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Recyclable Hypervalent Iodine(III) Reagent Iodosodilactone as an Efficient Coupling Reagent for Direct Esterification, Amidation, and Peptide Coupling

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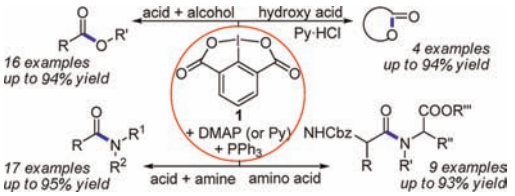
ABSTRACT



A hypervalent iodine(III) reagent plays a novel role as an efficient coupling reagent to promote the direct condensation between carboxylic acids and alcohols or amines to provide esters, macrocyclic lactones, amides, as well as peptides without racemization. The regeneration of iodosodilactone (1) can also be readily achieved. The intermediate acyloxyphosphonium ion C from the activation of a carboxylic acid is thought to be involved in the present esterification reaction.

Ester and amide functionalities are important structural units that serve as key components in a variety of natural products with biological activities, pharmaceuticals, and polymers. Accordingly, numerous synthetic methods have been developed to construct ester and amide linkages. A particularly successful strategy among them is the direct coupling of carboxylic acids with alcohols or amines using different kinds of coupling reagents.[1,2] Notably, the use of dicyclohexylcarbodiimide (DCC) or its analogues as a coupling reagent constitutes the most applied approach for both esterification and amidation including peptide synthesis.[3] Despite merits such as remarkable generality, high efficiency, and mild reaction conditions with the use of DCC, there are still problems, such as (a) racemization issue resulting in the use of additives such as 1-hydroxy-1*H*-benzotriazole (HOBt)[3c,d] or 1-hydroxy-7-azabenzotriazole (HOAt),[3d] although their potential explosive properties have been discussed,[2c,4] and (b) unrecyclability. Therefore, it is still highly desirable to develop an environmentally benign and readily recyclable coupling reagent to mediate the effective formation of ester and amide bonds.

Research interest in hypervalent iodine reagents has experienced a renaissance since the early 1980s with the discovery of Dess–Martin periodinane (DMP) which was commonly used as a mild oxidant for the effective transformation of alcohols into carbonyl compounds.[5] The environmentally benign nature of hypervalent iodine reagents is also a reason for chemists to pursue research on such reagents. With the continuing disclosure of the new findings on reactivities of hypervalent iodine reagents, they now can be regarded as multipurpose reagents in organic synthesis.[6] However, to the best of our knowledge,

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(2) (a) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447–2467. (b) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852. (c) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631. (d) Joullié, M. M.; Lassen, K. M. *ARKIVOC* **2010**, *8*, 189–250. (e) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471–479.

(3) (a) Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068. (b) Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1958**, *80*, 2902–2903. (c) Koenig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788–798. (d) Koenig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 2024–2033. (e) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed.* **1978**, *17*, 522–524. (f) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.

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there is no report describing the utilization of a hypervalent iodine reagent acting as a coupling reagent in the condensation of carboxylic acids with alcohols or amines. Herein, in connection with our ongoing research programs on chemistry of hypervalent iodine reagents,[7] we report that a hypervalent iodine(III) reagent iodosodilactone (**1**, Figure 1) can function as an efficient coupling reagent to promote the direct esterification including macrolactonization, direct amidation, and peptide coupling without racemization. An advantage with the use of **1** is that it can be easily regenerated from the reaction mixture.

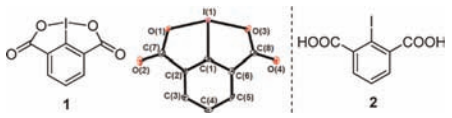

Figure 1. ORTEP drawing (the thermal ellipsoids drawn at the 50% probability level) of **1** and its synthetic precursor **2**.

Compound **1** can be quantitatively prepared from the commercially available 2-iodoisophthalic acid (**2**) by oxidation with sodium hypochlorite (NaOCl) in aqueous hydrochloric acid according to our reported procedure[7a] instead of the literature protocol involving the use of peracetic acid.[8a] The single crystal of **1** was first obtained from DMSO, and its X-ray crystallographic analysis showed a structure of overall planar shape unlike other usually employed aryl-λ^3-iodanes such as phenyliodine diacetate (PIDA) with a typical T-shape structure. Compound **1** is neither air nor moisture sensitive and can be stored for several months at room temperature without any detectable decomposition.

The study of the chemical reactivity of **1** was then carried out. Compound **1** was found to be able to promote the esterification between *n*-hexanoic acid (**3a**, 1.4 equiv) and 2-phenylethanol (**4a**, 1.0 mmol) in 91% yield together with 1.2 equiv of 4-dimethylaminopyridine (DMAP) and 1.0 equiv of PPh_3 in toluene under reflux for 1 h, which was one of the optimal reaction conditions. Another experiment showed that the reaction also proceeded very well in chloroform (for details of the optimization, see Table S1, Supporting Information). Two conventional hypervalent iodine(III) reagents PIDA and phenyliodine ditrifluoroacetate (PIFA) were also tested; however, the desired ester **5aa** was only isolated in 27% and 17% yield, respectively. The ready regeneration of **1** could be achieved after the esterification between **3a** (7 mmol) and **4a** (5 mmol) promoted by **1** (6 mmol). Upon quenching of the reaction with saturated aq $NaHCO_3$, the aqueous layer was collected and acidfied, followed by direct oxidation with aq NaOCl, and could yield **1** in 94% yield without the loss of reactivity.[7a]

To investigate the scope of the reaction, a variety of alcohols were examined under optimal reaction conditions (Scheme 1). The desired esters can be obtained in good to excellent yields regardless of primary alcohols (**5aa**−**ae**) or secondary alcohol (**5af**) with **3a**. Sterically hindered secondary alcohol L-menthol also performed well and yielded the corresponding optically pure ester product **5ag** with retention of configuration around the alkoxy carbon. Even the tertiary alcohol 2-methyl-1-phenylpropan-2-ol could be converted to the corresponding ester **5ah**, although it is less reactive than others. Moreover, the esterification of *p*- or *m*-nitrophenol could take place and the corresponding ester products were produced in good yields (**5ai** and **5aj**). Both aliphatic and aromatic carboxylic acids were employed and provided desired esters in good to excellent yields with **4a** (**5ba**−**fa**). Multiple C−C bond could be well tolerated under the present conditions (**5ad** and **5ae**). When *N*-Bz-proline was treated with **4a**, *N*-benzoylprolinate **5ga** was produced in 91% yield. Small amounts of byproduct from the condensation of **2** with **4a** were observed in two examples (**5da** and **5ea**). In a preliminary experiment, we tested the macrolactonization of HO-$(CH_2)_{11}CO_2H$ using **1** (2.0 equiv), DMAP (2.4 equiv), and PPh_3 (2.0 equiv) in toluene under reflux; however, only a trace amount of 12-dodecanolide (**5h**) was obtained (for details, see Table S2, Supporting Information). Inspired by Keck macrolactonization,[3f] the proton source compound pyridinium chloride was added together with the use of pyridine instead of DMAP, the desired product **5h** was produced in 56% yield. Under the optimal conditions, a series of hydroxy acids, $HO(CH_2)_nCO_2H$ (n = 11, 14, 15) were utilized in the macrolactonization. As indicated in Scheme 1, the desired lactones (**5h**−**j**) were formed in good to excellent yields, and a tendency was apparent that the longer carbon chain in the hydroxy acids would result in the better efficiency of macrolactonization. Notably, macrolactonization of (*R*)-(+)-ricinoleic acid provided **5k** with complete retention of the configuration around the alkoxy carbon, which has commercial importance in the fragrance industry.

To explore the mechanism, an experiment using ^{18}O-labeled 3-phenylpropanol (90% ^{18}O incorporation) was

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(6) For selected reviews and books on hypervalent iodine reagents, see: (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (c) *Topics in Current Chemistry*; Wirth, T., Ed.; Springer: Berlin, 2003; p 224. (d) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656–3665. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (f) Zhdankin, V. V. *ARKIVOC* **2009**, *1*, 1–62. (g) Brand, J. P.; González, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102–115. (h) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517–538.

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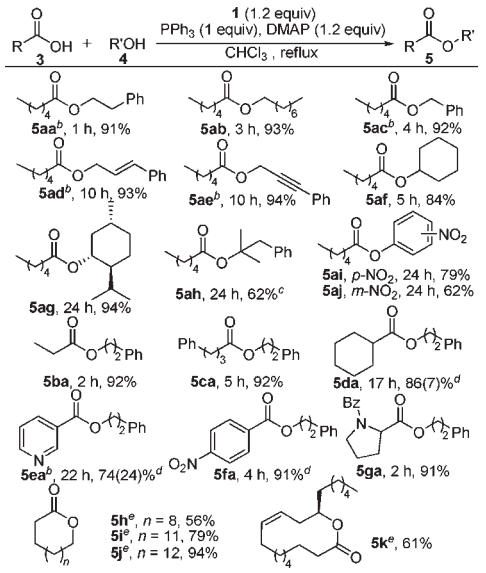
Scheme 1. Scope of Alcohols and Carboxylic Acids for Direct Esterification Promoted by **1**[a]



[a] Reaction conditions: **3** (1.4 mmol), **4** (1.0 mmol), **1** (1.2 mmol), DMAP (1.2 mmol), PPh_3 (1.0 mmol), $CHCl_3$ (10 mL), reflux; the isolated yields of the product were shown; the isolated yield of diphenethyl 2-iodoisophthalate is shown in parentheses.

[b] The solvent was toluene (10 mL).

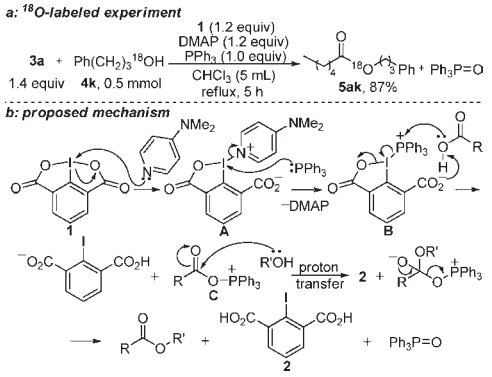
[c] Conversion of 2-methyl-1-phenylpropan-2-ol: 74%.

[d] 2.0 mmol of acid was used.

[e] Reaction conditions: the corresponding hydroxy acid (0.1 mmol), **1** (0.2 mmol), pyridine (0.24 mmol), pyridine·HCl (0.2 mmol), PPh_3 (0.2 mmol), toluene (250 mL), reflux, 12 h.

employed. When it reacted with normal *n*-hexanoic acid, an ^{18}O-labeled ester **5ak** (89% ^{18}O incorporation) was produced with the exclusive formation of normal triphenylphosphine oxide (Scheme 2a). Furthermore, the treatment of a chiral secondary alcohol L-menthol with *n*-hexanoic acid gave the ester **5ag** with excellent enantiomeric purity (ee > 99%), and according to the specific rotation of **5ag** ($[\alpha]^{25}_D = -61.2$ (*c* 2.0, CH_3OH); lit.[9] $[\alpha]^{25}_D = -60.6$), the stereochemistry about the alkoxy carbon was retained. These two observations suggested that the present esterification reaction proceeded via an acyloxyphosphonium ion intermediate **C**[10] from the activation of a carboxylic acid (Scheme 2b).

Scheme 2. Study of Mechanism



On the basis of the above two experiments and several literature reports, a working mechanism was hypothesized (Scheme 2b). Iodosodilactone was initially activated by DMAP to form the zwitterion **A**;[11] the similar aryliodines(III) species with *N*-heteroarenes including pyridine and DMAP as the ligands have been reported by Weiss and co-workers.[12] Intermediate **A** then underwent ligand exchange with PPh_3 to give the more reactive zwitterion **B**. ESI-mass analysis of a reaction mixture containing **3a**, **4a**, **1**, DMAP, and PPh_3 in $CHCl_3$ under reflux yielded a peak at $m/z = 570.03$, which was assigned to be $[\mathbf{B} + NH_4]^+$ (see the Supporting Information). Carboxylic acid would react with **B** to form the reactive acyloxyphosphonium salt **C** and the conjugate base of **2**. Makowiec and Rachon reported that the methyl acetate was obtained when treating PIDA with PPh_3 in methanol. In their studies, the acyloxyphosphonium salt was considered as the key intermediate.[10f] At last, the activated species **C** was attacked by an alcohol to give the product ester.

After the successful construction of an ester bond, we surmised that changing nucleophiles from alcohols to amines would give the corresponding amide products via a similar pathway, though amines are generally thought to be more susceptible to oxidation than alcohol counterparts. When **3a** (1.4 equiv) was treated with *n*-hexylamine (**6a**, 1.0 mmol) in the presence of **1** (1.2 equiv), DMAP (1.2 equiv) and PPh_3 (1.0 equiv) in $CHCl_3$ at 60 °C, the corresponding amide **7aa** was produced in 95% yield. To our satisfaction, employing equimolar amount of **3a** and **6a**, the amidation could still be achieved to give **7aa** in 95% yield. Under the optimal conditions (details of optimization presented in the Supporting Information, Table S3), the generality of the direct amide bond formation between carboxylic acids and amines was investigated (Scheme 3). Various aliphatic or aromatic primary amines and secondary amines effectively reacted with **3a** to provide the desired amides (**7aa**–**ai**) in good to excellent yields. Terminal alkynyl group (**7ad**) and morpholine ring (**7af**) were both

(9) Pavelich, W. A.; Taft, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 4935–4940.

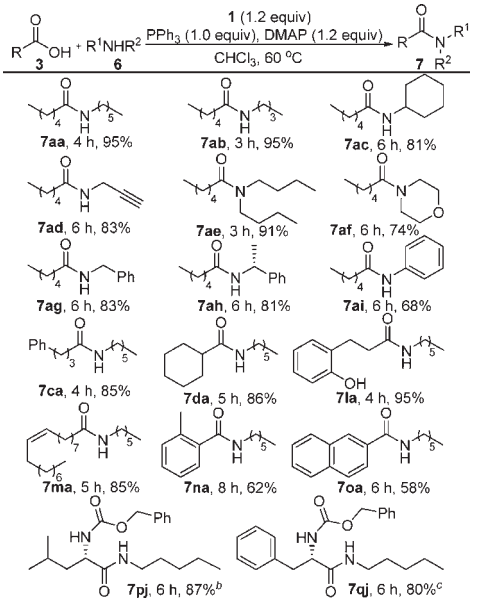
(10) (a) Taniguchi, T.; Hirose, D.; Ishibashi, H. *ACS Catal.* **2011**, *1*, 1469–1474. (b) Mukaiyama, T. *Angew. Chem., Int. Ed.* **1976**, *15*, 94–103. (c) Capretta, A.; Laritchv, V.; Dyck, J.; Robertson, A. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4051–4054. (d) Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Motevalli, S. *J. Org. Chem.* **2008**, *73*, 4882–4887. (e) Morcillo, S. P.; Álvarez de Cienfuegos, L.; Mota, A. J.; Justicia, J.; Robles, R. *J. Org. Chem.* **2011**, *76*, 2277–2281. (f) Makowiec, S.; Rachon, J. *Heteroatom Chem.* **2003**, *14*, 352–359.

(11) In our model esterification reaction, if all components were added all at once rather than following the standard procedure, that is, iodosodilactone and DMAP were mixed first under reflux for 1 h followed by the addition of other components, the reaction only gave the lower conversion (80%) of **4a** and yield (74%) of **5aa** after 12 h, which provided a clue that DMAP might function as a preactivator of iodosodilactone in the present esterification reaction.

(12) Weiss, R.; Seubert, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 891–893.

tolerated under the present conditions. (*R*)-1-Phenylethylamine having a chiral center also proceeded smoothly and

Scheme 3. Scope of the Direct Amidation between Carboxylic Acids and Amines Promoted by **1**[a]



[a] Reaction conditions: **3** (1 mmol), **6** (1 mmol), **1** (1.2 mmol), DMAP (1.2 mmol), PPh_3 (1 mmol), $CHCl_3$ (10 mL), 60 °C; the isolated yields of the product are shown.

[b] $D = 0$.

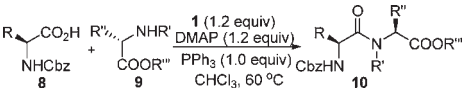
[c] $D = 0.18\%$.

gave the corresponding optically pure amide product **7ah** with retention of configuration in 81% yield. Then, many aliphatic carboxylic acids were studied and afforded desired amide products in high to excellent yields (**7ca**−**ma**) with **6a**. The reaction was compatible with the presence of phenolic hydroxyl group (**7la**) and no other side reaction was observed. Besides, one hindered aromatic acid also worked well to give **7na**. Additionally, protected natural amino acids were used to condense with *n*-pentylamine and the corresponding amides (**7pj** and **7qj**) were obtained in high yields without racemization.

Success in the racemization-free synthesis of chiral amide products (Scheme 3, **7ah**, **7pj**, and **7qj**) inspired us to explore the applications of the present condensation system in peptide coupling reactions. Various C-terminal carboxylic acids methyl or benzyl esters including sterically hindered amino acids (Pro, Leu, Ile) were employed to couple with N-protected amino acids, and the results are shown in Table 1. *N*-Cbz-leucine (Table 1, entries 1−4), *N*-Cbz-phenylalanine (entries 5−7), and *N*-Cbz-methionine (entries 8 and 9) all performed well to produce the corresponding dipeptides in good to excellent yields. Most importantly, no racemization occurred using the present **1**/DMAP/PPh_3 system.

To demonstrate the potential of this strategy, syntheses of higher polypeptides were targeted. Starting from

Table 1. Dipeptide Synthesis of Protected Amino Acids Promoted by **1**[a]



entry	product	time (h)	yield[b] (%)	D/DL[c] (%)
1	Z-L-Leu-Gly-OMe, **10aa**	8	93	0
2	Z-L-Leu-L-Ala-OMe, **10ab**	6	84	0.05
3	Z-L-Leu-L-Ala-OBzl, **10ac**	6	81	0.39
4	Z-L-Leu-L-Pro-OMe, **10ad**	8	72	0.03
5	Z-L-Phe-Gly-OMe, **10ba**	8	78	0
6	Z-L-Phe-L-Leu-OMe, **10be**	9	82	0.01
7	Z-L-Phe-L-lle-OMe, **10bf**	9	79	0
8	Z-L-Met-Gly-OMe, **10ca**	8	72	0
9	Z-L-Met-L-Val-OMe, **10cg**	9	70	0

[a] Reaction conditions: **8** (1.0 mmol), **9** (1.0 mmol), **1** (1.2 mmol), DMAP (1.2 mmol), PPh_3 (1.0 mmol), in $CHCl_3$ (10 mL), 60 °C. [b] Isolated yield. [c] The optical purity of products was determined by HPLC.

protected amino acids, the syntheses of a homo-tetrapeptide Z-L-Leu_4-OMe (**11**) and a heterotripeptide Z-L-Leu-L-Val-L-Ala-OMe (**12**) were achieved in good yields by building up the peptide chain one unit at a time from N-terminal to C-terminal.

In summary, for the first time, a hypervalent iodine(III) reagent iodosodilactone is presented that can function as a coupling reagent to promote the efficient syntheses of esters, macrocyclic lactones, and amides, as well as peptides without racemization. By the study of the mechanism, it was believed that the key intermediate acyloxyphosphonium ion **C** from the activation of a carboxylic acid was involved in the present esterification reaction. Iodosodilactone can be quantitatively prepared from the commercially available 2-iodoisophthalic acid by the oxidation with NaOCl and can be easily regenerated from the reaction mixture. Ready availability, stability, and recyclability of **1** and the easy workup make the present **1**/DMAP/PPh_3 system an alternative way to construct ester and amide bonds from carboxylic acids and alcohols or amines.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds and crystal data for **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.