Pergamon

Tetrahedron Letters 42 (2001) 5755–5757

TETRAHEDRON LETTERS

Cycloaddition reactions of thiazolidine derivatives. An approach to the synthesis of new functionalized heterocyclic systems

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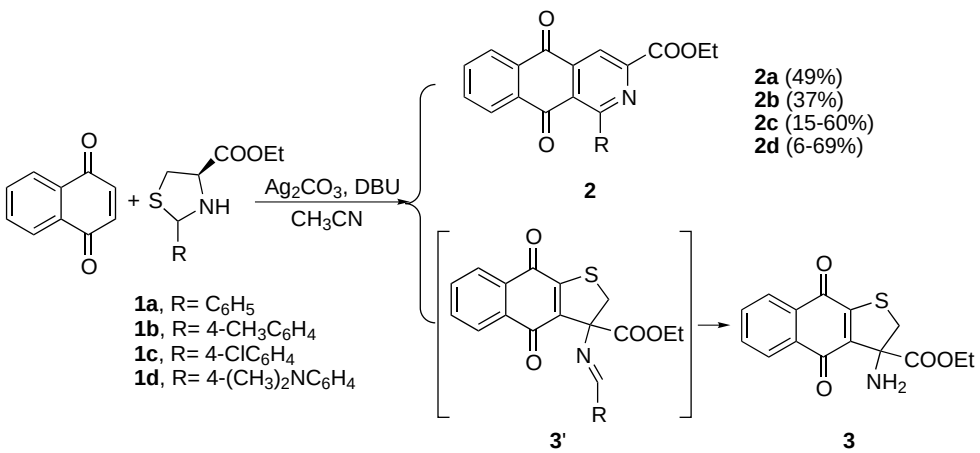
Received 12 March 2001; accepted 8 June 2001

Abstract—A one-pot procedure for the synthesis of two functionalized tricyclic systems having structures of benzo[*g*]isoquinoline-5,10-dione and dihydrothieno[2,3-*b*]naphto-4,9-dione (DTNQ) is described. These new series were synthesized from cycloaddition reactions between naphthoquinone and arylthiazolidine derivatives, the latter acting, respectively, as highly reactive *N*-arylidenedehydroalanine ethyl esters (2-AD) or as amino ester nucleophilic species.

Quinone-containing drugs such as adriamycin, daunorubicin, and mitoxantrone, have been established as one of the most effective classes of antitumor agents in clinical use today, with broad application against a number of malignant diseases.[1] However, some severe drawbacks in their use are the risk of dose-related cardiotoxicity, and development of resistance toward these compounds.[2,3] The therapeutic potential for modified aromatic quinones with improved pharmacokinetic properties, potency or spectrum, and lower side effects, prompted us to start a synthetic program devoted to explore new quinone derivatives.

Our approach was based on the known ability of quinone systems towards cycloaddition and nucleophilic addition reactions. In 1979, Ohler and Schmidt reported[4] the synthetic potential of thiazolidine derivatives as precursors of highly reactive *N*-arylidenedehydroalanine ethyl esters (2-AD) and also, as masked amino ester nucleophilic species. In the literature, the addition of nucleophiles like amino acid esters[5] as well as Diels–Alder reactions of the appropriate 1-aza-[6] or 2-azadienes supporting strongly electron-donating groups[7–9] to electron deficient quinones have been documented. Surprisingly, the cycloaddition reaction of



Scheme 1.

Keywords: quinones; thiazolidines; non-proteinogenic amino acids; cycloadditions.

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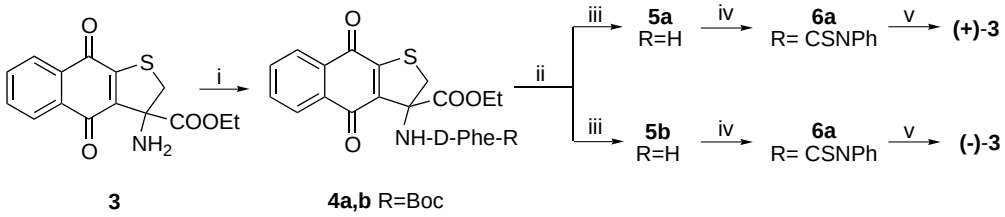
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01035-8



Scheme 2. *Reagents*: (i) Boc-D-Phe, HBTU, HoBT, DIEA, THF/DMF; (ii) HCl (g)/ether solution; (iii) chromatographic separation; (iv) phenylisothiocyanate, Cl_2CH_2, D; (v) TFA in Cl_2CH_2.

quinone systems with substituted 2-azadienes supporting one or more electron-withdrawing appended groups, remains unexplored.[10] On this basis, we now report an easy and versatile method directed towards the synthesis, in a one-step reaction, of the new benzo[*g*]isoquinoline-5,10-dione **2** and dihydrothieno[2,3-*b*]naphtho-4,9-dione (DTNQ, **3**) derivatives from naphthoquinone and arylthiazolidine derivatives.

Reaction of thiazolidines **1a**–**d**, which were prepared, in turn, from L-cystein ethyl ester and the corresponding aldehydes, with 1 equiv. of silver carbonate and an excess of naphthoquinone, under similar experimental conditions[11] from those reported by Gilchrist and coworkers,[10b] gave mixtures of the fully aromatized Diels–Alder cycloadducts **2a**–**c** and the DTNQ derivative **3** in different ratios and in 57–70% overall yield (Scheme 1). In the case of thiazolidines **1c**,**d**, the most stable intermediates **3′c**,**d**, can be detected by ^{1}H NMR or even isolated. Acid hydrolysis of these intermediates in 1N HCl solution gave DTNQ as the hydrochloride salt. It is interesting to note that when the reaction was carried out with the thiazolidines **1c**,**d**, under the conditions described by Ohler and Schmidt, i.e. using 3 equiv. of silver carbonate in the reaction mixture followed by addition of DBU 30 minutes later, the cycloadducts **2c** (60%) and **2d** (64%) were obtained as major products. The structures of all new compounds were elucidated from their analytical and spectroscopical data.[12] Furthermore, the structure of compound **3** was also confirmed through ^{1}H NMR analysis of the more stable intermediates **3′c**,**d**. Thus, these compounds showed all the signals corresponding to the two aromatic systems and the azamethylene protons as single signals at 8.20 or 8.30 ppm. The chemical shifts of 2-H and 2′-H protons of AB system are shifted 0.2–0.3 ppm to lower fields in relation to those of compound **3**.

As observed in the general reaction scheme, the new and unusual α-amino ester **3** was obtained as a racemic mixture of the (3*S*)- and (3*R*)-isomers, indicating that during the formation of this product, the configurational integrity of the C-4 thiazolidine ring is not preserved.[13] The mixture of two enantiomers was resolved following the Evans method for the resolution of racemic amines[14] (Scheme 2). Coupling of **3** with Boc-D-Phe by HBTU/HoBT method gave the derivative **4a**,**b** (63% yield) as 4:3 mixture of two diastereoisomers as determined by ^{1}H NMR and HPLC. After Boc deblocking and neutralization, preparative TLC of free amine **5a**,**b** with (90:10:1:1) CH_2Cl_2–MeOH–HAcO–H_2O yielded, isolated in decreasing order of R_f, the diastereoisomers **5a** and **5b**. Then, reaction of these compounds with benzylisothiocyanate gave the *N*-carbamoyl derivatives **6a** (80%) and **6b** (87%), respectively. Edman degradation of the higher R_f **6a** with trifluoroacetic acid led to enantiomer (+)**3** $[\alpha]_D^{25} = +21$ (*c* 1.2, MeOH) while the lower R_f diastereomer **6b** provided the enantiomer (**–**)**3** $[\alpha]_D^{25} = -19.9$ (*c* 1.5, MeOH). To date, unfortunately, the assignment of the absolute configuration of the stereogenic center has not been possible. Analytical and spectroscopic analysis of all intermediate compounds was accorded with the structure proposed.

In conclusion, the chemistry described here defines a versatile strategy for the synthesis of functionalized 1-aryl-3-ethoxycarbonylbenzo[*g*]isoquinoline-5,10-dione and 3-amino-3-ethoxy carbonyldihydrothieno[2,3-*b*]-naphtho-4,9-dione. The cycloaddition reaction used offers the possibility to prepare, in only a one-step reaction, two adducts having different chemical structures. Ours preliminary results showed that the selectivity of the reaction should be tuneable by selecting the reaction conditions. In addition, these chemotypes retain the planarity, spatial and electronic characteristics required for molecular recognition at the cellular level, which seem to determine the antineoplastic and antibacterial activities described for structurally related analogues.[15,16] The application of this method to the preparation of new quinone analogues and different chemical modification of the substituents in the amino position of DTNQ is in progress.

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11. General procedure: The thiazolidines **1a**–**d** (1–3 mmol) were dissolved in dry acetonitrile and the naphthoquinone (2 equiv.), silver carbonate (1 equiv. respect to thiazolidine) and DBU in acetonitrile (0.2 equiv. respect to thiazolidine) were added. After 12 h at room temperature, ether was added, the mixture was filtered and the solvents were evaporated. The residue of the reaction was dissolved in chloroform and treated with 1N HCl solution for 1 h. Then, chloroform and water were added, the organic phase was washed with 1N HCl, water and dried with Na_2SO_4. Removal of the solvent and flash chromatography of the residues, using $CHCl_3$ as eluant, yielded, in each case, the corresponding Diels–Alder adducts **2a**–**c**. In the other hand, the collected acid acqueous phases were neutralized with 10% $NaHCO_3$ solution and the free amine **3** was extracted with chloroform. Flash chromatography using a gradient of 0–30% ethyl ether in $CHCl_3$ gave the compound **3** as a orange oil: 11% from **1a**, 20% from **1b**, 45% from **1c**, and 63% from **1d**.
12. As an example, characterization data for **2c**: yellow crystalline solid, mp 217–219°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (s, 1H, 4-H); 8.34–8.32 and 8.19–8.17 (dd, 2H, 6-H and 9-H); 7.87–7.85 (m, 2H, 7-H and 8-H); 7.51–7.45 (dd, 4H, aryl); 4.55–4.51 (q, 2H, CH_2 ester); 1.48–1.45 (t, 3H, CH_3 ester). ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.1, 181.5 and 163.5 (C=O); 160.6 (1-C); 151.3 (3-C); 141.9 (10a-C); 138.1 (1′-C); 135.3 (4′-C); 135.2 (6-C); 134.4 (9-C); 133.9 and 132.1 (9a-C and 5a-C); 130.3 (2′ and 6′-C); 128.3 (3′ and 5′-C); 127.5 and 127.0 (7-C and 8-C); 126.7 (4a-C); 119.9 (4-C); 62.8 (*C*H$_2$ ester) and 14.2 (*C*H$_3$ ester). Anal. calcd for $C_{22}H_{14}ClNO_4$: C, 67.43; H, 3.57; N, 3.56; Cl, 9.07. Found: C, 67.60; H, 3.65; N, 3.82; Cl, 8.81.
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11–8.09 and 8.06–8.04 (dd, 2H, 8-H and 5-H); 7.76–7.69 (m, 2H, 6-H and 7-H); 4.31–4.27 (m, 2H, CH_2 ester); 3.85–3.82 (d, 1H, 2-H, $J_{2,2'}$ = 12.3 Hz); 3.29–3.26 (d, 1H, 2′-H); 1.28–1.25 (m, 3H, CH_3 ester). ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.5, 178.7 and 172.0 (C=O); 155.1 (9a-C); 141.6 (3a-C); 132.9 (6-C); 131.8 (7-C); 131.1 (8a-C and 4a-C); 125.1 (8-C and 5-C); 72.2 (3-C); 62.6 (*C*H$_2$ ester); 43.5 (2-C) and 13.9 (*C*H$_3$ ester). Anal. calcd for $C_{15}H_{13}NO_4S$: C, 59.04; H, 4.29; N, 4.62; S, 10.56. Found: C, 58.01; H, 4.60; N, 4.62; S, 10.21.
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