Bromination of Isoquinoline, Quinoline, Quinazoline and Quinoxaline in Strong Acid

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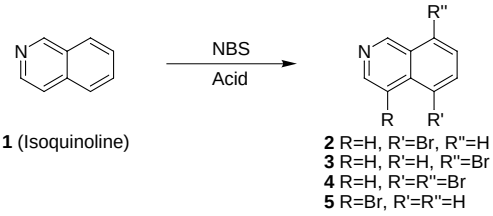
Abstract: Bromination of benzazines and benzodiazines most often gives a mixture of products. In this paper, we show that isoquinoline (**1**) may be regioselectively monobrominated in concentrated H_2SO_4 using NBS or in CF_3SO_3H using *N,N'*-dibromoisocyanuric acid (DBI) to give 5-bromoisoquinoline (**2**). The bromination was found to be highly sensitive to the choice of brominating agent, acid, temperature and concentration. Quinoline, quinazoline and quinoxaline may be brominated likewise, although with the strong regioselectivity reserved to isoquinoline.

Key words: bromination, electrophilic aromatic substitution, regioselective, benzazines, benzodiazines

The bromination of aromatic compounds have been a major subject of study[1] and a variety of brominating agents have been used, such as $KBrO_3$, Br_2, BrF/BrF_3, 1,3-dibromo-5,5-dimethylhydantoin (DBH), *N*-bromosuccinimide (NBS), and *N,N'*-dibromoisocyanuric acid (DBI).[2] To enhance the electrophilicity some of these reagent are often used in conjunction with strong acids. Thus, Duan et al.[3] recently used *N*-bromosuccinimide (NBS) in a mixture of trifluoroacetic acid (TFAA) and concentrated H_2SO_4 to synthesize 3-bromo(trifluoromethyl)benzene from trifluoromethylbenzene in a yield of 81%.

Bromobenzazines and bromobenzodiazines have been of interest for chemists as precursors for heterocyclic compounds with multifunctionality, giving accessability to a wide variety of compounds through, e.g. transition-metal couplings and Grignard reactions. These building blocks have especially been used within medicinal chemistry, as starting materials for numerous compounds with pharmacological activity.

During a recent optimization work we needed an efficient synthesis of 5-bromo-8-nitroisoquinoline, but found the known bromination procedures to be unsatisfactory for large-scale synthesis. These methods include the Sandmeyer reaction on 5-aminoisoquinoline to give 5-bromoisoquinoline,[4] and the direct bromination of isoquinoline by the use of $AlCl_3/Br_2$[5] or $Ag_2SO_4/Br_2/H_2SO_4$.[6] As a consequence of this, we investigated the electrophilic bromination of isoquinoline (**1**) using NBS in different acids (Scheme, Table 1).



1 (Isoquinoline)

2 R=H, R'=Br, R"=H
3 R=H, R'=H, R"=Br
4 R=H, R'=R"=Br
5 R=Br, R'=R"=H

Scheme

Table 1 Bromination of Isoquinoline (**1**) Using NBS in Different Acids

Solvent	Product Composition (%)[a]					
	1	**2**	**3**	**4**	**5**	Unidentified
CF_3SO_3H	11	62	5	21	–	–
oleum	–	–	–	–	–	100
concd H_2SO_4	13	53	9	25	–	–
92% H_2SO_4 (aq)[b]	11	42	20	27	–	–
72% H_2SO_4 (aq)[b]	28	31	22	2	–	16
CH_3SO_3H	17	40	32	11	–	–
CF_3CO_2H	82	14	4	–	–	–
12 M HCl	100	–	–	–	–	–
CH_3CO_2H	75	–	–	–	25	–

[a] Contents as determined by ^1H NMR spectroscopy of the reaction mixture at the time of no further conversion. Reaction conditions: isoquinoline (0.2 M), NBS (1.2 equiv) at r.t.
[b] Weight/weight.

The effect of the acid is dual; it deactivates isoquinoline (**1**) by N-protonation leading to higher selectivity between electrophilic attack at the 5-position vs. the 8-position[7] and the N–Br heterolytic bond breakage is enhanced under acidic conditions. The overall degree of conversion was highly dependent on the acidity of the media as seen from Table 1. This may reflect the degree of NBS activation. In acetic acid, substitution most likely occurs on the *non*-protonated species.[8] The lack of transformation in concentrated hydrochloric acid was probably due to insufficient solubility of NBS.

Focusing on concentrated H_2SO_4 and CF_3SO_3H as solvents, we investigated brominating reagents with different

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reactivities. Commercially available NBS, DBH, and easily prepared DBI[9] were tested. Gottardi has made comparative rate studies for the monobromination of deactivated aromatic compounds by DBI, DBH and NBS, and found DBI to be superior.[9,10]

During the course of these reactions, we found that NBS decomposes to some extent in CF_3SO_3H, especially after long term mixing, and that DBI is only slightly soluble in CF_3SO_3H. It was furthermore noted that the concentration and/or temperature had a pronounced impact on the outcome of the reaction, as seen by entry 6 vs. 7 in Table 2.

Table 2 Reactions of **1** with Different Brominating Agents

Entry	Reagent	Conditions	Product Composition (%)[a]			
			1	**2**	**3**	**4**
1	NBS[b]	1.2 equiv, r.t.	13	53	9	25
2	DBH[b]	0.65 equiv, r.t.	18	47	11	24
3	DBI[b]	0.65 equiv, r.t.	20	55	14	11
4	NBS[c]	1.2 equiv, r.t.	11	62	5	21
5	DBH[c]	0.65 equiv, r.t.	1	46	19	28
6	DBI[c]	0.65 equiv, r.t.	31	34	22	14
7	DBI[d]	0.76 equiv, 10 °C → r.t.	7	68	−10	15

[a] Contents as determined by ^{1}H NMR spectroscopy of the reaction mixture at the time of no further conversion.
[b] 0.2 M in concd H_2SO_4 with respect to **1**.
[c] 0.2 M in CF_3SO_3H with respect to **1**.
[d] 2.0 M in CF_3SO_3H with respect to **1**.

Two systems, DBI/CF_3SO_3H and NBS/H_2SO_4 seemed to work best (see Table 2). Clearly for CF_3SO_3H to be of general interest as a solvent, it would be preferable to dilute this very expensive acid. Attempts to use catalytic amounts of CF_3SO_3H (2 equiv with respect to **1**) in CH_2Cl_2, DMSO, and DMF were all unsuccessful in as much as no conversion was found. Dilution of H_2SO_4 with CH_2Cl_2 (1:1) or EtOH (1:1) lead to loss in selectivity, and mixtures of concentrated H_2SO_4 and CF_3SO_3H were no better than concentrated H_2SO_4 alone. Bromination using NBS in concentrated H_2SO_4 was chosen for further optimization with respect to temperature and concentration, due to the low costs.

Selectivity is highly dependent on the reaction temperature. Below –25 °C the reaction was very sluggish, and no reaction occurred below –35 °C due to solidification of the reaction mixture. No difference in selectivity was detected at 0.2, 0.5 or 1.0 molar concentrations of **1** in concentrated H_2SO_4, whereas a 2.0 M solution led to stirring difficulties, loss in selectivity and lengthy reaction times. The optimal concentration was thus found to be 1.0 M. It was furthermore found, that recrystallization of NBS[11] led to markedly improved yield of 5-bromoisoquinoline. Most importantly, the formation of 8-bromoisoquinoline (**3**), which requires tedious work to remove, is almost totally suppressed using an internal temperature of –25 to –18 °C, indicating strong kinetic control. A typical composition of the crude product using the optimized reaction conditions was: **1**:**2**:**3**:**4** = 2–4:90–94:0–1:2–5%, allowing **2** to be isolated in 72% yield. The use of 2.3 equivalents of NBS allowed the isolation of **4** in 76% yield.

The versatility of these brominating conditions, i.e. employing NBS/concd H_2SO_4 or DBI/CF_3SO_3H, was further investigated using quinoline (**6**), quinazoline (**7**) and quinoxaline (**8**).

Tochilkin et al.[12] have previously prepared 5-bromoquinoline (**9**) by bromination of **6** using NBS in concentrated H_2SO_4 at r.t. and 60 °C. We found the reaction to progress very sluggishly at –20 °C without higher selectivity than observed at r.t., thus differing from bromination of **2**. Conducting the reaction at r.t., changing the eluent for chromatography and finally isolating the product as the hydrochloride (**9a**), the isolated yield was improved from the reported 24% to 34%. When DBI/CF_3SO_3H was used, **9a** was isolated in 44% yield. Though not allowing strong regioselectivity, DBI/CF_3SO_3H was capable of brominating quinoline down to –70 °C.

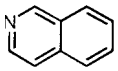
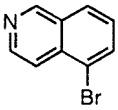
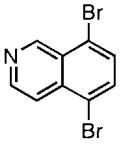
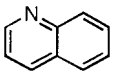
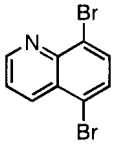
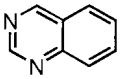
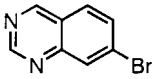
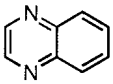
Using the the Derbyshire–Waters method ($Ag_2SO_4/Br_2/H_2SO_4$) or the "Swamping catalyst Effect" method ($AlCl_3/Br_2$), 5,8-dibromoquinoline[13,14] (**10**) has been synthesized in a moderate yield (34% for the latter method). Using NBS/H_2SO_4, **10** was easily synthesized in 61% yield.

Sidhu et al. have synthesized 6-bromoquinazoline (**11**) in a 3 step procedure.[15] Applying the NBS/H_2SO_4 system, **11** could be isolated in 27% yield by a one step procedure from commercially available quinazoline. Tri- and tetrabrominated quinazoline were also isolated from the reaction mixture in 16% yield (56:44). All substitution occurred in the homocyclic ring, as determined by ^{1}H NMR. Polybromination could not be suppressed by use of DBI/CF_3SO_3H or by means of temperature control. No bromination took place below 10 °C to 20 °C using NBS/concd H_2SO_4 or below –20 °C to –15 °C using DBI/CF_3SO_3H.

Hollstein and Krisov have prepared 5-bromoquinoxaline (**12**) in a 6 step procedure (yield not available).[16] Bromination of quinoxaline (**8**) was very slow and non-regioselective at room temperature using either NBS/H_2SO_4 or DBI/CF_3SO_3H. Using NBS/H_2SO_4 at room temperature to 60 °C, 5-bromoquinoxaline could be isolated in a yield of only 12%. In addition 6% 5,8-dibromoquinoxaline was isolated.

In conclusion, the present results indicate that the two main determinants for obtaining regioselective bromination are the temperature and acidity strength of the solvent. The conditions investigated, i.e. NBS/H_2SO_4 and DBI/CF_3SO_3H were especially suitable for bromination of isoquinoline, less so for quinoline and quinazoline and least for quinoxaline (see summarized results in Table 3). For the latter systems, both acid activated NBS and DBI seemed to be of too low brominating activity to allow an efficient and regioselective bromination.

Table 3 Bromination of Heterocycles **1**,**6**–**8**

Substrate		Product		Temp. (°C)	Method[a]	Time (h)	Mp (°C) (Lit.)	Yield[b] (%)
1		**2**		–22 to –18	A	5	81–82 (82–84)[c]	72
1		**4**		–25 to r.t.	A	4	113–115 (114–115)[d]	76
6		**9a**		r.t.	A	8	235[e] (-)	34
6		**9a**		–35	B	1.5	235[e] (-)	44
6		**10**		r.t.	A	8	126–128 (126–128)[d]	61
7		**11**		r.t.	A	21	136–138 (128–130)[f]	27
8		**12**		r.t. to 60	A	6	65–67 (66–67)[g]	12

[a] Method A = NBS/H_2SO_4, Method B = DBI/CF_3SO_3H.
[b] Yield of isolated purified product.
[c] Ref.[4]
[d] Ref.[5]
[e] Decomposes.
[f] Ref.[15]
[g] Ref.[16]

All reactions were conducted under N_2. All chemicals were obtained from Aldrich Chemical Co. and used without further purification except for NBS which was recrystallized prior to use.[11] All melting points are uncorrected. Silica gel Merck 60 (63–200 μm). NMR data were recorded on a Bruker 500 MHz spectrometer. The identity of **11** was based on NOE and ^1H NMR spectroscopy. TLC was performed using Merck 60 F_{254}.

General workup procedure for **2**, **9a** and **12**, unless otherwise stated: The reaction mixture was poured onto crushed ice (5 × the volume of H_2SO_4), pH was adjusted to 9.0 using concd aq NH_3 and the alkaline slurry was then extracted with diethyl ether (3 × double the volume of H_2SO_4). The combined organic fractions were washed with 1.0 M NaOH (2 × double the volume of H_2SO_4) and H_2O (1 × the volume of H_2SO_4), dried ($MgSO_4$), filtered, evaporated to dryness and purified by column chromatography (eluent: CH_2Cl_2–Et_2O, 9:1).

General workup procedure for **4**, **10** and **11**: The reaction mixture was poured onto crushed ice (5 × the volume of H_2SO_4) and the pH was adjusted to 7.0 using concd aq NH_3. The slurry was stirred for 1 h at 0 °C after which it was filtered and washed with ice-cold water [3 × triple the volume of H_2SO_4)]. The crude product was air-dried before purification by column chromatography.

5-Bromoisoquinoline (2)

To mechanically stirred concd H_2SO_4 (42.5 mL) at 0 °C was slowly added isoquinoline (**1**; 5 mL, 42.5 mmol). The mixture was cooled to –25 °C and NBS (9.83 g, 55.2 mmol) was added at such a rate that the reaction temperature was kept between at –25 °C and –22 °C. The mixture was stirred at –22 ±1 °C for 2 h and at –18 ±1 °C for 3 h. The mixture was then worked up as described above to give 6.16 g (72%) as a slightly off-white solid after chromatography; mp 81–82 °C. The solid was further purified by sublimation (75 °C/0.2 mmHg) to give **2** as a white powder (5.92 g, 69%); mp 81–82 °C; R_f 0.30 (CH_2Cl_2–Et_2O, 9:1).

^1H NMR (DMSO-d_6): δ = 7.62 (t, 1 H, J = 7.8 Hz),[17] 7.91 (d, 1 H, J = 6.0 Hz), 8.15 (d, 1 H, J = 7.5 Hz), 8.19 (d, 1 H, J = 8.2 Hz), 8.66 (d, 1 H, J = 6.0 Hz), 9.37 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 118.5, 120.3, 127.9, 128.4, 129.3, 133.9, 134.3, 144.6, 152.9.

Anal. Calcd for C_9H_6BrN: C, 51.96; H, 2.91; Br, 38.40; N, 6.73. Found: C, 52.06; H, 2.74; Br, 38.21, N, 6.65.

5-Bromoquinoline Hydrochloride (9a)

Method A: To a solution of **6** (1.8 mL, 15.3 mmol) in concd H_2SO_4 (15 mL) at r.t. was added NBS (3.5 g, 19.7 mmol). The reaction mixture was stirred for 8 h and worked up as described above to give 1.55 g as a slightly impure solid. The crude product was puri-

fied by sublimation (50–55 °C/0.2 mbar) to give 1.39 g of **9a** as an off-white solid. The solid was dissolved in EtOH (15 mL) and precipitated as the hydrochloride by addition of 12 M HCl (0.7 mL), yielding 1.23 g (34%) pure **9a** as a white powder.

Method B: To mechanically stirred CF_3SO_3H (15 mL) at 0 °C was slowly added **6** (1.8 mL, 15.3 mmol). The mixture was cooled to –40 °C and dibromoisocyanuric acid (3.06 g, 10.7 mmol) was added at such a rate that the temperature was kept between –40°C to –35 °C. The mixture was stirred at –40 °C to –35 °C for 1 h 40 min and worked up as in Method A to yield 1.56 g (44%) of **9a**; mp 235 °C (dec.); R_f 0.51 (CH_2Cl_2–Et_2O, 9:1).

^{1}H NMR (DMSO-d_6): δ = 7.86 (t, 1 H, *J* = 8.0 Hz),[17] 7.91 (dd, 1 H, *J* = 8.6, 4.6 Hz), 8.13 (d, 1 H, *J* = 7.5 Hz), 8.25 (d, 1 H, *J* = 8.5 Hz), 8.81 (d, 1 H, *J* = 8.6 Hz), 9.16 (dd, 1 H, *J* = 4.58, 1.4 Hz).

^{13}C NMR (DMSO-d_6): δ = 121.6, 123.4, 126.1, 127.2, 131.7, 132.1, 138.7, 144.7, 149.4.

Anal. Calcd for C_9H_7BrClN: C, 44.20; H, 2.88; Br, 32.68; Cl, 14.50; N, 5.72. Found: C, 43.89; H, 2.55; Br, 32.72; Cl, 14.48; N, 5.74.

5-Bromoquinoxaline (12)

To a solution of **8** (1.3 g, 10 mmol) in concd H_2SO_4 (10 mL) at r.t. was added NBS (1.3 g, 13 mmol). The reaction mixture was stirred for 20 min at r.t., 5.5 h at 60 °C and then worked up as described above, with the exception that CH_2Cl_2 (3 × 100 mL) was used for extraction and brine was added, until two separate phases were obtained. Column chromatography gave 260 mg (12%) pure **12** as an off-white powder; mp 65–67 °C; R_f 0.63 (CH_2Cl_2–Et_2O, 9:1).

^{1}H NMR (DMSO-d_6): δ = 7.80 (t, 1 H, *J* = 8.0 Hz),[17] 8.14 (dd, 1 H, *J* = 8.4, 1.1 Hz), 8.25 (dd, 1 H, *J* = 7.6, 1.1 Hz), 9.04 (d, 1 H, *J* = 1.7 Hz), 9.07 (d, 1 H, *J* = 1.7 Hz).

^{13}C NMR (DMSO-d_6): δ = 123.5, 129.3, 130.1, 133.6, 139.6, 143.3, 146.5, 146.6.

Anal. Calcd for $C_8H_5BrN_2$: C, 45.96; H, 2.41; Br, 38.22; N, 13.41 Found: C, 45.97; H, 2.13; Br, 38.18, N, 13.25.

5,8-Dibromoisoquinoline (4)

To mechanically stirred concd H_2SO_4 (17 mL) at 0 °C was slowly added **1** (2 mL, 17 mmol). The mixture was cooled to –25 °C and NBS (6.97 g, 39.2 mmol) was added at such a rate that the reaction temperature was kept between –25 °C to –20 °C. The mixture was stirred at –20 °C to –15 °C for 1 h and then allowed to reach r.t. in 1 h, at which temperature it was stirred for another 1 h. Workup was done as described above and column chromatography (eluent: CH_2Cl_2–EtOAc, 9:1 → 8:1) gave 3.88 g slightly impure **4**. Further purification by sublimation (90 °C/0.1–0.2 mbar) yielded 3.60 g (76%) of pure **4** as a white powder; mp 113–115 °C; R_f 0.63 (CH_2Cl_2–EtOAc, 9:1).

^{1}H NMR (DMSO-d_6): δ = 7.94 (d, 1 H, *J* = 8.0), 7.98 (d, 1 H, *J* = 5.9 Hz), 8.07 (d, 1 H, *J* = 8.0 Hz), 8.79 (d, 1 H, *J* = 5.9 Hz), 9.49 (d, 1 H, *J* = 0.5 Hz).

^{13}C NMR (DMSO-d_6): δ = 118.8, 120.5, 121.4, 126.8, 132.3, 134.9, 135.5, 145.7, 151.5.

Anal. Calcd for $C_9H_5Br_2N$: C, 37.67; H, 1.76; Br, 55.69; N, 4.88. Found: C, 37.41; H, 1.58; Br, 55.98; N, 4.87.

5,8-Dibromoquinoline (10)

To a solution of **6** (1 mL, 8.5 mmol) in concd H_2SO_4 (8.5 mL) at r.t. was added NBS (3.47 g, 19.49 mmol). The reaction mixture was stirred at r.t. for 8 h and worked up as described for **4** (sublimation at 95 °C/1.5 mbar) to give 1.84 g. The slightly impure product was further purified by recrystallization from heptane (30 mL) to give 1.42 g (61%) as a white powder; mp 126–128 °C. R_f 0.83 (CH_2Cl_2–EtOAc, 9:1).

^{1}H NMR (DMSO-d_6): δ = 7.81 (dd, 1 H, *J* = 8.5, 4.2 Hz), 7.91 (d, 1 H, *J* = 8.1 Hz), 8.10 (d, 1 H, *J* = 8.1 Hz), 8.57 (dd, 1 H, *J* = 8.5, 1.4 Hz), 9.10 (dd, 1 H, *J* = 4.2, 1.4 Hz).

^{13}C NMR (DMSO-d_6): δ = 120.9, 124.0, 124.4, 128.1, 131.0, 133.5, 135.7, 144.9, 152.4.

Anal. Calcd for $C_9H_5Br_2N$: C, 37.67; H, 1.76; Br, 55.69; N, 4.88. Found: C, 37.37; H, 1.50; Br, 55.42; N, 4.84.

6-Bromoquinazoline (11)

To a solution of **7** (1.04 g, 8.5 mmol) in concd H_2SO_4 (8 mL) at r.t. was added NBS (2.13 g, 12.0 mmol). The reaction mixture was stirred for 15 h. Further NBS (1.13 g, 6.35 mmol) was added and the mixture was stirred for another 6 h and worked up as described above. Column chromatography (eluent: CH_2Cl_2–MeOH, 20:1) yielded 450 mg (27%) of pure **11** as a white powder; mp 136–138 °C; R_f 0.40 (CH_2Cl_2–MeOH, 20:1).

^{1}H NMR (DMSO-d_6): δ = 7.98 (d, 1 H, *J* = 9.0 Hz), 8.17 (dd, 1 H, *J* = 9.0, 2.3 Hz), 8.45 (d, 1 H, *J* = 2.2 Hz), 9.35 (s, 1 H), 9.61 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 120.6, 125.8, 130.0, 130.1, 137.7, 148.0, 155.4, 160.0.

Anal. Calcd for $C_8H_5BrN_2$: C, 45.96; H, 2.41; Br, 38.22; N, 13.40. Found: C, 45.60; H, 2.04; Br, 38.31; N, 13.06.

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