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Halogenoheterocyclization of 2-(allylthio)-quinolin-3-carbaldehyde and 2-(propargylthio)-quinolin-3-carbaldehyde

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Abstract: The reaction of 2-allyl(propargyl)thioquinolin-3-carbaldehyde with halogens (Br or I) results in formation of 1-halogenomethyl(halogenomethylidene)-4-formyl-1,2-dihydrothiazolo[3,2-*a*]-quinolinium trihalogenide. In the case of the propargylic derivative the process is stereoselective.

Keywords: 2-allylthio-3-formylquinoline; dihydrothiazolo [3,2-*a*]quinolinium halogenide; halogenoheterocyclization; 2-propargylthio-3-formylquinoline; stereoselective.

Introduction

Derivatives of fused quinolines possess diverse biological properties such as antibacterial, antifungal [1–6], anti-inflammatory [7], antitubercular [8] and anticonvulsant [9] activity. Considering these observations, it was envisaged to synthesize new quinoline derivatives containing a fused thiazole ring. In recent years, heteroannulation processes based on electrophilic halocyclization have produced various heterocycles including furans [10–13], pyrroles [10, 14], selenophenes [15], pyrazoles [16], piperazines [17], imidazothiazoles [18], imidazotriazines [19], thiazolo(oxazolo)thienopyrimidines [20–23], thiazolopyrazolopyrimidines [24–27] and thiazolotriazoles [28]. Halogenoheterocyclization of unsaturated methallyl thioethers of quinoline has been described [28–36]. In continuation of these studies we now present halogenoheterocyclization of 2-allylthio and 2-propargylthio substituted quinolin-3-carbaldehydes **2** and **6**.

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Results and discussion

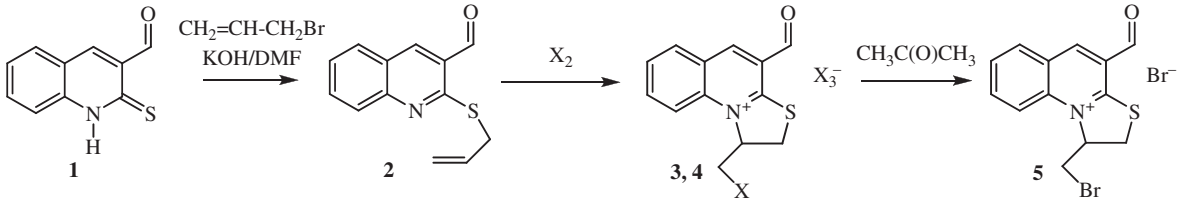
Compound **2** was obtained by alkylation of 3-formylquinolin-2-thione (**1**) with allyl bromide in DMF in the presence of KOH [37]. Bromine and iodine were used as electrophilic agents for halogenoheterocyclization. Halogenation was carried out in chloroform with a two-fold excess of halogen to give the respective 1-halogenomethyl-2,3-dihydrothiazolo[3,2-*a*]quinolinium trihalogenides **3** and **4**. The monobromide **5** was obtained after treatment of the tribromide **3** with acetone (Scheme 1).

Compounds **3** and **4** were extensively characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, COSY, NOESY, and by heteronuclear correlation methods HMQC and HMBC.

^{1}H NMR spectrum of compound **3** is fully consistent with the proposed structure and the proton assignments were obtained by analysis of two-dimensional spectra COSY and NOESY. Analysis of the COSY spectrum cross peaks gave the scheme of correlations shown in Figure 1. These assignments are fully consistent with the analysis of the NOESY spectrum of **3** (Figure 2).

The heteronuclear correlations in the HMQC and HMBC spectra were measured for full assimilation of signals in spectral data of compound **3**. Table 1 provides a complete list of observed correlations and these correlations are shown graphically in Figure 3.

In principle, halogenocyclization involving a propargylic substituent as unsaturated nucleophilic moiety in a quinoline system may result in the formation of two geometrical isomers. In our previous studies [31] we have found that the process of halogenocyclization of a similar propargyl thioether is stereoselective, however, the geometric configuration of the resulting product has not been established. In this work, halogenoheterocyclization of 7-methyl-2-propargylthioquinolin-3-carbaldehyde **6** [31] (Scheme 2), was carried out. ^{1}H NMR and ^{13}C NMR spectral data were used to establish structure of the synthesized compounds **7, 8**. The location of the halogen atom at the exocyclic double bond and the predominant conformation in solution of the aldehyde group are the main structural features which required additional investigation. This matter was addressed by using homonuclear overhauser



X = Br (**3**), I (**4**)

Scheme 1

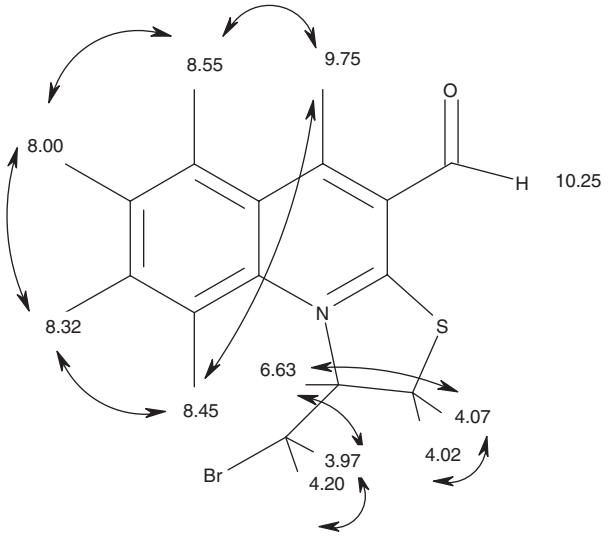


Figure 1 Correlations in the COSY spectrum of compound **3**.

Table 1 Heteronuclear ^{1}H-^{13}C correlations for compound **3**.

Signal in ^{1}H NMR spectrum, δ	The cross-peaks in ^{13}C NMR spectrum	
	HMQC	HMBC[a]
10.25	190.00	165.40; 126.64; 152.91 s
9.75	152.91	165.40; 138.63; 133.24; 126.64
8.55	133.24	152.91; 139.13; 126.57; 119.49s;
8.45	119.49	152.91s; 139.13; 133.24s; 129.93; 126.57;
8.32	139.13	138.63; 133.24; 129.93s; 126.57s; 119.49s
7.99	129.93	139.13; 133.24s; 126.57; 119.49
6.63	66.93	165.40
4.20	34.90	66.93; 32.82
4.07	32.82	66.93; 34.90;
4.02	32.82	66.93; 34.90
3.97	34.90	66.93; 32.82

[a]Correlation of low intensity.

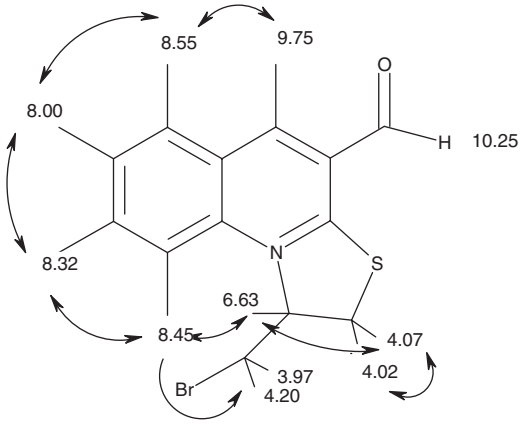


Figure 2 Correlations in the NOESY spectrum of compound **3**.

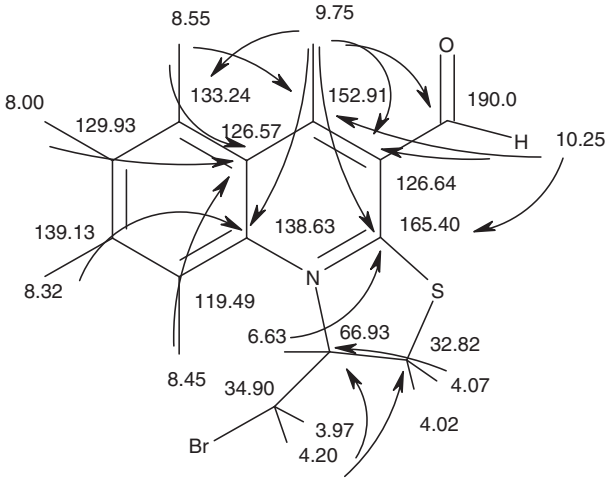
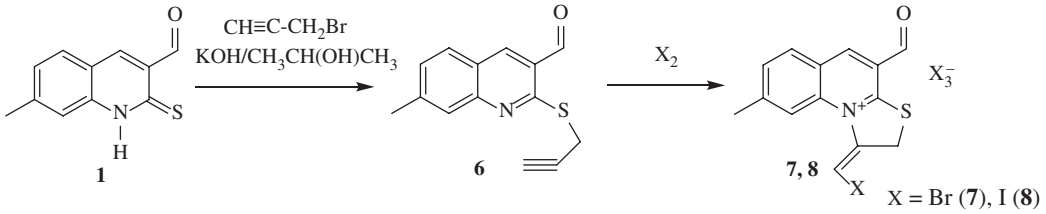


Figure 3 Heteronuclear correlations of compound **3**. Similar results were obtained for the iodo derivative **4**.

effect (NOE) and the results for compound **7** are shown in Figure 4.

The large NOE value for protons with chemical shifts at 8.34 ppm and 8.08 ppm indicates that the bromine atom in the olefin moiety has the E configuration relative to the thiazolium moiety. The large NOE value between the signals of the aldehyde proton and the aromatic proton with chemical shift of 9.72 ppm shows that the aldehyde group has *s-syn* orientation relative to the pyridinium moiety. Similar values of the chemical shifts for products



Scheme 2

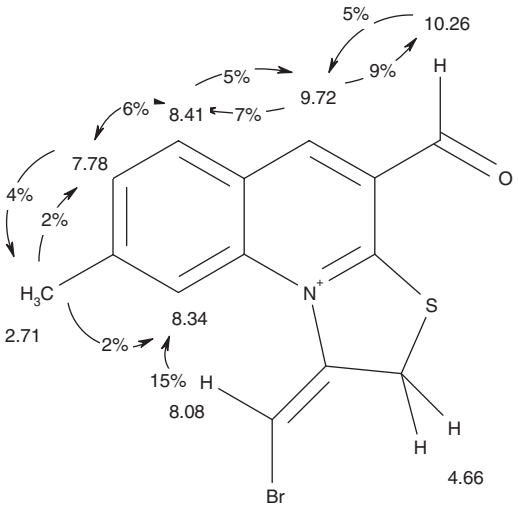


Figure 4 Correlations of NOE for compound **7**.

7 and **8** indicate identical stereochemical features in the products of bromination and iodination.

Conclusions

Heterocyclization of 2-allyl(propargyl)thioquinolin-3-carbaldehyde by reaction with halogens (Br and I) was investigated in detail.

Experimental

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $(CD_3)_2SO$ on a Varian Mercury-400 instrument. 2D-NOESY and COSY experiments were carried out for the compounds **3, 4, 7, 8** in $(CD_3)_2SO$ on the same instrument. Melting points were determined on a Stuart SMP30 instrument. Elemental analyses were performed on an Elementar Vario MICRO cube analyzer. All reagents were obtained from commercial suppliers and used without any further purification. Anhydrous solvents were prepared according to standard methods. Compounds **1** [38], **2** [37] and **6** [31] were synthesized as previously described. The R_f values were obtained using silica gel plates.

1-Bromomethyl-4-formyl-1,2-dihydro[1,8]thiazolo[3,2-*a*]quinolinium tribromide (3) A solution of bromine (7.2 mmol) in chloroform (7 mL) was added to a solution of allyl thioether **2** (3.6 mmol) in chloroform (15 mL) under constant stirring. After 5 h, the precipitated yellow solid was filtered and washed with chloroform; yield 71%; mp 132–133°C; R_f 0.81 (ethanol/hexane/diethyl ether, 1:2:3); ^{1}H NMR: δ 3.97 (d, *J* = 10.4 Hz, 1H), 4.02 (t, *J* = 7.6 Hz, 1H), 4.07 (d, *J* = 6.4 Hz, 1H), 4.20 (t, *J* = 10.4 Hz, 1H), 6.63 (m, 1H), 8.00 (t, *J* = 8.0 Hz, 1H), 8.32 (t, *J* = 8.0 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 9.75 (s, 1H), 10.25 (s, 1H); ^{13}C NMR: δ 32.8, 34.9, 66.9, 119.5, 126.6, 126.6, 129.9, 133.2, 138.6, 139.1, 152.9, 165.4, 190.0. Anal. Calcd for $C_{13}H_{11}Br_4NOS$: N, 2.55; Br, 58.23. Found: N, 2.48; Br 57.13.

1-Bromomethyl-4-formyl-1,2-dihydro[1,3]thiazolo[3,2-*a*]quinolinium bromide (5) A solution of tribromide **3** (0.001 mol) in acetone (10 mL) was slowly concentrated to give a crystalline residue of **5**; mp 245–247°C. Anal. Calcd for $C_{13}H_{11}Br_2NOS$: N, 3.60; Br, 41.07. Found: N, 3.49; Br, 40.28.

1-Iodomethyl-4-formyl-1,2-dihydro[1,3]thiazolo[3,2-*a*]quinolinium triiodide (4) A solution of allyl thioether **2** (1.8 mmol) in chloroform (15 mL) was stirred and slowly treated with a solution of iodine (3.6 mmol) in chloroform (20 mL). The mixture was stirred for 5 h and left for a day. The resultant precipitate of **4** was filtered off and washed with chloroform; yield 83%; mp 127–128°C; R_f 0.7 (ethanol/hexane/diethyl ether, 1: 2: 3); ^{1}H NMR: δ 3.66 (d, *J* = 10.5 Hz, 1H), 3.75 (t, *J* = 8.5 Hz, 1H), 3.92 (d, *J* = 12.3 Hz, 1H), 4.15 (t, *J* = 10.5 Hz, 1H), 6.43 (m, 1H), 7.99 (t, *J* = 6.9 Hz, 1H), 8.33 (t, *J* = 6.9 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 9.73 (s, 1H), 10.26 (s, 1H). Anal. Calcd for $C_{13}H_{11}I_4NOS$: N, 1.90; I, 68.93. Found: N, 1.85; I, 67.48.

1-Bromomethylidene-7-methyl-4-formyl-1,2-dihydro[1,3]thiazolo[3,2-*a*]quinolinium tribromide (7) To a solution of propargylic thioether **6** (0.62 mmol) in chloroform (15 mL) was added under constant stirring a solution of bromine (1.2 mmol) in chloroform (7 mL). After 5 h, the precipitated yellow solid of **7** was filtered and washed with chloroform; yield 73%; mp 178–179°C; R_f 0.80 (ethanol/hexane/diethyl ether, 1: 2: 3); ^{1}H NMR: δ 2.71 (s, 3H), 4.66 (s, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 8.08 (s, 1H), 8.34 (s, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 9.72 (s, 1H), 10.26 (s, 1H); ^{13}C NMR: δ 23.4, 36.4, 111.8, 119.8, 125.4, 125.5, 131.8, 133.0, 138.7, 140.1, 151.5, 152.2, 165.5, 189.5. Anal. Calcd for $C_{14}H_{11}Br_4NOS$: N, 2.50; Br, 56.98. Found: N, 2.41; Br, 56.25.

1-Iodomethylidene-7-methyl-4-formyl-1,2-dihydro[1,3]thiazolo[3,2-*a*]quinolinium triiodide (8) To a solution of propargylic thioether **6** (0.33 mmol) in chloroform (15 mL) was added under constant stirring a solution of iodine (0.66 mmol) in chloroform (15 mL). The mixture was stirred for 5 h and left for a day. The

precipitate was filtered off and washed with chloroform; yield 81%; mp 210–211°C; R_f 0.72 (ethanol/hexane/diethyl ether, 1: 2: 3); ^{1}H NMR: δ 2.73 (s, 3H), 4.64 (s, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 1H), 8.32 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 9.64 (s, 1H), 10.28 (s, 1H); ^{13}C NMR: δ 23.6, 36.1, 112.0, 119.6, 125.4, 125.5, 131.6, 133.0, 138.7, 140.1, 151.5, 152.2, 165.5, 189.6. Anal. Calcd for $C_{14}H_{11}I_4NOS$: N, 1.87; I, 67.78. Found: N, 1.85; I, 66.48.

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