

Hofmann-Type Rearrangement of Imides by in Situ Generation of Imide-Hypervalent Iodines(III) from Iodoarenes

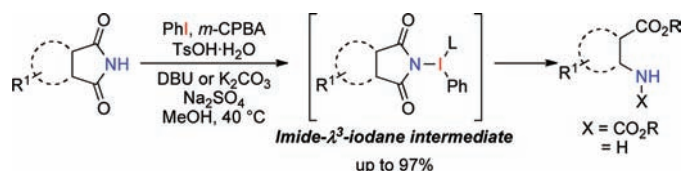
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ABSTRACT



The Hofmann-type rearrangement of aromatic and aliphatic imides using a hypervalent iodine(III) reagent generated in situ from PhI, *m*-CPBA, and TsOH·H₂O proceeded in the presence of a base in alcohol to provide anthranilic acid derivatives and amino acid derivatives in high yields, respectively. This reaction proceeds through a tandem reaction via alcoholysis followed by a Hofmann rearrangement promoted by the formation of an imide- λ^3 -iodane intermediate.

A variety of hypervalent iodine reagents are used as functional organic reagents for a wide range of organic synthesis.¹ In particular, (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, and [(hydroxy)(tosyloxy)iodo]benzene (Koser's reagent) are the most popular and utilizable trivalent iodine reagents for many kinds of oxidative conversions and are used in place of heavy metal reagents.² In recent years, the utility of hypervalent iodines has sparked the development of recyclable

analogues³ and catalytic reactions.⁴ We have also developed a hypervalent iodine(III) catalyzed reaction⁵ and a recyclable ion-supported catalyst,⁶ prepared from an iodoarene, oxidants (*m*-CPBA or Oxone), and *p*-toluenesulfonic acid in situ. Trivalent iodines are highly efficient reagents for the Hofmann rearrangement. They act to directly transform carboxamides into amines.⁷

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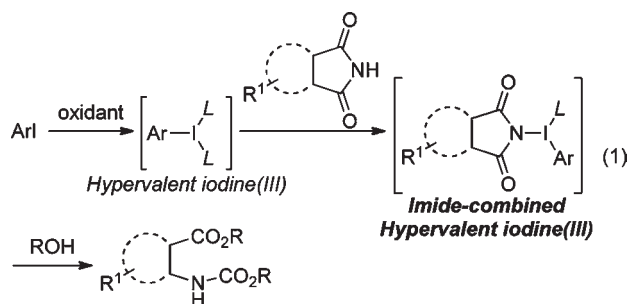
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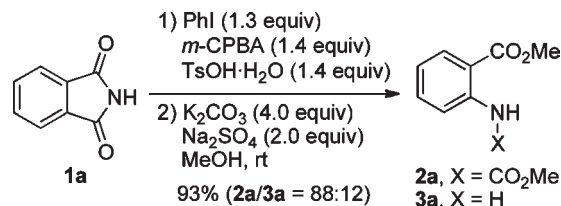
The groups of Zhdankin⁸ and Ochiai⁹ reported that active iodine(III) generated in situ from iodobenzene and oxidants could be finitely employed for the Hofmann rearrangement of aliphatic amides. Furthermore, the Hofmann rearrangement of aromatic and aliphatic imides is a very important strategy for the construction of anthranilic acid derivatives and amino acid derivatives possessing biological and medicinal activities¹⁰ and found in a variety of natural products.¹¹ Nevertheless, studies for the preparation of anthranilic acid derivatives by means of the Hofmann rearrangement are extremely limited and lacking in versatility,¹² and the desired product is obtained in low yield. To the best of our knowledge, the direct transformation into aromatic and aliphatic amino acid derivatives via the Hofmann-type rearrangement of cyclic imides using hypervalent iodines has not been established. Conventional methods for the preparation of anthranilic acid derivatives require transition metals, such as Pd¹³ and Cu.¹⁴

The potential of direct oxidative transformation using imide-combined hypervalent iodine(III) remains widely unexplored.¹⁵ We report here the metal-free direct transformation of phthalimides and aliphatic imides into the corresponding anthranilic acid derivatives and aliphatic amino acid derivatives by alcoholysis, followed by the Hofmann rearrangement of imides via the formation of imide-combined hypervalent iodines(III) generated in situ from an iodoarene and oxidant (eq 1).



Information). The optimum reaction was found to involve **1a**, K₂CO₃ (4.0 equiv), Na₂SO₄ (2.0 equiv), and hypervalent iodine, which was prepared from iodobenzene (1.3 equiv), *m*-CPBA (1.4 equiv), and TsOH·H₂O (1.4 equiv) in situ, in MeOH at room temperature (Scheme 1). In contrast, the previous active iodines(III) generated in situ from iodobenzene^{8,9} were not effective for the Hofmann-type rearrangement of **1a**.

Scheme 1. Hofmann-Type Rearrangement of Phthalimide **1a** by Hypervalent Iodine Generated in Situ



To explore the scope of the Hofmann-type rearrangement, various phthalimides **1** were examined using hypervalent iodine under the optimized reaction conditions (Scheme 2). The reactions of 4-monosubstituted phthalimides bearing an Me (**1b**), *t*-Bu (**1c**), Br (**1d**), or NO₂ (**1e**) group gave corresponding monosubstituted anthranilic acid derivatives (**2b–2e**) in high yields, respectively. Electron-donating 4-methoxy phthalimide (**1f**) was converted into desired product (**2f**) in 54% yield. 3-Fluoro phthalimide (**1g**) was also transformed into the corresponding product (**2g**) in high yield (90%). When symmetrical aromatic imides, such as 4,5-dimethylphenyl (**1h**), 4,5-dichlorophenyl (**1i**), naphthyl (**1j**), and biphenyl (**1k**) imides, were used, rearrangement products **2h**, **2i**, **2j**, and **2k** were obtained in good yields (62–72%), respectively. Heterocyclic 3,4-pyridine dicarboximide (**1l**) was efficiently converted into an aminoisonicotinic acid derivative (**2l**) in high yield. Moreover, the use of other alcohols, such as EtOH and CF₃CH₂OH, instead of MeOH as solvent for the rearrangement of **1a** provided corresponding esters **2m** and **2n** in good yields, respectively. Treatment of 4,4'-oxybisphthalimide (**1o**) with double the amount of each reagent gave an oxybisanthranilic acid derivative (**2o**) in 60% yield with three regioisomers (4,5'-/4,4'-/5,5'- = 61:22:17). In many cases, a small amount of decarboxylation product (**3**, X = H) was obtained as a byproduct with

First, we screened a series of iodoarenes and bases for the Hofmann-type rearrangement of phthalimide (**1a**) using hypervalent iodine (Table S1 in the Supporting

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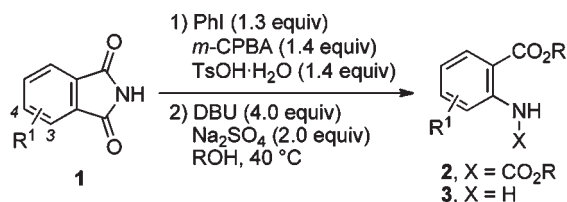
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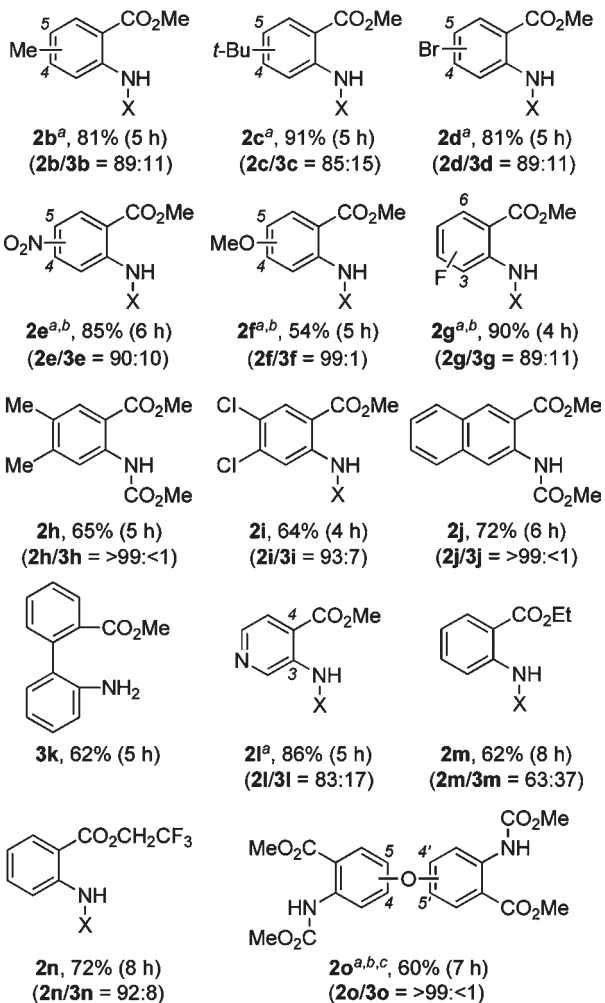
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Scheme 2. Hofmann-Type Rearrangement of Phthalimides **1** Using Hypervalent Iodine(III) Generated in Situ



product, yield (%), and reaction time (h)



^aRegioselectivities for **2b–g**, **2l**, **2o** appear in the Supporting Information. ^bThe reaction was carried out at rt. ^cThe reaction was carried out with PhI (2.3 equiv), *m*-CPBA (2.5 equiv), TsOH·H₂O (2.5 equiv), DBU (8.0 equiv), and Na₂SO₄ (4.0 equiv).

this methodology (2/3 = 83:17–99:1). Nevertheless, **3a** could be smoothly transformed into **2a** in quantitative yield by methoxycarbonylation with methyl chloroformate (Scheme S1 in the Supporting Information). Although the present rearrangement is a highly facile conversion method to obtain the desired products in satisfactory chemical yields, it exhibited low regioselectivity in the case of unsymmetrical imides (**1b–1g**, **1l**, **1o**) (see the Supporting Information). The optimized reaction conditions were subsequently applied to numerous aliphatic imides to give β- and γ-amino acid derivatives (Table 1). Succinimide **4a**

was efficiently converted into corresponding β-alanine derivative **5a** in 81% yield (entry 1). The same treatment of monosubstituted succinimide bearing Me, *n*-Bu, and Bn groups **4b**, **4c**, and **4d** also provided desired products **5b**, **5c**, and **5d** in 84%, 97%, and 87% yields, respectively (entries 2–4). The use of 1,2-disubstituted succinimide **4e** and 1,1-disubstituted succinimide **4f** bearing a tetrasubstituted carbon center furnished corresponding products **5e** and **5f** in 74% and 60% yields, respectively (entries 5 and 6). Glutarimide **4g** bearing a six-membered ring also gave γ-amino acid derivative **5g** in 91% yield (entry 7). Moreover,

Table 1. Hofmann-Type Rearrangement of Aliphatic Imides **4** Using Hypervalent Iodine(III) Generated in Situ

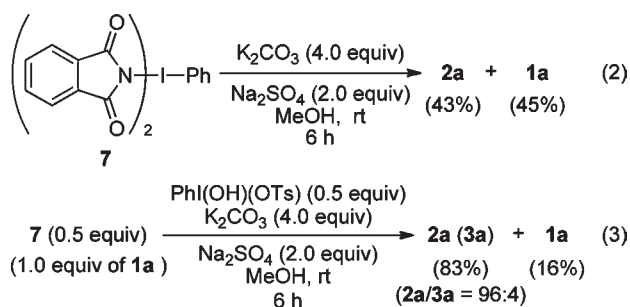
entry	5	time (h)	yield (%)
1	5a	5	81
2 ^a	5b	5	84
3 ^a	5c	5	97
4 ^a	5d	4	87
5	5e	21	74
6 ^a	5f	20	60
7	5g	5	91
8	5h	6	91

^aRegioselectivities for **5b–d**, **5f** were given in the Supporting Information.

the same treatment of 3-isobutylglutarimide **4h** provided pregabalin derivative **5h** in 91% yield (entry 8). Pregabalin is an anticonvulsant drug used to treat epilepsy and neuropathic pain.¹⁶ Fortunately, decarboxylation products in the form of primary amines were not observed in the reaction with aliphatic imides.

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Scheme 3. Mechanistic Study of Hofmann-Type Rearrangement of Phthalimide Derivatives^a



^a In eqs 2 and 3, the calculation of the yields of products **2a** and **1a** was based on an equivalence of phthalimide on **7**.

We then investigated the reactions with various phthalimide derivatives to ascertain the mechanism of the Hofmann-type rearrangement of imides using hypervalent iodines formed in situ (Scheme 3). High-resolution ESI-mass analysis of a reaction mixture containing **1a**, PhI(OH)(OTs), and K₂CO₃ in MeCN at room temperature yielded a peak at *m/z* = 349.9663, which was assigned to [PhI(phthalimide)]⁺ (**6**) (see the Supporting Information). When phenyliodine(III) bis[phthalimide] (**7**)¹⁷ was treated under similar conditions, the desired product **2a** was obtained in 43% yield, together with phthalimide **1a** (45% yield) (eq 2). Furthermore, the reaction of **7** and PhI(OH)(OTs) as the oxidant (1:1) produced anthranilic acid derivatives **2a** and **3a** in 83% yield (**2a/3a** = 96:4), and the yield of **1a** was decreased to 16% (eq 3). These investigations suggest that the Hofmann-type rearrangement of imides involves the formation of imide-combined hypervalent iodine(III) species prior to the ring-opening reaction of imides, which differs from the previous reaction of amides,^{7–9} and the imide-λ³-iodane is the key intermediate in the rearrangement step. In addition, the presence of TsOH·H₂O has a significant role in promoting this reaction (see the results for **2a**, **2h**, and **5a**).¹⁸

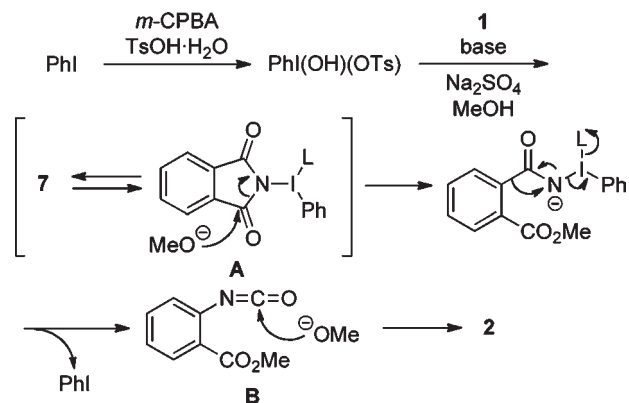
The proposed reaction mechanism is depicted in Scheme 4. Iodobenzene is oxidized by *m*-CPBA in the presence of TsOH·H₂O to generate PhI(OH)(OTs) in situ.^{5a} This is followed by the generation of an imide-λ³-iodane intermediate (**7** or **A**) via the reaction with cyclic imide (**1**)

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(18) Hofmann-type rearrangement of **1a**, **1h**, and **4a** in the absence of TsOH·H₂O was carried out to give the corresponding products **2a**, **2h**, and **5a** in 66% (**2a/3a** = 95:5), 54% (**2h/3h** = >99:<1), and 58% yields, respectively.

under basic conditions in alcohol. The alcoholysis of the activated imide-λ³-iodane intermediate (**A**) expeditiously leads to isocyanate **B** via a ring-opening reaction, followed by rearrangement with the elimination of iodobenzene. Isocyanate **B** immediately yields the corresponding carbamate (**2**) by the addition of alcohols.

Scheme 4. Plausible Reaction Mechanism for the Hofmann-Type Rearrangement of Imides



In conclusion, we have developed a new type of Hofmann-type rearrangement with aromatic and aliphatic imides via the generation of imide-combined hypervalent iodine(III) in situ from iodoarene and cyclic imides with *m*-CPBA, TsOH·H₂O, and a base. This activated imide-combined hypervalent iodine(III) can be easily prepared in situ from iodoarene and is utilized in the reactions with a broad range of aromatic and aliphatic imides. This new protocol is recognized as a direct method for the construction of aromatic and aliphatic amino acids under mild conditions, without the use of any transition metals and toxic reagents.

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Supporting Information Available. Experimental procedures, spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.