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Unexpected Rearrangement of 2-Bromoaniline under Biphasic Alkylation Conditions

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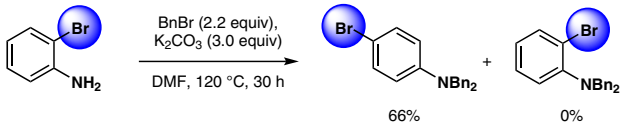
Dedicated to big brother Vic on the festive occasion of his entry into the ninth decade



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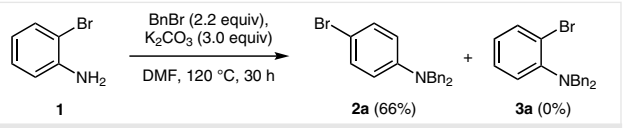
Abstract Alkylation of 2-bromoaniline with benzyl bromide under ostensibly basic N-alkylation conditions resulted in migration of bromine from the 2- to the 4-aryl position. Herein we report our studies to elucidate the mechanism of this rearrangement with the objective of suppressing this unexpected outcome. We find that careful choice of reagents is critical, and that this behavior may be extrapolated to alkylation reactions of electron-rich bromo- and iodoanilines in general.

Key words bromoaniline, alkylation, rearrangement, bromine

In the context of an ongoing investigation, we needed access to *N*,*N*′-dibenzyl-2-bromoaniline (**3a**) which we attempted to prepare by double benzylation of 2-bromoaniline. Much to our surprise, this process lead to the isolation of the *N*,*N*-dibenzyl-4-bromoaniline (**2a**) in 66% yield after recrystallization (Scheme 1). Furthermore, analysis of the crude reaction mixture showed that the 4-isomer was formed almost exclusively relative to the 2-isomer **3a**. Numerous examples of rearrangements of anilines are known, but most involve nitrogen-to-carbon migrations.[1] These may be divided into two categories in which the migrating group is either nucleophilic (e.g., the Bamberger[2] and quinamine[3] rearrangements) or electrophilic (e.g., the Hofmann–Martius,[4] Reilly–Hickenbottom,[5] Fischer–Hepp,[6] and Orton[7] rearrangements). To the best of our knowledge, there are no known rearrangements of anilines involving carbon-to-carbon migration of halogens from the 2- to 4-position under seemingly basic conditions, although the rearrangement of structurally related brominated benzothiazolones was reported by Mellor and Osbourne,[8] but this required concentrated HBr at reflux.



Scheme 1 Rearrangement of 2-bromoaniline under common biphasic alkylation conditions

Considering how often alkylation reactions are used, and the pervasiveness of haloanilines in synthesis, we sought to identify the mechanism of the rearrangement in hope of suppressing this undesired process and to establish if it is a general phenomenon. The reaction was investigated by varying substituents and conditions on a reduced scale. Authentic samples of 2- and 4-haloaniline isomeric products and putative intermediates (Figure 1) were independently synthesized (see Supporting Information), and the ^{1}H NMR spectra were compared with the spectra from the mechanistic experiments.[9] ^{1}H NMR spectroscopy was used for quantification and was confirmed by the unique ^{13}C NMR spectral fingerprint of each authentic sample. It should be noted that we chose to evaluate the reaction at

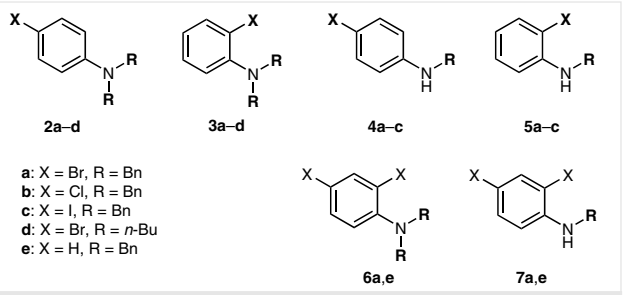
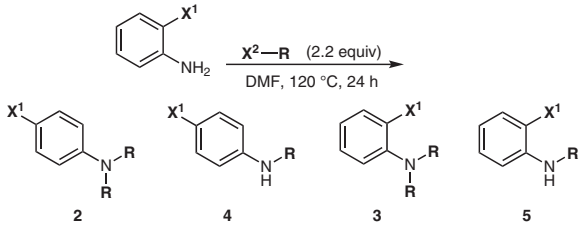


Figure 1 Variably halogenated and alkylated authentic standards were prepared and compared to test reactions

Table 1 Scope of 2-Haloaniline Rearrangement



Entry	X^1	X^2	R	Yield (%)[a]			
				2	**4**	**3**	**5**
1[b]	Br	Br	Bn	32	<1	15	21
2	Br	Br	Bn	67	<1	<1	2
3	Br	Br	*n*-Bu	9	52	22	<1
4	Br	Cl	Bn	0	0	53	32
5	Cl	Br	Bn	0	0	22	40
6	I	Br	Bn	0[c]	0[c]	0[c]	0[c]

[a] Yield determined by ^{1}H NMR spectroscopy against a known quantity of an internal standard (tetramethylurea) and standard error of the mean (SEM) for all reported values ≤ 3%.
[b] K_2CO_3 (3.0 equiv) added.
[c] Decomposition observed.

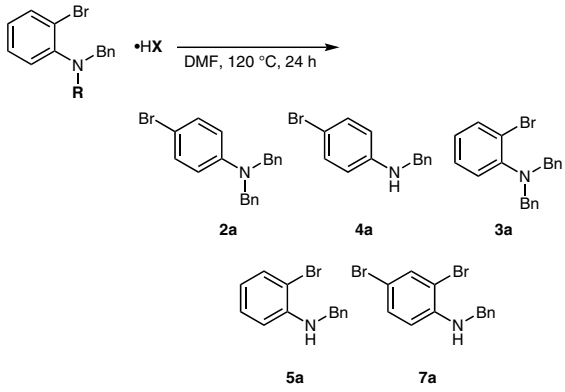
120 °C because this temperature is necessary to effect double alkylation, but significant amount of bromine migration was observed at lower temperatures as well (80 °C).

Under the original reaction conditions with K_2CO_3 (Scheme 1), the smaller-scale experiments afforded the rearranged product (Table 1, entry 1), albeit in diminished yield. Because K_2CO_3 is largely insoluble in DMF (7.5 g/L),[10] it is expected that the alkylation byproduct, HBr, must persist in the solution and may be causing the rearrangement. Indeed, in the absence of base the reaction resulted in nearly exclusive formation of the rearranged, dibenzylated product (Table 1, entry 2). Importantly, the rearrangement was not unique to benzyl bromide, as treatment of 2-bromoaniline with *n*-butyl bromide also afforded rearranged products (Table 1, entry 3).

To further test the scope of the process, the halogens on both the aniline and the benzyl halide were varied (Table 1). No rearrangement was observed in the alkylation of 2-bromoaniline by benzyl chloride (Table 1, entry 4), which suggested that HCl was not competent to induce the rearrangement. Interestingly, the reaction of 2-chloroaniline with benzyl bromide (Table 1, entry 5) also showed no rearrangement, despite the formation of HBr, probably because of the greater bond-dissociation energy of the C–Cl bond.[11] On the other hand, alkylation of 2-iodoaniline with benzyl bromide resulted in extensive decomposition (Table 1, entry 6).

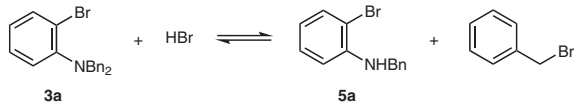
At this point it was uncertain if HBr could function as a catalyst for the rearrangement, and it was also unclear which benzylated intermediate (mono- or dibenzyl or both) was the competent bromine donor/acceptor. To address the first question, controlled quantities of hydrohalide salts of mono- and dibenzyl-2-bromoanilines were subjected to the reaction conditions without benzyl bromide. Interestingly, 0.1 equivalents of HBr (Table 2, entry 1) resulted only in debenzylation in an amount corresponding to the amount of acid added, with no indication of rearrangement. Therefore, HBr has the ability to facilitate debenzylation/benzylation to produce a source of benzyl bromide (Scheme 2). On the other hand, 1.0 equivalent of HBr (Table 2, entry 2) afforded a 33% yield of the *N*,*N*-dibenzyl-4-bromoaniline (**2a**) in addition to other products. The monobenzyl-2-bromoaniline hydrobromide salt also afforded a rearranged product (Table 2, entry 3), specifically 2,4-dibromoaniline **7a** and a corresponding amount of norbromoaniline **7e** (see Supporting Information). Predictably, the HCl salt did not effect rearrangement (Table 2, entry 4).

Table 2 Reactivities of 2-Bromoaniline Hydrohalide Salts



Entry	Aniline salt		Products (yield, %)[a]				
	R	HX	**2a**	**4a**	**3a**	**5a**	**7a**
1[b]	Bn	HBr	0	0	83	12	0
2	Bn	HBr	33	<1	21	43	8
3[c]	H	HBr	<1	0	0	26	21
4	Bn	HCl	0	0	56	34	0

[a] Yield determined by NMR spectroscopy against a known quantity of an internal standard (TMU) and standard error of the mean (SEM) ≤2% for all reported values.
[b] Using 9:1 free base/HBr salt.
[c] A significant amount of norbromoaniline **7e** also present.

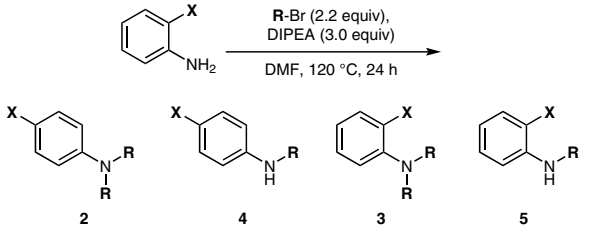


Scheme 2 Dynamic benzylation/debenzylation equilibrium

If HBr is the initiator for the rearrangement, and the insoluble K_2CO_3 does not neutralize this acid, it follows that a soluble base should effectively suppress bromine migration.

Predictably, addition of Hünig's base resulted in complete suppression of the rearrangement to afford only the expected dibenzylated product **3a** (Table 3, entry 1) with no evidence of the 4-isomer. This observation also held for the dibenzylation of 2-iodoaniline (Table 3, entry 2) as well as the di-*n*-butylation of 2-bromoaniline (Table 3, entry 3), for which absolutely no rearranged products were detected.

Table 3 Alkylations in the Presence of a Soluble Base



Entry	X	R	Yield (%)			
			2	**4**	**3**	**5**
1	Br	Bn	0	0	82[a]	<1
2	I	Bn	0	0	75[b]	<1
3	Br	*n*-Bu	0	0	83[b]	<1

[a] Yield determined by NMR spectroscopy against a known quantity of an internal standard (tetramethylurea), and standard error of the mean (SEM) <1% for the reported value.
[b] Isolated yield.

To obtain a better understanding of the intermediates involved, a time-course study was conducted to monitor the product profile at specific time points (Figure 2). Surprisingly, every proposed intermediate was present after one hour, including variably benzylated norbromo (**6e** and **7e**) and dibromo (**6a** and **7a**) anilines. After 12 hours, these intermediates converged upon a mixture enriched in *N*,*N*-dibenzyl-4-bromoaniline (**2a**) and persisted in their relative ratio until the last time point was taken, after 30 hours. Three nonexclusive explanations may account for the large number of intermediates: (1) the rearrangement is structurally indiscriminate; (2) complexity arises from reversible benzylation/debenzylation occurring in parallel to the rearrangement; or (3) the rearrangement is itself a dynamic system, and the ratio of intermediates reflects an equilibrium. Regarding this third hypothesis, Effenberger and others have shown that electron-rich bromoarenes reversibly isomerize in the presence of Lewis acids or HBr.[12]

To confirm that the rearrangement proceeds through a discrete electrophilic bromine source, 2-bromo and 2-chloroaniline together were subjected to the reaction conditions (Scheme 3). If the rearrangement is intermolecular, *N*,*N*-dibenzyl-4-bromo-2-chloroaniline (**9**) should be observed (since it was established that chloroanilines cannot rearrange). As shown in Scheme 3, this product clearly formed. Additional crossover experiments showed that the

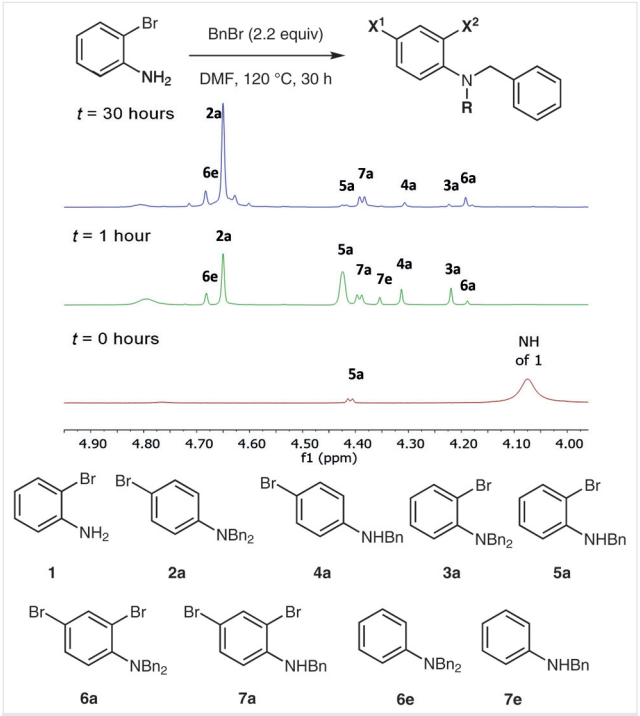
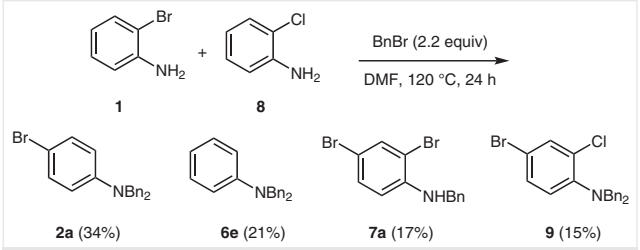


Figure 2 Time course for the rearrangement of 2-bromoaniline, in δ = 5.0–4.0 ppm window. Labeled peaks are those of benzyl methylenes.

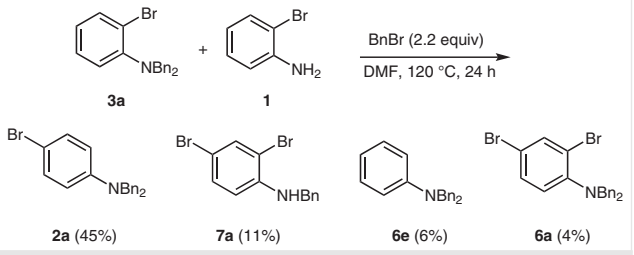


Scheme 3 Crossover experiment showing the intermolecularity of the rearrangement

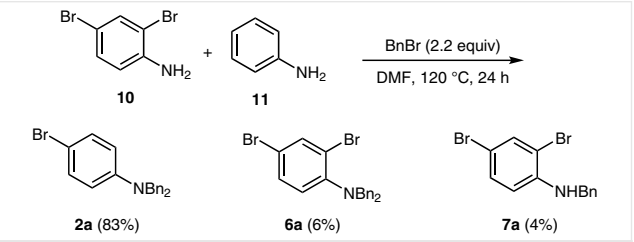
N,*N*-dibenzyl-2-bromoaniline (**3a**, Scheme 4), as well as dibrominated anilines derived from **10** (Scheme 5), were competent in transferring a bromine.

Interestingly, each experiment in which rearrangement occurred exhibited a deep blue color which was quenched upon aqueous workup. Such colors have been reported for stable arenium cations,[13] and it is highly probable that the rearrangement proceeded through such an intermediate, formed though protonation by a strong acid and stabilized by the electron-donating ability of the aniline nitrogen. This is also a likely point for bromine abstraction.

Three possible scenarios through which bromine may have been abstracted from the putative arenium cation intermediate can be formulated (Figure 3), involving attack by: (1) bromide ion, to form Br_2; (2) a nitrogen nucleophile, to form an N–Br species; or (3) a carbon nucleophile, in an



Scheme 4 Crossover experiment showing that *N*,*N*-dibenzyl-2-bromoaniline (**3a**) can undergo rearrangement



Scheme 5 Crossover experiment showing that 2,4-dibromoanilines are competent bromine donors in the rearrangement

S_EAr process. Although not observed directly, the evidence implicates the first scenario and the formation Br_2, because HCl (which could effect processes 2 and 3) does not induce rearrangement. It has been shown that both HBr and HCl effect bromoisomerization of similarly electron-rich arenes (bromocresols and dimethylanilines) though arenium cation intermediates,[12] and that the rate was dependent on the nucleophilicity of the bromine-abstracting nucleophile; consequently, HCl was substantially slower. Accordingly, rearrangement in the presence of HCl should be observed if either chloride, the aniline nitrogen, or the 4-carbon was the bromine-abstracting nucleophile, but this was not the case (Table 1, entry 4, and Table 2, entry 3); therefore, chloride, nitrogen, and carbon nucleophiles are not competent.

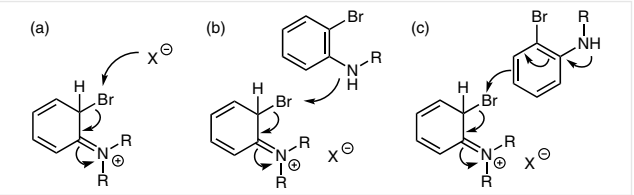
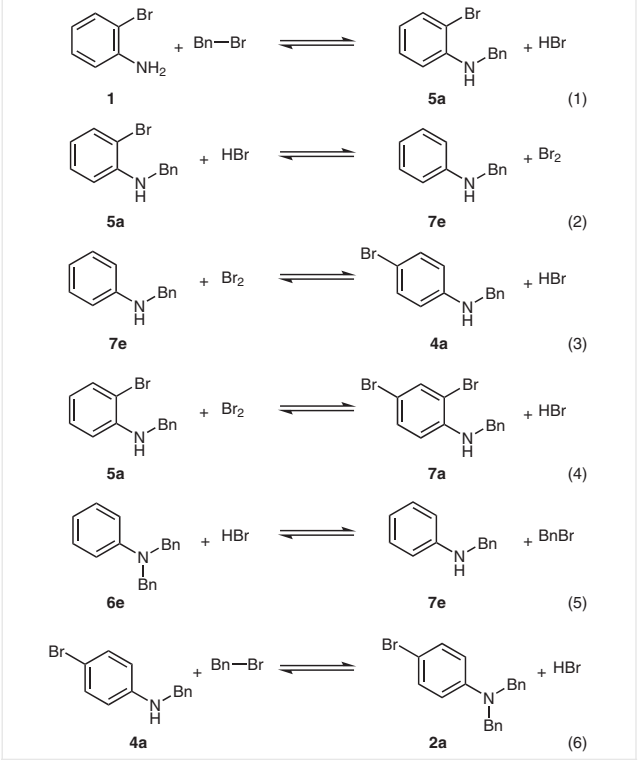


Figure 3 Three scenarios for bromine abstraction from an arenium cation, involving (a) halide, (b) nitrogen, or (c) carbon nucleophiles

Taken together the experimental evidence allows the following simplified mechanism to be proposed (Scheme 6). Benzylation of 2-bromoaniline affords the *N*-benzyl-2-bromoaniline (**5a**) and HBr (Scheme 6, eq. 1). It is likely that the arenium cation is derived from the monobenzyl aniline, as the dibenzyl anilines are expected to adopt a conformation that minimizes steric interaction with the arene, thereby twisting the nitrogen lone pair out of conjugation with the ring and diminishing its ability to stabilize a cation. Accordingly, *N*-benzyl-2-bromoaniline (**5a**) reacts with HBr to form *N*-benzylaniline (**7e**) and Br_2 (Scheme 6, eq. 2). It is again likely that the most nucleophilic species, the monobenzylanilines, react with Br_2 to preferentially form 4-bromo- and 2,4-dibromoaniline intermediates (Scheme 6, eq. 3 and 4). This step is made feasible by the larger pool of *N*,*N*-dibenzylaniline (**6e**) compared to *N*-benzylaniline (**7e**, see Figure 2), where *N*,*N*-dibenzylanilines would be expected to either react slowly or await debenzylation before undergoing bromination (Scheme 6, eq. 5). Benzylation of *N*-benzyl-4-bromoaniline (**4a**) affords *N*,*N*-dibenzyl-4-bromoaniline (**2a**, Scheme 6, eq. 6), and its enrichment may be attributed to a nitrogen conformation that diminishes stabilization of the arenium cation and thus susceptibility to further bromoisomerization.

In conclusion, we have clarified the mechanistic details of a rearrangement of 2-bromoanilines under alkylation conditions with a small set of strategically selected substrates, the results of which agreed with what little literature exists.[14] It is likely that other electron-rich bromo- and iodoarenes (not just simple bromoanilines) are susceptible to this type of rearrangement. Therefore, the significance lies not in synthetic utility but in the awareness of conditions that may lead to rearrangement. For optimal N-alkyla-



Scheme 6 Proposed mechanistic steps of the bromoaniline rearrangement

tion, use of soluble bases under single-phase reaction conditions, or the alternative use of alkyl chlorides, is recommended.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590882.

References and Notes

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(14) **General Procedure for Rearrangement Experiments**
The relevant aniline (0.5 mmol) was weighed into an oven-dried, threaded dram vial, followed by the sequential addition of anhydrous DMF (1 mL), an additional reagent (if required), and an alkyl halide (if required) last. The vial was tightly capped and placed in a pre-heated aluminum block (80 °C or 120 °C). After 24 h, the vial was removed from the block and allowed to cool to ambient temperature (23 °C), at which point it was *cautiously* opened (may be pressurized). The most common reaction colors are: colorless, black, amber, green, and blue. The reaction mixture was diluted with 1:1 hexanes/EtOAc (20 mL) and washed with 10% aq $NaHCO_3$ (30 mL), 10% aq LiCl (30 mL), and brine (30 mL), dried over anhydrous Na_2SO_4 (1 g), decanted, and concentrated on a rotovap (30 °C, 15 mm Hg). The crude product was then dried further under high vacuum (0.1 mm Hg) for 1 h before being diluted with a solution of a known quantity of tetramethylurea (TMU) in $CDCl_3$ (1 mL). The targeted quantity was 0.05 mmol TMU/1 mL $CDCl_3$, prepared as stock solutions in 10 mL volumetric flasks at 23 °C. TMU was measured by mass, and the actual quantity per mL $CDCl_3$ is reported. The solution was then transferred to a 5 mm NMR tube and analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy (600 MHz, ^{1}H).