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A Mild and Effective Iodination Method Using Iodine in the Presence of Bis-(trifluoroacetoxy)iodobenzene

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Abstract : Herein is described a mild and effective iodination method using bis-(trifluoroacetoxy)iodobenzene-iodine as reagent to be applied to electron deficient heterocyclic systems (protected indoles, coumarin...) Moreover, sensitive protecting groups such as acetyl and tert-butyldimethylsilyl were found to be stable under the new iodination reaction conditions. © 1998 Elsevier Science Ltd. All rights reserved.

The synthetic potential of vinyl iodides is far from being fully exploited. This might be due to the fact that in the case of chemically sensitive compounds mild and efficient iodination preparation procedures are not always available. It is surprising that among iodinating reagents, trifluoroacetylhypoiodide, which is supposed to be formed *in situ* by a simple treatment of a solution of bis-(trifluoroacetoxy)iodobenzene with iodine, has received little attention. To the best of our knowledge, the former reagent has been used to iodinate aromatic compounds only[1]. We herein report on the extension of this methodology, to obtain in a convenient manner a variety of iodo compounds in satisfactory yields compared to standard procedures (Table).

To illustrate the interest of the proposed reagent system, we chose to prepare derivatives of 3-iodoindole which due to their relative chemical instability are otherwise difficult to obtain. To date there are best prepared in modest overall yield by iodine treatment of indole followed by *N*-derivatization of the resulting unstable 3-iodoindole[2a-c] or in two steps from protected indoles by mercuration-iodination procedures[2d-f]. We have now found that indole, protected either as its *N*-phenylsulfonyl or *N-tert*-butyloxycarbonyl (Boc) derivatives **1** (X= H) and **2** (X= H), respectively can be readily iodinated by the bis-(trifluoroacetoxy)-iodobenzene/iodine reagent system (Entries 1 and 2).

In the case of **2** (X= H), the reaction conditions are the following: to a solution of iodine (152 mg, 0.6 mmole) in methylene chloride (2 mL) was added pyridine (194 µl, 2.4 mmole) and bis-(trifluoroacetoxy)iodobenzene (516 mg, 1.2 mmole). Then the solution was stirred 15 min until disappearance of iodine coloration. At that time indole derivative (2 mmole) was added and the reaction mixture stirred for an additional 1.5 h. Then it was diluted by addition of heptane (10 mL) and the solution was filtered over a pad of silica to remove traces of iodine. This procedure allowed the isolation of the corresponding 3-iodo indole **2** (X= I) in good yield (Table, entries 1 and 2).

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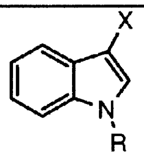
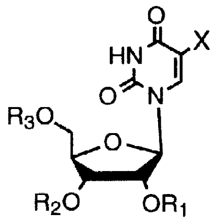
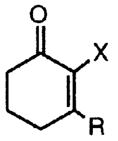
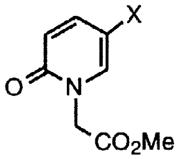
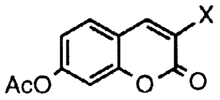
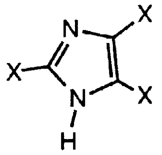
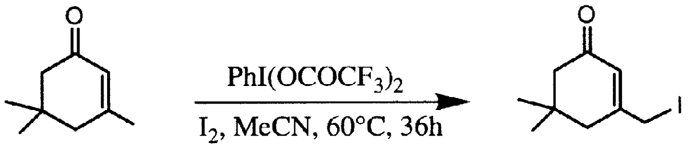
Table: Iodination of various heterocyclic and unsaturated carbonyl derivatives[12]

Entry	Substrate	Ri	δ ^{13}C-H X = H	δ ^{13}C-I X = I	Reaction time (h)[a]	Yield[b]	Lit.[h]
1		**1** R = SO_2Ph	109.19	67.15	2	73	48-88[2a-c]
2		**2** R = Boc	107.28	65.54	2	92	-
3		**3** R_1= R_2= R_3= Ac	103.10	69.61	5	96	89-96[3a,b]
4		**4** R_1-R_2= isopropylidene, R_3 =TBDMS	102.21	68.54	5	87	-
5		**5** R= H	129.65	103.76	2	96	60-81[6a,b]
6		**6** R= Me	126.61	106.70	4	82	70-75[6a,b]
7		**9**	106.14	64.53	2	79	48[8]
8		**10**	110.48	85.39	36	56	-
9		**11**	121.88 135.42	89.45 90.01	3	95	76[10]

[a] Reagent: I_2 (0.6 eq.), $PhI(OCOCF_3)_2$ (0.6 eq.), pyridine (1.2 eq.), CH_2Cl_2; rt. [b] Yield of pure product after column chromatography. [c] Reaction was run at 0°C. [d] The corresponding 3,5-diiodopyridin-2-one was isolated (9%). [e] MeCN was used. [f] Reaction was run at 60°C with 1.2 eq. of reagent. [g] 3 eq. of reagent was used. [h] Litterature yields.

Another heterocyclic system of interest is uracil since in the nucleoside series, 5-iodo derivatives[3] of this pyrimidine can serve as intermediates to give access to C-5 substituted uridines which have been found useful as therapeutic agents[4] or building blocks to be incorporated within modified oligonucleotides[5]. Under our iodination reaction conditions, both acetyl and *tert*-butyldimethylsilyl protecting groups were found to be stable. Thus starting from **3** (X= H) and **4** (X= H) the corresponding 5-iodinated products were obtained in high yield (Entries 3 and 4).

Application of the reagent could also be successfully extended to a number of unsaturated ketones[6]. In particular, 2-cyclohexenone **5** (X= H) and 3-methylcyclohexenone **6** (X= H) were transformed in their corresponding 2-iodo derivatives in almost quantitative yield using 0.6 eq. of iodosobenzene derivative (Entries 5 and 6). When we tried to iodinate isophorone **7** (X= H) without pyridine, we unexpectedly isolated in low yield (not optimized) compound **8** resulting from allylic iodination of the vinylic methyl position (Scheme). This probably reveals the steric hindrance of a methyl group at C-5 which prevents the formation of the required iodonium intermediate. Unfortunately, the more constrained 4-cholesten-3-one could not be iodinated under these conditions.



7 $\delta\ ^{13}C(\underline{C}H_3)$: 24.21 **8** (23%) $\delta\ ^{13}C(\underline{C}H_2I)$: 8.18

Scheme

The case of *N*-alkylpyridin-2-one is remarkable because of the presence of two reactive centers (positions 3 and 5) due to the enamine and enone character of this molecule. We have observed that treatment of *N*-methoxycarbonylmethylpyridin-2-one **9** (X= H)[7] led to its corresponding 5-iodo derivative[8] in good overall yield, together with a little amount of 3,5-diiodopyridin-2-one (mp 161-162°C; 9%) (Entry 7). We tried, without success, to find reaction conditions to give the 5-iodo derivative **9** (X= I) as a single product. The results of this regioselective iodination can be explained by the higher nucleophilicity of the C-5 position compared to the C-3 position as supported by both ^{13}C chemical shift data ($\delta\ ^{13}C$-3: 120.50, $\delta\ ^{13}C$-5: 106.14) and electronic density calculation. In this series it is worthy of note that so far only a few examples of such derivatives are known. In particular, Edgar[1c] has recently reported the preparation of 5-iodopyridin-2-one in a modest 48% yield by an oxydative method using NaI in the presence of NaOCl. To obtain the corresponding *N*-substituted derivative the later compound had to be alkylated.

Finally, it was of interest to observe that, compared to the substrates studied so far, the less electrophilic 7-acetoxycoumarin **10** (X= H) could be iodinated in modest yield by the above reagent at its 3-position, exclusively (Entry 8). This is a remarkable observation since iodine tris-(trifluoroacetate)/ NaI reagent was reported to give mixtures of mono- and diodinated coumarins[9].

We also felt that the reagent could be used to define a reproductive preparation of 2,4,5-triiodoimidazole[10a] which is well known to serve as an efficient iodinating agent[10b]. Thus the treatment of imidazole in acetonitrile with 3 equivalents of reagent gave 2,4,5-triiodoimidazole which was isolated in 95% yield after addition of triethylamine to the reaction medium followed by solvent evaporation and filtration of the crude product over a silica gel column (mp 190-192°C)[10a] (Entry 9).

In conclusion, the above series of examples indicates that the bis-(trifluroacetoxy)iodobenzene/ iodine/ pyridine reagent system can be applied to iodinate under mild conditions a wide range of enones and highly functionalized heterocyclic systems. In view of the importance of vinylic iodo derivatives in synthetic applications[11] the herein described procedure might offer a safe alternative to prepare such compounds when difficulties are encountered with more classical methods.[12]

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12 All compounds were characterized by their analytical and spectral data. For selected spectral data: **4** (X= I): Foam; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02 (s, 6H, 2MeSi), 0.81 (s, 9H, *t*Bu), 1.25 and 1.48 (2s, 6H, 2Me), 3.70 and 3.82 (2dd, 2H, J_1 = 16.6 Hz, J_2= 2.5 Hz, CH_2OSi), 4.29 (m, 1H, H-4'), 4.62 (m, 2H, H-2' and H-3'), 5.77 (d, 1H, J = 2.5 Hz, H-5'), 7.85 (s, 1H, H-6), 9.65 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ −5.16, 18.27, 25.15, 25.66, 27.03, 63.30, 68.54, 80.54, 85.08, 86.64, 92.82, 113.94, 144.87, 150.06, 160.44; MS (EI) *m/z*: 495 (M^+). **8**: oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (s, 6H, 2Me), 2.22 (s, 2H, CH_2CO), 2.41 (s, 2H, CH_2), 4.01 (s, 2H, CH_2I), 6.22 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 8.18, 28.06, 33.71, 42.51, 51.03, 125.64, 157.81, 199.86; MS (EI) *m/z*: 264 (M^+). **10** (X= I): oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H, Me), 7.07 (dd, 1H, J_{ortho}= 8.2 Hz, J_{meta}= 2.3 Hz, H-6), 7.12 (d, J_{meta}= 2.3 Hz, H-8), 7.44 (d, J_{ortho}= 8.2 Hz, H-5), 9.34 (s, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 21.19, 85.39, 110.37, 117.98, 118.83, 127.62, 151.64, 153.49, 154.52, 158.60, 168.59; MS (EI) *m/z*: 330 (M^+).