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A facile nuclear bromination of phenols and anilines using NBS in the presence of ammonium acetate as a catalyst☆

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Abstract

An efficient nuclear monobromination of phenols and anilines has been achieved by treatment with NBS in the presence of a catalytic amount of NH_4OAc at room temperature. The method is rapid, regioselective and high-yielding.

Keywords: Phenol; Aniline; NBS; NH_4OAc; Monobromination

Brominated aromatic compounds are important as pharmaceuticals, agrochemicals, flame retardants and specialty chemicals [1]. They can also undergo C–C bond formation via transmetalation reactions such as Heck, Stille and Suzuki reactions [2]. The direct bromination of aromatic compounds using bromine produces toxic and corrosive HBr and therefore various other improved brominating agents have been developed [3]. However, in terms of ease of handling and activity, NBS in the presence of a suitable catalyst, has been found to be a superior brominating agent. NBS alone was also previously used [4] for bromination of activated aromatic compounds but the conversion time was long and the reaction was generally conducted under reflux using CCl_4 as the solvent. Moreover, with some substrates the selectivity of the reaction was poor and the yields were unsatisfactory.

Recently we required some brominated phenols and anilines for the synthesis of anticancer agents. We have observed that these compounds can conveniently be prepared by treatment of phenols and anilines with NBS along with a catalytic amount of ammonium acetate (NH_4OAc) (Scheme 1).

The method is highly efficient for the preparation of a series of brominated phenols and anilines (Table 1). The conversion occurred at room temperature and the products were formed in excellent yields. The reaction times were short and most of the anilines underwent the conversion immediately. Even 4-nitroaniline (Table 1, entry o) also afforded the brominated product quantitatively. The bromination of this compound was difficult by earlier methods [3]. Alkyl, ether, halogen, carbonyl and nitro groups remained here unaffected.

The present conversion yielded only the monobrominated products and the formation of these compounds is highly regioselective. Phenols and anilines afforded the corresponding *para*-bromo compounds as the sole products. However, when the *para*-position of a substrate was blocked with a substituent *ortho*-products were obtained.

The method is suitable for bromination of hydroxycoumarins (Table 1, entries u–w). The bromination took place at C-3 position and the products were formed in very high yields.

2-Amino picoline and 2-amino pyridine (entries s and t) were also underwent the desired monobromination with a short period of time.

Regarding mechanism of the reaction it may be mentioned here that the reaction of NBS with NH_4OAc is known [5] to produce HOAc and HBr which can polarize the >N–Br bond of NBS and facilitate the nuclear bromination of phenols and anilines. In absence of NH_4OAc the reaction of phenols and anilines with NBS required longer time to form the products and the yields and selectivity were lower. As for an example, phenol on treatment with NBS in the presence of a catalytic amount of

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Table 1
Bromination of phenols and anilines with NBS catalyzed by NH_4OAc[a]

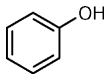
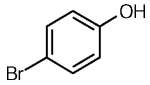
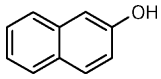
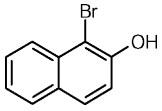
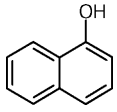
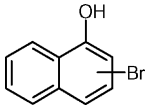
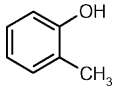
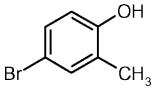
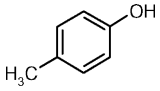
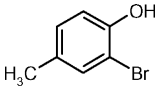
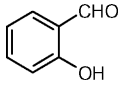
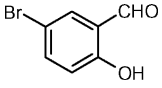
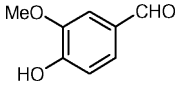
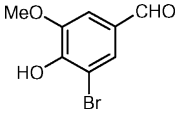
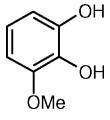
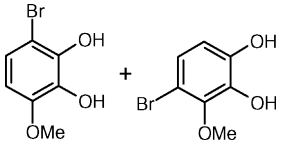
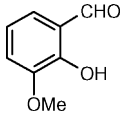
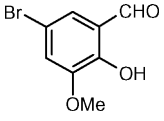
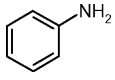
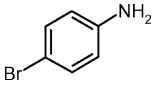
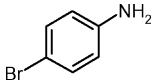
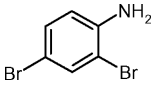
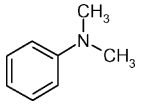
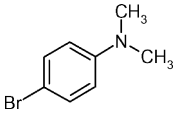
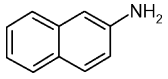
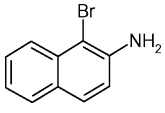
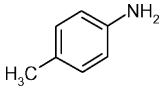
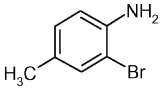
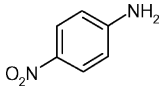
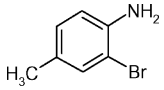
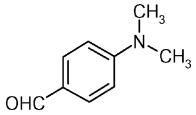
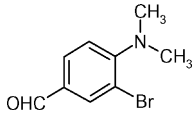
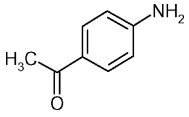
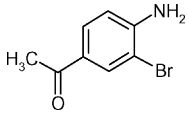
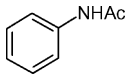
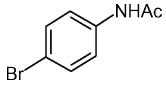
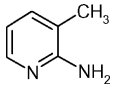
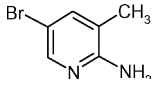
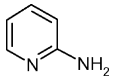
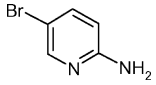
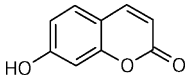
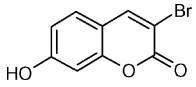
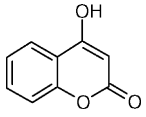
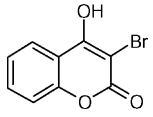
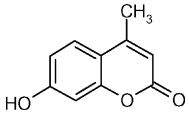
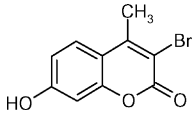
Entry	Substrate	Time (min)	Product	Isolated yield (%)
a		5		98
b		1		99
c		2		23, 77 (2-bromo, 4-bromo)
d		10		96
e		10		97
f		45		94
g		60		89
h		10		68 and 18, respectively
i		75		81
j		1		99
k		1		99
l		1		99
m		1		99
n		2		99

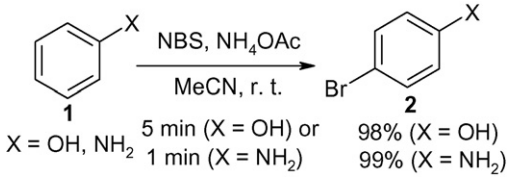
Table 1 (*Continued*)

Entry	Substrate	Time (min)	Product	Isolated yield (%)
o		10		98
p		1		99
q		2		97
r		5		95
s		10		90
t		1		98
u		20		95
v		45		91
w		45		90

[a] The structures of the products were settled from their spectral (^{1}H NMR and MS) data, ^{13}C NMR spectra of some of the compounds were also studied.

NH_4OAc afforded solely *p*-bromophenol in 5 min in an yield of 98% under the present experimental conditions (Table 1, entry a) while the similar reaction in absence of NH_4OAc furnished a mixture of products in 24 h in an yield of 68%. Thus the catalytic role of NH_4OAc is clearly established and it is also proved that the present method is superior to earlier methods [4] where NBS alone was used for bromination of activated arenes.

In conclusion, NBS in the presence of a catalytic amount of NH_4OAc is a simple and efficient brominating agent for nuclear monobromination of phenols and anilines at room temperature. The mild reaction conditions, rapid conversion, excellent yields and high regioselectivity are the impressive advantages of the present protocol.



Scheme 1.

1. Experimental

1.1. General procedure for bromination of phenols and anilines

To a mixture of a phenol or aniline (1 mmol) and NH_4OAc (10 mol%) in MeCN (5 ml) NBS (1.05 mmol) was added and the mixture was stirred at room temperature. After completion of the reaction as indicated by TLC the mixture was concentrated in vacco and extracted with EtOAc–H_2O (1:1) (3 × 5 ml). The organic portion was separated from the extract, dried and concentrated. The residue was subjected to column chromatography (silica gel, hexane–EtOAc, 10:1) to obtain pure monobromo phenol or aniline.

The spectral (^{1}H NMR and MS) data of some representative compounds are given below.

*1.1.1. 4-Bromo-2-methyl phenol (**2d**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18 (1H, d, $J = 2.0$ Hz), 7.10 (1H, dd, $J = 8.0$, 2.0 Hz), 6.56 (1H, d, $J = 8.0$ Hz), 4.86 (1H, brs), 2.18 (3H, s); EIMS: (*m/z*) 188, 186 ($M^{+\bullet}$).

*1.1.2. 3-Bromo-4-hydoxy-5-methoxy benzaldehyde (**2g**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.01 (1H, brs), 9.72 (1H, s), 7.59 (1H, s), 7.28 (1H, s), 3.96 (3H, s); EIMS: (*m/z*) 232, 230 ($M^{+\bullet}$).

*1.1.3. 3-Bromo-4(N,N-dimethyl)amino benzaldehyde (**2p**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.68 (1H, s), 7.86 (1H, d, $J = 2.0$ Hz), 7.59 (1H, dd, $J = 8.0$, 2.0 Hz), 6.94 (1H, d, $J = 8.0$ Hz), 2.82 (6H, s); EIMS: (*m/z*) 229, 227 ($M^{+\bullet}$).

*1.1.4. 4-Amino-3-bromo acetophenone (**2q**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99 (1H, d, $J = 2.0$ Hz), 7.66 (1H, dd, $J = 8.0$, 2.0 Hz), 6.70 (1H, d, $J = 8.0$ Hz), 4.82 (2H, brs), 2.46 (3H, s); EIMS: (*m/z*) 215, 213 ($M^{+\bullet}$).

*1.1.5. 2-Amino-5-bromo-3-picoline (**2s**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (1H, d, $J = 2.0$ Hz), 7.32 (1H, d, $J = 2.0$ Hz), 5.02 (2H, brs), 2.01 (3H, s); EIMS: (*m/z*) 188, 186 ($M^{+\bullet}$).

*1.1.6. 3-Bromo-7-hydroxy-4-methyl coumarin (**2w**)*

^{1}H NMR (200 MHz, $CDCl_3 + d_6$-DMSO): δ 10.21 (1H, brs), 7.48 (1H, d, $J = 8.0$ Hz), 6.78 (1H, dd, $J = 8.0$, 2.0 Hz), 6.78 (1H, d, $J = 2.0$ Hz), 2.58 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3 + d_6$-DMSO): δ 161.8, 156.7, 153.2, 150.8, 125.6, 114.2, 112.3, 107.5, 102.2, 19.4; EIMS: (*m/z*) 256, 254 ($M^{+\bullet}$).

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