Side Chain Bromination of Mono and Dimethyl Heteroaromatic and Aromatic Compounds by Solid Phase *N*-Bromosuccinimide Reaction without Radical Initiator under Microwave

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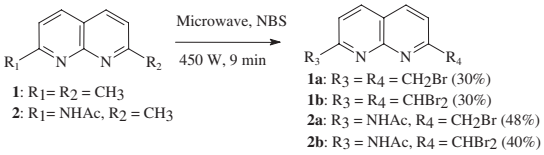
A series of side chain mono and dibromo derivatives of mono and dimethyl heteroaromatic and aromatic compounds (**1**–**17**) were synthesized by one step solid phase *N*-bromosuccinimide (NBS) reaction without radical initiator by microwave irradiation. The benzylic mono and dibromo products were exclusively preferred except in the case of 6-methylpyridine amides (**8** and **9**) where nuclear and also side chain bromination resulted. Naphthyridine systems resulted improved yields. By this method, we also report the synthesis of 2-pivaloylaminopterin-6-carbaldehyde.

Bromomethyl aromatic and heteroaromatic compounds (e.g. pyridine, pterin, or naphthyridine derivatives) are important substrates and they have been used as the precursors for benzylic coupling reactions,[1a–1c] oxidation reactions,[1c] synthesis of liquid crystals,[2] and they have applications in the synthesis of artificial receptors for molecular recognition research.[3] Pterin-6-carbaldehyde and 6-bromomethylpterin compounds are also important substrates for the synthesis of anticancer drug methotrexate and the nutrient cofactor folic acid. NBS reactions[4a] under different conditions (NBS in NaOH,[4b] in aqueous or catalytic amount of conc. H_2SO_4,[4c] *p*-toluenesulfonic acid[4d]) have also been used for electrophilic substitution of aromatic rings.[5] This experiment was also carried out varying the solvents[6] (polar and nonpolar) with the most used halogen donor like NCS[5c] and NBS, using AIBN as an initiator. We have previously reported[7] side chain versus nuclear bromination in the presence or absence of water. Solid phase bromination[8a,8b] with molecular bromine[8c] and over HZSM-5 have also been reported.[8d]

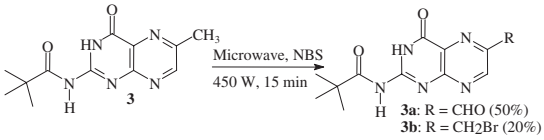
In an effort towards the preferred benzylic bromination compared to ring bromination, we sought to extend the NBS chemistry by a straightforward and mild reaction under solvent free condition utilizing microwave heating.[9]

We report here that heating under microwave assists exclusively side chain bromination (mono and bis) by NBS without the necessity of a radical initiator (Scheme 1 and Table 1). This method also conveniently produces 2-pivaloylaminopterin-6-carbaldehyde **3a** (50%) (from dibromomethyl derivative, which is not isolable by thin layer or preparative chromatography) along with the monobromomethyl product **3b** (20%) (Scheme 2).

One representative reaction procedure: A thoroughly ground mixture of 2-acetylamino-7-methyl-1,8-naphthyridine **2** (100 mg, 0.49 mmol) and freshly recrystallized NBS (90 mg, 0.50 mmol) in an open-mouth conical flask was irradiated at 450 W with a domestic microwave oven (BPL 800G) for an optimum time of 9 min (Scheme 1). The solid residue upon silica gel column chromatography afforded the benzylic bromomethyl derivative **2a**[3e] (48%) as a light yellow semi solid along with dibromo derivative **2b** (40%) as a brown solid.[10] However, a longer reaction time did not improve the yield. The heterocycles having more nitrogen atoms and more fused pyridine rings did not give nuclear bromination, but afforded side chain mono and dibromo derivatives. The solid starting substrates during the reaction turned brownish and nothing liquefied. In the case of liquid substrates, a brownish semisolid mixture was obtained.



Scheme 1. Microwave irradiation with NBS in solid phase.

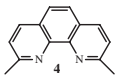
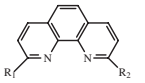
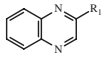
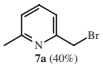
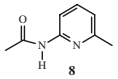
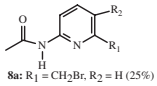
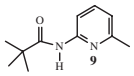
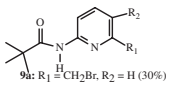
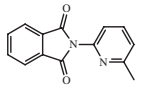
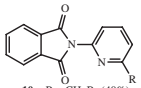


Scheme 2. Synthesis of 2-pivaloylamionopterin-6-carbaldehyde.

It is clear from Table 1 that this methodology is applicable for benzylic bromination to a wide variety of mono and dimethyl heteroaromatic and aromatic compounds in moderate to good yield within a very short time. Only in case of protected 2-amino-6-picolines, benzylic (**8a** and **9a**) as well as nuclear bromo derivatives (**8b** and **9b**) resulted, whereas 2,6-lutidine **7** and 2-*N*-phthalimido-6-methylpyridine **10** gave only side chain bromo products which may be due to less electron density in the rings of **7** and **10** compared to **8** and **9**. It is also suggested from Table 1 that the electron density in all the methyl substituted starting substrates having simple aromatic and heterocyclic rings like pyridine, pyrazine or phenanthroline is less compared to pyridine amides (**8** and **9**) and thus precludes ring bromination, but exclusively favors side chain bromination. We have also found that using excess NBS (three equivalents instead of usual one equivalent per methyl), the ratio of the products i.e. benzylic mono and di, or the yield of simple nuclear bromination product remained practically unchanged.

Ross et al. have reported[11] that predominantly nuclear bromination with NBS in propylene carbonate occurred in aromatic hydrocarbons. During our investigation, van Koten et al. have also reported[12] α-bromination of xylene derivatives using NBS and AIBN under microwave in methyl acetate medium. In our condition, the findings are also different where we have isolated both mono bromo (**11a**–**13a**) as well as bis monobromo (**11b**–**13b**) products from the xylenes **11**–**13**. The nitrotoluenes (**14**, **15**) led to the benzylic mono bromination. However, minor bis benzylic bromomethyl derivative, **16b** was isolated in case of

Table 1. Microwave-assisted NBS reactions without radical initiator and solvent

Starting Material	MW Conditions[a] Watt, min	Products Yield
 **4**	450, 9	 **4a**: $R_1 = R_2 = CH_2Br$ (40%) **4b**: $R_1 = R_2 = CHBr_2$ (25%)
 **5**	300, 6	 **5a**: $R_1 = CH_2Br$ (25%) **5b**: $R_1 = CHBr_2$ (20%)
 **6**	450, 6	 **6a** (30%)
 **7**	450, 9	 **7a** (40%)
 **8**	450, 3	 **8a**: $R_1 = CH_2Br$, $R_2 = H$ (25%) **8b**: $R_1 = CH_3$, $R_2 = Br$ (70%)
 **9**	450, 6	 **9a**: $R_1 = CH_2Br$, $R_2 = H$ (30%) **9b**: $R_1 = CH_3$, $R_2 = Br$ (33%)
 **10**	450, 9	 **10a**: $R = CH_2Br$ (40%) **10b**: $R = CHBr_2$ (40%)
 **11**: *o*-isomer **12**: *m*-isomer **13**: *p*-isomer	450, 9	 **11a**: R = CH_3 (45%) **11b**: R = CH_2Br (40%) **12a**: R = CH_3 (40%) **12b**: R = CH_2Br (42%) **13a**: R = CH_3 (43%) **13b**: R = CH_2Br (40%)
 **14**: *o*-isomer **15**: *m*-isomer **16**: *p*-isomer	450, 9	 **14a**: R = CH_2Br (30%) **15a**: R = CH_2Br (70%) **16a**: R = CH_2Br (70%) **16b**: R = $CHBr_2$ (20%)
 **17**	450, 6	 **17a** (45%)

[a] 1:1 Molar ratios of NBS per methyl group of the substrate were used.

16 along with the major mono bromomethyl product **16a**. Only the dibromo derivatives **6a** and **17a** were obtained in the case of pyrazine and acetyl protected *o*-toluidine,[13] respectively.

Thus this method of side chain bromination is more straightforward and environmentally friendlier as no solvent or initiator like AIBN are necessary compared to those reported earlier.[12] Interestingly, when a mixture of **9** (1 mmol) and NBS (1 mmol) in CCl_4 is refluxed for a period of 4 h without using AIBN, the products are different compared to the microwave heating where the nuclear bromination (**9b**) results without any side chain bromination. Though it is difficult to predict the exact reaction mechanism under this condition, microwave irradiation may help easy cleavage of N–Br bond to generate bromine radical for benzylic bromination in the solid phase.

We have thus developed a new method for the side chain bromination of aromatic as well as heteroaromatic methyl groups by microwave-assisted solid phase NBS reaction without radical initiator. The isolation of the tetrabromo compounds is important because of their subsequent facile hydrolytic conversion to the corresponding dialdehydes. The synthesis of pterin-6-carbaldehyde is important by this method as no other dibromo or tetrabromo heterocyclic compounds studied here, yield the corresponding aldehyde under the similar condition of the reaction or isolation.

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