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Efficient Halogenation of 2-Aminopyrazine

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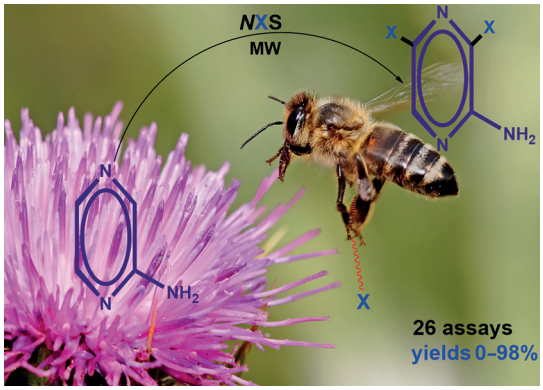

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Abstract 2-Aminopyrazine was halogenated with NIS, NCS, and NBS under different reaction conditions. Chlorination and bromination were achieved with good yields by using acetonitrile as the solvent. However, iodination was only obtained in poor yields. Undoubtedly, the best conditions for both mono- and dihalogenation were the use of NBS, acetonitrile, and microwave assistance for short periods. 3,5-Dibromo-2-aminopyrazine is an excellent functionalized starting material for the synthesis of nitrogen heterocycles.

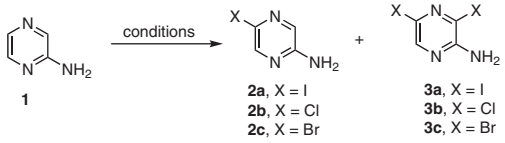
Key words *N*-halosuccinimide, 2-aminopyrazine, nitrogen heterocycles, halogenation

Halogenated heterocyclic compounds are attractive intermediate compounds for the chemical synthesis of other more complex systems and used for the synthesis of condensed heterocyclic compounds of potential industrial and therapeutic interest.[1] Specifically the pyrazine nucleus is part of the structure of antitumor compounds[2] (zibotentan and oltipraz), antivirals (telaprevir),[3] and anti-inflammatory compounds[4] among others. In general, the introduction of a halogen atom to the core of nitrogenated unsaturated heterocycles allows the attachment of different nucleophilic groups directly or indirectly.[5] Likewise, the reaction can be carried out with electrophiles by using lithium derivatives.[6] The presence of electron-donating groups on the pyrazine nucleus facilitates the halogenation as an electrophilic substitution reaction compared with the unsubstituted diazines.[7]

This work focuses on the halogenation of 2-aminopyrazines and the search for the best conditions by studying reagents and solvents. Several authors reported the process to be a complicated reaction with low yields.[8] Previous studies showed different methods for the halogenation of 2-aminopiperazine and the results are collected in Table 1.

The commercial 2-aminopyrazine (**1**) was selectively brominated at position 5 (compound **2**) by using NBS in dichloromethane under stirring at room temperature during four hours, giving the desired intermediate in 50% yield (Table 1, entry 3).[9] More recently, other authors have confirmed these results by using similar conditions (Table 1, entry 4).[10] The exchange of the solvent dichloromethane by DMF entailed an increase in yield according to the results provided by the Isobe and co-workers (Table 1, entry 1).[11] The results of this last work also show that bromination occurs with better performance than iodination (Table 1, entries 1 and 2).[11]

Table 1 Halogenation of 2-Aminopyrazine, Literature Data



Entry	Conditions	Yield of **2** (%)	Yield of **3** (%)	Ref.
1	NBS, DMF 0 °C, overnight	88		11
2	NIS, DMF 28 °C, overnight	61		11
3	NBS, CH_2Cl_2, r.t. 4 h	50		9
4	NBS, CH_2Cl_2, r.t. 1.5 h	52		10
5	DBH, DMF–MeCN, r.t. 0.5 h	65		15
6[a]	Br_2/HBr/H_2O 5 °C		82	12
7	Br_2, pyridine, $CHCl_3$, r.t.		36	13
8	NBS, CH_2Cl_2		63	14
9	NBS, DMSO–H_2O, 15 °C, 6 h		85	16a
10	NBS, DMSO–H_2O, 15 °C, 16 h		77	17
11	NBS, DMSO–H_2O, r.t. 6 h		90	16b

[a] From 2-amino-3-bromopyrazine.

Regarding the dibromation, the first results refer to the work of Brachwitz, who prepared the dibrominated derivative **3** from 2-amino-3-bromopyrazine (Table 1, entry 6).[12] More recently, Pastor and co-workers[13] used Br_2 in pyridine–chloroform and obtained only the dibrominated compound in 36% yield (Table 1, entry 7). Using dichloromethane as a solvent and NBS as halogenating agent, Zimmermann and co-workers[14] improved the result (Table 1, entry 8).

With other halogen agents such as 1,3-dibromo-5,5-dimethylhydantoin (DBH), the monobrominated derivative was also obtained with 65% yield (Table 1, entry 5).[15] Other authors used DMSO–H_2O as a solvent and obtained higher yields when operating at room temperature (Table 1, entry 11)[16] or even lower (Table 1, entries 9 and 11).[17] In this work we have tried to reproduce these results following the described conditions, but in no case has the 77% yield been exceeded. The greatest difficulty lies in the total elimination of DMSO that requires distillation at high temperatures and recrystallization from water for obtaining **3** in 99% purity.

The halogenation of the 2-aminopyrazine (**1**) is the basis of this work. Given the difficulties that we face in the preparation of halogenated pyrazine derivatives, especially the isolation and purification of the products, we wanted to find a method that will facilitate our work and allow us to obtain the isolated product in good yields.[18]

Iodination with NIS in MeCN gave very poor results and 2-amino-5-iodopyrazine (**2a**) was mostly obtained (Table 2, entries 1–3). Modifying the temperature, the NIS equivalents, or the reaction time did not improve the results. The exchange of MeCN by methanol slightly increased the yield (Table 2, compare entry 5 with entry 1). The improvement in performance was lower when exchanging MeCN by DMF. However, changes in temperature do not particularly affect the result (Table 2, entries 6–8). The use of LDA as a base and subsequent addition of molecular iodine as the electrophile allowed to obtain 39% yield of monoiodinated pyrazine (**2a**), the best performance achieved (Table 2, entry 9).

With regard to chlorination, by using 2.2 equivalents of NCS, a mixture of 2-amino-3,5-dichloropyrazine (**3b)** and 2-amino-3,5,6-trichloropyrazine (**5b**) was obtained in low yields (Table 2, entry 10). When 1.1 equivalents were used at 100 °C a mixture of **2b**, **3b**, and **4b** was obtained in 57, 13, and 17% respectively (Table 2, entry 11). While maintaining the above conditions but operating at room temperature, monochlorinated pyrazine (**2b**) was regioselectively obtained in good yield (Table 2, entry 12).

Finally, bromination was attempted. NBS was used as halogenating agent with MeCN as the solvent and the reaction was tested at different temperatures. The addition of 3.3 equivalents of NBS led to the dibrominated product (**3c**) in 38% yield (Table 2, entry 13). By using 1.1 equivalents of NBS and heating at 100 °C a mixture of mono- and dihalogenated products was obtained in poor yield (Table 2, entry 14). However, these conditions at room temperature led to the monobrominated pyrazine (**2c**) with high performance (Table 2, entry 15) which coincides with the chlorination carried out previously (Table 2, entry 12). In order to improve the yields and decrease the reaction times, halogenation assisted by the radiation of a microwave oven was carried out. By using 1.1 equivalents of NBS monobrominated product (**2c**) was obtained in good yield accompanied by the dibromopyrazine (**3c**) in only 6% yield (Table 2, entry 16). Other trials such as reducing the reaction time (five to two minutes) or the equivalents of NBS (1.1 equivalents to one equivalent) did not substantially improve the results. However, with 2.2 equivalents, dibrominated pyrazine (**3c**) was obtained in practically quantitative yield, the best according to the bibliography data (Table 2, entry 17). When using DMF as a solvent and heating by microwave irradiation, the yields were very low (Table 2, entry 21). When using methanol instead of MeCN the results at both room temperature and 100 °C were not good (Table 2, entries 19 and 20). By isolating the monobrominated derivative (**2c**) and subjecting it to a new bromination, the dibrominated pyrazine was obtained in 77% yield (Table 2, entry 18). The addition of CuBr as a catalyst slightly improved the result by providing yields of the same order as when the reaction was carried out under radical conditions (Table 2, entries 22 and 23). In this work, we tried to reproduce the conditions described above by Caldwell and co-workers[17] by using a mixture of DMSO–H_2O as the solvent and NBS as a halogenating agent, but in no case 50% yield was exceeded (the authors describe 77%). The reaction was also tested with bromodioxane as the halogenating agent and in this case, the best result was obtained when the reaction was carried out at 100 °C during 30 minutes (Table 2, entries 25–27).

Other halogenation conditions (KI, $CuCl_2$, I_2, cyclodextrin or Celite, r.t., 2–20 h; NIS, DMF, MW, 100 °C, 1 h; SmI_2, NIS, DMF, MW, 100 °C, 1.15 h; or NCS, ACN, 0 °C, 3 h) afforded the starting material and no traces of the halogenation products were obtained.

In summary, we have developed a method and set up conditions that allow to prepare both 2-amino-5-bromopyrazine and 2-amino-3,5-dibromopyrazine in excellent yields depending on the amount of halogenating agent added. Acetonitrile has proved to be the ideal solvent and the assistance of microwave irradiation is essential to obtain halogenated 2-aminopyrazine.

Acknowledgment

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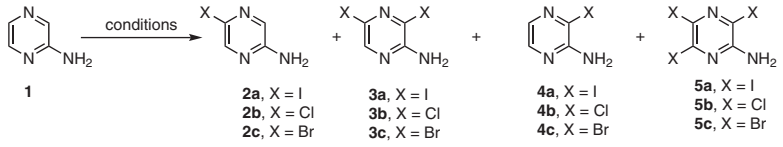
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690183.

Table 2 Halogenation of 2-Aminopyrazine, Experimental Data



Entry	Conditions	X	**2** (%)	**3** (%)	**4** (%)	**5** (%)
1	NIS (3 equiv), MeCN, 100 °C, 20 h	I	9	–	–	–
2	NIS (3 equiv), MeCN, r.t., 3 h	I	11	–	–	–
3	NIS (1.1 equiv), MeCN, r.t., 6 h	I	14	28	–	–
4	NIS (1.1 equiv), MeOH, r.t., 3 h	I	13	–	–	–
5	NIS (1.1 equiv), MeOH, 100 °C, 3 h	I	34	–	–	–
6	NIS (1.1 equiv), DMF, r.t., 3 h	I	25	–	–	–
7	NIS (1.1 equiv), DMF, 100 °C, 3 h	I	22	–	–	–
8	NIS (1.1 equiv), DMF, –30 °C, 3 h	I	15	–	–	–
9	I_2 (1.1 equiv), LDA (1.5 equiv), THF, –78 °C, 3 h	I	39	–	–	–
10	NCS (2.2 equiv), MeCN, r.t., 72 h	Cl	–	12	–	14
11	NCS (1.1 equiv), MeCN, 100 °C, 3 h	Cl	57	13	17	–
12	NCS (1.1 equiv), MeCN, r.t. 3 h	Cl	89	–	–	–
13	NBS (3 equiv), MeCN, r.t., 3 h	Br	–	38	–	–
14	NBS (1.1 equiv), MeCN, 100 °C, 6 h	Br	22	11	–	–
15	NBS (1.1 equiv), MeCN, r.t., 3 h	Br	89	–	–	–
16	**NBS (1.1 equiv), MeCN, MW, 5 min**	**Br**	**88**	**6**	–	–
17	**NBS (2.2 equiv), MeCN, MW, 5 min**	**Br**	–	**98**	–	–
18[a]	NBS (2.2 equiv), MeOH, r.t., 3 h	Br	–	78	–	–
19	NBS (1.1 eqiuv), MeOH, r.t., 3 h	Br	26	19	–	–
20	NBS (1.1 equiv), MeOH, 100 °C, 3 h	Br	28	25	–	–
21	NBS (1.1 equiv), DMF, MW, 100 °C, 1 h	Br	5	15	–	–
22	NBS (1.1 equiv), CuBr, MeCN, r.t., 3 h	Br	41	–	–	–
23	NBS (1.1 equiv), AIBN, CCl_4, *hv*, 3 h	Br	46	–	9	–
24	NBS (2.2 equiv), DMSO, H_2O, 0 °C to r.t., 16 h[17]	Br	–	48 (77)[17]	–	–
25	bromodioxane (1.1 equiv), dioxane, 0 °C to r.t., 3 h	Br	–	6	–	–
26	bromodioxane (0.5 equiv), dioxane, 0 °C to r.t., 3 h	Br	32	–	5	–
27	bromodioxane (1 equiv), dioxane, 100 °C, 30 min	Br	48	–	6	–

[a] From 2-amino-5-bromopyridine (1 equiv).

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(18) **Halogenation; General Procedure**
To a solution of pyrazine-2-amine (1.0 mmol) in methanol, acetonitrile, dimethylformamide, or lithium diisopropylethylamine (5–10 mL) was added *N*-iodosuccinimide (NIS) (**procedure A**) (1.1–3.0 mmol) or I_2 (1.1 mmol) or *N*-chlorosuccinimide (NCS) (**procedure B**) or *N*-bromosuccinimide (NBS) (**procedure C**) [in the reaction with I_2 also LDA (1.5 mmol) was added]. The reaction mixture was stirred until no starting material could be detected by thin-layer chromatography. Then, the solvent was removed under reduced pressure to give the crude product, which was purified by silica gel column chromatography.
Reaction under Microwave Irradiation; General Procedure
To a solution of the pyrazine-2-amine (1.0 mmol) in acetonitrile (5 mL) in a glass tube (10 mL) sealed with a silicon septum was added *N*-iodosuccinimide (NIS) (**procedure A**) (1.1–3.0 mmol) or I_2 (1.1 mmol) or *N*-chlorosuccinimide (NCS) (**procedure B**) or *N*-bromosuccinimide (NBS) (**procedure C**) (1.1–2.2 mmol) containing magnetic stirring. The tube was introduced to the microwave oven, heated to 100 °C, and subjected to a variable MW power until 300 W (an IR sensor measured the temperature of the glass tube surface) until no starting material could be detected by thin-layer chromatography. Then, the solvent was removed under reduced pressure to give the crude product, which was purified by silica gel column chromatography. Alternatively, the crude reaction mixture can be extracted with diethyl ether/water (3×15 mL), dried with sodium sulfate, filtered, and the solvent can be removed to dryness. Representative product:
2-Amino-3,5-dibromopyrazine
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18 (br s, 2 H, NH_2), 8.04 (s, 1 H, H-6). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 123.6 (C3), 124.0 (C5), 143.1 (CH, C6), 151.9 (C2). Mp: 118–120 °C (Lit.[16a]mp 117–118 °C).