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Mild and regioselective oxidative bromination of anilines using potassium bromide and sodium perborate

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Abstract

The selective monobromination of various deactivated anilines using potassium bromide and sodium perborate as oxidant has been achieved. The use of ammonium molybdate as catalyst accelerates the rate of reaction but is not essential to obtain good yields and high selectivities. © 2000 Elsevier Science Ltd. All rights reserved.

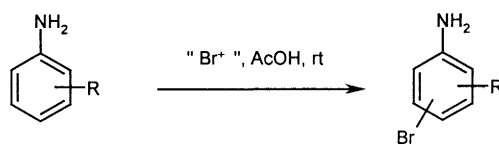
Historically, aromatic primary amines have been converted to the corresponding anilides prior to bromination if monosubstitution was desired.¹ However, new methods allowing good control over selectivity and polybromination of unprotected anilines have been reported in the past decade.^{2a–f} Among them, oxidative bromination using potassium bromide, hydrogen peroxide and various metal–oxo catalysts have gained much interest.^{2e,f} This method has the advantage not only of providing high selectivity but is also economical. In the course of our study on the oxidative bromination of methyl anthranilate, we investigated sodium perborate ($\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$) as the potassium bromide oxidant. Sodium perborate is widely recommended^{3a–c} as a cheap, safe and convenient alternative to hydrogen peroxide and its use in oxidative brominations has been reported, but mainly for anilides.^{2f} We wish to report herein our results on the bromination of a representative range of deactivated anilines using potassium bromide and sodium perborate in presence or absence of ammonium molybdate catalyst.

In contrast to what is reported on the oxidative bromination using hydrogen peroxide,^{2e} the presence of vanadium or molybdate catalyst is not required to obtain good selectivities and good yields of brominated materials. Indeed, the bromination of methyl anthranilate and anthranilonitrile using $\text{KBr}/\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ in acetic acid without molybdate catalyst (Table 1: entries 2 and 5) provided *o/p* ratios comparable with the known procedures^{2e} (entries 1 and 4) and better control over polybromination. This result could be well explained by the higher redox potential of sodium perborate compared to hydrogen peroxide at acidic pH. However, the rate of reaction was greatly increased in the presence of 1 mol% of ammonium molybdate (entries 3 and 6). Two to three hours were usually necessary to drive the reaction to completion versus 14 h in the absence of catalyst, rendering the use of catalyst more

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appealing. 2'-Aminoacetophenone was as well brominated with high *para* selectivity (94.2% *para*) in the presence (entry 8) or absence (entry 7) of catalyst. It is worth noting that although sodium perborate in AcOH has been used as a reagent to promote Baeyer–Villiger reactions at room temperature,⁴ ketones are compatible with the reaction conditions. Acid functionalities are compatible as well (entry 20), although bromination of anthranilic acid led to a moderate yield (entry 9). Excellent results were obtained with *ortho*-halogenated anilines (entries 10–13) which are attractive intermediates in organic synthesis.⁵ However, bromination of the strongly deactivated *ortho*-nitroaniline gave a mixture of mono and polybrominated compounds. Our method was extended to the bromination of *para*-substituted anilines (entries 15–20) which gave *ortho*-brominated compounds with good to excellent control over dibromination.

Table 1
Regioselective *mono* bromination of anilines



Entry	Substrate	Method	Reaction time (h)	SM	% Conversion ^a			Yield
					<i>para</i> ^d	<i>ortho</i> ^d	dibromo ^d	
1	methyl anthranilate	A	0.5	0	87.1	3.2	9.7	n.d.
2	"	B	14.5	4.3	92.0	3.7	0	88% ^c
3	"	C	4.0	1.3	95.4	3.2	0	99% ^b
4	anthranilonitrile	A	0.75	0	96.5	1.5	2.0	n.d.
5	"	B	14.5	0	98.2	<1	1.1	98% ^b
6	"	C	3.0	0	97.7	<1	2.2	98% ^b
7	2'-aminoacetophenone	B	14	0	91.4	5.3	<2	85% ^c
8	"	C	2	0	94.2	5.8	0	100% ^b
9	anthranilic acid	C ^e	2	3.7	82.0	7.5	n.d.	51% ^{c,f}
10	2-bromoaniline	B	14.5	0	96.9	<1	3.0	85% ^c
11	"	C	2	5	95.0	<1	0	98% ^b
12	2-iodoaniline	C	2.2	0	98.6	1.4	0	100% ^{b,f}
13	2-fluoroaniline	C	1	1.3	97.5	1.2	0	88% ^{b,f}
14	2-nitroaniline	C	1.25	23.2	48.9	2.3	25.6	n.d.
15	4-nitroaniline	C	2	1.4	-	98.6	0	95% ^b
16	4-aminobenzonitrile	C	1.5	0	-	>99	0	96% ^b
17	4-bromoaniline	C	2.25	0	-	96.3	3.7	87% ^c
18	4-iodoaniline	C	2	5.4	-	68.6	1.17	79% ^{b,f}
19	4-fluoroaniline	C	1.5	2.8	-	91.4	n.d.	87% ^{b,f}
20	4-aminobenzoic acid	C	2.25	0	-	85.6	0	75% ^c

Method A: KBr (1.2 eq.), 35% H₂O₂ (1.2 eq.), (NH₄)₆Mo₇O₂₄·4 H₂O (0.01 eq), AcOH, rt. Method B: KBr (1.2 eq.), NaBO₃·4H₂O (1.2 eq.), AcOH, rt. Method C: KBr (1.2 eq.), NaBO₃·4H₂O (1.05 eq.), (NH₄)₆Mo₇O₂₄·4H₂O (0.01 eq.), AcOH, rt. a) Determined by HPLC (λ 250 nm) and correlated by ¹H NMR; b) isolated material after aqueous workup; c) isolated yield after recrystallization; d) the products were characterized by NMR and MS; e) 1.3 eq. of NaBO₃·4H₂O and 1.4 eq. of KBr were used; f) charcoal filtration was used during the workup.

In a typical experiment, NaBO₃·4H₂O (9.3 mmol) was added at once to a suspension of KBr (10.1 mmol), anthranilonitrile (8.5 mmol) and ammonium molybdate (0.08 mmol) in AcOH (10 mL) at rt.

After stirring for 3 h, the reaction was quenched with a saturated solution of Na_2CO_3 and extracted with EtOAc. The organic extract was washed with a saturated solution of Na_2CO_3 , dried over MgSO_4 , filtered and concentrated to give 5-bromoanthranilonitrile (1.65 g, 98% yield, 98% *para*). Alternatively, the reaction was quenched with ice water. The resulting suspension was filtered, the white precipitate thoroughly washed with water and dried under vacuum at 40°C to give 5-bromoanthranilonitrile (1.5 g, 90% yield, 100% *para*).

In conclusion, we have developed a practical method using sodium perborate as an interesting alternative to hydrogen peroxide in the oxidative bromination of unprotected aromatic amines. Brominated anilines are obtained in good to excellent yields, and several chemical functionalities are compatible with the reaction conditions.

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