



Photochemical conversion of 4-chloroaniline into 4-alkylanilines[†]

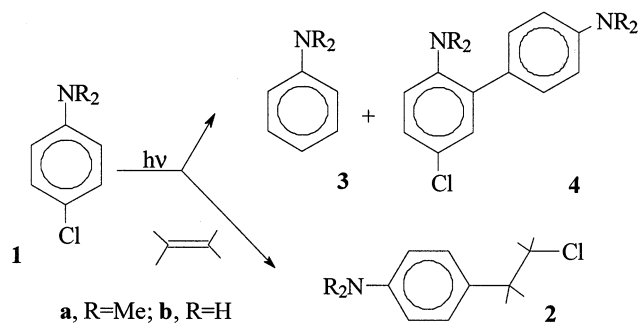
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Abstract—Irradiation of 4-chloroanilines in the presence of alkenes gives 4-(2'-chloroalkyl)-anilines. When the irradiation is carried out in the presence of NaBH₄, 4-alkylanilines are obtained directly. The reaction appears to occur via the corresponding phenyl cation. © 2001 Elsevier Science Ltd. All rights reserved.

Methods for the preparation of ring-alkylated anilines are scarce. As for alkylation of anilines, the Friedel–Crafts reaction has been applied only to some tertiary derivatives¹ and palladium-catalysed coupling occurs only with amides.² Other examples involve elaborate procedures such as metallation of chromium carbonyl complexes³ or reactions via *N*-sulfonium salts.⁴ Conversely, the seemingly appealing S_{RN}1 amination of alkylphenylhalides is restricted to a few applications.⁵ Therefore, entry to ring-alkylated anilines usually involves multistep procedures, generally the nitration of alkylbenzenes—with the associated problems of regioselectivity and side-reactions—followed by reduction.⁶ As an example, the reported synthesis of 4-alkylanilines, a class of compounds active as strong and selective aromatase inhibitors, involves a low-yielding multi-step procedure via the nitro derivative.⁷



Scheme 1.

Keywords: alkylation; photochemistry; alkyl halides; fragmentation reaction.

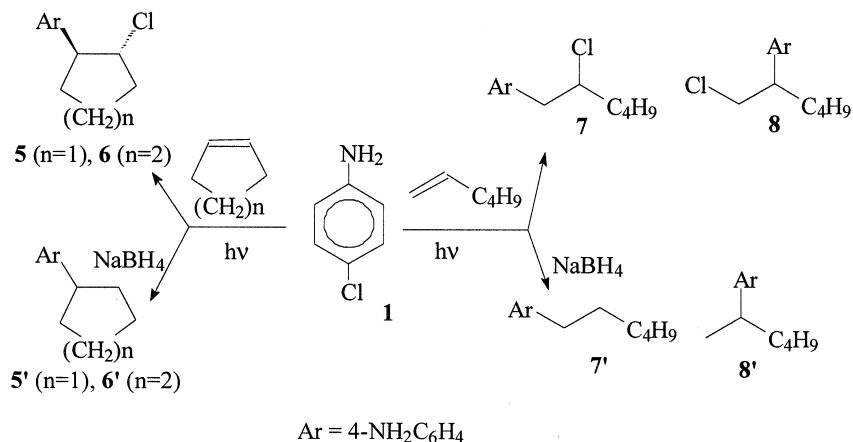
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We have recently reported⁸ that irradiation of 4-chloro-*N,N*-dimethylaniline (**1a**, Scheme 1) in the presence of benzene, as well as some alkenes, results in substitution of the chloro group by the phenyl or alkyl group (see formula **2**), whereas in the absence of such traps reductive dechlorination to give **3a** and coupling to give the monochloro diphenyldiamine **4a** occur. This offered an alternative entry to alkylanilines and we were eager to explore whether the reaction could be extended and, in particular, whether it also occurred with a primary amine such as **1b**.

In fact, we found that irradiation of 4-chloroaniline **1b** in neat acetonitrile proceeded in a manner similar to that of **1a**, yielding diamine **4b** and aniline **3b**. When the reaction was carried out in the presence of alkenes (1 M), the yield of products **3b** and **4b** was strongly reduced and 4-(β-chloroalkyl)anilines were formed in reasonable yields (55–73%). Thus, with both cyclopentene (*n*=1) and cyclohexene (*n*=2) the corresponding β-chloroalkylated compounds **5** and **6** were the main products (*trans* stereochemistry, see Scheme 2, Table 1). We then tested a non-symmetrically substituted olefin, 1-hexene, and found that the two regioisomeric adducts **7** (main product) and **8** were formed (ratio of **7/8** 1.9).⁹

Our current rationalisation is that the initial step is heterolytic photocleavage of the C–Cl bond, followed by the addition of the resulting phenyl cation (**9**, see Scheme 3)—and then of chloride—onto the alkenes. We carried out some experiments to test this mechanism (versus an alternative hypothesis where homolytic cleavage occurred and where the phenyl radical (**10**) was involved). Thus, the photoreaction of chloroanilines required a polar medium (e.g. both **1a** and **1b** were ca. 20 times less photoreactive in cyclohexane than in acetonitrile). 4-Iodoaniline, expected to undergo



Scheme 2.

Table 1. Results from the irradiation of 4-chloroaniline (**1b**) in acetonitrile in the presence of alkenes and NaBH₄

Alkene	Anilines (%)	Products (% yields)	
		Chloroalkylanilines	Alkyilanilines
None	3b (50), 4b (38)		
None, NaBH ₄	3b (95)		
<i>c</i> -C ₅ H ₈	3b (18), 4b (trace)	5 (60)	
<i>c</i> -C ₅ H ₈ , NaBH ₄	3b (28)	5 (8)	5' (48)
<i>c</i> -C ₆ H ₁₀	3b (25), 4b (trace)	6 (55)	
<i>c</i> -C ₆ H ₁₀ , NaBH ₄	3b (25)	6 (7)	6' (43)
<i>n</i> -C ₆ H ₁₄	3b (14), 4b (trace)	7 (48), 8 (25)	
<i>n</i> -C ₆ H ₁₄ , NaBH ₄	3b (25)	7 (2), 8 (3)	7' (39), 8' (21)

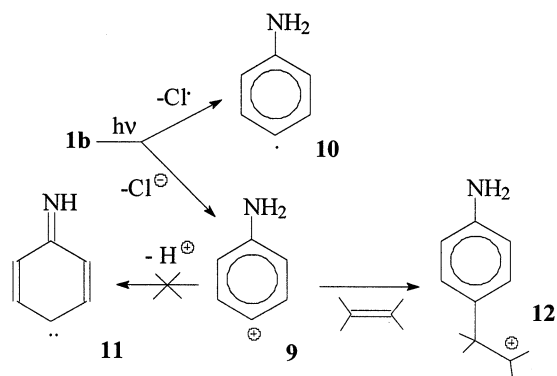
homolytic cleavage more easily, was also shown to be photoreactive, though less than **1b**. Indeed in this case the course of the reaction was suggestive of a radical, not of a cation, as the intermediate. Thus, in the presence of alkenes the main process was reduction rather than addition, and irradiating iodoaniline in the presence of acrylonitrile caused polymerisation of the latter, while this did not occur with **1b**. A further hypothesis was that cation **9** underwent *N*-deprotonation before addition to the alkene and that an iminocyclohexadienyl carbene **11**¹⁰ was involved. This, however, was discounted by the fact that both aniline **1b** and its *N,N'*-dimethyl derivative **1a** added to 1-hexene gave the same type of products (**7** and **8** and their dimethyl analogues) in similar yields.

Since our goal was that of obtaining alkyilanilines directly, we experimented with the effect of irradiation in the presence of a weak reducing agent. Thus, when a concentrated aqueous solution of NaBH₄/K₂CO₃ was added dropwise to a MeCN solution of **1b** during the irradiation, in the presence of the above alkenes, the yield of aniline **2b** was only slightly increased and the major change was that the chlorine-free alkylated anilines **5'**–**8'** replaced the corresponding chloroalkyl derivatives **5**–**8**. In the initial phase of the conversion, replacement was complete, but at the end of the reaction, probably because of the growing concentration of chloride, a small amount of products **5**–**8** were again formed. At any rate, the final ratio between non-chlori-

nated and chlorinated derivatives ranged from ca. 6 to 12. On the other hand, irradiation in the presence of NaBH₄ and omitting the alkene resulted in a clean reduction of **1b** to **3b** (yield 95%).

It appears that the intermediate phenyl cation **9** is reduced by NaBH₄, but in the presence of a large excess of alkene, it is preferentially trapped by the latter and it is the cationic adduct **12** (see Scheme 3) that is reduced to give directly the alkyilaniline.¹¹

Alkyilanilines **5'**–**8'** are easily freed from lower molecular weight anilines such as **1b** and **3b** and purified by bulb-to-bulb distillation. Thus, even if the yields are



Scheme 3.

moderate (43–60%), irradiation under these conditions has some preparative interest and derivatives that, as mentioned above, have pharmaceutical interest can be obtained in a single operation. Work aiming to establish the scope of this alkylation reaction and to clarify the mechanistic issues is under way.

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11. Irradiation of a solution of β -chloroalkylanilines in the presence of $\text{NaBH}_4/\text{K}_2\text{CO}_3$ does not cause their reduction. Thus, the reductive step occurs at the cation stage.