Indian Journal of Chemistry
Vol. 49B, January 2010, pp. 115-118

Note

Synthesis of 2-alkyl/arylalkyl/phenacylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-dione

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Received 3 December 2008; accepted (revised) 10 September 2009

2,3-Dichloronaphthoquinone is condensed with 5-(alkyl/arylalkyl/phenacylthio)-1,3,4-thiadiazol-2-amine in acetic acid to furnish a novel and hitherto unknown 2-alkyl/aralkyl/phenacylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-dione. The structure of the synthesized compound has been confirmed by converting it into the corresponding reductive acetate. The structures of newly prepared compounds have been confirmed by analytical and spectral data

Keywords: 2,3-Dichloronaphthoquinone, thiadiazole, reductive acetylation

The quinone moiety is involved in a wide variety of biochemical processes including electron transport and oxidative phosphorylation[1]. Various biological properties including enzyme inhibition, antibacterial, antifungal, and anticancer activities have been reported for quinones and quinone derivatives[2-9]. The antitumor activity of the quinone moiety has been thoroughly studied and it is known that they act as topoisomerase inhibitors *via* the DNA-intercalation[10-12] and the reduction of the quinone moiety by DT-diaphorase (quinone oxidoreductase)[13-15]. In continuation of the earlier work[16,17] on the naphthaquinones, in this communication is reported the synthesis of 2-substituted sulfanyl-1-thia-3,3*a*,10-triaza-pentaleno-[1,2-*b*]naphthalene-4,9-diones.

The required starting material 5-thiol-1,3,4-thiadiazole-2-amino was prepared by a known procedure[18] and treated with different alkyl, aralkyl and phenacyl halides in KOH solution to yield the corresponding thioethers **2** (Ref. 19).

A series of 2-alkyl/aralkyl/phenacylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-diones **3** have been prepared by the condensation of 2,3-dichloronaphthoquinone **1** with 5-(alkylthio)-1,3,4-thiadiazol-2-amines **2** in glacial acetic acid. They also revealed the presence of quinone moiety by the reduction and aerial oxidation test with Zn/AcOH. Compound **3b** on reductive acetylation gave the corresponding reductive acetate **4** (**Scheme I**).

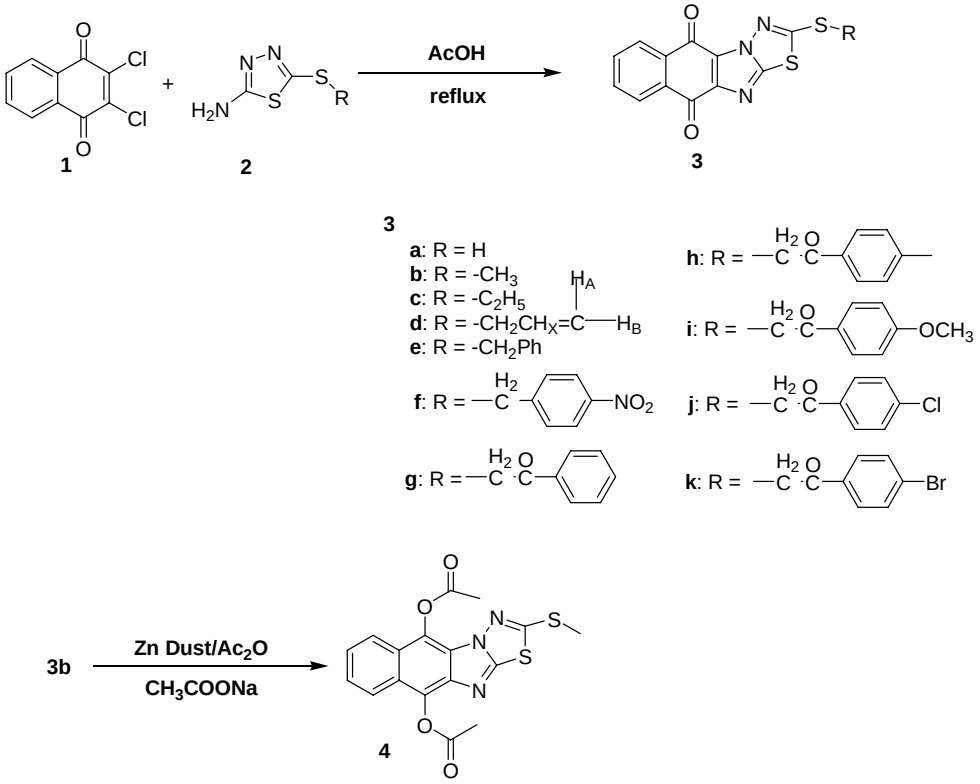
The IR spectrum of **3a** displayed bands in the region 1157 (-C=S), 1557 (C=C), 1587 (-C=N-), 1678 (-C=O), and 2840 cm^{-1} (SH weak). The ^1H NMR ($CDCl_3$) spectrum of **3a** displayed characteristic singlet at δ 1.25 assignable to SH group and two complex multiplets centered at δ 7.8 and 8.2 for the four aromatic protons. In mass spectrum of **3a,** the molecular ion was detected at *m/z* 287. The IR spectrum of **4** displayed a peak at 1771 (ester carbonyl), 1496(-C=N-) cm^{-1}. The ^1H NMR ($CDCl_3$) spectrum of **4** displayed singlet at δ 2.50 ($-CH_3$ of acetyl group) and the aromatic protons appeared as complex multiplets at δ 7.6 and 7.8. Compound **4** exhibited molecular ion peak at *m/z* 387 (M^+).

Experimental Section

All reagents and solvents were purchased from commercial sources and used as received unless otherwise stated. Melting points were determined in open capillaries with a Cintex melting point apparatus, Mumbai, India. Melting points are uncorrected and CHNS analysis was performed using Carlo Erba EA 1108 automatic elemental analyzer. The homogeneity of the compounds was checked using TLC plates (E. Merck, Mumbai, India), IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^1H NMR spectra were recorded on a Bruker WM-300 MHz spectrometer (δ, ppm) using TMS as internal standard. Mass spectra (EI-MS) were determined on Perkin-Elmer (SCIEX API-2000, ESI) at 12.5 eV.

General procedure for the synthesis of 2-mercapto-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-dione, 3

A mixture of 2,3-dichloronaphthalene-1,4-dione (2.27 g, 0.01 mole) and 5-amino-1,3,4-thiadiazole-2-thiol or its thio ether derivative (1.33 g, 0.01 mole) in acetic acid (20 mL) was refluxed for 8 hr. The reaction mixture was cooled to RT and poured over crushed ice. The solid thus separated was filtered, dried and purified by recrystallization from methanol.



Scheme I

Synthesis of acetic acid 9-acetoxy-2-methylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4-yl ester, 4

To compound **3b** (0.301 g, 1 mmole) in 10 mL of acetic anhydride, Zn dust (0.5 g), anhydrous powdered sodium acetate (0.1 g) were added and refluxed on a water bath for 6 hr. The reaction mixture was cooled to RT and poured into ice-cold water. The resulting solid was purified by recrystallization from ethanol.

2-Mercapto-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-dione, 3a. Brown solid, yield 92%, decomposes at 160-62°C. IR (KBr): 1157 (C=S) (Ref. 20), 1557 (C=C), 1587 (-C=N-), 1678 (-C=O), 2840 cm^{-1} (SH weak); ^1H NMR ($CDCl_3$): δ 1.23 (s, 1H, D_2O exchangable SH), 7.80 (m, 2H, Ar-H) and 8.20 (m, 2H, Ar-H); MS: *m/z* 287 $(MH)^{+\cdot}$. Anal. Calcd for $C_{12}H_5N_3O_2S_2$: C, 50.16; H, 1.75; N, 14.62; S, 22.32. Found: C, 50.19; H, 1.69; N, 14.65; S, 22.36%.

2-Methylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno-[1,2-*b*]naphthalene-4,9-dione, 3b. Light brown solid, yield 89%, decomposes at 145-47°C. IR (KBr): 1138 (C=S), 1560 (C=C), 1587(-C=N-), 1680 cm^{-1} (-C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 3.30 (s, 3H, CH_3), 7.90 (m, 2H, Ar-H) and 8.10 (m, 2H, Ar-H); MS: *m/z* 302 $(MH)^{+\cdot}$. Anal. Calcd for $C_{13}H_7N_3O_2S_2$: C, 51.81; H, 2.34; N, 13.94; S, 21.28. Found: C, 51.84; H, 2.31; N, 13.98; S, 21.32%.

2-Ethylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno-[1,2-*b*]naphthalene-4,9-dione, 3c. Light brown solid, yield 91%, decomposes at 142-44°C. IR (KBr): 1560 (C=C), 1586 (C=N), 1698 cm^{-1} (-C=O). Anal. Calcd for $C_{14}H_9N_3O_2S_2$: C, 53.32; H, 2.88; N, 13.32; S, 20.33. Found: C, 53.38; H, 2.90; N, 13.30; S, 20.36%.

2-Allylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno-[1,2-*b*]naphthalene-4,9-dione, 3d. Light brown solid, yield 89%, decomposes at 128-30°C. IR (KBr): 1559 (C=C), 1587 (C=N), 1678 cm^{-1} (-C=O); ^1H NMR ($CDCl_3$): δ 3.64 (d, *J*=7 Hz, 2H, S-CH_2), 5.20 (d, *J*=H_X, H_A, *J*=8 Hz, H_A of allyl group), 5.30 (d, *J*=H_X, H_B, *J*=16.8 Hz, H_B of allyl group), 5.98 (m, 1H, H_X), 7.80 (m, 2H, Ar-H) and 8.20 (m, 2H, Ar-H). Anal. Calcd for $C_{15}H_9N_3O_2S_2$: C, 55.03; H, 2.77; N, 12.84; S, 19.59. Found: C, 55.10; H, 2.80; N, 12.88; S, 19.62%.

2-Benzylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno-[1,2-*b*]naphthalene-4,9-dione, 3e. Light brown solid, yield 87%, decomposes at 120-22°C. IR (KBr): 1555 (C=C), 1588 (C=N), 1678 cm^{-1} (-C=O); ^1H NMR

($CDCl_3$): δ 4.50 (s, 2H, S-CH_2), 7.30 (m, 5H, Ar-H), 8.10 (m, 2H, Ar-H) and 8.40 (m, 2H, Ar-H). Anal. Calcd for $C_{19}H_{11}N_3O_2S_2$: C, 60.46; H, 2.94; N, 11.13; S, 16.99. Found: C, 60.49; H, 2.98; N, 11.17; S, 16.95%.

2-p-Nitrobenzylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-dione, 3f. Light brown solid, yield 92%, decomposes at 122-24°C. IR (KBr): 1138 (C=S), 1559 (C=C), 1588(-C=N-), 1690 cm^{-1} (-C=O); ^1H NMR ($CDCl_3$): δ 4.80 (s, 2H, S-CH_2), 7.2-7.40 (m, 4H, Ar-H), 8.10 (d, *J*=8.2 Hz, 2H, of *p*-nitrophenyl), 8.38 (d, *J*=8.2 Hz, 2H, of *p*-nitrophenyl). Anal. Calcd for $C_{19}H_{10}N_4O_4S_2$: C, 54.02; H, 2.39; N, 13.26; S, 15.18. Found: C, 54.10; H, 2.36; N, 13.30; S, 15.22%.

2-(2-Oxo-2-phenyl-ethylsulfanyl)-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-dione, 3g. Light brown solid, yield 95%, decomposes at 155-57°C. IR (KBr): 1678 (-C=O), 1456 cm^{-1} (-C=N-); ^1H NMR ($CDCl_3$): δ 4.70 (s, 2H, S-CH_2), 7.00-7.10 (m, 5H, Ar-H), 7.80 (m, 2H, Ar-H), 8.20 (m, 2H, Ar-H). Anal. Calcd for $C_{20}H_{11}N_3O_3S_2$: C, 59.25; H, 2.73; N, 10.36; S, 15.82. Found: C, 50.20; H, 2.76; N, 10.31; S, 15.85%.

2-(2-Oxo-2-*p*-tolyl-ethylsulfanyl)-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4,9-dione, 3h. Light brown solid, yield 92%, decomposes at 126-28°C. IR (KBr): 1590 (C=C), 1604 (C=N), 1680 cm^{-1} (-C=O); ^1H NMR ($CDCl_3$): δ 2.60 (s, 3H, Ph-CH_3), 4.60 (s, 2H, S-CH_2), 7.05-7.10 (m, 4H, Ar-H), 7.8 (d, *J*=8.2 Hz, 2H, ArH) and 8.1 (d, *J*=8.2 Hz, 2H, ArH). Anal. Calcd for $C_{21}H_{13}N_3O_3S_2$: C, 60.13; H, 3.12; N, 10.02; S, 15.29. Found: C, 60.16; H, 3.15; N, 10.10; S, 15.32%.

2-[2-(4-Methoxy-phenyl)-2-oxo-ethylsulfanyl]-1-thiaza-[1,2-*b*]naphthalene-4,9-dione, 3i. Light brown solid, yield 88%, decomposes at 132-34°C. IR (KBr): 1559 (C=C), 1586 (-C=N-), 1669 cm^{-1} (-C=O); ^1H NMR ($CDCl_3$): δ 3.90 (s, 3H, O-CH_3), 4.40 (s, 2H, S-CH_2), 7.00-7.10 (m, 4H, Ar-H), 7.65 (d, *J*=8.2 Hz, 2H, ArH), 7.90 (d, *J*=8.2Hz, 2H, ArH). Anal. Calcd for $C_{21}H_{13}N_3O_4S_2$: C, 57.92; H, 3.01; N, 9.65; S, 14.73. Found: C, 57.95; H, 3.00; N, 9.69; S, 14.77%.

2-[2-(4-Chloro-phenyl)-2-oxo-ethylsulfanyl]-1-thiaza-[1,2-*b*]naphthalene-4,9-dione, 3j. Light brown solid, yield 87%, decomposes at 145-47°C. IR (KBr): 1138 (C=S), 1560 (C=C), 1587(-C=N-), 1680 cm^{-1} (-C=O); ^1H NMR ($CDCl_3$): δ 4.80 (s, 2H, S-CH_2), 7.00-7.10 (m, 4H, Ar-H), 7.9 (d, *J*=8 Hz, 2H, ArH), 8.2 (d, *J*=8 Hz, 2H, ArH). Anal. Calcd for $C_{20}H_{10}ClN_3O_3S_2$: C, 54.61; H, 2.29; N, 9.55; S, 14.58. Found: C, 54.61; H, 2.31; N, 9.59; S, 14.61%.

2-[2-(4-Bromo-phenyl)-2-oxo-ethylsulfanyl]-1-thiaza-[1,2-*b*]naphthalene-4,9-dione, 3k. Light brown solid, yield 90%, decomposes at 158-60°C. IR (KBr): 1556 (C=C), 1589, (C=N), 1679 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.60 (s, 2H, S-CH_2), 7.05-7.1 (m, 4H, Ar-H), 7.90 (d, *J*=8 Hz, 2H, ArH), 8.2 (d, *J*=8 Hz, 2H, ArH). Anal. Calcd for $C_{20}H_{10}BrN_3O_3S_2$: C, 49.60; H, 2.08; N, 8.68; S, 13.24. Found: C, 49.62; H, 2.10; N, 8.64; S, 13.25%.

Acetic acid 9-acetoxy-2-methylsulfanyl-1-thia-3,3*a*,10-triaza-pentaleno[1,2-*b*]naphthalene-4-yl ester, 4. Yellow solid, yield 85%, decomposes at 208-10°C. IR (KBr): 1444(-C=N-), 1577 (C=C), 1771 cm^{-1} (-C=O); ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H, S-CH_3), 2.50 (s, 6H, -OCOCH_3), 7.60 (m, 2H, Ar-H) and 7.80 (m, 2H, Ar-H); MS: *m/z* 388 $(M+H)^+$. Anal. Calcd for $C_{17}H_{13}N_3O_4S_2$: C, 52.70; H, 3.38; N, 10.85; S, 16.55. Found: C, 52.65; H, 3.40; N, 10.81; S, 16.51%.

Conclusions

In summary, a mild and single step method for preparation of the title compounds in high yield has been developed without application of any catalyst. The testing of bioactivity of these compounds is in progress.

Acknowledgement

Financial support from UGC, New Delhi for the sanction of the project [F.No. 32-201/2006 (SR)] is gratefully acknowledged. The authors also thank Director, NIT Warangal for providing research facilities.

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