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A cheap and efficient method for selective *para*-iodination of aniline derivatives

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Abstract—A new and cheap protocol for controlled iodination in the *para*-position of various aniline derivatives is presented. It operates under mild conditions by reacting the aniline derivatives with molecular iodine in a mixture of pyridine/dioxane (1/1 vol) at 0 °C.

Iodinated aniline derivatives are useful compounds in many domains of synthetic organic chemistry. They are widely used as intermediates for the synthesis of biologically active molecules, including drugs, pesticides and fungicides.[1,2] Furthermore, the strong electron donating character of the amino group is currently exploited for the development of compounds where charge transfer is required, such as organic dyes or push–pull electro-optic chromophores for NLO.[3,4] They are also employed in a great number of metal-catalysed cross-coupling reactions since they display a much higher reactivity than the corresponding brominated or chlorinated derivatives. In these latter reactions, electron rich substrates, such as amino derivatives, react usually sluggishly with the metal catalyst in the initial oxidative addition step, imposing sometimes the use of the iodo derivatives to achieve good yields.[5]

However, selective iodination of aniline derivatives in the *para*-position is quite a complicated task when mild conditions are required. Amongst the numerous examples found in the literature, most of them imply the use of activators such as toxic heavy metals[5] (lead, mercury and chromium), strong oxidising agents[6–8] (IO_3 anions, silver complexes, H_2O_2 and NaOCl), or strong acidic[9,10] or basic conditions (trifluoroacetic acid, H_2SO_4 and KOH). Most of these methods are particularly harsh, costly, environmentally hazardous[11] and are not compatible with fragile functional groups.

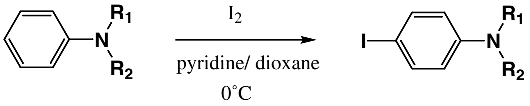

Figure 1. General procedure for iodination of aniline derivatives.

In this letter, we report an exceedingly simple, mild and efficient procedure for the *para*-selective iodination of aniline derivatives (Fig. 1).[12] In this procedure, besides the aromatic amine, the only reagent is molecular iodine dissolved in a mixture of pyridine and dioxane. The reaction is carried out at low temperature (0 °C), and offers in most cases, generally within 1 h, a quantitative conversion of the starting reactant. The results of this study are summarised in Table 1. The first models we used were the *N*-ethyl-*N*-hydroxyethylaniline and *N*,*N*-dihydroxyethylaniline (Table 1, entries 4 and 5), which are highly useful precursors in material sciences.[3] In both cases, the reaction worked with an almost quantitative isolated yield. These two examples demonstrated that this reaction is totally compatible with the presence of free hydroxy groups.

The reaction conditions were also successfully applied on alkyl substituted anilines, namely the *N*,*N*-dimethylaniline and *N*,*N*-dihexylaniline (Table 1, entries 2 and 3).

Keywords: Aniline iodination; Para-selective; Mild conditions.

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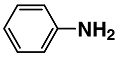
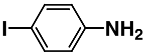
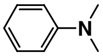
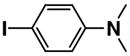
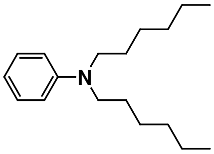
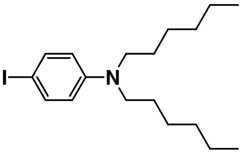
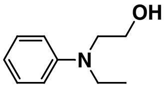
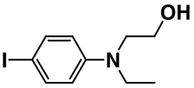
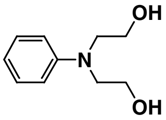
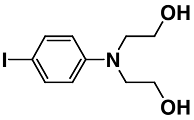
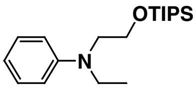
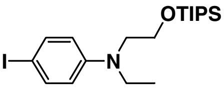
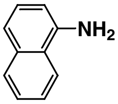
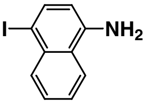
Table 1. Yield of isolated products following the reaction in Figure 1

Entry	Reactant	Product	Yield (%)
1			85
2			98
3			80
4			96
5			94
6			94
7			92

The isolated yield turned out to be lower in the case of the dihexyl substituted aniline, although an apparently quantitative conversion of the monomer was observed by TLC of the raw reaction mixture. This probably resulted from a partial decomposition of the product on silica gel, which progressively took a light blue color during the flash column chromatography. The isolated yield for 4-iodo-*N*,*N*-dimethylaniline was slightly higher than those reported in previous papers (98%) using different reagents.[10] More interestingly, the same protocol was applied on the unsubstituted aniline (Table 1, entry 1). Selective *para*-iodination of this molecule is known to be particularly tricky, as one can hardly avoid the formation of the *ortho*-isomer or poly-iodinated material.[7] Moreover, it generally operates with modest yields. To our satisfaction, such problems were not encountered with this protocol and the iodinated product was formed with a high yield and with an excellent selectivity. The successful iodination of the *O*-silyl protected analogue of the previously used *N*-ethyl-*N*-hydroxyethylaniline (Table 1, entry 6) evidences the softness of the procedure. Such silylated compounds are indeed especially sensitive to harsh acidic or basic conditions, and we shall notice that absolutely no deprotection of the product was observed consecutively to the reaction. Iodination of α-aminonaphthalene (Table 1, entry 7) also operated with a high yield, evidencing the possibility to carry out this reaction with amino naphthyl derivatives.

In summary the procedure presented in this letter is a mild and efficient way for controlled iodination in the *para*-position of aniline derivatives.

General procedure: the aromatic compound (5 mmol) was dissolved in dioxane (30 mL) and pyridine (30 mL) and the solution was cooled to 0 °C. Iodine (1.90 g, 15 mmol) was added in one portion. The solution progressively took a dark brown colour. After 1 h, the ice bath was removed and a supplementary portion of iodine (630 mg, 5 mmol) was added if needed. The solution was further stirred for one hour at room temperature. A saturated solution of sodium thiosulfate was then added until the brown colour disappeared. The mixture was extracted with dichloromethane (200 mL) and washed with water (200 mL). After evaporation, the product was filtered through a short plug of silica, eluted with the appropriate solvent.

Acknowledgment

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