Simple and scalable iodination of 2,6–dialkylanilines: useful building blocks for synthesis.

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Method Article

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Abstract

The syntesis of 2,6-dimethyl-4-iodoaniline and 2,6-diisopropyl-4-iodoanilne is described. Both compounds were easily obtained in using an aromatic iodination reaction with molecular iodine. The desired products were isolated in nearly quantitative yields after a simple extraction. The crude materials are pure according to NMR.

Introduction

4–iodo–2,6–dialkylanilines are useful building blocks for chemical synthesis as highlighted in several recent publications describing diversified applications: medicinal chemistry[1,2,3], materials[4] and ligand design for catalysis[5]. These synthons are usually obtained by aromatic iodination of commercial 4,6-diiodoanilines. Most protocols imply the use of iodine monochloride, a hazardous fuming liquid[1,4,5], sophisticated reagents \(benzyltrimethylammonium dichloroiodate[3,6], \[K\(18-crown-6)]\(ICl_2)[7] or molecular iodine in combination with other reagents \(Ag_2SO_4[8] or iodic acid[2]). However, almost 50 years ago, the first publication describing the aromatic iodination of 2,6–dimethylaniline[9] implied a much simpler procedure using molecular iodine, which is also less hazardous than ICl. However, the isolation of the desired was reported only in moderate yield after a lengthy steam–distillation. While repeating this experiment we discovered that the crude material quantitatively recovered prior to distillation was analytically pure and could be used for further reactions. This simple protocol was simply scaled up to about 100 g of 4–iodo–2,6–dimethylaniline and 4–iodo–2,6–diisopropylaniline. See figure in Figures section.

Reagents

• 2,6–dimethylaniline \(liquid) • 2,6–diisopropylaniline \(liquid) • molecular diiodine \(solid) • diethyl ether • saturated aqueous sodium carbonate • saturated aqueous sodium thiosulfate • $CDCl_3$ for NMR sample preparation

Equipment

• balance • fume hood • 2 L two-necked round-bottomed flask • funnel • 2L separation funnel • 1 L or 2 L round-bottomed evaporation flask • 100 mL dropping funnel • mechanical stirrer • rotary evaporator • high vacuum pump • large crystallising dish • NMR spectrometer and tubes for NMR characterisation

Procedure

Synthesis of 4-iodo-2,6-diisopropylaniline 1) Equip a 2 L two-necked flask with a mechanic agitator 2) Weigh out 119 g \(0.466 mol) of iodine in a 500 mL round-bottomed flask. Dissolve it in 400 mL of diethyl ether. Pour the resulting solution into a 2 L two-necked flask using a funnel. Wash the funnel with a minimal amount of diethyl ether. CAUTION: if the balance is not inside a fume hood, iodine must be weighed in a stoppered flask. In this case, the zero of the balance must be set with the round bottomed flask and the stopper. The flask is then removed from the balance and iodine added inside a fume hood. The flask is stopper and weighed. This process is repeated until the desired mass is reached. 3) Add 1 L of a saturated sodium bicarbonate solution. 4) Charge a dropping funnel with 80.0 mL \(75.2 g, 424 mmol) of 2,6–diisopropylaniline. Add the aniline dropwise in the stirred reaction mixture \(approximate duration: 5 min). Gas evolution is observed. CAUTION: In the case the gaseous evolution becomes too vigorous, addition and stirring can be temporarily halted. 5) Stir vigorously the resulting biphasic mixture for 2 h. Gas evolution continues in the beginning of this period. PAUSEPOINT: It is possible to check the complete conversion by thin layer chromatography \(stationary phase SiO_2, elution with ethyl acetate/cyclohexane v/v 2:8 R_f\(2,6-dimethylaniline) = 0.60, R_f\(4-iodo-2,6-dimethylaniline) = 0.55) 6) Destroy excess iodine by addition of sodium thiosulfate until the aqueous phases becomes perfectly colourless. PAUSEPOINT: The colour of the aqueous phase is better observed by temporarily stopping agitation. 7) Separate the ethereal layer and extract the aqueous phase with 200 mL of diethyl ether. 8) Wash the combined organic phase with 300 mL of water, dry it over anhydrous sodium sulfate and evaporate using a rotary evaporator. 9) Dry the resulting dark liquid in high vacuum overnight. 10) Characterise the oily product by ^{1}H-NMR in $CDCl_3$. **Synthesis of 4-iodo-2,6-dimethylaniline** 1) Equip a 2 L two-necked flask equipped with a mechanic agitator 2) Weigh out 119 g \(0.466 mol) of iodine in a 500 mL round-bottomed flask. Dissolve it in 400 mL of diethyl ether. Pour the resulting solution into a 2 L two-necked flask using a funnel. Wash the funnel with a minimal amount of diethyl ether. CAUTION: If the balance is not inside a fume hood, iodine must be weighed in a stoppered flask. In this case, the zero of the balance must be set with the round bottomed flask and the stopper. The flask is then removed from the balance and iodine added inside a fume hood. The flask is stopper and weighed. This process is repeated until the desired mass is reached. 3) Add 1 L of a saturated sodium bicarbonate solution. 4) Charge a dropping funnel with 52.4 mL \(51.4 g, 424 mmol) of 2,6–dimethylaniline. Add the aniline dropwise in the stirred reaction mixture \(approximate duration: 5 min). Gas evolution is observed. CAUTION: In the case the gaseous evolution becomes too vigorous, addition and stirring can be temporarily halted. 5) Stir vigorously the resulting biphasic mixture for 2 h. Gas evolution continues in the beginning of this period. PAUSEPOINT: It is possible to check the complete conversion by thin layer chromatography \(stationary phase SiO_2, elution with ethyl acetate/cyclohexane v/v 2:8 R_f\(2,6-dimethylaniline) = 0.50, R_f\(4-iodo-2,6-diisomethylaniline) = 0.45) 6) Destroy excess iodine by addition of sodium thiosulfate with stirring until the aqueous phases becomes perfectly colourless. PAUSEPOINT: The colour of the aqueous phase is better observed by temporarily stopping agitation. 7) Transfer the reaction mixture to the 2 L separation funnel. Separate the ethereal layer and extract the aqueous phase with 200 mL of diethyl ether. 8) Wash the organic phase with 300 mL of water, dry it over anhydrous sodium sulfate and evaporate using a rotary evaporator using a 2 L . 9) Pour the resulting oil in a crystallizing dish along with a minimal amount of diethyl ether to wash the flask . During the drying process 4-iodo-2,6-dimethylaniline crystallises. CAUTION: Crystallisation, which is exothermic, may occur abruptly resulting in the dish to become hot. 10) Characterise the oily product by 1H-NMR in CDCl3.

Timing

4–iodo–2,6–diisopropylaniline: 4h + overnight drying. 4–iodo–2,6–dimethylaniline: 4h + overnight drying.

Anticipated Results

Typical isolated yield for 4–iodo–2,6–diisopropylaniline 97 % \(124.7 g). Yields obtained in smaller-scale preparations: 96% \(61.7 g), 94%** \(24.1g), 94%** \(10.4 g). *performed with magnetic instead of mechanic stirring. See figure in Figures section. Typical isolated yield for 4–iodo–2,6–dimethylaniline 81 % \(84.7 g). Yields obtained in smaller-scale preparations: 81% \(61.2 g), 94%\(47.7 g), 93%** \(9.6 g), 95%** \(5.8 g). *performed with magnetic instead of mechanic stirring. See figure in Figures section.

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Figures

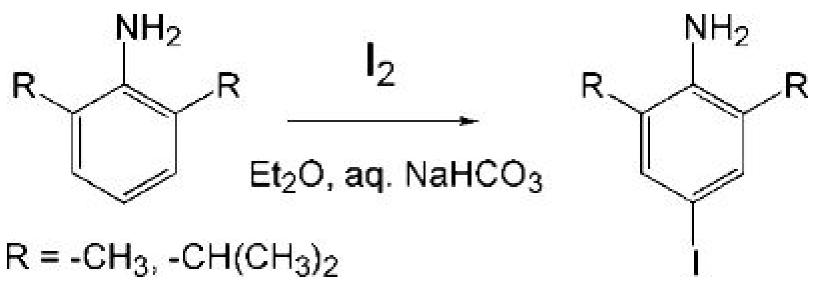

Figure 1

Scheme 1 Iodination reaction

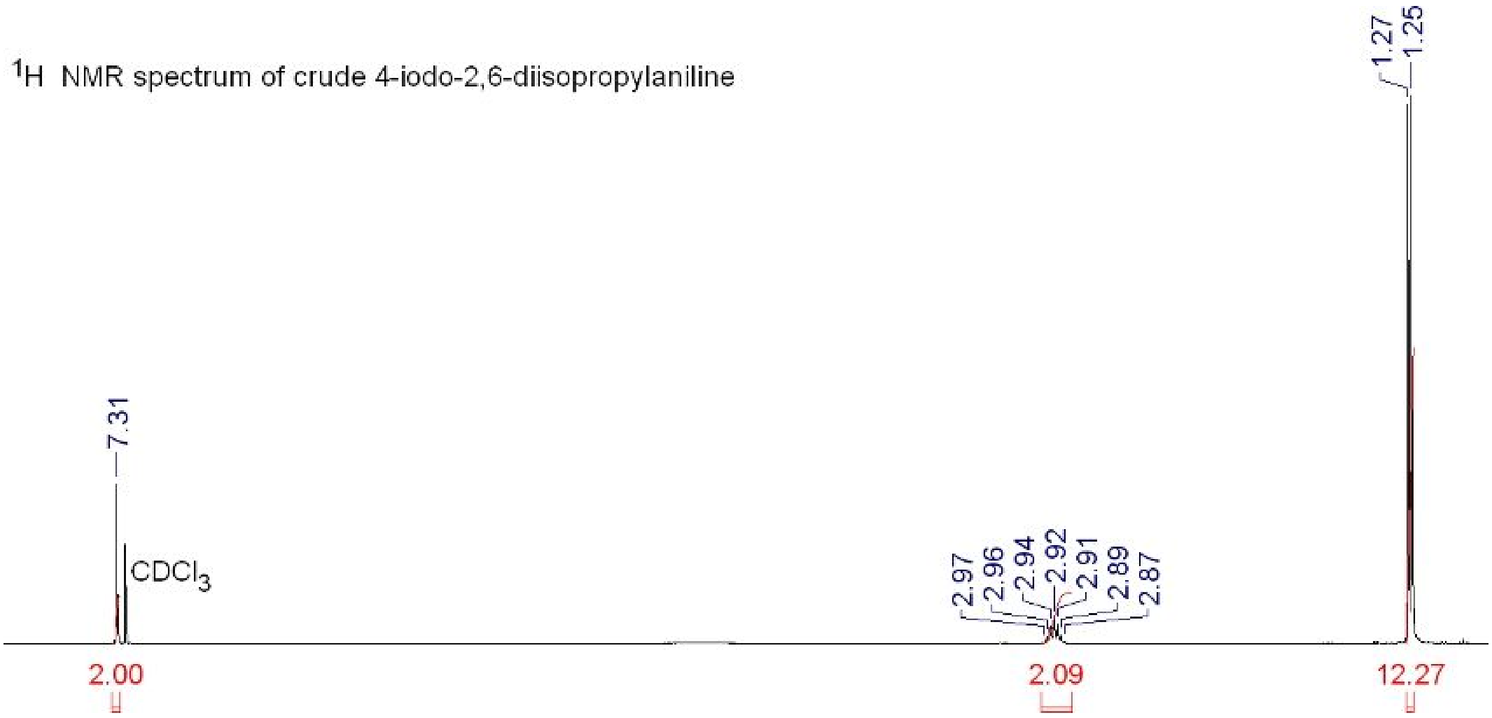

Figure 2

Figure 1 ^1^H NMR spectrum of 4-iodo-2,6-diisopropylaniline

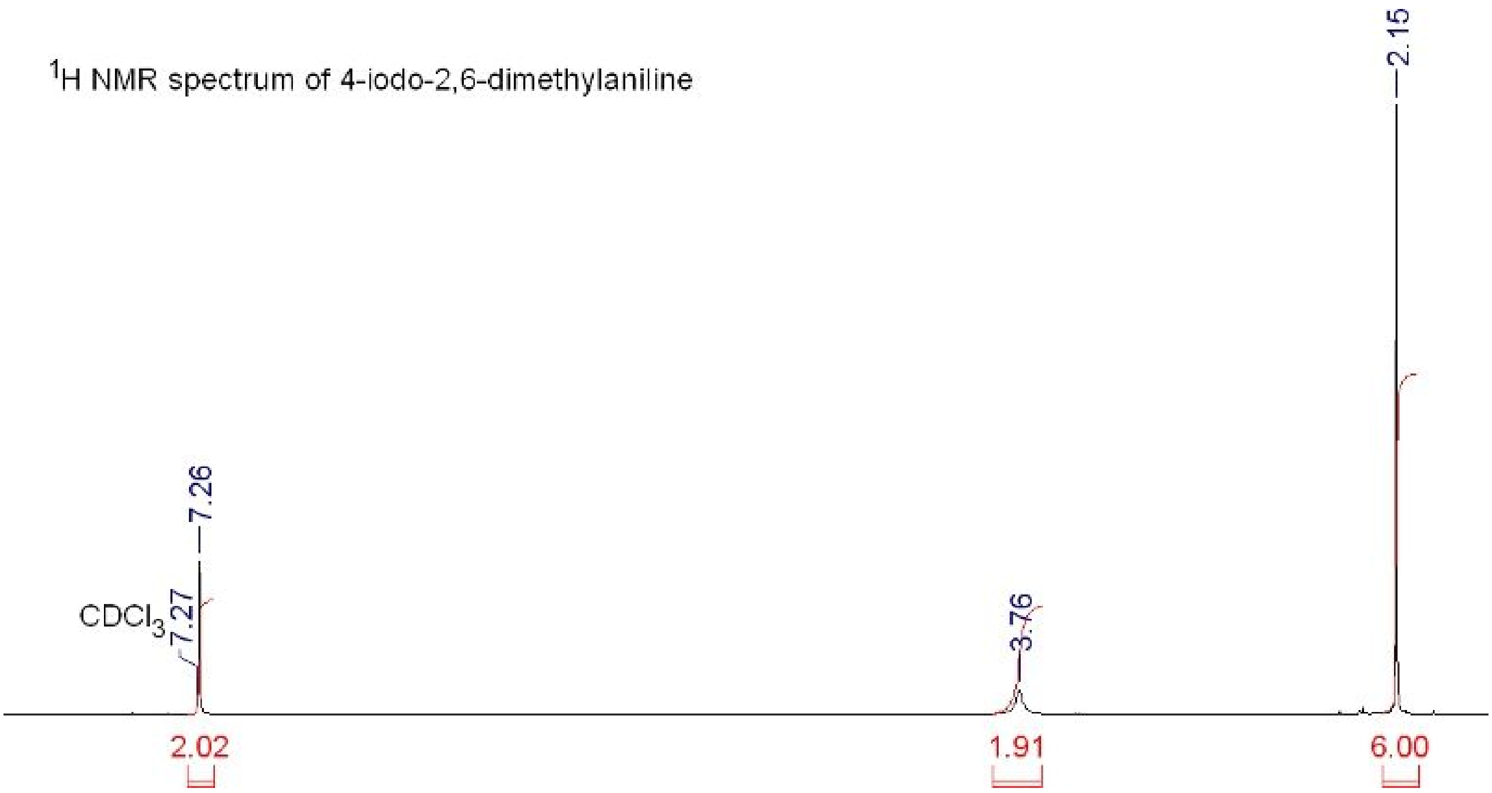

Figure 3

Figure 2 ^1^H NMR spectrum of 4-iodo-2,6-dimethylaniline