ORGANIC LETTERS

2002
Vol. 4, No. 23
4129−4131

Amino Acid-Based Dithiazines: Synthesis and Photofragmentation of Their Benzaldehyde Adducts

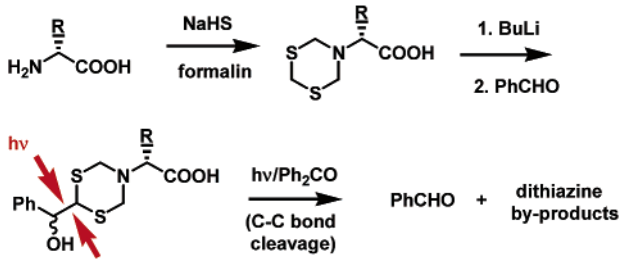
Alexei N. Kurchan and Andrei G. Kutateladze*

Department of Chemistry and Biochemistry, University of Denver, Denver, Colorado 80208-2436

akutatel@du.edu

Received September 10, 2002

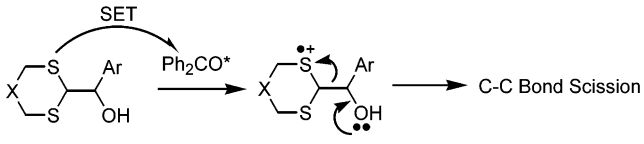
ABSTRACT



α-Amino acids and GABA are functionalized with dithiazine rings via reaction with sodium hydrosulfide in aqueous formaldehyde. The resulting dithiazines are lithiated at −78 °C and reacted with benzaldehyde furnishing amino acid-based 2,5-bis-substituted dithiazines. These adducts undergo externally sensitized photofragmentation with quantum efficiency comparable to that of the parent dithiane adducts, thus offering a novel approach to amino acid-based photolabile tethers.

We are developing a general strategy for assembly and photoinduced disassembly of modular photolabile molecular objects, designed for applications in chemical biology. At the core of this approach is the recently discovered photofragmentation in dithiane- or trithiane-carbonyl adducts, which is initiated by photoinduced electron transfer followed by mesolytic C−C bond scission in the generated cation-radical, Scheme 1.[1]

Scheme 1

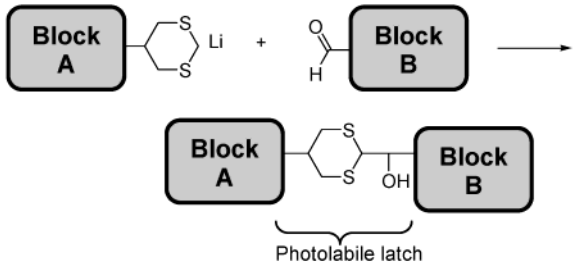


We use such adducts as photolabile "latches" that can hold together various molecular blocks and at the same time are capable of releasing them upon photoirradiation (Scheme 2).

This approach was utilized to link calixarenes,[2a,c] crown ethers,[2c,d] carbohydrates,[2c] hydrophobic tails and hydrophilic headgroups of photolabile amphiphiles,[2e] and even the blocks equipped with hydrogen bond-based elements of molecular recognition, for example ureas or aminopyridines.[2b]

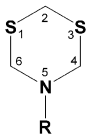
Successful implementation of this methodology requires a systematic search for photolabile tethers capable of photoinduced fragmentation and at the same time outfitted

Scheme 2



10.1021/ol0268790 CCC: $22.00
Published on Web 10/19/2002

with functional groups suitable for interconnecting the desired modules in a straightforward manner. In the course of these studies, we turned our attention to 1,3,5-dithiazines, a potentially interesting class of S,N-heterocycles.[3]



Our rationale is that the nitrogen atom at the 5-position of the dithiazine ring is perfectly suited for linking various functionalities and modules to the photolabile latch. It is known that dithiazines are readily deprotonated by butyllithium producing carbanions, which can add to carbonyl compounds[4] or react with other electrophiles.[5] Such deprotonation occurs faster than in dithianes, even when it is carried out at lower temperatures. The dithiazine ring also hydrolyzes under much milder conditions than the dithiane ring.[6] In most reported dithiazines, nitrogen is either free of substitution or carries a simple alkyl substituent, although chiral dithiazines based on 1-phenylethylamine were also synthesized.[7]

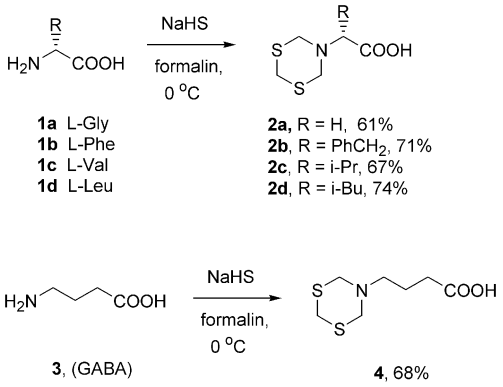
In view of our particular interest in biological systems, we chose amino acids as the dithiazine building blocks. Our long-term objective is in developing artificial photolabile amino acids that can be incorporated into a polypeptide/protein chain with negligible structural perturbation. The carboxylic group can also be utilized for attaching a variety of other potentially useful "blocks" to the photolabile latch.

As far as biocompatibility is concerned, dithiazines appear to be quite benign compounds. They have been studied and used in food chemistry, and there is a detailed review on their remarkable organoleptic properties.[8]

In this communication, we report on (i) synthesis of N-carboxyalkyl-substituted 3,4-dihydro-1,3,5-dithiazines based on α-amino acids and GABA (γ-aminobutyric acid), (ii) addition of lithiated dithiazines to benzaldehyde, and (iii) externally sensitized photofragmentation of the adducts.

Amino Acid-Based Dithiazines. Dithiazines **2a**−**d** and **4** were obtained in good yield by treating basic aqueous solutions of (L)-amino acids **1a**−**d** or GABA (**3**) with aqueous formaldehyde and sodium hydrosulfide, Scheme 3, according to described procedures.[9]

Scheme 3

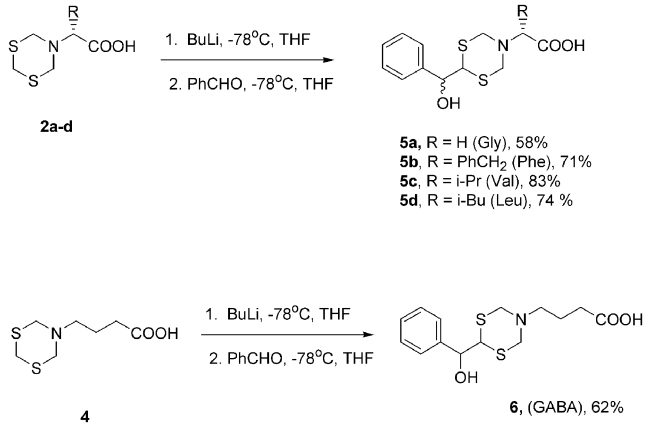


Most of the synthesized dithiazines are stable white crystalline solids except **2b**, the phenylalanine-based heterocycle, which is a viscous oil. Interestingly, the dithiazine functionality can itself be considered an N-protecting group for amino acids due to the fact that it can be hydrolyzed under relatively mild conditions, for example, $HgCl_2$/HgO in wet dichloromethane.[6]

Benzaldehyde Adducts. The dithiazinyl addition to a simple aldehyde, benzaldehyde, was used as a model for the "assembly" of more complex photolabile molecular latches. Butyllithium added in excess at −78 °C deprotonates **2a**−**d** and **4** in anhydrous THF within 1−2 h, whereas parent dithianes require much higher temperatures (−20 °C) for efficient deprotonation with BuLi.[10] The observed acceleration is probably due to both the electronic and chelating[6] effect of nitrogen.

The generated dithiazine anions were reacted with benzaldehyde at −78 °C to furnish 2-(α-hydroxybenzyl)-dithiazines **5a**−**d** and **6** in moderate to good yields,[11] Scheme 4.

Scheme 4



(1) (a) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924. (b) Vath, P.; Falvey, D. E.; Barnhurst, L. A.; Kutateladze, A. G. *J. Org. Chem.* **2001**, *66*, 2886.

(2) (a) Wan, Y.; Mitkin, O.; Barnhurst, L.; Kurchan, A.; Kutateladze, A. *Org. Lett.* **2000**, *2*, 3817. (b) Mitkin, O. D.; Kurchan, A. N.; Wan, Y.; Schiwal, B. F.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 1841. (c) Mitkin, O.; Wan, Y.; Kurchan, A.; Kutateladze, A. *Synthesis* **2001**, 1133. (d) Barnhurst, L. A.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 2633. (e) Wan, Y.; Angleson, J. K.; Kutateladze, A. G. *J. Am. Chem. Soc.* **2002**, *124*, 5610.

(3) First synthesized: Braithwaite, E. R.; Graymore, J. *J. Chem. Soc.* **1953**, 143.

(4) (a) Bauermeister, H.; Riechers, H.; Schomberg, D.; Washausen, P.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 191. (b) Redlich, H.; Lenfers, J. B. *Liebigs Ann. Chem.* **1988**, 597. (c) Flores-Parra, A.; Khuong-Huu, F. *Tetrahedron* **1986**, *42*, 5925. (d) Paulsen, H.; Mielke, B.; Von Deyn, W. *Liebigs Ann. Chem.* **1987**, 439 (e) Brown, C. A.; Chapa, O.; Yamaichi, A. *Heterocycles* **1982**, *18*, 187.

(5) (a) Kumar, A.; Coe, P. L.; Jones, A. S.; Walker, R. T.; Balzarini, J.; De Clercq, Eric. *J. Med. Chem.* **1990**, *33*, 2368. (b) Juaristi, E.; Gonzalez, E. A.; Pinto, B. M.; Johnston, B. D.; Nagelkerke, R. *J. Am. Chem. Soc.* **1989**, *111*, 6745.

(6) Balanson, R. D.; Kobal, V. M.; Schumaker, R. R. *J. Org. Chem.* **1977**, *42*, 393.

(7) Cadenas-Pliego, G.; de Jesus Rosales-Hoz, M.; Contreras, R.; Flores-Parra, A. *Tetrahedron*: *Asymmetry* **1994**, *5*, 633.

(8) Werkhoff, P.; Guentert, M.; Hopp, R. *Food Rev. Int.* **1992**, *8*, 391.

Chiral dithiazines **2b**−**d** (based on α-amino acids) were expected to produce diastereomeric adducts **5b**−**d**. Given the considerable spatial separation of the two stereogenic centers, which are five bonds apart, we did not expect the diastereomers to exhibit large differences in their NMR spectra. In fact, it was only adduct **5b** (phenylalanine-based dithiazine) that clearly showed an approximately 0.006 ppm difference in chemical shifts of the benzylic Ph−C*H*−OH protons. Both adducts **5c** (valine-based) and **5d** (leucine-based) have this doublet broadened but not resolved into two doublets. Presented in Figure 1 is the expansion of the doublets of these benzylic protons in **5b** and **5c** for comparison.

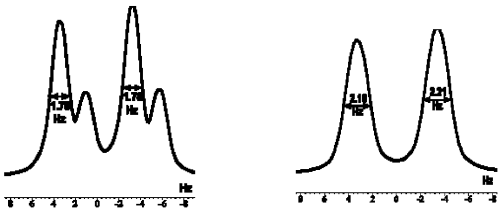


Figure 1. Expanded portion of ^{1}H NMR spectra of **5b** and **5c** showing resonances of benzylic (Ph−CH−OH) protons.

The ratio of diastereomers **5b** determined by NMR is approximately 2:1. The line width derived from the left spectrum is about 1.8 Hz. We suggest that the 0.4 Hz broadening in **5c** is due to the presence of the second diastereomer.

(9) **General Procedure.** Amino acid (20 mmol) was dissolved upon stirring in 50 mL of 0.4 M aqueous KOH. The solution was cooled to 0 °C, and 6.3 mL of 38% formalin was added dropwise. The resulting solution was stirred at 0 °C for 1.5 h, and then 25 mL of 2 M aqueous NaHS was added dropwise. The reaction mixture was stirred for an additional 2 h at 0 °C and then allowed to warm overnight. Workup included addition of 1 mL of concentrated HCl and extraction with 20 mL of $CHCl_3$. The first organic extract was discarded, and the aqueous layer was further acidified to pH = 6 by adding more concentrated HCl. The water phase was extracted again with chloroform (3 × 40 mL); organic layers were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Resulting products were purified by recrystallization or flash chromatography (for further details and spectra, see Supporting Information; this procedure is a modification of the N-*methyl*dithiazine synthesis described in ref 5b).

(10) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(11) **General Procedure.** To a solution of dithiazine (2 mmol) in 25 mL of anhydrous THF at −78 °C was added 3.1 mL of 1.6 M BuLi in hexane (5 mmol) under nitrogen. The reaction mixture was stirred for 2 h at −78 °C, and a solution of benzaldehyde (3 mmol) in 10 mL of anhydrous THF was added dropwise. The resulting solution was stirred at −78 °C for 1 h and then allowed to warm to room temperature. The reaction mixture was washed with a solution prepared from 30 mL of saturated ammonium chloride and 10 mL of 3% HCl. The aqueous layer was extracted twice with 20 mL of ethyl acetate. The organic extracts were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by flash chromatography using chloroform as an eluent. (For further details and spectra, see Supporting Information.)

Photoinduced Fragmentation. Synthesized adducts **5** and **6** were then irradiated in acetonitrile with a medium-pressure mercury lamp using a Pyrex filter (∼300 nm cutoff) in the presence of benzophenone. The photoinduced C−C bond cleavage was followed by proton NMR monitoring of the release of benzaldehyde. It is not possible to follow the release of the dithiazine fragment due to its degradation in secondary photoprocesses in the presence of benzophenone. In all the cases studied, the cleavage occurred with an efficiency similar to that of the parent di- or trithiane-based system.

As a representative example, the quantum yield of photocleavage in **6** was determined in a carousel Rayonet-type photoreactor using the standard benzophenone-benzhydrol actinometer system at conversions below 10−15% and found to be 0.078. This value is similar to the quantum efficiency of the cleavage of benzaldehyde-trithiane adduct (0.069) and slightly smaller than that of the benzaldehyde-dithiane adduct (0.119), Figure 2.[2b]

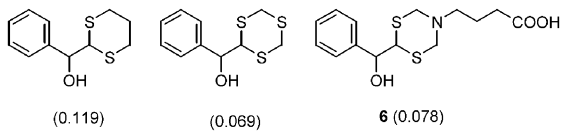


Figure 2. Quantum efficiencies of the photoinduced cleavage of benzaldehyde adducts of dithiane, trithiane, and dithiazine **4** (adduct **6**), sensitized by benzophenone.

In conclusion: we synthesized novel amino acid-based dithiazines that can potentially be utilized as linkers in photolabile molecular systems. Specifically, we have shown that carboxylate functionality does not interfere with dithiazines' deprotonation by butyllithium and their addition to benzaldehyde. Externally sensitized irradiation of the benzaldehyde adducts triggers a photofragmentation reaction, similar to that of the parent tri- and dithiane-aldehyde adducts. Benzaldehyde adducts **5** and **6** represent a model system designed to prove the concept. Work is in progress in our laboratories to synthesize photolabile tethers via addition of lithiated dithiazines **2** and **4** to aldimines or substituted aldehydes possessing auxiliary functionalities suitable for anchoring useful molecular blocks.

Acknowledgment. Support of this research by the National Science Foundation (Career Award CHE-9876389) is gratefully acknowledged.

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

OL0268790