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p-Iodinations in hydrocarbon media: continuous flow reactor application

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ABSTRACT

Regiospecific iodination of aryl amines, that is, aryl compounds possessing strong electron donating groups (EDG's) in the *p*-position, is described. This procedure features not only unique use of hydrocarbon media for such substitutions but also the absence of any oxidants aside from iodine itself. Further potential of this hydrocarbon media based electrophilic aromatic substitution is demonstrated by the coupling of the iodination with an in situ halogen/lithium exchange and product forming nucleophilic addition in a batch process. The protocol was ultimately scaled to a continuous flow reactor using an isolated *p*-iodoarylamine. Constituted as described, these procedures possess enhanced atom-economical, green and safety aspects compared to existing literature protocols.

Electrophilic aromatic substitution (EAS) has long been the mainstay for the preparation of specifically substituted aromatic compounds. In spite of the many protocols developed for such substitutions, several drawbacks persist, for example, lack of regioselectivity, strong acid conditions, oxidative conditions and metal and/or acid containing hazardous waste streams. Not all drawbacks will exist simultaneously, but seldom will fewer than two of them be absent. In spite of these drawbacks, chemists have been able to devise conditions and modify reagents and aromatic substrates to effect reasonably efficient syntheses of numerous substituted arenes and hetarenes.

Halogenated arenes, particularly arylbromides and -iodides, are useful intermediates for further synthetic elaboration. Procedures for such elaborations are the halogen/metal (X/Li) exchange, Grignard formation and Pd intermediate formation. The X/Li exchange and Grignard intermediates provide entry to countless nucleophilic additions and substitutions while Pd intermediate formation leads to Heck, Stille, Suzuki and a multitude of related coupling reactions.

Classically, arylbromides and -chlorides are prepared using Cl_2 or Br_2 in an EAS reaction catalyzed by a small amount of an oxidative catalyst in a halogenated solvent. Textbook preparations of aryliodides often invoke use of I_2 and HNO_3. This latter protocol affords only modest yields. Neither of these approaches provides regiospecific aromatic substitution. Classically, all four halides can be regiospecificly prepared via diazonium salts.

Over the past two decades or so a number of papers have appeared describing novel routes to regiospecific *p*-iodination and *p*-bromination of arenes. Usually, but not exclusively, the aromatic substrates are activated, often highly activated, towards EAS. In each case an oxidant was found necessary. A few examples of these oxidants are: KIO_3[1] or $NaIO_4$,[12] $NaNO_3$[3] or $NaNO_2$,[6] $[S_2O_8^{2-}]$,[2,8,9,16] Urea·H_2O_2 solvent free complex,[13] HgO,[10] CrO_3[5] and Selectfluor™.[15] Solvent systems utilized were combinations of acetonitrile/$CHCl_3$,[14–16] CH_2Cl_2[10] Ac_2O/HOAc/H_2SO_4[3–5,9,11,12] or aqueous ether/alcohol.[1,2,7] Four distinct sources of iodine have been utilized, KI,[1,2,11] ICl,[7] I_2[3,5,6,8–10,12,13,15,16] and N-iodosuccinamide (NIS).[4,14] One procedure involving KI invoked an intermediate produced by thallation.[11] Although these approaches provide regioselectivity, they do so for the most part at the expense of raising both the hazardous components of the reactions and the toxic waste streams from the reactions. In these days of atom-economy, sustainability and overall emphasis on green chemistry, these procedures do not appear especially attractive.

We now bring to the community's attention the regiospecific *p*-iodination of eleven activated aryl amines under novel conditions that are both safer and greener than those in the literature (Table 1). These conditions feature use of I_2 in cyclohexane media (Eq. 1). The reactions are mostly run at room temperature in the presence of an aqueous phase of saturated Na_2CO_3 to neutralize the HI generated. Yields were lower when the HI was not neutralized. It is important that we point out, in addition to the novel use of cyclohexane as the reaction medium, that no external oxidant is necessary. Compared to the extant conditions for these iodinations, the absence of oxidative catalyst and the use of hydrocarbon media

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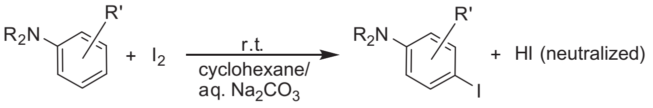
Table 1
GC and isolated yields of *p*-iodinated aryl amines

Substrates	Reaction time (h)	GC yield (%)	Isol. yield (%)	Lit. mp (°C)	Exp. mp (°C)
Aniline (**1**)	7	91	60	63.5–64.0[17]	63.5–64.5
2-Toluidine (**2**)	3	95	73	86[18]	86.5–87.0
3-Toluidine (**3**)	0.5	95	70	49.5–50[19]	40.5–42.0
N-Methylaniline (**4**)	2	90	80	30–32[20]	Oil
DMA[a] (**5**)	4.5	95	75	80–81[12]	81.5–82
2-Methyl-DMA (**6**)	24	21	12	Unknown	Oil
3-Methyl-DMA (**7**)	24	95	80	Unknown	61.5–63.0
3,5-Dimethyl-DMA (**8**)	24	85	64	54.5–55.0[21]	56.0–56.5
3-Methoxy-DMA (**9**)	24	81	65	Unknown	48.0–49.0
DEA[b] (**10**)	6	95	80	26–27[22]	Oil
Acetanilide (**11**)	24	70[c]	45	188–189[5]	182.0–183.0

[a] *N*,*N*-Dimethylaniline.
[b] *N*,*N*-Diethylaniline.
[c] NIS utilized as the iodinating agent (60 °C).

afford a much safer, greener and unique approach to these unusual *p*-substitutions.



(1)

Initial studies of the solvent media involved examination of 80% aqueous ethanol, ethanol, toluene, pentane, and hexanes in addition to cyclohexane. Most of these media afforded yields of iodination that were 10–20% lower than those realized using cyclohexane although for a few substrates yields obtained in hexanes and pentane were nearly comparable. Most of these initial runs were performed at a 0.67 M concentration. Once cyclohexane was chosen, further experiments were performed at 1.0 M, 1.67 M, and 2.2 M with 1.67 M ultimately chosen as the routine concentration. For maximum conversion, the reaction times varied for many of the anilines from 0.5 to 7 h, but for all the substituted DMA's and acetanilide 24 h was necessary. All the iodinations save that for acetanilide (**11**) utilized I_2. For acetanilide very low yields were obtained using this reactant; yields were greatly increased by switching to NIS as the sources of iodine. The other substrate affording a low yield, 2-methyl-DMA (**6**), also experienced significant yield enhancement (64%) using NIS. We attribute greater iodination reactivity to NIS compared to I_2 itself for these iodinations as a result of the enhanced yields observed for these two substrates. Isolated yields were not optimized. Curiously, we found no cases where mild heating provided benefit for iodinations using I_2. In two instances heating caused some decomposition.

A comparison was made of the yields afforded by our procedure and several of those found in the literature (Table 2). We note that for aniline itself, not only is a relatively high yield obtained, there is an improved *para*/*ortho* ratio. For the most part we conclude that a substituent with any dimension whatsoever will possess sufficient steric bulk to inhibit the transition state for *ortho*-iodination. This would be minimally true for both aniline (–NH_2 substituent) and phenol (–OH substituent) (not studied here).

Table 2
Reported yields from *p*-iodinations[a]

Substrate	Overall % yield	% *o*-	% *p*-
$PhNH_2$	(65)[1], (63)[2], 37[3], 20–83[13]	(6.5)[1](8)[2]	(58.5)[1], (55)[2]
PhNHAc	80[1], (47)[3], (80)[8]	Not reported	
DMA	83[1], 58[2]	Not reported	
$PhNH_2$[b]	(96) 60	(4.5)[c]	(91.4)
PhNHAc[b]	(70) 45	0	
DMA[b]	(95) 75	(<1)	

[a] Numbers in parenthesis represent GC yields.
[b] This Letter.
[c] 0.5% Diiodo product.

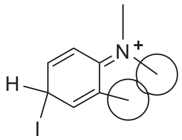


Figure 1.

The observation that an improved *p*-/*o*-ratio for aniline iodinated in cyclohexane compared to other media suggests, in addition to higher yields, that even greater regioselectivities can be realized under these conditions. It should be noted that both *o*- and *m*-toluidine are each *p*-iodinated with no detection of any *o*-iodinated product (Table 1).

Mechanistically, some evidence has been accumulated that supports an electrophilic substitution even under these non-polar conditions. The *p*-regiospecificity alone suggests an *ortho*-inhibited electrophilic mechanism. Moreover, protection from light radiation during several repeat runs for the iodination of DMA brought no observed change in reaction profile. Lastly, the low GC yield (21%) observed for the *p*-iodination of the 2-methylDMA, **6**, with I_2 suggests an increase in the transition state energy by an inhibition of resonance stabilization by steric inference (Fig. 1). The canonical structure involving delocalization of the positive charge to nitrogen is the principal contributor to the transition state resonance structure for *p*-iodination. Its inhibition as depicted in Figure 1 raises the transition state energy resulting in a significantly retarded reaction.

Use of I_2 in the reaction generates HI which must be neutralized to move the reaction towards completion. Accordingly, all of these reactions save one have been run as two-phase systems with the second phase being constituted of saturated Na_2CO_3. This procedure did not work well for acetanilide, a less activated substrate. NIS was found to afford an acceptable yield in this instance. Use of NIS avoided the need for the use of aqueous Na_2CO_3.

The success of this approach to the synthesis of *p*-iodinated arenes provides a potential for, essentially, a one-pot elaboration of the iodoarene. Both the X/Li exchange and Grignard formation could be effected by the simple expedient of drawing off the aqueous layer and directly subjecting the cyclohexane medium containing the generated iodoarene to either an alkyllithium reagent or a Grignard-forming reagent. This strategy cannot be employed for those arenes containing acidic hydrogens. Such a strategy is outlined for DMA (Eq. 2).