing samples of several rhodium catalysts. The assistance of L. LaBean in administrative support of this work is greatly appreciated.

Supporting Information Available: Tables of solvent and catalyst effects on reaction 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. Efficient Rh(II) binaphthol phosphate catalysts for enantioselective intramolecular tandem carbonyl ylide formation-cycloaddition of α-diazo-*β*-keto esters. *J. Chem. Soc., Chem. Commun*. **1999**, 2185−6. Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-i. Enantiocontrol in tandem carbonyl ylide formation and intermolecular 1,3-dipolar cycloaddition of α-diazo ketones mediated by chiral dirhodium(II) carboxylate catalyst. *J. Am. Chem. Soc.* **1999**, *121*, 1417−8.