IODINATION OF BENZOCYCLIC AMINES WITH MERCURY(II) OXIDE-IODINE REAGENT

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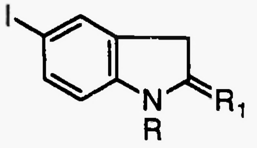
Abstract: By treatment with mercury(II) oxide-iodine reagent in dichloromethane at room temperature, 5-,6- and 7-membered benzocyclic amines, such as indole, indoline, 1,2,3,4-tetrahydroquinoline and 2,3,4,5-tetrahydro-1*H*-benzazepine, were readily converted to the corresponding monoiodo compounds, regioselectively.

Introduction

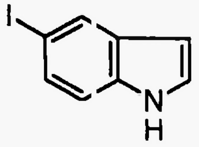
Most of the currently used methods for the direct iodination of aromatic amines, such as I_2-AcOH (1), I_2-HNO_3 (2), I_2-DMSO (3), KI-I_2-EDA (4), I_2-morpholine (5), I_2-$NaHCO_3$ (6), I_2-DMF-KOH (7), I_2-$CuCl_2$ (8), I_2-$F_3CCOOAg$ (9), I_2-Ag_2SO_4 (10), I_2-$HgCl_2$ (11), I_2-Al_2O_3 (12), IF (13), IF_5 (14), DIDH (15), ICl (16-20), PSVP (19), BTMA-ICl_2 (20), $KICl_2$ (21), NaOCl-NaI (22), PyICl (21,23), IPy_2BF_4 (24), and $I(collidine)_2PF_6$ (25), require acidic or basic reaction conditions, and liberate strong acids. Iodination of alkoxy-substituted benzenes with HgO-I_2 reagent was first introduced using hydroquinone dimethyl ether as a substrate by Kauffmann and Fritzs in 1908 (26). We have recently reported on a high regioselectivity of this reagent to iodination of alkyl aryl ethers in dichloromethane (27). Because of the neutral and mild reaction conditions provided by this reagent and an easy work-up, application of this procedure to the initial functionalizations in the synthesis of aromatic heterocyclic compounds has become a subject of interest. In this paper, we report the results of a study focused on preparation of monoiodo derivatives of 5-, 6- and 7-membered benzocyclic amines by direct iodination with HgO-I_2 reagent.

Results and Discussion

On the basis of the results of iodination of alkoxybenzenes (27) and of aniline and its derivatives (28), a suspension of an appropriate benzocyclic amine, mercury(II) oxide (red) and iodine in dichloromethane (0.2 mol/l) was stirred at room temperature, and the reaction was monitored by TLC. After removal of precipitates, the filtrate was washed with water (29), dried, and evaporated. In this manner, iodination of indoline and N-methylindoline (30) took place exclusively at their 5 position to give **1a,b** in moderate yields, as shown in Table. Iodination of N-acetylindoline and oxindole proceeded more slowly to give the corresponding 5-iodo derivatives **1c,d** in good yields. It should be noted that 5-iodoindole **2** can be prepared by the reported method *via* DDQ



1a : R=H, $R^1=H_2$
1b : R=Me, $R^1=H_2$
1c : R=Ac, $R^1=H_2$
1d : R=H, $R^1=O$



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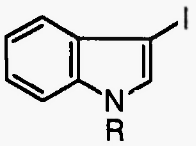
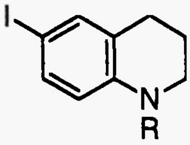


3a: R=H
3b: R=Me



4a : R=H
4b : R=Me

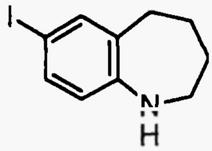


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Table : Iodination of Benzocyclic Amines with $HgO\text{-}I_2$[a]

entry	HgO/I_2 (mol.equiv)	reaction time	product	yield	m.p. or b.p.	Lit. m.p. (°C)
1	1/1	5h	**1a**	55%		
2	1/1	6 h	**1b**	60%		
3	2/2	20 h	**1c**	78%	139.5-140°C (MeOH)	139.5-140.5°C[18] 142.5-143.5°C[36]
4	2/2	20 h	**1d**	77%	212-215°C (MeOH)	
5	1/1	16 h	**3a**	84%	75-77°C (ether-hexane)	75°C,[17] 76°C[7] 80-82°C[23]
6	1.5/1.5	20 h	**3b**	86%	oil	oil[7]
7	2/2	3 h	**4a**	80%		
8	1/1	6 h	**4b**	70%		
9	1.4/1.4	5 h	**5**	70%.		

[a] The reaction equation:

$$\text{Ar-H} + 0.5\,\text{HgO} + I_2 \longrightarrow \text{Ar-I} + 0.5\,\text{HgI}_2 + 0.5\,H_2O$$

oxidation of **1c** (18,31). A careful treatment of indole and N-methylindole with this reagent gave 3-iodo derivatives **3a,b** (32). Purification of the crude purple-colored 3-iodoindole **3a** was achieved by recrystallization (84%), and 3-iodo-N-methylindole **3b** (86%) could be chromatographed on silica gel with CH_2Cl_2. Quinoline, isoquinoline and pyridine were inert to this reagent. 1,2,3,4-Tetrahydroquinoline and its N-methyl derivative (33) were easily converted to their 6-iodo derivatives **4a** (80%) and **4b** (70%), respectively. 7-Iodo derivative **5** of 2,3,4,5-tetrahydro-1*H*-benzazepine (34) was also produced in a similar yield (35).

Thus, it has been shown that monoiodo derivatives of 5-, 6- and 7-membered benzocyclic amines can be efficiently prepared by direct iodination with mercury(II) oxide-iodine reagent.

Selected spectral data:

1a: a colorless liquid; IR (neat) 3386, 1601 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.03 (2H, t, *J* = 8.2 Hz, 2-H), 3.55 (2H, t *J* = 8.2 Hz, 3-H), 6.42 (1H, d, *J* = 8.1 Hz, 7-H), 7.28 (1H, dd, *J* = 8.1, 1.0 Hz, 6-H), 7.37 (1H, d, *J* = 1.0 Hz, 4-H); EI-MS (rel. int.) *m/z* 245 (M$^+$, 100), 118 [(M - I)$^+$, 29.1], 117 (69.8); EI-HR-MS *m/z* 244.9699 (calcd for C_8H_8IN: 244.9695).

1b: a colorless liquid; IR (neat) 1598 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.72 (3H, s, 1-CH_3), 2.92 (2H, t, *J* = 8.3 Hz, 2-H), 3.30 (2H, t, *J* = 8.3 Hz, 3-H), 6.25 (1H, d, *J* = 8.3 Hz, 7-H), 7.31 (1H, d, *J* = 1.0 Hz, 4-H), 7.33 (1H, dd, *J* = 8.3, 1.0 Hz, 6-H); EI-MS (rel. int.) *m/z* 259 (M$^+$, 100), 131 (7.2); EI-HR-MS *m/z* 258.9856 (calcd for $C_9H_{10}IN$: 258.9864).

4a: a colorless liquid; IR (neat) 3414, 1594, 1573 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.89 (2H, q, *J* = 6.3 Hz, 3-H), 2.71 (2H, t, *J* = 6.3 Hz, 2-H), 3.28 (2H, t, *J* = 5.3 Hz, 4-H), 6.24 (1H, d, *J* = 7.92 Hz, 7-H), 7.17 (1H, d, *J* = 2.0 Hz, 5-H), 7.21 (1H, d, *J* = 1.3 Hz, 7-H); EI-MS *m/z* (rel. int.) 259 (M$^+$, 100), 132 [(M - I)$^+$, 6.8], 131 (3.6), 130 (7.2); EI-HR-MS *m/z* 258.9873 (calcd for $C_9H_{10}IN$: 258.9858).

4b: a colorless liquid; IR (neat) 1589, 1557, 1500 (N-H) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.93 (2H, *J* = 6.6 Hz, 3-H), 2.70 (2H, t, *J* = 6.6 Hz, 2-H), 2.84 (3H, s, 1-CH_3), 3.20 (2H, t, *J* = 5.6 Hz, 4-H), 6.32 (1H, d, *J* = 8.6 Hz, 7-H), 7.20 (1H, d, *J* = 2.0 Hz, 5-H), 7.21 (1H, dd, *J* = 8.6, 2.0 Hz 7-H); EI-MS *m/z* 273 (M$^+$, 100), 272 [(M$^+$ - H), 45.5], 146 [(M - I)$^+$, 10.7], 145 (13.5), 144 (26.0); EI-HR-MS *m/z* (rel. int.) 273.0031 (calcd for $C_{10}H_{12}IN$: 273.0014).

5: a colorless liquid; IR (neat) 3384 (N-H) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.57-1.66 (2H, m, 3-H), 1.73-1.82 (2H, m, 4-H), 2.69 (2H, t, *J* = 5.6 Hz, 2-H), 3.02 (2H, t, *J* = 5.3 Hz, 5-H), 6.49 (1H, d, *J* = 8.3 Hz, 9-H), 7.21 (1H, dd, *J* = 8.3, 2.3 Hz, 8-H), 7.40 (1H, d, *J* = 2.3 Hz, 6-H); EI-MS (rel. int.) *m/z* 273 (M$^+$, 100), 272 [(M - H)$^+$, 24.5], 146 [(M - 1)$^+$, 6.9], 145 (5.0), 144 (8.9); EI-HR-MS *m/z* 273.0014 (calcd for $C_{10}H_{12}IN$: 273.0017).

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(28) Iodination of N,N-diethylaniline with HgO-I$_2$ (1/1 mol equiv, 20 min) in CH$_2$Cl$_2$ at room temperature provided N,N-diethyl-4-iodoaniline (92%), exclusively. A similar treatment afforded 4-iodoaniline (0.5/1, 15min, 68%), 4-iodo-N-methylaniline (1/1, 1h, 75%) and 4-iodoacetanilide (3/3, 17h, 72%).

(29) The solution may be washed with a hypo solution to remove excess iodine.

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