Tetrahedron Letters, Vol. 33, No. 10, pp. 1299-1302, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

A FACILE α-IODINATION REACTION OF UNSATURATED AMIDES

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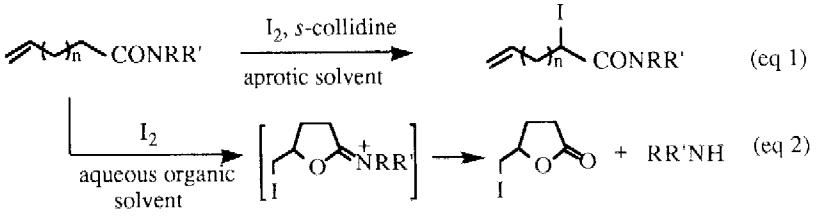
Key Words: iodination, unsaturated amide, iodine, collidine, imidate

Abstract: A novel and mild α-iodination of carboxamides was developed. Unsaturated amides could be converted to the α-iodoamides in moderate to good yields by treatment with I_2 in the presence of *s*-collidine.

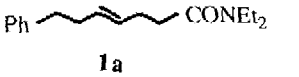
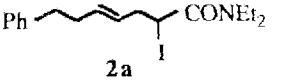
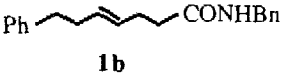
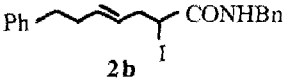
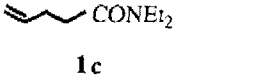
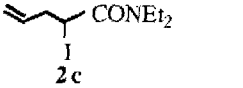
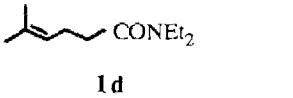
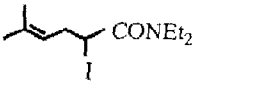
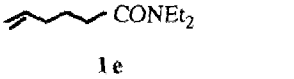
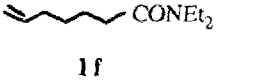
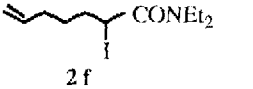
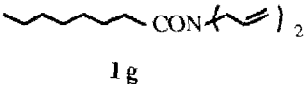
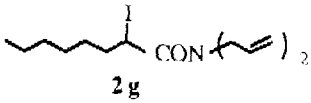
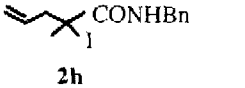
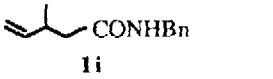
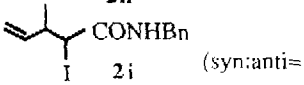
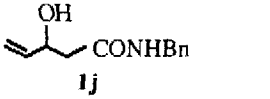
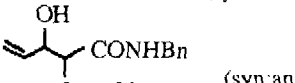
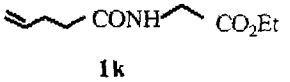
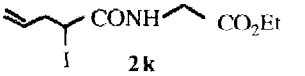
In contrast to relative ease of α-halogenation, commonly bromination or chlorination of aldehydes or ketones, α-halogenation of esters or carboxamides (amides) requires a certain activating process.[1,2] Thus, it has been widely documented that the synthetic method of α-haloesters or amides involves the conversion of parent esters or amides to the enolate anions by treatment with a strong base such as lithium dialkylamide or to the corresponding enol derivatives followed by reaction with an appropriate halogenating reagent.[2] It has hardly been possible to conduct these procedures in the case of *N*-monosubstituted or *N*-unsubstituted amide, probably due to the difficulty in bringing about the activation. In this paper, we report a facile α-iodination reaction of unsaturated amides featuring readily available starting materials and which proceeds under mild conditions. Futhermore, the reaction pathway of the present reaction involving the reversible activating process is also described.



It is reported that the reaction of γ,δ-unsaturated amides with I_2 in aqueous organic solvent produces the γ-iodolactone through hydrolysis of the intermediacy imidate (eq 2).[3] In contrast to the above, we found that α-iodination of the amide cleanly proceeds when the reaction is carried out in the presence of *s*-collidine in aprotic solvent (eq 1). For example, the reaction of *N*,*N*-diethyl-7-phenyl-4-heptenamide **1a** with I_2 and *s*-collidine in dry CH_2Cl_2 at room temperature for 14 h gave the α-iodoamide **2a** in 84% yield along with recovery of a small amount of **1a** (13%), but the corresponding iodolactone could not be detected (Table 1, entry 1).[4] The yield of **2a** was affected little by the solvent used [THF(**2a**, 76%), CH_3CN(**2a**, 69%)], but strongly by the additive. That is, **2a** was obtained in lower yield when triethyl amine (**2a**, 40%) or $Ti(Oi\text{-}Pr)_4$ (**2a**, 31%) was used instead of *s*-collidine, and no iodide **2a** was produced without these additives. Furthermore, the presence of olefinic

moiety at the suitable position is essential (see Table 1) and with saturated amide such as *N,N*-diethyl-7-phenylheptanamide no reaction occured under the same conditions.

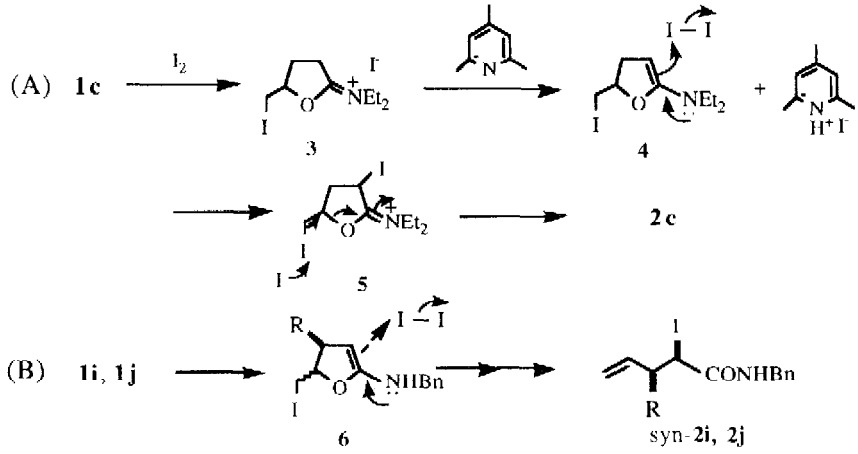
Table 1. α- Iodination of Unsaturated Amides[a)]

Entry	Substrate	Temp	Time (h)	Products	Yield (%)[b)]
1	 **1a**	r.t	18	 **2a**	84
2	 **1b**	r.t	40	 **2b**	78
3	 **1c**	r.t	14	 **2c**	81
4	 **1d**	r.t	18	 **2d**	81
5	 **1e**	r.t	15	 **2e**	57
6	 **1f**	r.t	15	 **2f**	44
7	 **1g**	r.t	20	 **2g**	36
8	 **1h**	45 °C	20	 **2h**	58
9	 **1i**	0 °C - r.t	14	 **2i**	43 (syn:anti=11.3:1)[c)]
10	**1i**	45 °C	20	**2i**	76 (syn:anti=2.8:1)[c)]
11	 **1j**	40 °C	14	 **2j**	67[d)] (syn:anti=15:1)[c)]
12	 **1k**	45 °C	20	 **2k**	42

a) α-Iodination: amide (1mmol), I_2 and *s*-collidine (1.5mmol), CH_2Cl_2 (6-7ml). b) Isolated yield.
c) Determined by 400 MHz ^{1}H-NMR. d) amide (0.5mmol), I_2 and *s*-collidine (1.5mmol), DMF (7 ml).

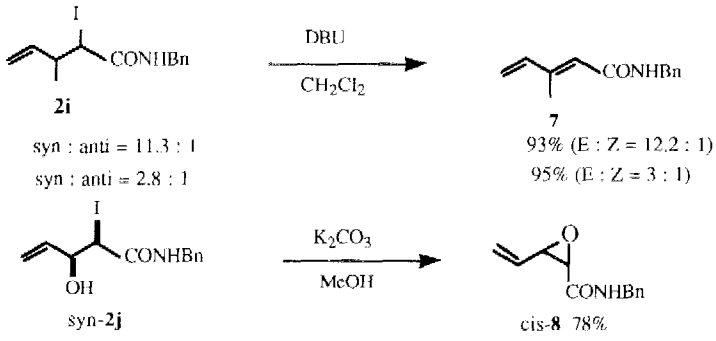
Various unsaturated amides were iodinated as summarized in Table 1. From these results followings are worth to note. Similar to **1a**, amides **1c**, **1d** having mono- or trisubstituted olefin gave the iodide **2c**, **2d** in good yield (entries 3, 4). The present reaction was also applicable to *N*-monosubstituted amides; thus, **1b** was converted to the iodide **2b** under the same conditions (entry 2, see also entries 8-12).[5] *N*,*N*-Diethylamide of 5-hexenoic acid **1e** and 6-heptenoic acid **1f** also gave the iodides **2e**, **2f** under the same conditions, although the yields were slightly lower than those of 4-pentenoic acid derivatives (entries 5, 6). Iodination of the amide of saturated carboxylic acid was possible giving the iodide in moderate yield when *N*-allyl amide was used (entry 7). In the case of 2-alkylsubstituted amide **1h**, slightly higher temperature (45 °C) was required (entry 8). Iodination of *N*-benzyl-3-substituted-4-pentenamide **1i**, **1j** gave the iodide **2i**, **2j** with relatively high syn-selectivity (syn /anti = 11.3, entry 9; syn/anti = 15, entry 11).[6,7] Syn-selectivie formation of **2j** from **1j** is significant contrary to anti-selectivity in iodination of lithium enolate of β-hydroxy ester.[8] Even if there exists another acidic hydrogen in the same molecule as in the case of **1k**, the iodide **2k** can be obtained in moderate yield (entry 12). As shown here, the present reactions can be carried out with a variety of unsaturated amides under mild conditions by simple procedures.

The reaction pathway may be explained by considering the conversion of the cyclic imidate **3**, an intermediate of halolactonization, into the ketene *N*,*O*-acetal form **4**, which, in turn, reacts with I_2 to form the α-iodocyclic imidate **5** and the ring cleavage subsequently occurs by nucleophilic attack of iodide to the iodo atom at the 5-position of **5** to produce **2c** and I_2 [Scheme 1 (A)]. ^{1}H- and ^{13}C-NMR spectra data of a mixture of **1c** (1mol equiv.) and I_2 (1.5 mol equiv.) in $CDCl_3$ indicated the quantitative formation of the imidate **3**.[9] In ^{1}H-NMR of **3**, downfield shifts of the α-hydrogens of **3** by 1.2-1.3ppm compared with those of **1c** indicated the considerable increase in acidity of α–hydrogens, resulting in abstraction of α-hydrogen by a weak base such as *s*-collidine to form **4**. Observed syn-selectivity in iodination of **1i**, **1j** may also be explained by considering the cyclic enamine structure as an intermediate, as shown in Scheme 1 (B).



(Scheme 1)

The followings, conversion to the trisubstituted diene **7** and to the epoxide **8** are the typical examples of synthetic use of the iodides.



(Scheme 2)

In conclusion, a facile α-iodination reaction of unsaturated amides, which involves reversible activating process, was developed. Asymmetric iodination using chiral amides and further application of the present reaction are currently being carried out.

References and Notes

1. House, H. O. in *Modern Synthetic Reactions*, W. A. Benjamin, Inc., (Melon Park), **1972**, Chap. 8.
2. For example, see: Lithium enolate of esters: Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995-3998. Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1977**, 43, 3687-3690. Ketene silylacetal: Oppolzer, W.; Dudfield, P. *Tetrahedron Lett.* **1985**, 26, 5037-5040. Boron enolate of active amide: Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, 28, 1123-1126.
3. Lawson, W. B.; Witkop, B. *J. Org. Chem.* **1961**, 26, 247-248. Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 18, 1625-1628. Cardillo, G.; Orena, M. *Tetrahedron.* **1990**, 46, 3321-3408.
4. Under similar reaction conditions, methyl 7-phenyl-4-pentenoate was almost unchanged (70% of recovery) and the α-iodoester could not be detected.
5. In general, the reaction rates of *N*-monoalkylamides are slower than those of *N,N*-dialkylamides.
6. Stereochemical assignment of **2i** was determined by converting **2i** to the diene compound **7** through out *E2*-elimination (see Scheme 2).
7. Stereochemical assignment of **2j** was determined by converting **2j** to the epoxide **8** [J = 4.8Hz (cis-**8**) and J = 2.0Hz (trans-**8**) for vicinal ring protons, respectively].
8. Seebach, D.; Beck, A. K.; Renaud, P. *Angew. Chem. Int. Ed. Eng.* **1986**, 25, 98-102. Lin, J. T.; Yamazaki, T.; Takeda, M.; Kitazume, T. *J. Fluorine Chem.* **1989**, 44, 113-120.
9. **1c**: ^{1}H-NMR($CDCl_3$, 400 MHz) δ: 1.04(3H, t, J=7.1Hz, Me), 1.10(3H, t, J=7.1Hz, Me), 2.22-2.43(4H, m, 2-3-H), 3,24(2H, q, J=7.1Hz, NCH_2), 3.31(2H, q, J=7.1Hz, NCH_2), 4.91(1H, d, J=10.3Hz, 5-H), 4.98(1H, d, J=17Hz, 5-H), 5.72-5.88(1H, m, 4-H); ^{13}C-NMR($CDCl_3$, 125 MHz) δ: 12.39, 14.19, 29.32, 32.25, 39.96, 41.78, 114.81, 137.59, 171.15.
3: ^{1}H-NMR($CDCl_3$, 400 MHz) δ: 1.49(3H, t, J=7.3Hz, Me), 1.54(3H, t, J=7.3Hz, Me), 2.39(1H, ddt, J=13.2, 10.6 and 7.5Hz, 3-H), 2.97(1H, dddd, J=4.3, 7.5, 10.7 and 13.2Hz, 3-H), 3.52(1H, ddd, J=4.3, 10.3 and 18.9Hz, 2-H), 3.64(1H, dd, J=4.0 and 11.4Hz, 5-H), 3.72(1H, ddd, J=7.5, 10.6 and 18.9Hz, 2-H), 3.78(1H, dd, J=5.4 and 11.4Hz, 5-H), 3.71-3.96(4H, m, NCH_2), 5.49(1H, ddt, J=4.0, 5.4 and 7.5Hz, 4-H); ^{13}C-NMR($CDCl_3$, 125 MHz) δ: 6.98, 12.73, 13.18, 28.79, 32.73, 47.08, 49.60, 90.63, 178.79.

(Received in Japan 28 October 1991)