New and Efficient Rout for One Pot Synthesis of acenaphtho[1,2-b] quinoxalines

Zahra haghighi ju

Department of Medicinal Chemistry , Mazandaran University of Medical Sciences , Sary, Iran

E-mail : zhaghighiju@gmail.com

Abstract -Acenaphtho derivatives have been reported as antitumor agents. So, the reaction of acenaphthylene-1,2-dione with 3,4-diaminobenzenethiol, and then with the alkyl chloride derivatives for the synthesis of acenaphtho [1,2-b] quinoxalines are reviewed. Excellent yields of the products, short reaction times and simple work-up are attractive features of this suitable protocol.

Keywords: Synthesis; Acenaphthene-1,2-dione; pyrimidine , quinoxalines

Introduction

Economic generation of bioactive compounds has been a major concern in modern organic chemistry [1]. In this regard, development of novel compounds and especially diverse small molecule scaffolds caused higher attention of medicinal and biological chemists [2-4].

quinaxolines are of chemical and pharmacological interest 5,6 and compounds containing the polycyclic ring systems have been shown to possess antitumor, antibacterial, antifungal, antimalarial and anticonvulsant activities.5–8 Some are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children and adult granulocytic leukemia.

Polycyclic aromatic hydrocarbon (PAH) heterocycles are highly important structural units in a variety of pharmacologically active substances [8-12]. At first glance, rigid polycyclic structures seem to have role in the development of antitumor agents owing to their ability in insertion between stacked base pairs of oligonucleotides and action as intercalator [13-15]. Particularly important is that when these planar polycyclic heterocycles bear appropriate side chains, further interactions with other important macromolecules might be envisaged [14,16].
In the frame work of our program to develop the chemistry of compounds and in connection with our ongoing interests in MCRs [17,18]., We would like to introduce a facile procedure for the synthesis of 9-(alkylthio) acenaphtho pyrimidines via the reaction of acenaphthylene-1,2-dione with 3,4-diaminobenzenethiol, and then with the alkyl chloride derivatives (Scheme 1).
We investigated the reaction of acenaphthylene-1,2-dione, 3,4-diaminobenzenethiol and alkyl bromoides in the presence of catalytic amounts of AcOH. Various parameters were investigated to obtain the optimum reaction conditions. The results on the synthesis of quinaxolines in the presence of catalytic amounts of AcOH are summarized in Table 1.

Experimental

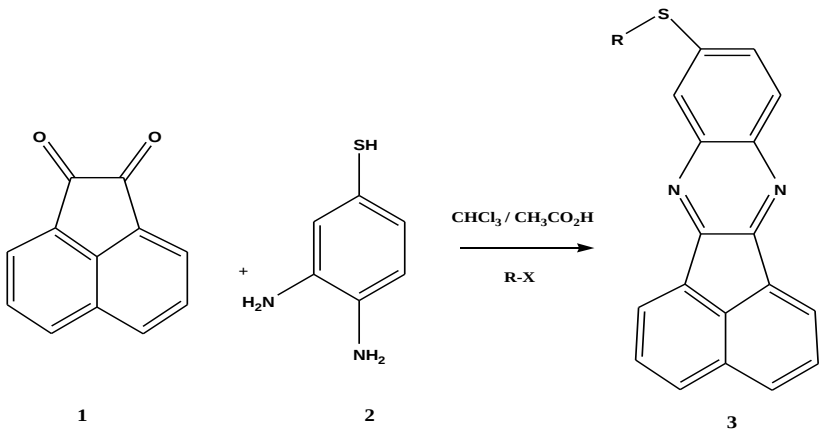
Material and methods

All of the reagents were purchased from commercial sources and were freshly used after being purified by standard procedures. Melting points were determined on the Electrothermal Melting Point apparatus and were uncorrected. Infrared spectra were recorded on the Shimadzu-420

infrared spectrophotometer.[1]H-NMR and [13]C-NMR spectra were recorded in $CDCl_3$-d6 or $CDCl_3$ on Brucker 300 MHz spectrometer (Chemical shifts are given in parts per million or ppm). Elemental analyses (C, H, N) were performed by the Microanalytical Unit.

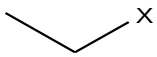
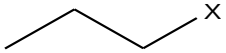
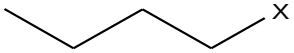
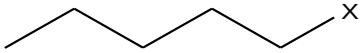
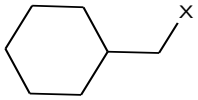
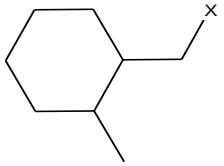
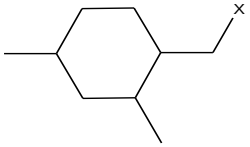
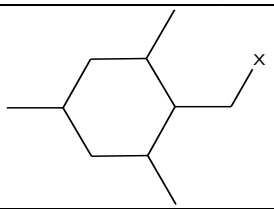
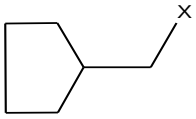
General procedure for preparation of acenaphtylene pyrimido thoalyles

To the acenaphtylene-1,2-dione (5 mmol) and 3,4-diaminobenzenethiol (5 mmol) in chloroform(30 mL) , various alkyl bromids was added and continuously stirred at reflux condition. small amount of acetic acid was added as an catalyst. The reaction mixture was stirred under reflux condition. The progress of the reaction was monitored with TLC and at the completion of the reaction, The precipitated product was filtered off, washed with mixture of H_2O / EtOH, dried and recrystallized from ethanol to give yellow crystalline 9-(alkylthio) acenaphtho[1,2-b] quinoxaline derivatives (Scheme 1).



Scheme 1: synthesis of 9-(alkylthio)acenaphtho[1,2-b] quinoxaline derivatives

Table 1: synthesis of various 9-(alkylthio) acenaphtho[1,2-b] quinoxalines

entry	R-X	X	Time (min)	Yield (%)	m.p (°C)
3a		Cl	35	78	130
3b		Cl	30	70	134
3c		Cl	43	81	130
3d		Cl	46	73	126
3e		Cl	40	76	135
3f		Cl	25	82	147
3g		Cl	28	77	153
3h		Cl	27	72	150
3i		Cl	36	70	159
3j		Cl	22	84	152

Spectral characteristic data:

acenaphtho[1,2-b]quinoxaline-9-thiol (2)

IR (KBr, cm^{-1}): 3245, 3151,2572 , 2920 , 2400 , 1689, 1607, 1050 ; ^{1}HNMR (300 MHz, DMSO-d6) δ: 7.81 (d, 2H, J = 7.5Hz, CHaromatic), 7.65 (dd, 2H, J = 7.6, 5.9 Hz, CH-aromatic),

7.46 (d, 2H, J = 8Hz CH-aromatic), 3.21 (s, 1H, SH); ^{13} C-NMR (75 MHz, DMSO-d6) δ: 163, 150, 131, 128, 126, 124, 123; Anal. Calcd for C18H10N2S: C, 75.50; H, 3.50; N, 3.52 , S ; 11.20. Found: C, 75.65; H, 3.56; N, 3.41 ; S , 11.32.

9-(methylthio) acenaphtho[1,2-b]quinoxaline (3a)

IR (KBr, cm^{-1}): 3230, 3175,2490 , 2935 , 2560 , 1650, 1575, 1050; ^{1}HNMR (300 MHz, $CDCl_3$-d_6) δ: 7.95 (s, 1H, , CH aromatic), 7.90 (d, 2H, CH-aromatic), 7.81 (d, 2H, CH-aromatic), 7.65 (dd, 4H, CH-aromatic), 7.81 (d, 2H, CH-aromatic), 2.85 (s, 3H,S- CH_3), ; ^{13}C-NMR (75 MHz, $CDCl_3$-d_6) δ: 148,145,139,136,131,127,124, 46; Anal. Calcd for $C_{19}H_{12}N_2S$: C, 75.95; H, 4.05; N, 9.33 ; S , 10.67. Found: C, 75.81; H, 4.1; N, 9.35 ; S , 10.55

9-(methylthio)acenaphtho[1,2-b]quinoxaline (3b)

IR (KBr, cm^{-1}): 3250, 3122, 2480 , 2900 , 2438 , 1680, 1664, 1078; ^{1}HNMR (300 MHz, $CDCl_3$-d_6) δ: 7.95 (s, 1H, , CH aromatic), 7.90 (d, 2H, CH-aromatic), 7.81 (d, 2H, CH-aromatic), 7.65 (dd, 4H, CH-aromatic), 7.81 (d, 2H, CH-aromatic), 2.35 (s, 3H,S- CH_3), ; ^{13}C-NMR (75 MHz, $CDCl_3$-d_6) δ: 148,145,139,136,131,127,124,44,21; Anal. Calcd for $C_{20}H_{14}N_2S$: C, 75.41; H, 4.49; N, 8.91 ; S , 10.2. Found: C, 75.32; H, 4.54; N, 9.05 ; S , 10.15

9-(propylthio)acenaphtho[1,2-b]quinoxaline (3c)

IR (KBr, cm^{-1}): 3286, 3165, 2482 , 2900 , 2430 , 1650, 1635, 1050; ^{1}HNMR (300 MHz, $CDCl_3$-d_6) δ: 7.92 (s, 1H, , CH aromatic), 7.81 (d, 2H, CH-aromatic), 7.84 (d, 2H, CH-aromatic), 7.65 (dd, 4H, CH-aromatic), 7.81 (d, 2H, CH-aromatic), 2.21 (t, 2H,S- CH_2), 1.81 (m, 2H, CH_2- CH_3) ; 1.51 (t, 3H, CH_3) . ^{13}C-NMR (300 MHz, $CDCl_3$-d_6) δ: 148,145,139,136,131,127,124,44,21 , 18 ; Anal. Calcd for $C_{20}H_{14}N_2S$: C, 75.41; H, 4.49; N, 8.91 ; S , 10.2. Found: C, 75.32; H, 4.54; N, 9.05 ; S , 10.15

9-(butylthio)acenaphtho[1,2-b]quinoxaline (3d)

IR (KBr, cm–1): 3310, 3120, 2870 , 2475 , 2430 , 1640, 1585, 1130 . ^{1}HNMR (300 MHz, $CDCl_3$-d6) δ: 7.87 (s, 1H, , CH aromatic), 7.78 (d, 2H, CH-aromatic), 7.7 (d, 2H, CH-aromatic),

7.65 (dd, 4H, CH-aromatic), 7.57 (d, 2H, CH-aromatic), 2.16 (t, 2H,S- CH_2), 1.75 (m, 4H, -CH_2-) ; 1.62 (t, 3H, CH_3) . 13C-NMR (300 MHz, $CDCl_3$-d6) δ: 148,145,139,136,131,127,124,47,23 , 16 , 14 ; Anal. Calcd for C20H14N2S: C, 77.16; H, 5.34; N, 8.19 ; S , 9.36. Found: C, 77.21; H, 5.28; N, 8.23 ; S , 9.42

9-(pentylthio) acenaphtho[1,2-b]quinoxaline (3e)

IR (KBr, cm^{-1}): 3350, 3160, 2820 , 2520 , 2482 , 1600, 1522, 1191; ^{1}HNMR (300 MHz, $CDCl_3$-d_6) δ: 7.81 (s, 1H, , CH aromatic), 7.78 (d, 2H, CH-aromatic), 7.75 (d, 2H, CH-aromatic), 7.62 (dd, 4H, CH-aromatic), 7.57 (d, 2H, CH-aromatic), 2.16 (t, 2H,S- CH_2), 1.75 (m, 6H, -CH_2-) ; 1.51 (t, 3H, CH_3) . $_{13}$C-NMR (300 MHz, $CDCl_3$-d_6) δ: 148,145,139,136,131,127,124,47,23 , 16 , 14 ,10; Anal. Calcd for $C_{20}H_{14}N_2S$: C, 77.49; H, 5.65; N, 7.86 ; S , 8.99. Found: C, 77.43; H, 5.72; N, 7.73 ; S , 8.84 .

9-(cyclohexylmetylthio) acenaphtho[1,2-b]quinoxaline (3f)

IR (KBr, cm^{-1}): 3250, 3100, 2870 , 2450, 2370 , 1640, 1585, 1130; ^{1}HNMR (300 MHz, $CDCl_3$-d_6) δ: 7.81 (s, 1H, , CH aromatic), 7.78 (d, 2H, CH-aromatic), 7.75 (d, 2H, CH-aromatic), 7.62 (dd, 4H, CH-aromatic), 7.57 (d, 2H, CH-aromatic), 2.16 (t, 2H,S- CH_{2-}), 1.25 (m, 11H, cyclohexyl) . ^{13} C-NMR (300 MHz, $CDCl_3$-d_6) δ: 148,145,139,136,131,127,124,44,25 , 14 ,; Anal. Calcd for $C_{25}H_{22}N_2S$: C, 78.50; H, 5.80; N, 7.32 ; S , 8.38. Found: C, 78.58; H, 5.70; N, 7.47 ; S , 8.46 .

9-((2-methylcyclohexyl)methylthio)acenaphtho[1,2-b]quinoxaline (3g)

IR (KBr, cm–1): 3260, 3075, 2790 , 2475 , 2420 , 1640, 1585, 1115; ^{1}HNMR (300 MHz, $CDCl_3$-d6) δ: 7.88 (s, 1H, , CH aromatic), 7.78 (d, 2H, CH-aromatic), 7.71 (d, 2H, CH-aromatic), 7.55 (dd, 4H, CH-aromatic), 7.46 (d, 2H, CH-aromatic), 2.15 (t, 2H,S- CH_{2-}), 1.21 (m, 14H, 2-methylcyclohexyl) . ^{13} C-NMR (300 MHz, $CDCl_3$-d6) δ: 148,145,139,136,131,127,124,41,22 , 16 ,; Anal. Calcd for C26H24N2S: C, 78.56; H, 6.15; N, 7.06 ; S , 8.12. Found: C, 78.51; H, 6.28; N, 6.92 ; S , 8.19 .

9-((2,6-dimethylcyclohexyl)methylthio)acenaphtho[1,2-b]quinoxaline(3h)

IR (KBr, cm_{-1}): 3250, 3143, 2870 , 2470 , 2430 , 1590, 1566, 1130; ^{1}HNMR (300 MHz, $CDCl_3$-d_6) δ: 7.76 (s, 1H, , CH aromatic), 7.72 (d, 2H, CH-aromatic), 7.77 (d, 2H, CH-aromatic), 7.43 (dd, 4H, CH-aromatic), 7.38 (d, 2H, CH-aromatic), 2.23 (t, 2H,S- CH_{2-}), 1.17 (m, 17H, 2,6-dimethylcyclohexyl) . ^{13} C-NMR (300 MHz, $CDCl_3$-d_6) δ: 148,145,139,136,131,127,124,43,18 , 14 ; Anal. Calcd for $C_{27}H_{26}N_2S$: C, 78.95; H, 6.38; N, 6.82 ; S , 7.81. Found: C, 78.77; H, 6.45; N, 6.77 ; S , 7.80 .

9-((2,4,6-trimethylcyclohexyl)methylthio)acenaphtho[1,2-b]quinoxaline (3i)

IR (KBr, cm–1): 3300, 3215, 2768 , 2539 , 2430 , 1640, 1585, 1070; ^{1}HNMR (300 MHz, $CDCl_3$-d6) δ: 7.71 (s, 1H, , CH aromatic), 7.75 (d, 2H, CH-aromatic), 7.66 (d, 2H, CH-aromatic), 7.35 (dd, 4H, CH-aromatic), 7.30 (d, 2H, CH-aromatic), 2.20 (t, 2H,S- CH_{2-}), 1.22 (m, 20H, 2,4,6-trimethylcyclohexyl) . ^{13} C-NMR (300 MHz, $CDCl_3$-d6) δ: 152,148,141,137,130,127,124,38,16 , ; Anal. Calcd for C27H26N2S: C, 79.20; H, 6.65; N, 6.60 ; S , 7.55. Found: C, 79.32; H, 6.53; N, 6.77 ; S , 7.65 .

9-(cyclopentylmethylthio) acenaphtho[1,2-b]quinoxaline(3j)

IR (KBr, cm–1): 3260, 3147, 2835 , 2475 , 2477 , 1622, 1490, 1088; ^{1}HNMR (300 MHz, $CDCl_3$-d6) δ: 7.77 (s, 1H, , CH aromatic), 7.70 (d, 2H, CH-aromatic), 7.64 (d, 2H, CH-aromatic), 7.43 (dd, 4H, CH-aromatic), 7.32 (d, 2H, CH-aromatic), 2.22 (t, 2H,S- CH_{2-}), 1.19 (m, 9H, cyclopentyl) . ^{13} C-NMR (300 MHz, $CDCl_3$-d6) δ: 152,148,141,137,130,127,124,38,16 , ; Anal. Calcd for C24H20N2S: C, 78.23; H, 5.47; N, 7.61 ; S , 8.73. Found: C, 78.14; H, 5.52; N, 7.54 ; S , 8.85 .

Results

Our strategy for the synthesis of 9-(alkylthio) acenaphtho[1,2-b] quinoxaline derivatives (3a-j) , which are potential precursors for further heterocyclic systems, is a alkyl substitution of the sulfur atom of ***acenaphtho[1,2-b]quinoxaline-9-thiol (2)*** . The structures assigned to compounds 3a–j were substantiated by spectral data. The ^{1}H NMR spectra were devoid of the

signals at *ca.* 3 ppm (δ) for S-H groups of the precursor's 2 and showed further downfield shifts for alkyl protons with a signal at < 2.35 ppm for the alkyl groups of products 3a-j indicating the construction of a planar alkylated ring. Further proof came from their IR spectra, which lacked the S–H stretching frequencies of their precursor's 2 and confirmed the presence of the H group and the S-H in 2 by stretching frequencies at about 1150 cm^{-1}, respectively. Mass spectra showed the expected molecular ion peak, and the fragmentation pattern indicated the loss of alkylthio groups from compounds 3a-j, which is in line with the proposed structure as shown in Schemes 1. It seemed from the table 1, that specially in the case of cyclo hexyl and cyclo pentyl chloride groups (3f-3g) , the time and yield of products was reduced in contrast with alkyl chloride (3a-e) substitution .

Conclusion

In conclusion, the condensation of acenaphthylene-1,2-dione with 3,4-diaminobenzenethiol and further replacement of the S-H atom with alkyl is a convenient and general procedure for preparation of 9-(alkylthio) acenaphtho[1,2-b]quinoxaline derivatives. In the majority of cases, this methodology was allowed access in simple steps to a diverse range of quinoxaline derivatives . This work represents a new, general method for preparation of acenaphtho[1,2-b]quinoxaline, which are useful precursors for the synthesis of novel heterocyclic poly aromatic systems.

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