# High Regioselectivity of Bromination of Anilines by Tetraethylammonium Chloride / Methanol System as Cocatalysts under Mild Conditions

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Abstract : An efficient and high regioselectivity for monobromination of a family of anilines in the para position is reported. Tetraethylammonium Chloride / Methanol are used as cocatalysts.

Several procedures have been described for direct introduction of bromine into aromatic nuclei of aniline derivatives. The bromination with molecular bromine is one of the classical methods  $^{1}$ .

Generally, the electron releasing substituents in the phenyl group create an ortho/para orienting effect, with low o/p ratio. The isomer distribution is strongly dependent on the nature of the bromine source which is employed.

Recently, the parabromination of anilines has been achieved by using the complex of molecular bromine with quaternary ammonium halides <sup>2-4</sup>.

Berthelot<sup>2</sup> and coworkers reported the reaction of commercially available tetrabutylammonium tribromide (TBABr<sub>3</sub>) with aromatic amines in aprotic and non basic solvents at room temperature. Surprisingly, in contrast with molecular bromine, acetanilide is not brominated in the described conditions.

Kajigaeshi <sup>4a</sup> et al. found that quaternary ammonium polyhalides in dichloromethane and methanol as cosolvents are more efficient. Even tetrabutylammonium tribromide brominated acetalinide in high yield (95 %) after 12 hours of reaction time <sup>4b</sup>.

Two drawbacks of these methodologies must be taken into account :

- first : the need for stoechiometric amounts of quaternary ammonium salt,
- second : due to the high molecular weight of the brominating reagents, the
- reactions are run in high dilution.

Consequently, these procedures are not suitable when multigrams of 4-Bromo products are needed.

An elegant paper of Heasley and coworkers 5 demonstrated that Lewis acids transform the sluggish hypohalites into highly reactive electrophiles. Shellhamer et al. 6 activate alkylhypochlorites via formation of a complex between xenon difluoride and the alkylhypochlorites.

Recently Sanson and Dakka <sup>7</sup> reported that quaternary ammonium salts can function as alternative Friedel-Crafts aromatic bromination catalysts. This group of catalysts is less efficient than iron and aluminium salts.

The main role of the catalyst in aromatic bromination consists in polarising the reagent in such a way that the bromine atom is as positive as possible. These results show that high active hypobromide produced from quaternary ammonium salt and methanol generates Br<sup>+</sup>.

This way, we anticipated that we could be able to brominate anilines with the triethylammonium chloride (TEACl) / methanol system as cocatalysts according to the following scheme.



#### **GENERAL BICATALYTIC SCHEME**

We found that when one equivalent of bromine in dichloromethane is added into a solution of dichloromethane containing one equivalent of aniline derivatives, 0.01 eq of TEACl and 0.5 eq of methanol, para-bromo derivatives are obtained in nearly quantitative yield <sup>8</sup>.



- 1.  $R^1 = R^2 = Me$
- 2.  $R^1 = CH_3, R_2 = H$
- 3.  $R^1 = COCH_3, R_2 = H$
- 4.  $R^1 = R^2 = CH_2 CH_2 OAc$
- 5.  $R^1 = R^2 = CH_2 CH_2 OH$
- 6.  $R^1 = R^2 = CH_2 CH_2 OTHP *$
- 7.  $R^1 = R^2 = CH_2 CH_2 OSi Me_2 Bu^t *$

\* The protecting group is removed : 5B is isolated (~ 99 %).

The addition of base in order to neutralize the acidity of the medium lowers the yield and requires longer reaction time. We conclued that hydrogen bromide activates the ammonium salts.

It is interesting to notice that 5B has been recently described as a precursor of organic materials for opto-electronic and nonlinear optical applications  $^{9}$ .

The extensions of this methodology will be published later.

Acknowledgements : the authors would like to thank Prof. J.F. Fauvarque for his encouragement during this work.

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### **Typical Procedure :**

Under argon atmosphere, to a well stirred solution of dichloromethane (100 mL) containing 26.5 g (0.1 M) of 4A, 1.65 g (0.01 M) of TEACl and 2 mL (0.05 M) of methanol, is added dropwise, a solution of bromine 16 g (0.1M) diluted in 100 mL of dichloromethane. CAUTION!! The reaction is exothermic and the temperature of the medium must not raise above 35 °C. During the addition, the brown coloration disappears instantaneously. The end of the reaction is determined by persistency of slight brown coloration. Triethylamine : 15 mL is added dropwise. The usual work-up gives 4B (99 %).

#### Note :

The bromination of 5A, 6A and 7A is identical to the procedure described above. After the addition of triethylamine, the solvent is removed ; flash chromatography on silica gel using diethylether as eluent gives 5B in quantitative yield.

(Received in France 8 December 1992; accepted 26 January 1993)