ORGANIC LETTERS

2002
Vol. 4, No. 25
4411−4414

Ketene Dithioacetals in the Aza-Diels–Alder Reaction with *N*-Arylimines: A Versatile Approach to Tetrahydroquinolines, 2,3-Dihydro-4-quinolones, and 4-Quinolones

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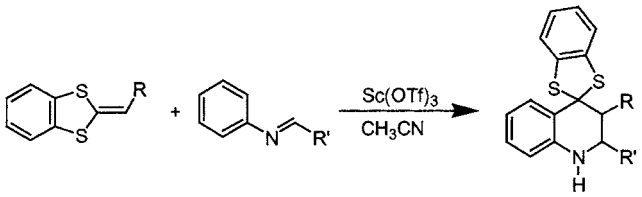
Received September 4, 2002

ABSTRACT



The first successful use of ketene dithioacetals as dienophiles in the aza-Diels–Alder reaction with *N*-arylimines is described. Among the ketene dithioacetals tested, 1,4-benzodithiafulvenes are most effective in assembling the tetrahydroquinoline core. Subsequent chemical manipulations provide a concise and divergent approach to the synthesis of 2,3-tetrahydroquinolines, 2,3-dihydro-4-quinolones, and 4-quinolones.

The acid-promoted aza-Diels−Alder reaction between *N*-arylimines and electron-rich alkenes has been a topic of continuing interest for forty years.[1,2] Due to its efficiency, the ready availability of starting materials, and relatively mild reaction conditions, this reaction constitutes the most attractive strategy for the synthesis of 1,2,3,4-tetrahydroquinolines.[1,4] The use of a highly convergent three-component reaction among aldehydes, anilines, and alkenes in which the heterocycle is assembled in one pot is of particular note[2b−f] and especially valuable for its potential application in combinatorial synthesis.[2e]

The synthetic scope of this reaction is limited by two factors: the generally low reactivity of imines and alkenes and the requirement of electron-rich alkene dienophiles that direct the electron-donating group toward the 4-position of the tetrahydroquinoline ring.[2,3,5] Because of this, the introduction of substituents at the 3-position has proven to be

(1) For reviews on hetero Diels−Alder reactions, see: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (b) Weinreb, S. M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergmon: Oxford, 1991; Vol. 5, p 401.

(2) For leading references for aza-Diels−Alder reaction between alkenes and *N*-arylimines or iminium salts, see: (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656−670. (b) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855−5858. (c) Mellor, J. M.; Merriman, G. D. *Tetrahedron* **1995**, *51*, 6115−6132 and references therein. (d) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423−424. (e) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977−8978. (f) Narasaka, K.; Shibata, T. *Heterocycles* **1993**, *35* (2), 1039−1053. (g) Crousse, B.; Begue, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009−5013. (h) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973−1976.

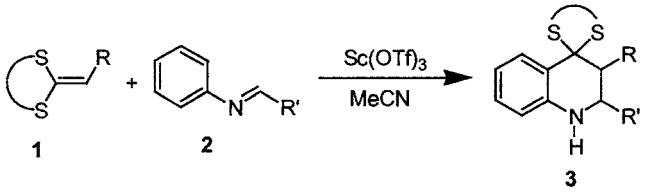
(3) For a review on the synthesis and applications of 1,2,3,4-tetrahydroquinolines, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070 and references therein.

(4) For the most recent developments of tetrahydroquinoline synthesis *via* other strategies, see: (a) Larock, R. C.; Yang, H.; Pace, P. *Tetrahedron Lett.* **1998**, *39*, 1885−1888. (b) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595−3607. (c) Bunce, R. A.; Herron, D. M.; Johnson, L. B.; Kotturi, S. *J. Org. Chem.* **2001**, *66*, 2822−2827.

10.1021/ol020179d CCC: $22.00
Published on Web 11/20/2002

difficult. Moreover, an approach to access 2,3-disubstituted tetrahydroquinolines *via* this highly efficient aza-Diels–Alder reaction has yet to be established. We sought to address this problem by employing cyclic[6] ketene dithioacetals[7] **1** as dienophiles (Scheme 1). To our knowledge, ketene

Scheme 1. Cycloaddition Reactions of Cyclic Ketene Dithioacetals **1a–c** with *N*-Phenylimine **2a**



dithioacetals have not been reported in Diels–Alder reactions with 2-azadienes despite their synthetic potential.[7a,8] The electron-donating effect of the mercapto groups of the ketene dithioacetal should not only provide a sufficiently reactive dienophile for the construction of the tetrahydroquinoline ring system but also dictate placement of the R group at the 3-position of the heterocyclic core. The relatively straightforward preparation of ketene dithioacetals[7] from aldehydes would also provide a source of variation of the R group and a means to conveniently modify the 3-position of tetrahydroquinolines. Subsequent manipulations of the dithioacetals **3** should provide access not only to 2,3-disubstituted tetrahydroquinolines **4** that are inaccessible through conventional [4 + 2] cycloaddition strategies but also to 2,3-dihydro-4-quinolones **5** and 4-quinolones **6** (Scheme 2, see below), compounds of extensive interest for their biological activities.[3,9]

(5) For example, with styrene as a dienophile in reactions with *N*-arylimines, the phenyl group would be introduced exclusively at the 4-position,[2c,3] rather than at the 3-position. The ketene dithioacetal approach described in this paper successfully places the phenyl group at the 3-position as demonstrated on product **4a**, providing a formally "reversed" substitution pattern.

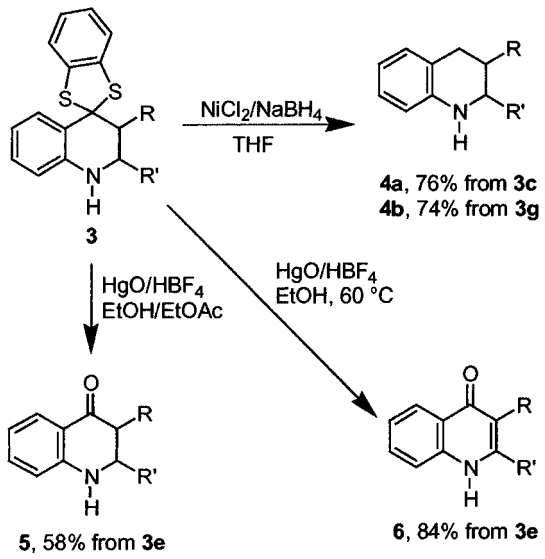
(6) (a) Using acyclic ketene dithioacetals would expose the tetrahydroquinoline thus formed to β-hydrogen elimination of the mercapto group (activated by the benzene ring and the nitrogen atom) from the 4-position, similar to using vinyl ethers as dienophiles.[2a] In addition, cyclic ketene dithioacetals such as **1a–c** are more sterically confined and expected to be more reactive. (b) There has been a report[2f] on an unsuccessful attempt to react an acyclic ketene dithioacetal with an *N*-arylimine in the presence of $BF_3{\cdot}Et_2O$.

(7) (a) For a review on the preparations and synthetic applications of ketene dithioacetals, see: Kolb, M. *Synthesis* **1990**, 171–190. (b) Barbero, M.; Cadamuro, S.; Ceruti, M.; Degani, I.; Fochi, R.; Regondi, V. *Gazz. Chim. Ital.* **1987**, *117*, 227–235. (c) Bellesia, F.; Boni, M.; Ghelfi, F.; Pagnoni, U. M. *J. Heterocycl. Chem.* **1994**, *31*, 1721–1723.

(8) There have been reports on ketene dithioacetals in Diels–Alder reactions with other hetero dienes. See, for example: (a) Denmark, S. E.; Sternberg, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 8277–8279 and references therein. (b) Tietze, L. F.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1998**, 1629–1637.

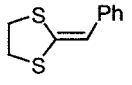
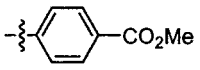
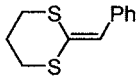
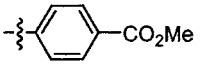
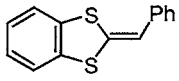
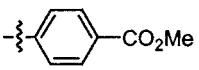
(9) For applications of 4-quinolones, see: (a) Pesci, E. C.; Milbank, J. B. J.; Pearson, J. P.; McKnight, S.; Kende, A. S.; Greenberg, E. P.; Iglewski, B. H. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11229–11234. (b) Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 3932–3936. (c) Cecchetti, V.; Parolin, C.; Moro, S.; Pecere, T.; Filipponi, E.; Calistri, A.; Tabarrini, O.; Gatto, B.; Palumbo, M.; Fravolini, A.; Palu, G. *J. Med. Chem.* **2000**, *43*, 3799–3802. (d) Wang, J.-P.; Raung, S.-L.; Huang, L.-J.; Kuo, S.-C. *Biochem. Pharmacol.* **1998**, *56*, 1505–1514. (e) Ruiz, M.; Ortiz, R.; Perello, L.; LaTorre, F.; Server-Carrio, F. *J. Inorg. Biochem.* **1997**, *65*, 87–96.

Scheme 2. Conversion of Products **3** to Tetrahydroquinolines **4a**,**b**, 2,3-Dihydro-4-quinolone **5**, and 4-Quinolone **6**



The choice of an adequate ketene dithioacetal for this conversion is critical.[6b] We first compared the reactivity of three cyclic ketene dithioacetals shown in Table 1. Reaction

Table 1. Cycloaddition Reactions of Cyclic Ketene Dithioacetals **1a–c** with *N*-Phenylimine **2a** (Scheme 1)

entry	ketene dithioacetal **1**	R'	product **3** yield (%)
1	 **1a**	 **2a**	**3a** 38
2	 **1b**	 **2a**	**3b** 35
3	 **1c**	 **2a**	**3c** 81

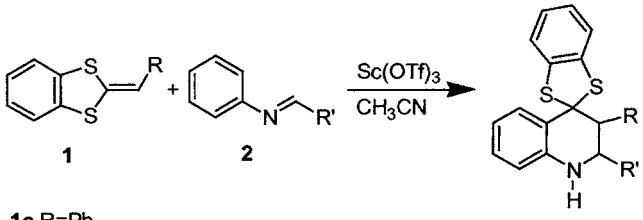
of 1,3-dithiolane **1a** and 1,3-dithiane **1b** with imine **2a** in acetonitrile in the presence of scandium triflate[2d] at 64 °C for 3 h gave the corresponding cycloaddition products **3a** and **3b** in 38 and 35% yields, respectively. In contrast, 1,4-benzodithiafulvene **1c** gave product **3c** in a yield of 81% under the same conditions. The increase in yield can be rationalized by the extra electron-donating effect of the benzo system and the aromatic nature of the corresponding carbocation (Figure 1),[10] no matter whether the reaction mechanism is concerted or stepwise.[11]

The next study focused on the formation of the tetrahydroquinolines **3** from a series of substituted 1,4-benzo-

Figure 1. Resonance structures of 1,4-benzodithiafulvenes.

dithiafulvenes **1c**−**f** and imines **2a**−**d** as described in Table 2. The basic protocol for the transformation involved the

Table 2. Cycloaddition Reactions of 1,4-Benzodithiafulvenes **1c**−**f** with *N*-Phenylimines **2a**−**d**



1c R=Ph
1d R=CH_2Ph
1e R=$CH(CH_3)_2$
1f R=H

2a R'=*p*-$(C_6H_4)CO_2Me$
2b R'=$CH_2CH(CH_3)_2$
2c R'=Ph
2d R'=$CH(CH_3)_2$

3c R=Ph, R'=*p*-$(C_6H_4)CO_2Me$;
3d R=Ph, R'=$CH_2CH(CH_3)_2$;
3e R=CH_2Ph, R'=Ph;
3f R=CH_2Ph, R'=$CH_2CH(CH_3)_2$;
3g R=$CH(CH_3)_2$, R'=*p*-$(C_6H_4)CO_2Me$;
3h R=H, R'=Ph;
3i R=H, R'=$CH(CH_3)_2$.

product	protocol	yield	reaction time	anti/syn
3c	A	81%	180 min	23/1
3d	B	64%	60 min	2/1
3e	A	82%	75 min	28/1
3f	B	66%	60 min	1/1
3g	A	38%	240 min	100/0
3h	C	92%	15 min	
3i	D	64%	15 min	

reaction of 1,4-benzodithiafulvene with Schiff base in acetonitrile in the presence of scandium triflate at 64 °C (see protocol A in Supporting Information). Alternative protocols were developed where either the imine (protocol B) or 1,4-benzodithiafulvene (protocol C) could not be isolated. In these cases, the respective intermediate was generated *in situ*. For the 1,4-benzodithiafulvene **1f**, the reactivity of this reagent was such that the tetrahydroquinoline formation was performed at room temperature. A complementary protocol (protocol D) was also established for the *in situ* generation of both intermediates where neither reagent was stable. In this way, a highly convergent approach was realized that covered combinations of various substituents at both 2- and 3-positions.

The use of anhydrous solvent and the amount of scandium triflate were found to be crucial in order to achieve the yields that are summarized in Table 2. Scandium triflate was used in proportions of 1.2 equiv relative to imine **2** for the synthesis of tetrahydroquinolines from substituted 1,4-benzodithiafulvenes **1c**−**e**. For the highly reactive 1,4-benzodithiafulvene **1f**, 0.2 equiv of scandium triflate was used. The use of other Lewis acids such as boron trifluoride diethyl etherate and trifluoroacetic acid was unsuccessful in terms of effecting this transformation, which is consistent with previous observations.[2d]

As summarized in Table 2, the readily prepared 1,4-benzodithiafulvenes **1c**−**e**[7] were reacted with preformed or *in situ*-generated *N*-phenylimines **2a**−**d** to give the tetrahydroquinolines **3c**−**g** with combinations of aliphatic or aromatic substituents at both 2- and 3-positions. This methodology could also be applied to the synthesis of systems lacking the 3-substituent as exemplified by **3h** and **3i** by using the *in situ*-generated **1f**. From the results in Table 2, it appears that the *anti*/*syn* stereoselectivity depends on the steric demands of the two substituents R and R′. High preference for anti isomers[12] was observed for examples **3c**, **3e**, and **3g** where both R and R′ were relatively bulky, while there was little or no discrimination in relative stereochemistry for **3d** and **3f** for the less hindered *iso*-butyl group at the 2-position.

The true versatility of this method lies in the opportunity to chemically manipulate the dithioacetal moiety within the tetrahydroquinolines **3** (Scheme 2). Reduction of dithioacetals **3c** and **3g** with $NiCl_2/NaBH_4$[13] afforded the 2,3-disubstituted 1,2,3,4-tetrahydroquinolines **4a** and **4b**. These compounds have a substitution pattern that is formally opposite to those obtained if styrene or 3-methyl-1-butene were used as dienophiles in the cyclization.[5] Hydrolysis of the ketene dithioacetal group, as illustrated for example **3e**, occurred readily at room temperature with mercuric oxide in tetrafluoroboric acid ether solution[14] to yield the corresponding 2,3-dihydro-4-quinolone **5**. When the reaction was carried out at 60 °C overnight, the oxidized 4-quinolone **6** was isolated. The successful conversion of dithioacetal **3e** to either 2,3-dihydro-4-quinolone **5** or 4-quinolone **6** demonstrates a more concise and mild alternative to the existing methods of synthesis of these classes of compounds.[15,16]

In summary, we have successfully demonstrated the aza-Diels−Alder reaction between *N*-arylimines and ketene

(10) Soder, L.; Wizinger, R. *Helv. Chim. Acta*. **1959**, *42*, 1733−1737 and 1779−1785.

(11) For the mechanistic aspect of this type of reactions, see: (a) refs 1a (pp 258−260) and 2c,d,g. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem*. **1985**, *50*, 5678−5686. (c) Lucchini, V.; Prato, M.; Scorrano, G.; Stivanello, M.; Valle, G. *J. Chem. Soc*., *Perkin Trans. 2* **1992**, 259−266. (d) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195−1202. (e) Linkert, F.; Laschat, S.; Kotila, S.; Fox, T. *Tetrahedron* **1996**, *52*, 955−970.

(12) Structure assignments were based on NOE experiments and coupling constants.

(13) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem*. **1993**, *58*, 2407−2413.

(14) Degani, I.; Fochi, R.; Regondi, V. *Synthesis* **1981**, 51−53.

(15) For methods of 4-quinolone synthesis, see: (a) Reynolds, G.; Hauser, C. In *Organic Syntheses*; Wiley & Sons: New York, 1955; Collect. Vol. III., pp 593 and 374. (b) Heindel, N. D.; Kennewell, P. D.; Fish, V. B. *J. Heterocycl. Chem*. **1969**, *6*, 77−81 and references therein. (c) Potts, K. T.; Ehlinger, R.; Nichols, W. M. *J. Org. Chem*. **1975**, *40*, 2596−2600. (d) Chen, B.-C.; Huang, X.; Wang, J. *Synthesis* **1987**, 482−483.

(16) For methods of 2,3-dihydro-4-quinolone synthesis, see: (a) Elderfield, R. C.; Maggiolo, A. *J. Am. Chem. Soc*. **1949**, *78*, 1906−1910. (b) Kano, S.; Ebata, T.; Shibuya, S. *J. Chem. Soc*., *Perkin Trans. 1* **1980**, 2105−2111. (c) Ongania, K.; Hohenlohe-Oehringen, K. *Chem. Ber*. **1981**, *114*, 1203−1205. (d) Donnelly, J. A.; Farrell, D. F. *J. Org. Chem*. **1990**, *55*, 1757−1761. (e) Nieman, J. A.; Ennis, M. D. *J. Org. Chem*. **2001**, *66*, 2175−2177 and references therein.

dithioacetals. Construction of the tetrahydroquinoline core is most efficiently realized through the use of substituted 1,4-benzodithiafulvenes. Subsequent chemical manipulations provide a convenient and divergent approach to the synthesis of substituted tetrahydroquinolines, 4-quinolones and 2,3-dihydro-4-quinolones. To our knowledge, this represents the first synthetic methodology that allows access to 2,3-disubstituted tetrahydroquinolines *via* a highly efficient aza-Diels−Alder pathway.

Acknowledgment. We thank Catherine Jolivet for assistance with the NMR characterization of the compounds presented, Karla Savage and Robyn Rourick for assistance in obtaining High-Resolution Mass data, and Sabine Hadida-Ruah, Mark Suto, and Theodore Cohen for critical review of this manuscript.

Supporting Information Available: Experimental procedures and details of compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020179D