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Hypervalent (III) Iodine Reagent Catalyzed Highly Efficient *N*-Formylation in Water with Oxone® as a Co-oxidant

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***Abstract*—**Treatment of structurally diverse aniline derivatives with formic acid in the presence of catalytic amount of aq. $NaICl_2$ (25 mol%), carbon and oxone® in water at reflux temperature resulted highly efficient *N*-formylation to afford superior excellent yield of corresponding formamides.

***Keywords*—** *N*-formylation, *N*-acylation, Aq. Sodium Dichloroiodate, Hypervalent Iodine Reagent.

I. INTRODUCTION

N-FORMYLATION is an important process for the production of formamides, a versatile moiety in organic synthesis. Formamides have been widely used as precursor for synthesis of pharmaceutically important compounds such as 1,2-dihydroquinolines [1], oxalidinones [2], substituted aryl imidazoles [3] and nitrogen bridged heterocycles [4] etc. In addition, they are useful reagents in asymmetric allylation [5], hydrosilylation [6], Vilsmeier formylation [7], synthesis of formamidines [8] and isocyanides [9]; and as an amino protecting group in peptide synthesis [10]. Though number of methods has been reported for N-formylation using different formylating agents [11]-[19], most of them suffer from drawbacks such as use of expensive and toxic reagents, unavailability of reagents, long reaction time, thermal instability, strict anhydrous conditions and formation of byproducts.

Hypervalent iodine reagents have attracted a wide attention of the organic chemists to explore new and safe reagents. The advantages of different hypervalent iodine reagents have been widely demonstrated and successfully applied for various organic transformations. Our research group is highly active in the development of new methodologies using hypervalent iodine reagents [20]. Our decennial interest in new applications of hypervalent iodine reagents motivated us to discover novel, simple and highly efficient method for *N*-formylation.

II. RESULTS AND DISCUSSION

Initially, we selected to compare performance of various hypervalent (III) iodine reagents using aniline as moderate substrate (Table I). Very minor reaction was observed when (diacetoxyiodo)benzene was reacted with aniline and formic acid for 24 h. With dichloroiodobenzene as a reagent, reaction proceeded unsatisfactory with 55% yields. It was observed that when 2M aq. Sodium dichloroiodate ($NaICl_2$) solution was used, the product showed very minute evidence of desired *N*-formylation product. However, product was characterized as 2,6-diiodoaniline resulting from iodination of aniline. To overcome this undesired iodination, it was decided to add activated carbon (carbon) in reaction mass; as it is well known that iodine is well adsorbed on carbon. The reaction proceeded smoothly in water at reflux temperature to afford formanilide exclusively without any undesired byproducts. To improve reaction yield, oxone® was used as co-oxidant and this afforded high yield product at reflux temperature in 3 h.

TABLE I
INFLUENCE OF REAGENT RATIO ON *N*-FORMYLATION

Sr. No.	Reagent[a]	Time (h)	Yield (%)
1	(diacetoxyiodo) benzene	24	10
2	dichloroiodobenzene	13	55
3	Aq. $NaICl_2$	10	12
4	Aq. $NaICl_2$ and carbon	8	70
5	Aq. $NaICl_2$, oxone® and carbon	3	85
6	Aq. $NaICl_2$, (50 mol%), oxone® and carbon	3	86
7	Aq. $NaICl_2$, (25 mol%), oxone® and carbon	3	86
8	Aq. $NaICl_2$, (10 mol%), oxone® and carbon	6	61
9	Aq. $NaICl_2$, (1 mol%), oxone® and carbon	12	42

[a] All reagents are used in 1equivalence if not mentioned.

Encouraged by above results, the reagent system of aq. $NaICl_2$, oxone® and carbon was applied to investigate the role of various reaction parameters to optimize reaction conditions. The reaction was carried out with 50 mol% aq. $NaICl_2$, and surprisingly, the time taken for reaction completion remained the same. These results indicated that catalytic amount of aq. $NaICl_2$ was sufficient to drive the reaction to completion. The amount of aq. $NaICl_2$ varied from

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50 mol% to 1 mol% to check minimum amount of aq. NaICl$_2$ required for conversion of aniline to formanilide. Decreasing the amount of aq. NaICl$_2$ below 25 mol% led to perceptible change in reaction time and moreover yields were also slightly decreased. Though exact mechanism is yet to be established, we postulate that high surface area and excellent adsorption of iodine on carbon enhances availability of all ions and promotes catalytic reaction. The effect of oxone® on reaction efficiency was also examined and it was observed that a molar equivalent of oxone® produced best results. Indeed, the reduction of amount of oxone® below a molar equivalent significantly suppressed the yield of reaction and use of higher equivalents of oxone® resulted to undesired side products. Compared to various contents of carbon, the best results were obtained when one gram of carbon was used per ml of aq. NaICl$_2$. Although lesser amount of carbon did not affect the yield of reaction, higher amount of carbon eased the work up as it adsorbed colored impurities formed. Comparison of various solvents such as water, methanol, chloroform and DMF revealed that best yields were obtained using water. Subsequently, examination of reaction at various temperatures exhibited that reflux temperature was best choice with respect to the reaction time and yield (Fig. 1).

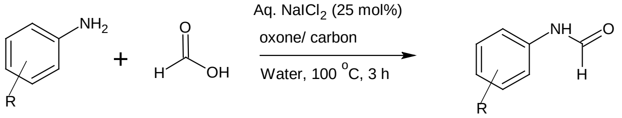
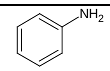
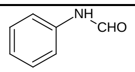
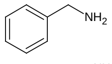
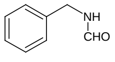
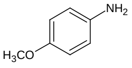
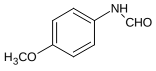
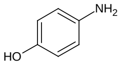
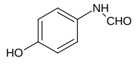
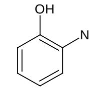
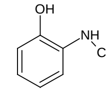
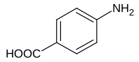
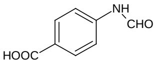
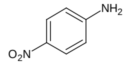
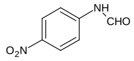
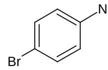
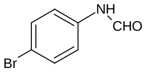
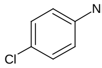
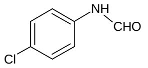
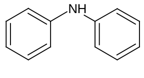
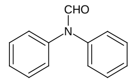


Fig. 1: Reaction of aniline derivatives with aq. NaICl$_2$ (25 mol%), oxone® (1 equiv), carbon (g/mL of aq. NaICl$_2$) and formic acid (2 equiv) in water at 100 °C to obtain corresponding formanilide derivatives

To evaluate potential of this novel reagent system, different structurally diverse primary and secondary amines were subjected to reaction parameters optimized for aniline. The reaction time and yields are summarized in Table II. The reaction proceeded well with various electron-rich, electron-deficient aniline derivatives to afford high to excellent yields of desired formamides.

TABLE II

N-FORMYLATION OF ANILINE DERIVATIVES USING OPTIMIZED REACTION CONDITION[a]

Sr. No.	Substrate	Product[b]	Time (h)	Yield (%)
1			3	86
2			3	86
3			3	87
4			3	84
5			3	84
6			3	79
7			3	80
8			3	85
9			3	85
10			5	68

[a] All reactions of aniline derivatives (1 mmol) were performed at 100 °C in the presence of formic acid (2 mmol), aq. NaICl$_2$ (25 mol%), Carbon (g/ cm^3 of aq. NaICl$_2$) and oxone® (1mmol) in water.

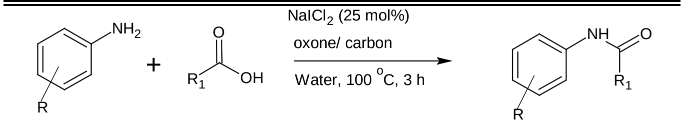
[b] All previously reported products were identified by comparison of their NMR spectra, GC-MS, and melting points with literature data.

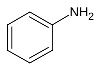
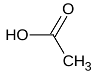
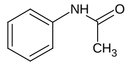
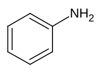
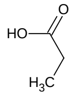
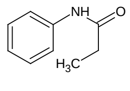
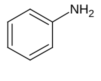
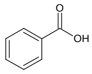
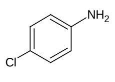
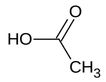
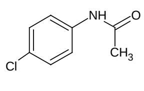
[c] Isolated yields of analytically pure products.

The accomplishment of *N*-fomylation encouraged us to investigate whether the *N*-acylation can be realized via this new protocol. It was observed that, the reaction of aliphatic acids with aniline derivatives proceeded in facile manner giving rise to 65-70% yield, but no reaction was observed when aromatic acid such as benzoic acid was used. The results are shown in Table III.

TABLE III

N-ACYLATION OF ANILINE DERIVATIVES



Sr. No.	R	R$_1$	Product[b]	Time (h)	Yield (%)
1				3	70
2				3	69
3			No reaction	-	-
4				3	67

[a] All reactions of anilines (1 mmol) were performed at 100 °C with corrosponding acid (2 mmol), aq. NaICl$_2$ (25 mol%), Carbon (g/ cm^3 of aq. NaICl$_2$) and oxone® (1mmol) in water.

[b] All previously reported products were identified by comparison of their NMR spectra, GC-MS, and melting points with literature data.

[c] Isolated yields of analytically pure products.

III. CONCLUSION

A highly efficient *N*-formylation of anilines with formic acid catalyzed by aq. $NaICl_2$, carbon and oxone® is revealed. Reaction conditions are optimized using different hypervalent iodine reagents and various reaction parameters. It should be noted that, reaction proceeds well with various electron-rich, electron-deficient aniline derivatives to afford high to excellent yields of desired formamides. Study of *N*-acylation adds an additional credit to the present work.

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(d) V. N. Telvekar, and K. A. Sasane, "Simple and facile benzylic C-H oxidation using (diacetoxyiodo)benzene and catalytic sodium azide," *Synth. Commun.*, vol. 42, pp. 1325–1329, 2012.
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[21] **Typical Experimental procedure:**
Aniline (0.1 g, 1.08 mmol) and formic acid (0.08 g, 2 mmol) were added to a suspension of 2 M aq. $NaICl_2$ (0.13 cm^3, 0.26 mmol), carbon (0.13 g) and oxone® (0.3 g, 1.08 mmol) in water (10 cm^3) and mixture was stirred at 100 ^oC for 3 h. Upon completion of reaction, the mixture was filtered to remove carbon. The filtrate was extracted with ethyl acetate (2 ×10 cm^3) and organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and crude residue was purified by column chromatography to yield pure formanilide.