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## ARTICLE TYPE

## Hypervalent Iodine -Catalyzed Oxidative Amidation of Methylarens

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Hypervalent iodine-catalyzed oxidative amidation of methylarens to the corresponding amides by using an oxidant (*tert*-butyl hydroperoxide, 70% aqueous solution) is discussed. This oxidizing agent presented a high degree of selectivity for the oxidation of toluene to amide without oxidation to carboxylic acid. This reaction involves the metal-free oxidation, mild reaction condition and *tert*-butyl alcohol as the only by-product.

Hypervalent refer to molecules with elements of groups 15-18 that break the octet rule and formally have more than 8 electrons in their valence shell.<sup>1</sup> The predominant use of hypervalent iodine compounds is that of oxidizing reagent replacing many toxic reagents based on heavy metals (Hg(II), Tl(III), Pb(IV)).<sup>2</sup> Mild reaction conditions, ease of handling, and commercial availability of these compounds are factors leading to revival of interest to hypervalent iodine compounds over the past decade.<sup>3</sup>

Iodine is most stable with an oxidation state -1; however, it forms stable polycordinate, multivalent compounds.<sup>4</sup> Current researches focus on its use in carbon-carbon and carbon-heteroatom bond forming reactions.<sup>5</sup>

Zhang et al. demonstrated that 1-(4'-diacetoxyiodo benzene)-3-methylimidazolium tetrafluoroborate [dibmim][BF<sub>4</sub>] catalyze the selective oxidation of alcohols to carbonyl compounds.<sup>6</sup> Zhdankin and co-worker presented that 2-Iodolphenol ethers can selectively oxidize sulfides to sulfoxides and alcohols to the respective aldehydes or ketones.<sup>7</sup> Also,  $\alpha$ -Acetoxylation of ketones in the presence of iodobenzene using acetic anhydride and 30% aqueous hydrogen peroxide was reported.<sup>8</sup> A 1-chloro-1, 2-benziodoxol-3(1*H*)-one/TEMPO catalyst system enables an efficient and selective oxidation of various alcohols to their corresponding carbonyl compounds.<sup>9</sup> Ishihara has reported the oxidation of alcohols to carbonyl compounds in the presence of *in situ*-generated 2-iodoxybenzenesulfonic acid from 2-iodobenzenesulfonic acid sodium salt.<sup>10</sup>

Aqueous oxidations of phenolic substrates to dearomatized quinones was first reported in 2012 by using  $\mu$ -oxo-bridged hypervalent iodine trifluoroacetate reagent.<sup>11</sup> An oxidative desulfurization method enabled the construction of oxadiazole and thiadiazoleheterocycles using iodobenzene and Oxone.<sup>12</sup> Recently, an intermolecular diamination of alkenes catalyzed by dinuclear iodine(III) reagents was reported.<sup>13</sup>

Amides are a highly important category of compounds with a variety of biological activities.<sup>14</sup> Therefore, the amide bond formation is of importance in view of synthetic and biological

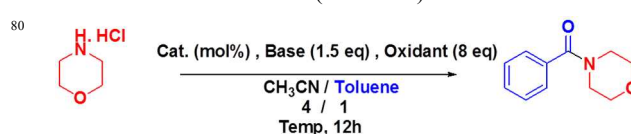
aspects.<sup>15</sup> Coupling of activated carboxylic acid derivatives and amine is one of the most conventional methods for the synthesis of amides.<sup>16</sup> Traditional approaches often require stoichiometric amounts of coupling reagents and produce toxic chemical waste.<sup>17</sup> Subsequently, several groups have described new methods for the synthesis of amides using metal-free oxidative amidation such as conversion of benzylic alcohols and benzylic halides into amides in the presence of molecular iodine in NH<sub>3</sub>, followed by treatment with H<sub>2</sub>O<sub>2</sub>,<sup>18</sup> Oxidative amidation of aldehydes and alcohols with primary amines catalyzed by KI-TBHP,<sup>19</sup> and the direct amidation of alcohols with N-Substituted formamides for the synthesis of *N*, *N*-dimethyl-substituted amide.<sup>20</sup>

The selective oxidation of primary C-H bonds due to the high energy of C-H bonds, and the selectivity issues arising from the increased reactivity of products as compared to starting materials has been represented one of the greatest challenges in catalysis.<sup>21</sup>

Moreover, the oxidation of aromatic hydrocarbons to benzyl alcohol, benzaldehyde and benzoic acid has been carried out in the presence of copper manganese oxides,<sup>22</sup> Mn/Si mixed oxides,<sup>23</sup> and Au-Pd/C<sup>24</sup> as catalyst.

Recently, Mizuno and co-workers have demonstrated for the first time that the aerobic oxidative amidation of methylarenes using ammonia in the presence of amorphous MnO<sub>2</sub>.<sup>25</sup>

This reported oxidative amidation of methylarenes rely on ammoxidation of methylarenes to nitriles, and followed by hydration to form the corresponding primary amides. Herein, we demonstrate that the direct oxidative amidation of methylarenes with hydrochloric salts of amines in the presence of hypervalent iodine with TBHP for the first time. Various secondary and tertiary amides were synthesized in good to excellent yields in one-pot manner under our conditions (Scheme 1).



**Scheme 1:** Synthesis of *N*-morpholinebenzamide catalyzed by hypervalent iodine

Initial experiments were performed with hydrochloride salt of morpholine in toluene as model substrates.

The presence of 10 mol % I<sub>2</sub> promoted the yield of **1a** to 33% (Table 1, Entry 1). However, this reaction did not work in the absence of hypervalent iodine as the catalyst. **1a** was formed in 40 % yield when catalyzed by NaI and TBHP as the oxidant in toluene at 80 °C (Entry 2). When the catalyst was replaced by PhI, the yield of

product decreased to 25 % (Entry 3). After a deal of screening of other hypervalent iodine as catalysts, the highest yield (57%) was achieved when KI was employed (Entry 4). Encouraged by these results, we examined the effects of solvents on the yield of product.

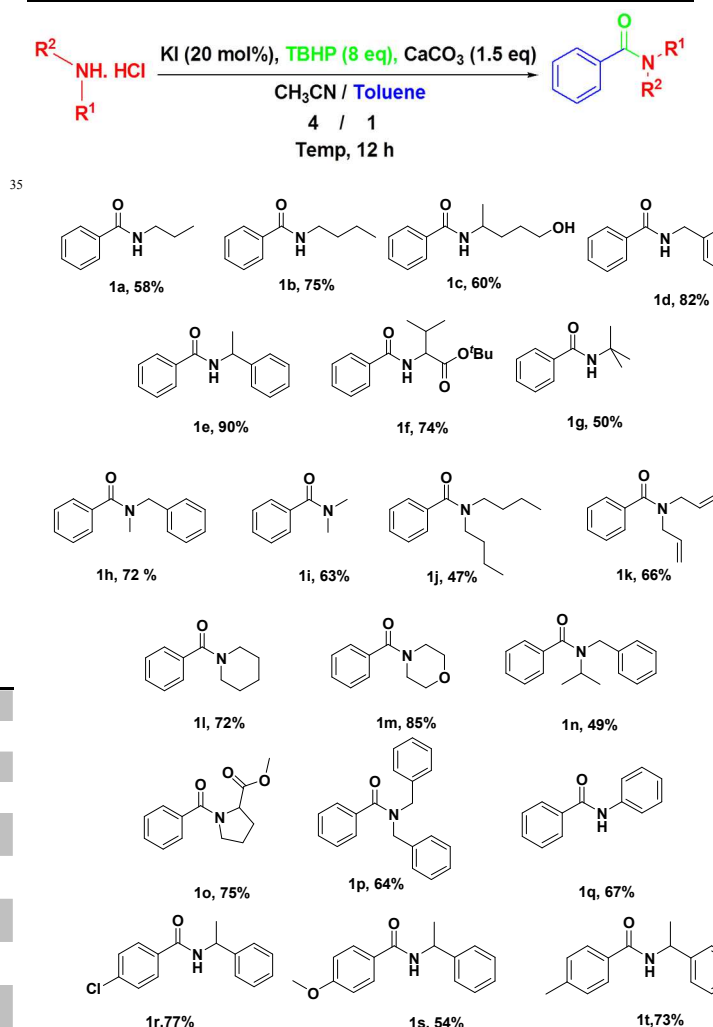
Since the formation of *N*-morpholinebenzamide wasn't favoured in toluene, we foresaw that dissolving the salt would be disfavoured in non-polar solvent. We therefore calculated that oxidative amidation would be more facile in polar solvents and attempted the oxidative amidation of toluene with hydrochloride salt of morpholine in a variety of solvents (Entries 5-8). In particular, acetonitrile / toluene (4/1) stood out as an excellent solvent for the synthesis of *N*-morpholinebenzamide (Entry 8). After that, we wanted to determine temperature which would further improve the yield of product. Temperature optimization revealed that 100 °C is suitable to provide identical yields of *N*-morpholinebenzamide **1a** after 12 h reaction time (Entry 12). We were pleased to find that the reaction in the presence of CaCO<sub>3</sub> as the base afforded the desired product with a yield of 70% (Entry 12). The *tert*-butyl hydroperoxide efficiency in this reaction was higher than other oxidants, confirming the ability of it to activate KI (Entry 12). With a catalyst loading of 20 mol%, the best result was achieved, which gave 85% yield after 12 h. Interestingly, the reaction with 25 mol% did not lead to comparable yield after 12 h reaction time. Moreover, in the absence of an oxidant or catalyst, the yield of benzamide **1a** was either much lower, or null. Attempts to investigate other different parameters, gratifyingly, furnishing benzamide **1a** was formed as the product in 85% yield when catalyzed by KI (20 mol %) and TBHP (8 equiv.) as the oxidant in toluene /acetonitrile (1:4) at 100 °C.

**Table 1:** Investigation of hypervalent iodine -catalyzed oxidative amidation<sup>a</sup>

Entry	Cat	mol (%)	Oxidant	Solv.	Base	Temp.	Yield <sup>b</sup>
1	I <sub>2</sub>	10	TBHP	Toluene	CaCO <sub>3</sub>	80	33
2	NaI	10	TBHP	Toluene	CaCO <sub>3</sub>	80	40
3	PhI	10	TBHP	Toluene	CaCO <sub>3</sub>	80	25
4	KI	10	TBHP	Toluene	CaCO <sub>3</sub>	80	57
5	KI	10	TBHP	THF/Toluene (4/1)	CaCO <sub>3</sub>	80	60
6	KI	10	TBHP	DMSO/Toluene (4/1)	CaCO <sub>3</sub>	80	61
7	KI	10	TBHP	Dioxane/Toluene (4/1)	CaCO <sub>3</sub>	80	47
8	KI	10	TBHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	80	64
9	KI	10	TBHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	25	30
10	KI	10	TBHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	40	41
11	KI	10	TBHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	60	53
12	KI	10	TBHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	100	70
13	KI	10	TBHP	Acetonitrile/Toluene (4/1)	Na <sub>2</sub> CO <sub>3</sub>	100	<5
14	KI	10	TBHP	Acetonitrile/Toluene (4/1)	K <sub>2</sub> CO <sub>3</sub>	100	36
15	KI	10	TBHP	Acetonitrile/Toluene (4/1)	Et <sub>3</sub> N	100	31
16	KI	10	<i>m</i> CPBA	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	100	29
17	KI	10	H <sub>2</sub> O <sub>2</sub>	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	100	48
18	KI	10	UHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	100	55
19	KI	5	TBHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	100	30
20	KI	15	TBHP	Acetonitrile/Toluene (4/1)	CaCO <sub>3</sub>	100	76

21	KI	20	TBHP	Acetonitrile / Toluene (4/1)	CaCO <sub>3</sub>	100	85
22	KI	25	TBHP	Acetonitrile / Toluene (4/1)	CaCO <sub>3</sub>	100	85
23	KI	-	TBHP	Acetonitrile / Toluene (4/1)	CaCO <sub>3</sub>	100	<10
24	KI	20	-	Acetonitrile / Toluene (4/1)	CaCO <sub>3</sub>	100	N.R.
25	KI	10	TBHP	Acetonitrile / Toluene (8/1)	CaCO <sub>3</sub>	100	70

<sup>a</sup> The reactions were carried out with hydrochloride salt of morpholine (1.5 mmol), base (1.5 eq), oxidant (8 equiv), toluene (0.5ml), under Ar at 100 °C for 12 h. <sup>b</sup> Isolated yield.



**Scheme 2:** Oxidative amidation of methylarenes using hypervalent iodine with hydrochloride salt of amines (1.5 mmol), CH<sub>3</sub>CN (2 ml), oxidant (8 equiv), toluene (0.5ml) under Ar at 100 °C for 12h

To calculate the isolated yield when 0.183 g of hydrochloride salt of morpholine (1.5 mmol) was reacted with an excess of toluene. The reaction gave a percent yield of 85%.

$$\begin{aligned}
 &0.183 \text{ g morpholine hydrochloride} \times \frac{1 \text{ mmol morpholine hydrochloride}}{0.122 \text{ mmol morpholine hydrochloride}} \times \frac{1 \text{ mmol amide}}{1 \text{ mmol morpholine hydrochloride}} \\
 &\times \frac{0.191 \text{ g amide}}{1 \text{ mmol amide}} = 0.40 \text{ g Theoretical Yield} \\
 &\frac{0.34 \text{ Actual yield}}{0.40 \text{ g Theoretical Yield}} \times 100 = 85 \%
 \end{aligned}$$

After that, the scope of the present KI/TBHP system with regard to

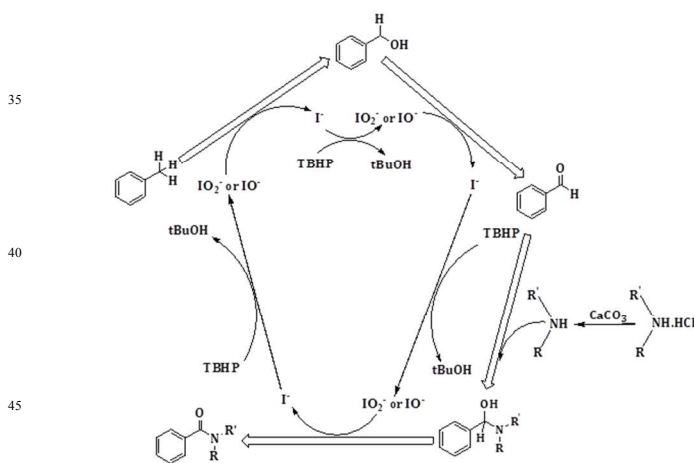
a series of secondary and tertiary amides was examined. KI/TBHP showed high catalytic activity for this transformation. As can be seen in table 2, aliphatic amines such as propyl amine, butyl amine, 2-amino-1-butanol and *tert*-butyl amine were converted into their corresponding amides in moderate to good yield (respectively 58, 75, 60 and 50%). Notably, no oxidation was observed in alcoholic function in 1c.

Under standard conditions toluene was replaced by *para*-anisole, *para*-chlorotoluene and *para*-xylene and after 12 hours afforded respectable yields. Assessment of table 2 reveals that the reaction is compatible with a series of primary and secondary amines and both aromatic and aliphatic amines. The reaction is also compatible with amino esters (1f, 1o). All these products were characterized by recording melting points (in some cases), IR, <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR spectra.

Wei and colleagues detected unstable iodite (IO<sub>2</sub><sup>-</sup>) and hypoiodite (IO<sup>-</sup>) species by means of negative ion ESI-MS analysis. According to these observations, they suggested that *in situ* generated hypoiodite or iodite species should be the actual oxidant in the presence of H<sub>2</sub>O<sub>2</sub> and Bu<sub>4</sub>Ni.<sup>26</sup>

After these pioneering findings, a plausible reaction pathway for the oxidative amidation of toluene is shown in Scheme 3. The highly reactive iodine (I) intermediate (IO<sup>-</sup>) or iodine (III) intermediate (IO<sub>2</sub><sup>-</sup>) are the actual oxidants to afford benzyl alcohol. Next, benzaldehyde will potentially be generated, and this will be followed by the formation of hemiaminal. Actually, benzaldehyde reacts with the free amine that is obtained from the reaction of the amine.HCl salt with calcium carbonate to generate hemiaminal.<sup>27</sup>

Benzamide will then be obtained from this intermediate *via* the oxidation and regenerate (I<sup>-</sup>).



**Scheme 3:** Plausible mechanism for the oxidative amidation of toluene with hydrochloric salts of amines in the presence of KI-TBHP

In summary, hypervalent iodine (KI) can serve as an efficient catalyst in the oxidative amidation of toluene using TBHP as an oxidant. Mild reactivity with good yields, availability, non-toxic, and benign environmental character are factors using KI as catalyst. More studies about other catalytic methods, in this reaction class, are ongoing.

## Notes and references

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