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I_2/Aqueous TBHP-Catalyzed Coupling of Amides with Methylarenes/Aldehydes/Alcohols: Metal-Free Synthesis of Imides

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Supporting Information

ABSTRACT: We present a metal-free method for the synthesis of imides by the direct coupling of NH-amides with methylarenes under iodine/aqueous TBHP conditions. The optimized conditions worked very well with benzaldehydes and benzyl alcohol and furnished the corresponding imides in good to excellent yields. A series of control and radical scavenger experiments were also performed, which suggested the involvement of radical pathways. The labeling experiment in the presence of ^{18}O-labeled H_2O suggested water as a source of oxygen in the imides.

The wide occurrence of imides from nature to pharmaceutical to material explains their importance in chemical space. The natural products containing an imide moiety are rebeccamycin,[1a] fumaramidmycin,[1b] palauimidine,[1c] berkeleyamide B and C,[1d] penimidine A,[1e] pestalamides A and B,[1f] granulatimide,[1g] isogranulatimide,[1h] and brabantamides A−C.[1i] The pharmaceutical products having an imide moiety are thalidomide,[1j] anircetam,[1k] and ethosuximide.[1l] Similarly, examples of fungicide and polymer are capton and Kapton, respectively.[2] Considering their wide occurrence and importance, the methods for their synthesis are of high interest. Historically, these were synthesized either by acylation of amides, by coupling of amines with dicarboxylic acids (or anhydride),[3a] or by Mumm rearrangement of isoimides.[3b] Alternatively, oxidation of *N*-alkylamides was also used for the synthesis of imides, which was reviewed recently.[4] By comparing all these methods, acylation of amides is considered as one of the easy and direct methods, but it has limited substrate scope due to the weak nucleophilicity of amides and the requirement of activated acyl partners. To counter these limitations, C−H activation methods provide an attractive strategy, and recently, few attempts were made where copper- and iron-based C−H activation methods were employed for the acylation of amides using aldehyde as a coupling partner (Figure 1).[5,6] By employing aldehyde as an acyl coupling partner, Hong et al. also reported a Ru-catalyzed (Shivo's catalyst) method for the synthesis of imides.[7] In last two decades, iodide/iodine in the presence of oxidant represents a metal-free and effective alternative method for C−H activation to construct C−C and C−heteroatom bonds.[8] Moreover, iodide/iodine along with TBHP has been successfully utilized for

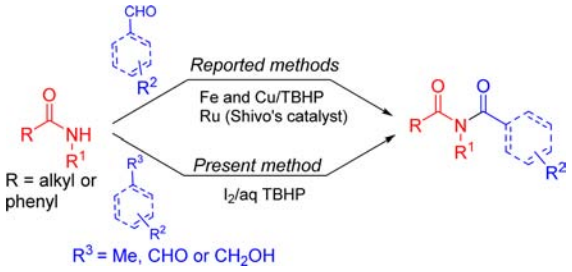

Figure 1. Previous and present approaches.

activation of benzylic and aldehydic C−H to construct amides;[9] however, to the best of our knowledge, no reports have been demonstrated for the synthesis of imides. Here, we have developed a metal-free method for the synthesis of imides employing an iodine/TBHP catalytic system.

In a first attempt, reaction between **1a** and **2a** in the presence of a TBAI/TBHP catalytic system, a trace amount of required product **3a** was obtained (Table 1, entry 1) along with some quantity of benzaldehyde. Upon replacement of TBAI with I_2, 24% of product **3a** was obtained (Table 1, entry 2) along with some quantity of benzaldehyde. Next, the addition of additive such as Na_2CO_3 gave the required product **3a** in a yield of 72% (Table 1, entry 3). After this, the reaction was again attempted with TBAI along with TBHP and Na_2CO_3, but only a trace amount of product **3a** was observed (Table 1, entry 4). In a

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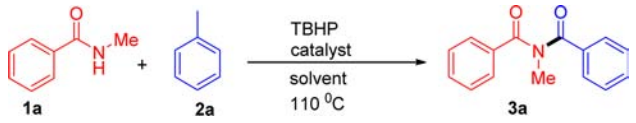
Table 1. Optimization Studies[a]



entry	catalyst	solvent	additive	yield[b] (%)
1	TBAI	neat		trace
2	I_2	neat		24
3	I_2	neat	Na_2CO_3 (0.5 equiv)	72
4	TBAI	neat	Na_2CO_3 (0.5 equiv)	trace
5	KI	neat	Na_2CO_3 (0.5 equiv)	65
6	I_2	neat	Na_2CO_3 (1 equiv)	71
7[c]	I_2	neat	$ZnBr_2$	69
8[c]	I_2	neat	$FeCl_3{\cdot}6H_2O$	54
9[c]	I_2	neat	CuI	trace
10	I_2	DCE	Na_2CO_3	trace
11	I_2	ACN	Na_2CO_3	trace

[a]All of the reactions were performed with 1 mmol of amide **1a**, 20 mmol of toluene **2a**, 6 mmol of aq TBHP, 0.2 mmol of catalyst, 0.5 mmol of additive at 110 °C, 20 h. [b]Isolated yields. [c]0.2 mmol of additive was used.

further attempt, replacement of catalyst I_2 with KI furnished 65% of product **3a** (Table 1, entry 5). An increase in the amount of Na_2CO_3 from 0.5 equiv to 1 equiv did not affect the product formation (Table 1, entry 6). Screening with other additives such as $ZnBr_2$, $FeCl_3{\cdot}6H_2O$, and CuI as additives was also attempted, but none gave any improvement (Table 1, entries 7−9). The screening in different solvents such as DCE and ACN suppressed the formation of coupled product (Table 1, entries 10 and 11). In the optimization reactions, the benzaldehyde was observed as a side product with varying quantities; however, the quantification of benzaldehyde was not made, as the same was taken as 20-fold excess. The reaction with 0.2 equiv of iodine, 6 equiv of TBHP, and 0.5 equiv of Na_2CO_3 was considered as the best condition (Table 1, entry 3).

After the optimization study, the generality of the optimized conditions with different substituted methylarenes was investigated (Scheme 1). Substituted methylarenes on reaction with *N*-methylbenzamide **1a** gave moderate to good yields of coupled products along with some quantity of the corresponding aldehydes and alcohols. Reaction of *N*-methylbenzamide **1a** with *p*-methoxytoluene and *p*-*tert*-butyltoluene proceeded smoothly and gave **3b** and **3c** in a yield of 69 and 71%, respectively. Reaction of **1a** with *p*-chloro-, bromo-, and iodo-

Scheme 1. Coupling of *N*-Methylbenzamide with Various Methylarenes

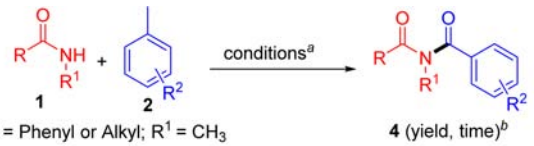
3a, R_2 = H, (72%, 18 h)
3b, R_2 = *p*-OMe, (69%, 20 h)
3c, R_2 = *p*-*tert*-butyl, (71%, 18 h)
3d, R_2 = *p*-chloro, (72%, 24 h)
3e, R_2 = *p*-bromo, (67%, 22 h)
3f, R_2 = *p*-iodo, (65%, 18 h)
3g, R_2 = *o*-bromo, (58%, 18 h)
3h, R_2 = 2-naphthyl, (64%, 18 h)
3i, R_2 = *m*,*m*′-dimethyl, (62%, 18 h)

[a]Reaction conditions: amide **1**(0.22 mmol), methylarene **2** (4.4 mmol), aq TBHP (1.32 mmol), I_2 (20 mol %), Na_2CO_3 (50 mol %), 110 °C. [b]Isolated yield.

substituted toluenes gave coupled products **3d**, **3e**, and **3f** in yields of 72, 67, and 65% respectively. *Ortho*-substituted toluenes such as *o*-bromotoluene also reacted with **1a** and gave the corresponding product **3g** in a yield of 58%. A bicyclic system such as 2-methylnapthalene also successfully underwent reaction with **1a** and furnished the corresponding product **3h** with 64% yield. Interestingly, a disubstituted methylarene such as mesitylene also reacted smoothly with **1a** and furnished monosubstituted product **3i** in a yield of 62%.

To further extend the generality of this method, different substituted NH-amides were also explored (Scheme 2). *o*-

Scheme 2. Coupling of Various *N*-Methylbenzamide with Methylarenes



4a, R = *o*-fluorophenyl, R^2 = H, (74%, 20 h)
4b, R = *o*-fluorophenyl, R^2 = *p*-OMe, (67%, 20 h)
4c, R = *o*-fluorophenyl, R^2 = *p*-*t*-butyl, (72%, 20 h)
4d, R = *o*-fluorophenyl, R^2 = *p*-Cl, (71%, 20 h)
4e, R = *p*-tolyl, R^2 = H, (75%, 20 h)
4f, R = *p*-tolyl, R^2 = *p*-Cl, (71%, 20 h)
4g, R = *p*-tolyl, R^2 = 1-naphthyl, (48%, 20 h)
4h, R = *p*-tolyl, R^2 = 2-naphthyl, (57%, 20 h)
4i, R = *m*-methoxyphenyl, R^2 = H, (68%, 20 h)
4j, R = *o*-tolyl, R^2 = H, (74%, 20 h)
4k, R = methyl, R^2 = H, (65%, 20 h)
4l, (62%, 20 h)

[a]Reaction conditions: amide **1** (0.22 mmol), methylarene **2** (4.4 mmol), aq TBHP (1.32 mmol), I_2 (20 mol %), Na_2CO_3 (50 mol %), 110 °C. [b]Isolated yield.

Fluoro-*N*-methylbenzamide successfully benzoylated under the optimized conditions with methylarene and gave corresponding product **4a** in a yield of 74%. Similarly, reaction of *o*-fluoro-*N*-methylbenzamide with *p*-methoxy, *p*-*tert*-butyl, and *p*-chlorotoluene furnished the corresponding products **4b**, **4c**, and **4d** in yields of 67, 72, and 71%, respectively. *p*-Tolyl-*N*-methylbenzamide also reacted with methylarene and 4-chlorotoluene and produced 75 and 71% of the corresponding products **4e** and **4f**, respectively. *p*-Tolyl-*N*-methylbenzamide smoothly reacted with sterically hindered 1-methylnapthalene and 2-methylnapthalene and furnished 48 and 57% of corresponding imides **4g** and **4h**, respectively. *m*-Methoxy-*N*-methylbenzamide and *o*-methyl-*N*-methylbenzanmide also reacted with toluene and gave **4i** and **4j** in yields of 68% and 74%, respectively. Aliphatic amides such as *N*-methylacetamide and caprolactam also underwent reaction with toluene and produced the corresponding imides **4k** and **4l** in yields of 65% and 62%, respectively. Under the optimized conditions, primary amides such as benzamides did not give acylated products.

Under the optimized conditions, the compatibility of bulky groups bearing amides was also investigated (Scheme 3). *N*-Propyl, *N*-cyclobutyl, *N*-(1-phenylethyl), and *N*-phenethylbenzamide reacted with toluene and furnished the corresponding products **5a**−**d** with moderate to good yields.

During the optimization and generality study with methylarenes, most of the reactions also gave the corresponding aldehydes and alcohols along with the required products, indicating the same could be explored for the coupling. When the reaction was performed between *p*-tolyl-*N*-methylbenzamide and benzaldehyde under an optimized catalytic system, the corresponding coupled product was obtained in trace quantities.

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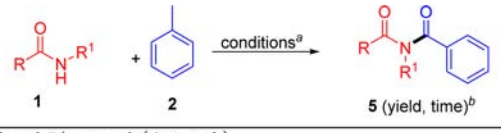
Scheme 3. Coupling of Various *N*-Alkylbenzamides with Methylarenes

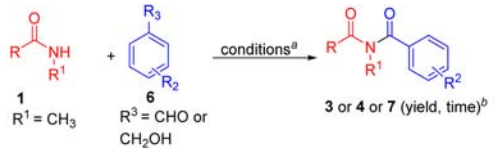


5a, R = phenyl, R^1 = propyl, (67%, 22 h)
5b, R = phenyl, R^1 = cyclobutyl, (65%, 22 h)
5c, R = phenyl, R^1 = $PhCHCH_3$, (51%, 22 h)
5d, R = phenyl, R^1 = $PhCH_2CH_2$, (67%, 22 h)

[a]Reaction conditions: amide **1** (0.22 mmol), methylarene **2** (4.4 mmol), aq TBHP (1.32 mmol), I_2 (20 mol %), Na_2CO_3 (50 mol %), 110 °C. [b]Isolated yield.

Surprisingly, when the same reaction was performed in 1,2-dichloroethane (DCE) as solvent, the corresponding product **4e** was obtained in a yield of 92% (Scheme 4). Other benzaldehydes

Scheme 4. Coupling of Various *N*-Alkylbenzamides with Aldehydes



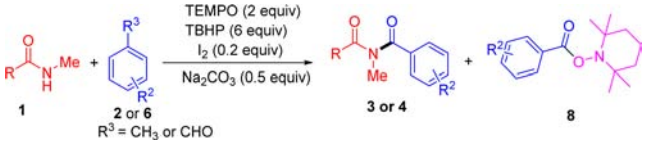
4e, R = *p*-tolyl, R^2 = H (92%)[c];(85%)[d]
3b, R = Ph, R^2 = *p*-OMe (82%);(74%)[d]
7a, R = Ph, R^2 = 3,4-di-OMe (75%)[c]
7b, R = Ph, R^2 = *p*-F (72%)[c]
7c, R = Ph, R^2 = *p*-NO_2 (52%)[c]
7d, R = Ph, R^2 = *p*-COOMe (54%)[c]
3d, R = Ph, R^2 = *p*-Cl (70%)[d]
7e, R = Ph, R^2 = *p*-OCF_3 (72%)[d]
7f, R = Ph, R^2 = *p*-CF_3 (68%)[d]

[a]Reaction conditions (unless otherwise noticed): amide **1** (0.22 mmol), aldehyde **6** (0.22 mmol), aq TBHP (0.44 mmol), I_2 (10 mol %), Na_2CO_3 (50 mol %), DCE, 80 °C, 12 h. [b]Isolated yield. [c]Reaction with benzaldehyde. [d]Reaction with benzyl alcohol, aq TBHP (0.66 mmol), I_2 (10 mol %), Na_2CO_3 (50 mol %), DCE, 80 °C, 15 h.

such as *p*-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde on reaction with *N*-methylbenzamide gave the corresponding imides **3b** and **7a** in yields of 82% and 75%, respectively. Similarly, when reactions between *N*-methylbenzamide and electron-withdrawing groups substituted benzaldehyde were attempted, good to moderate yields of their corresponding products were obtained (**7b**−**d**, **3d**). On the other hand, benzyl alcohols were used as acyl sources for coupling with *HN*-amides. Various un/substituted benzyl alcohols on coupling with *N*-methylbenzamide furnished corresponding products (**4e**, **3b**,**d**, **7e**,**f**) in good to excellent yields (Scheme 4).

To gain insight into the mechanism, a series of control experiments were performed. When the reactions were performed in the presence of free-radical scavengers such as TEMPO and 1,1-diphenylethylene (DPE), product formation was significantly suppressed (Table 2, entries 1−5), indicating the involvement of radical pathway. Interestingly, the reaction with 3,4-dimethoxybenzaldehyde in the presence of TEMPO gave TEMPO-aldehyde adduct **8**, further confirming the radical pathway (Table 2, entry 5). During optimization and diversity generation studies with methylarenes, the existence of benzyl alcohol and benzaldehyde was always noticed on TLC (by comparing with commercial standards), suggesting the possibility of conversion of methylarenes to alcohols and then to benzaldehyde, which ultimately reacted with amides and

Table 2. Radical Scavenger Experiments

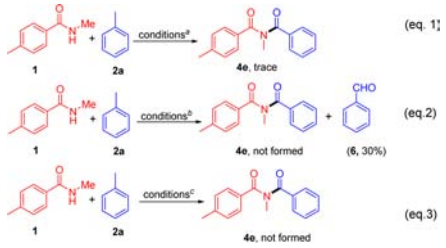


entry	$R/R^2/R^3$	conditions	yield (**3** or **4**) (%)	yield (**8**) (%)
1	*p*-tolyl/H/Me	*a*	nf	no
2[c]	*p*-tolyl/H/Me	*a*	nf	no
3	Ph/H/CHO	*b*	30	no
4[d]	Ph/H/CHO	*b*	nf	no
5	Ph/3,4-di-OMe/CHO	*b*	nf	71

[a]Reaction conditions: Amide **1** (0.22 mmol), methylarene **2** (4.4 mmol), aq TBHP (1.32 mmol), I_2 (20 mol %), Na_2CO_3 (50 mol %), 110 °C, 20 h: [b]amide **1** (0.22 mmol), aldehyde **6** (0.22 mmol), TEMPO (0.44 mmol), aq TBHP (0.44 mmol), I_2 (10 mol %), Na_2CO_3 (50 mol %), 80 °C, 12 h, DCE; [c]0.44 mmol of 1,1-diphenylethylene was used instead of TEMPO; [d]TEMPO (2.2 mmol); nf: not formed; no: not observed

furnished the corresponding imides. The intermediacy of alcohol and aldehyde was also confirmed by performing an independent reaction with benzyl alcohol and benzaldehyde, where the corresponding required product **4e** was obtained in a yield of 92 and 85% (Scheme 4). These experiments confirmed the above proposed path. Next, the intake of oxygen was also understood by performing the reaction under dry conditions, where only a trace amount of required product **4e** was observed (Scheme 5, eq

Scheme 5. Control Experiments



[a]Conditions: amide **1** (0.22 mmol), dry toluene **2a** (4.4 mmol), TBHP in decane 5−5.5 M (1.32 mmol), I_2 (20 mol %), Na_2CO_3 (50 mol %), N_2 atmosphere, 110 °C, 20 h. [b]Conditions: amide **1** (0.22 mmol), methylarene **2a** (4.4 mmol), aq TBHP (1.32 mmol); 110 °C, 20 h. [c]Conditions: amide **1** (0.22 mmol), methylarene **2a** (4.4 mmol), I_2 (20 mol %), 110 °C, 20 h.

1), suggestimg the water might be the source for oxygen. In another reaction, when *p*-tolyl-*N*-methylbenzamide reacted with toluene in the presence of only TBHP, no required product formation was observed, but instead benzaldehyde formation was noticed (Scheme 5, eq 2). On the other hand, when the reaction was performed between *p*-tolyl-*N*-methylbenzamide and toluene in the presence of I_2, no product formation was observed (Scheme 5, eq 3). These experiments suggested that activation of methylarenes was initiated by TBHP. The incorporation of oxygen was further confirmed through labeling experiments by performing the reaction with ^{18}O-labeled H_2O, where LC−MS analysis showed the presence of ^{18}O in the product (Figure 2).

On the basis of the above experiment and previous literature reports,[9,10] a plausible pathway is proposed as shown in Figure 3. On the basis of the intermediate capturing and labeling experiments, the present reaction undergoes the following

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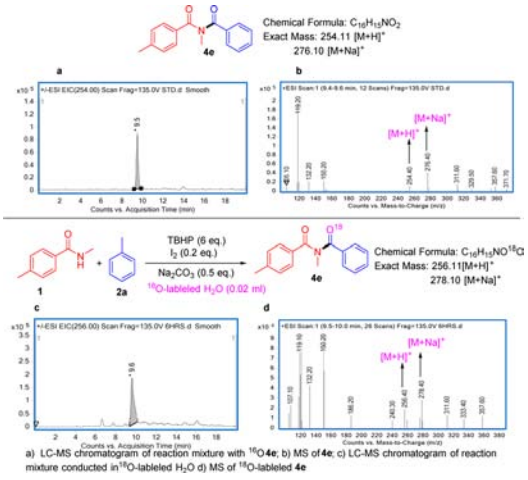

Figure 2. Labeling experiments.

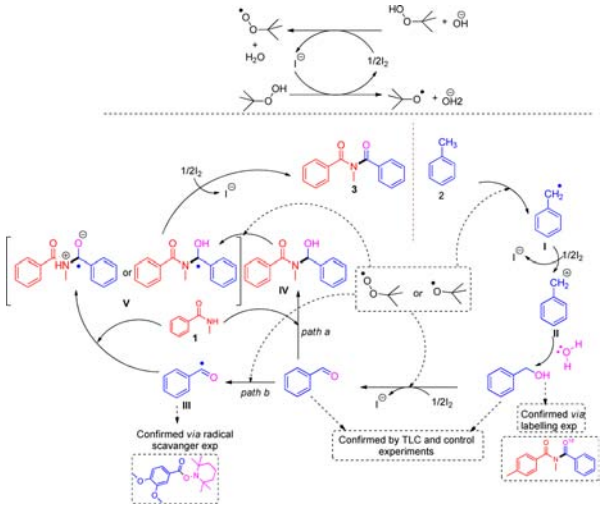

Figure 3. Plausible mechanism.

sequence, wherein methylarene is first converted into benzyl alcohol and then to benzaldehyde, which ultimately reacts with amide and finally furnishes the required imide. The reaction is initiated by redox reaction between iodine and TBHP, which generates *tert*-butoxy and *tert*-butylhydroperoxide radicals. The generated *tert*-butoxy and *tert*-butylhydroperoxide radicals abstract hydrogen atom from methylarene and give benzyl radical **I**, which further undergoes a single-electron reaction and furnishes benzyl carbocation **II**. The benzyl cation reacts with water to generate benzyl alcohol. The generated benzyl alcohol again gets oxidized by *tert*-butoxy and *tert*-butyl hydroperoxide radicals and iodine to form the key intermediate benzaldehyde. On the basis of the literature reports, two pathways (path a and b) are proposed for the coupling of benzaldehyde with amide.[9a,c] In our radical scavenger experiments (Table 2, entries 3−5), formation of TEMPO−aldehyde adduct **8** was observed, suggesting the intermediacy of benzoyl radical **III** and involvement of path b (as also reported previously for amide synthesis),[9b,10] wherein benzoyl radical undergoes nucleophilic reaction with amide, followed by single electron release and deprotonation to generate final product **3**.

In summary, a metal-free method for the *N*-acylation of *NH*-amides with methylarenes, benzaldehydes, and benzyl alcohol was developed involving a I_2/TBHP catalytic system.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01684.

Detailed experimental procedures and characterization data for all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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