N-HALOSUCCINIMIDE/SULFURIC ACID: AN EFFICIENT REAGENT FOR THE SYNTHESIS OF FUSED BENZOTHIAZOLES

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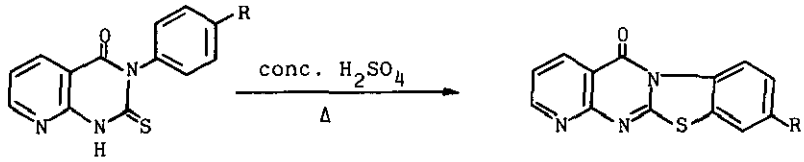
Abstract- A new version of Hugershoff's synthesis is reported. The cyclizing agent, N-halosuccinimide/sulfuric acid permits the preparation of complex fused benzothiazoles in very good yields.

One of the most classical routes to 2-aminobenzothiazoles (Hugershoff's synthesis) involves the oxidation of arylthioureas[1], a reaction which has been carried out using different reagents. Thus, bromine in an inert solvent has been widely used, although $Br_2/HOAc$[2], Br_2/H_2SO_4[3], I_2/H_2SO_4[3] and other halogen-transfer reagents, such as sulfuryl chloride[4], thionyl chloride[5] and sulfur monochloride[6], have also been reported as cyclizing agents.

Nevertheless, according to the literature these reagents have mainly been used in the synthesis of relatively simple systems.

As we have developed a very simple and general method for the synthesis of benzo-[7] and heterofused[8,9] 2-thioxopyrimidines it was thought that 1, 2 and 3 might prove to be useful starting compounds for the preparation of the corresponding tetracyclic benzothiazole derivatives 4, 5 and 6 respectively.

In fact, a few 5-oxo-5H-pyrido[2',3':4,5]pyrimido[2,1-b]benzothiazoles 4 had been prepared by us[8] using concentrated sulfuric acid as an oxidizing agent[10], though the yields were only moderate (Scheme I).



1
R=H, CH_3

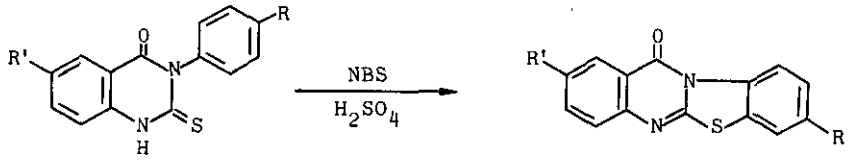
4
Yield: 36%

Scheme I

In a similar way, the treatment of compounds 2 with hot (140°C) concentrated sulfuric acid gave 5 in low yields (20-45%). In order to avoid side-reactions, such as the formation of sulfonated by-products, 50% aqueous sulfuric acid was used, but this treatment resulted in acidic hydrolysis of the thioxo group and the main products were the corresponding 3-aryl-2,4-dioxo-1,2,3,4 -tetrahydroquinazolines, identified by comparison with authentic samples prepared independently[11].

A better method for the oxidation of this type of thioureas was sought, and we found that the treatment of structures 2 and 3 with N-halosuccinimide/H_2SO_4 (halo= chloro or bromo) gave the corresponding fused benzothiazole derivatives 5 and 6 respectively, with yields ranging from good to nearly quantitative.

Thus, the treatment of 2 with an equimolar amount of N-bromosuccinimide in H_2SO_4 yielded the corresponding 12-oxo-12H-benzothiazolo[2,3-b]quinazolines 5 (Scheme II), identified by their spectral data. The molecular ion constitutes the base peak of the mass spectrum in every case and, in their ^{1}H-nmr spectra, the downfield shift of H-10 is specially noticeable. The main spectral features of these compounds are summarized in Table 1.



2 5

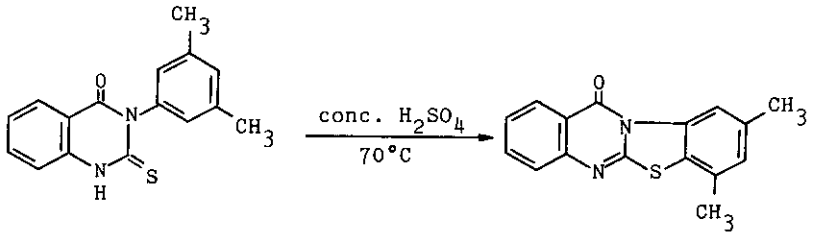
Scheme II

Table 1. Ir (Nujol) and ^{1}H-nmr spectra of compounds 5

Compound	R'	R	ν(C=O)cm^{-1}	δ(ppm); solvent CF_3-COOH H-1	H-10
5a	H	H	1690	8.6(dd,J=8Hz,J'=2Hz)	9.1(m)
5b	H	Cl	1690	8.6(d,J=7Hz)	9.1(d,J=9Hz)
5c	H	CH_3	1695	8.6(d,J=8Hz)	9.0(d,J=9Hz)
5d	Cl	H	1700	8.5(d,J=2Hz)	9.2(m)
5e	Cl	Cl	1705	8.5(d,J=2Hz)	9.0(d,J=9Hz)
5f	Cl	CH_3	1695	8.5(d,J=2Hz)	9.0(d,J=9Hz)
5g	CH_3	H	1695	8.4(s)	9.0(m)
5h	CH_3	Cl	1690	8.4(s)	9.1(d,J=9Hz)
5i	CH_3	CH_3	1695	8.4(s)	9.0(d,J=9Hz)

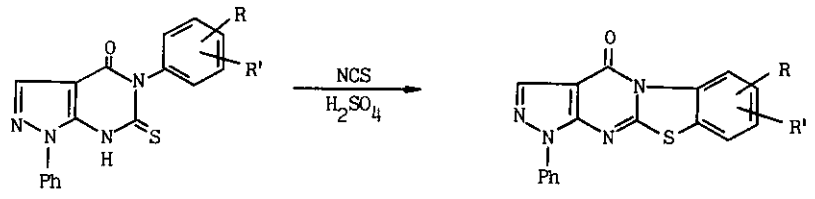
Products 5 were also prepared using N-chlorosuccinimide/H_2SO_4 but with lower yields (except for 5e). In both cases shorter reaction times and lower temperatures were required when activating groups were present in the 3-aryl substituent. Nevertheless, when this ring was highly activated, as in the case of R=OCH_3, substrate 2 becomes over-reactive and, under a variety of conditions (protic or Lewis acids) only complex mixtures resulted.

An intermediate example is the 3-(3,5-dimethylphenyl) derivative shown below (Scheme III), which was smoothly oxidized by conc. sulfuric acid alone, while the use of NBS/H_2SO_4 yielded once again a mixture of products.



Scheme III

Similar results were obtained with the pyrazolo[3,4-d]pyrimidines 3, but the use of NBS/H_2SO_4 led, under a variety of conditions, to the expected products 6 together with varying amounts of brominated derivatives. When N-chlorosuccinimide was used instead of NBS, however, the corresponding 1H,4H-4-oxo-1-phenylpyrazolo-[3',4':4,5]pyrimido[2,1-b]benzothiazoles 6 were obtained in good yields (Scheme IV). Insignificant amounts of chlorinated by-products resulted with the more activated aryl groups, but were easily removed by recrystallization.



3 6

Scheme IV

Again, the presence of a methoxy group in the phenyl ring, as in 3 (R=H, R'=4-OCH_3), gave rise to a number of by-products, and the corresponding compound 6 could not be isolated.

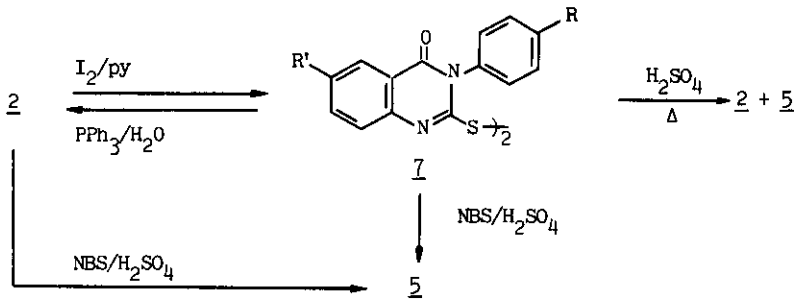
The structure of products 6 were mainly determined from their mass spectra (in all cases M^+ is the base peak) and ^{1}H-nmr spectra, where a "peri" effect on H-6

was observed. Some spectral features are summarized in table 2.

Table 2. Ir (Nujol) and ^{1}H-nmr spectra of compounds 6

Compound	R	R'	ν(C=O)cm^{-1}	δ(ppm);solvent CF_3-COOH	
				H-3 + H-6	Aromatics
6a	H	H	1710	9.2-9.0(m,1H);8.9(s,1H)	8.0-7.6(m,8H)
6b	H	8-CH_3	1700	9.0-8.8(m,2H)	7.8-7.5(m,7H)
6c	H	8-Cl	1700	8.8(d,J=9Hz,1H);8.7(s,1H)	7.7-7.3(m,7H)
6d	6-CH_3	8-CH_3	1720	8.9(s,1H)	7.6(br.s,5H); 7.4(s,2H)
6e	7-CH_3	9-CH_3	1710	8.9(s,1H);8.7(s,1H)	7.7(br.s,5H); 7.2(s,1H)

In an effort to extend the scope of this reaction, solvents other than H_2SO_4 were used. But when the reactions of 2 with NBS in dioxane, or formic acid or acetic acid were carried out, the isolated products were not the corresponding 5, but disulfides 7, as demonstrated by an independent synthesis using the well-known system I_2/pyridine (Scheme V)

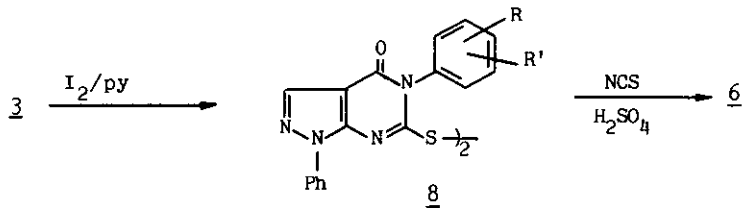


Scheme V

The structure of these disulfides was confirmed by their reactivity, since it was possible either to reduce 7 to 2 with PPh_3/H_2O[12] or oxidize it[13] to 5 with NBS/H_2SO_4. (Disulfide 7j (R'=H,R=OCH_3) was easily synthesized but the corresponding 5 could not be prepared using this procedure either). Moreover, when disulfides 7 were heated with conc. H_2SO_4 in the absence of NBS, a disproportionation reaction took place and equimolar amounts of compounds 2 and 5 were formed, as expected.

Similarly, disulfides 8 were obtained from 3 and oxidized to 6 with NCS/H_2SO_4 (ex-

cept for 8f(R=H,R'=4-OCH_3)) as shown in Scheme VI.



Scheme VI

ACKNOWLEDGEMENT

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EXPERIMENTAL

Melting points were determined using a Büchi 510 apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 283 instrument. ^{1}H-nmr spectra were obtained on a Bruker WP 80 CW spectrometer with TMS as internal reference. Mass spectra were recorded on a Hewlett-Packard 5995 C instrument.

12-Oxo-12H-benzothiazolo[2,3-b]quinazolines 5 (General Procedure)

A solution of the corresponding 3-aryl-4-oxo-2-thioxo-1,2,3,4 -tetrahydroquinazoline[7] 2 (2 mmol) and N-bromosuccinimide (0.356g, 2 mmol) in concentrated sulfuric acid (6 ml) was heated with stirring for several hours (see time and temperature under each product). The solution was then cooled, poured into water (50 ml) in an ice-water bath and made alkaline (pH=9) by dropwise addition of 20% aqueous sodium hydroxide. The resulting precipitate was washed with 5% aqueous sodium hydroxide and then with water, dried and recrystallized.

An identical procedure can be followed when using N-chlorosuccinimide, but yields are lower, except for 5e. In this case, the reported yield was that of the reaction with NCS.

5a: (Reaction time and temperature: 7h, 70°C). Yield 96%. Mp 189-190°C (MeOH). Reported[10] m.p.190-191°C. Anal. Calcd. for $C_{14}H_8N_2OS$(252.29):C,66.65; H,3.20;N,11.11. Found: C,66.49; H,3.12; N, 11.28%.

5b: (7h, 100°C) Yield 94%. Mp 262-264°C(n-BuOH). Anal. Calcd. for $C_{14}H_7ClN_2OS$ (286.73):C,58.64;H,2.46;N,9.77. Found: C,58.45;H,2.60;N,9.66%.

5c: (5h,70°C). Yield 96%. Mp 226-227°C(n-BuOH). Anal. Calcd. for $C_{15}H_{10}N_2OS$(266.31): C,67.65;H,3.79;N,10.52. Found: C,67.59;H,3.60;N,10.62%.

5d: (7h,70°C). Yield 83%. Mp 225-226°C(n-BuOH). Anal. Calcd. for $C_{14}H_7ClN_2OS$(286.73): C,58.64;H,2.46;N,9.77. Found: C,58.48;H,2.49;N,9.89%.

5e: (7h,100 °C). Yield 76%. Mp 265-266 °C(n-BuOH). Anal. Calcd. for $C_{14}H_6Cl_2N_2OS$ (321.18):C,52.35; H,1.88;N,8.72. Found: C,52.51;H,1.99;N,8.64%.

5f: (5h,70°C). Yield 98%. Mp 209-210°C(n-BuOH). Anal. Calcd. for $C_{15}H_9ClN_2OS$(300.76): C,59.90; H,3.02;N,9.32.Found:C,60.08;H,3.15;N,9.20%.

5g: (7h, 70°C). Yield 73%. Mp 203-204°C(n-BuOH). Anal. Calcd. for $C_{15}H_{10}N_2OS$ (266.31):C,67.65;H,3.79;N,10.52.Found:C,67.47;H,3.64;N,10.61%.

5h: (7h, 100 °C). Yield 81%. Mp 235-236 °C(DMF/H_2O). Anal. Calcd. for $C_{15}H_9ClN_2OS$ (300.76):C,59.90;H,3.02;N,9.32.Found:C,60.11;H,3.08;N,9.19%.

5i: (5h, 70°C). Yield 80%. Mp 212-213°C (DMF). Anal. Calcd. for $C_{16}H_{12}N_2OS$(280.34): C,68.55;H,4.31;N,9.99. Found:C,68.42;H,4.40;N,9.83%.

7,9-Dimethyl-12-oxo-12H-benzothiazolo[2,3-b]quinazoline

3-(3,5-Dimethylphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline(0.564g,2mmol) was dissolved in concentrated sulfuric acid (6 ml) and the solution was heated with stirring at 70°C for 3h. After cooling of the solution, the work-up was identical to the one previously described. Yield 75%. Mp 239-240 °C(n-BuOH). Anal. Calcd. for $C_{16}H_{12}N_2OS$(280.34):C,68.55;H,4.31;N,9.99. Found: C,68.38;H,4.39;N,9.86%. Ir(Nujol) 1695 cm^{-1}. ^{1}H-nmr(TFA) δ 8.85(s,1H),8.6(d,J=8Hz,1H),8.3-7.7(m,3H),7.45(s,1H),2.6 (s,6H). Ms,m/z 280(M^+,100%), 265(11), 140(M^{++},12).

1H,4H-4-Oxo-1-phenylpyrazolo[3',4':4,5]pyrimido[2,1-b]benzothiazoles 6 (General Procedure)

A mixture of the corresponding 5-aryl-4-oxo-1-phenyl-6-thioxo-1H-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine[9] 3(2 mmol) and N-chlorosuccinimide (0.267g, 2mmol) in concentrated sulfuric acid (6 ml) was heated with stirring for several hours (see time and temperature under each product). After cooling, the work-up was identical to the one described for the synthesis of compounds 5.

6a: (Reaction time and temperature: 3h, 60°C). Yield 70%. Mp 206-208°C(DMF). Anal. Calcd. for $C_{17}H_{10}N_4OS$(318.35):C,64.13;H,3.16;N,17.60.Found:C,64.22;H,3.07;N,17.69%.

6b: (2h,90°C). Yield 72%. Mp 242-244°C(DMF). Anal. Calcd. for $C_{18}H_{12}N_4OS$(332.38): C,65.04;H,3.64;N,16.86.Found:C,65.12;H,3.72;N,16.69%.

6c: (4h,90°C). Yield 68%. Mp 256-258°C(DMF). Anal. Calcd. for $C_{17}H_9ClN_4OS$(352.80): C,57.87;H,2.57;N,15.88.Found:C,57.96;H,2.69;N,15.70%.

6d: (3h, 70°C). Yield 88%. Mp 170-172°C(DMF). Anal. Calcd. for $C_{19}H_{14}N_4OS$(346.41): C,65.87;H,4.07;N,16.18.Found:C,65.93;H,4.19;N,16.04%.

6e: (2h, 90°C). Yield 63%. Mp 216-218°C(DMF). Anal. Calcd. for $C_{19}H_{14}N_4OS$(346.41): C,65.87;H,4.07;N,16.18. Found:C,65.72;H,4.15;N,16.26%.

Bis(3-aryl-4-oxo-3,4-dihydroquinazolin-2-yl)disulfides 7 (General Procedure)

To a vigorously-stirred suspension of the corresponding compound 2 (2 mmol) in water/pyridine (25/10 ml), a solution of iodine (0.254 g, 1 mmol) in ethanol (20 ml) was added dropwise at room temperature. The mixture was stirred for 30 min and the resulting precipitate was filtered off, washed with water and dried.

7a: (R=R'=H). Yield 88%. Mp 277-278°C. Ir (nujol) 1690 cm^{-1}. Anal.Calcd. for $C_{28}H_{18}N_4O_2S_2$(506.59): C,66.38;H,3.58;N,11.06.Found:C,66.29;H,3.67;N,11.10%.

7b: (R=Cl, R'=H). Yield 63%. Mp 281-282°C. Ir(nujol) 1705 cm^{-1}. Anal.Calcd. for $C_{28}H_{16}Cl_2N_4O_2S_2$(575.48):C,58.43;H,2.80;N,9.74. Found:C,58.32;H,2.76;N,9.81%.

7c: (R=CH_3, R'=H). Yield 91%. Mp 272-273°C. Ir(nujol) 1690 cm^{-1}. Anal.calcd. for $C_{30}H_{22}N_4O_2S_2$(534.64):C,67.39;H,4.15;N,10.48.Found:C,67.47;H,4.20;N,10.29%.

7g: (R=H, R'=CH_3). Yield 75%. Mp 273-274°C. Ir(nujol) 1690 cm^{-1}. Anal. Calcd. for $C_{30}H_{22}N_4O_2S_2$(534.64):C,67.39;H,4.15;N,10.48.Found:C,67.45;H,4.06;N,10.60%.

7j: (R=OCH_3, R'=H). Yield 74%. Mp 279-280 °C. Ir(nujol) 1680 cm^{-1}. Anal. Calcd. for $C_{30}H_{22}N_4O_4S_2$(566.64):C,63.58;H,3.91;N,9.89.Found:C,63.70;H,3.87;N,9.95%.

Reduction of Disulfides 7 to 2 (General Procedure)

A mixture of the corresponding disulfide 7 (1 mmol), triphenylphosphine (0.262 g, 1 mmol), dioxane (8 ml), water (2 ml) and conc. hydrochloric acid (0.1 ml) was stirred at room temperature for 20 min and then poured into water (100 ml). The precipitate was filtered off, thoroughly washed with water, dried and recrystallized to afford pure products 2, identified by comparison with authentic samples[7].

2a: Yield 88%. 2b: 94%. 2c: 97%. 2g: 81%. 2j: 95%.

Oxidation of Disulfides 7 to 5 (General Procedure)

The disulfide 7 (1 mmol) and N-bromosuccinimide (0.178g, 1 mmol) were dissolved in conc. sulfuric acid (6 ml). The stirred mixture was heated (see time and temperature under each product) and then cooled. Subsequent work-up was identical to the one described for the synthesis of 5.

5a: (Reaction time and temperature: 7 h, 70°C). Yield 98%. 5b: (7h, 100°C). Yield 32%. 5c: (5h, 70°C). Yield 45%. 5g: (7h, 70°C). Yield 86%.

Disproportionation of Bis(3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl)disulfide 7a

A solution of 7a (0.506 g, 1 mmol) in conc. H_2SO_4(6 ml) was heated at 70°C for 7 h, cooled and poured into water (50 ml) in an ice-water bath.

The crude precipitate was filtered off, suspended in 30% aqueous sodium hydroxide (25 ml) and stirred for 10 min. The resulting solid was filtered, washed with 5% aqueous NaOH, then with water and dried, to afford 5a (0.182 g, recovery: 72 %). The mother and washing liquors were neutralized to litmus with conc. hydrochloric acid (ice-water bath); the precipitate thus obtained was filtered off, washed with water and dried to afford 2a (0.152 g, recovery: 60%).

Bis(5-aryl-4-oxo-1-phenyl-1H-4,5-dihydropyrazolo[3,4-d]pyrimidin-6-yl)disulfides 8 (General Procedure)

This procedure is identical to that described for the synthesis of compounds 7, but with 3 as starting materials.

8a: (R=R'=H). Yield 86%. Mp>300°C(DMF). Ir(nujol) 1700 cm^{-1}. Anal.Calcd. for $C_{34}H_{22}N_8O_2S_2$(638.72):C,63.93;H,3.47;N,17.55. Found:C,63.85;H,3.36;N,17.64%.

8b: (R=H, R'=4-CH_3). Yield 91%. Mp>300°C(DMF). Ir(nujol) 1730 cm^{-1}. Anal.Calcd. for $C_{36}H_{26}N_8O_2S_2$(666.78):C,64.84;H,3.93;N,16.81.Found:C,64.92;H,3.87;N,16.75%.

8c: (R=H,R'=4-Cl). Yield 75%. Mp>300°C(DMF). Ir(nujol) 1730 cm^{-1}. Anal. Calcd. for $C_{34}H_{20}Cl_2N_8O_2S_2$(707.61):C,57.71;H,2.85;N,15.84. Found:C,57.62;H,2.76;N,15.90%.

8d: (R=2-CH_3, R'=4-CH_3). Yield 87%. Mp>300°C(DMF). Ir(nujol) 1710 cm^{-1}.Anal. Calcd. for $C_{38}H_{30}N_8O_2S_2$(694.83): C, 65.68;H,4.35;N,16.13.Found:C,65.79;H,4.28;N,16.26%.

8e: (R=3-CH_3,R'=5-CH_3) Yield 87%. Mp>300°C(DMF). Ir(nujol) 1710 cm^{-1}. Anal. Calcd. for $C_{38}H_{30}N_8O_2S_2$(694.83):C,65.68;H,4.35;N,16.13. Found: C,65.52;H,4.49;N,16.21%.

8f: (R=H, R'=4-OCH_3). Yield 75%. Mp>300°C(DMF). Ir(nujol) 1770 cm^{-1}. Anal. Calcd. for $C_{36}H_{26}N_8O_4S_2$(698.78):C,61.87;H,3.75;N,16.04.Found:C,61.70; H,3.66; N,16.16%.

Oxidation of Disulfides 8 to 6 (General Procedure)

The disulfide 8 (1 mmol) and N-chlorosuccinimide (0.134 g, 1 mmol) were dissolved in conc. sulfuric acid (6 ml). The stirred mixture was heated (see time and temperature under each product) and then cooled. Subsequent work-up was identical to the one described for the synthesis of 5.

6a: (Reaction time and temperature: 4h,90°C). Yield 72%. 6b:(3h, 80°C). Yield 74%. 6c:(4h, 90°C). Yield 63%. 6d: (3h, 80°C). Yield 88%. 6e: (2h, 90°C). Yield 79%.

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