Ring contraction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones with [hydroxy(tosyloxy)iodo]benzene to *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates

Ashok Kumar, Sunil Kumar, Rakesh K. Gupta and Devinder Kumar*

Department of Chemistry, Guru Jambheshwar University of Science and Technology, Hisar-125001, Haryana, India

The ring contraction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones with [hydroxy(tosyloxy)iodo]benzene to *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates in trimethylorthoformate in good yield is described.

Keywords: [hydroxy(tosyloxy)iodo]benzene, 4-quinolones, 2,3-dihydroindoles

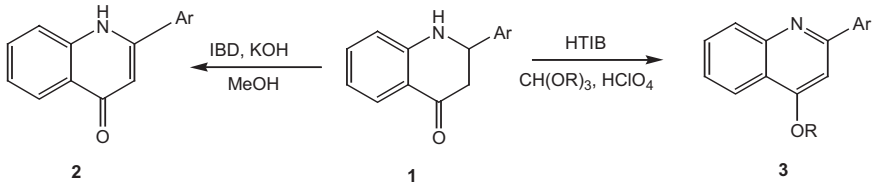
Hypervalent iodine reagents have been widely used in organic synthesis over the past few years.[1] These reagents have been found to be excellent substitutes for metal-containing oxidising agents, such as lead(IV), thallium(III) and mercury(II) salts. Oxidation of quinolones with hypervalent iodine reagents, particularly iodobenzene diacetate (IBD) and [(hydroxytosyloxy)iodo] benzene (HTIB) have been shown to afford different products depending upon the reaction conditions[2,3] (Scheme 1).

Oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones (**1**) with IBD under basic conditions in methanol gave 2-aryl-4-quinolones (**2**) via dehydrogenation[2] whilst treatment of compound **1** with HTIB under acidic conditions in trialkyl orthoformate resulted in the naturally occurring 4-alkoxy-2-arylquinoline (**3**) alkaloids.[3] These compounds have also been obtained by oxidation with iodine-methanol.[4] Further, oxidation of 2-methyl-4-quinolones using HTIB afforded 2-methyl-3-iodo-4-phenoxyquinolines with the intermediacy of isolable α-phenyliodonio tosylates and novel monocarbonyl iodonium ylides.[5] In continuation of our earlier work on oxidation of quinolones by hypervalent iodine,[2,5] the oxidative ring contraction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones to *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates in trimethylorthoformate (TMOF) using HTIB is described.

The 2,3-dihydroindole ring is present in many naturally occurring compounds including biologically active alkaloids.[6,7] 2,3-Dihydroindoles have also been found to behave as selective monoamine oxidase inhibitors[8] and as non-peptide angiotensin II receptor antagonists.[9] 2,3-Dihydroindoles are also potential intermediates for the synthesis of other indoles.[10]

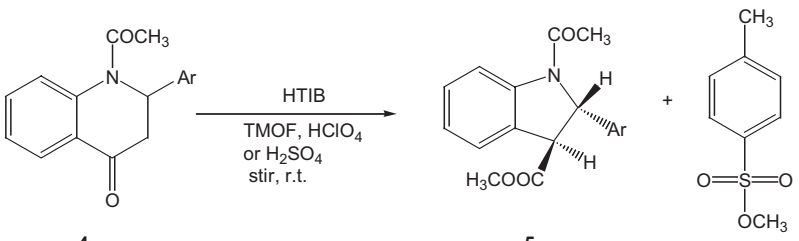
Results and discussion

The reaction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones (**4**) with HTIB was examined in trimethyl orthoformate (TMOF) in the presence of a few drops of either $HClO_4$ or H_2SO_4 at room temperature. The stereoselective ring-contracted products which were formed were identified as *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates (**5**). A side product, methyl *p*-toluenesulfonate (**6**), was also isolated (Scheme 2) in small quantity. The structures of **5a–e** and **6**[11] were established by physical and spectroscopic techniques (IR, ^1H and ^{13}C NMR). The characteristic feature in the ^1H NMR spectrum of compounds **5a–e** was the doublet (or broad singlet) of C_3–H at δ 3.79–3.97 (J = 1.8 Hz, broad singlet of C_2–H at δ 5.73–5.99 and downfield signal of C_7–H at δ 8.24–8.43 (probably due to its deshieding by N-acetyl group). The *trans* stereochemistry of dihydroindole ring in **5a–e** was established by comparing the coupling



2 **1** **3**

Scheme 1

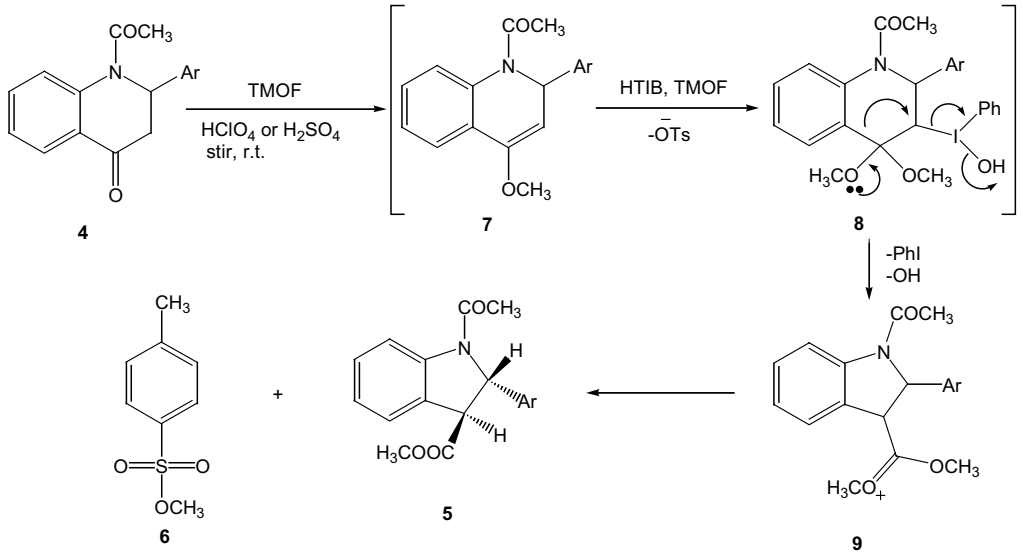


4 **5** **6**

4, **5**; a, Ar = C_6H_5
b, Ar = C_6H_5Br (p)
c, Ar = C_6H_5OMe (p)
d, Ar = $C_6H_5NO_2$ (p)
e, Ar = C_6H_5Cl (p)

Scheme 2

* Correspondent. E-mail: dk_ic@yahoo.com



Scheme 3

constant between C_2–H and C_3–H with that of reported *cis* and *trans* 2,3-dihydroindoles.[12] The coupling constant between C_2–H and C_3–H of *cis* 2,3-dihydroindoles where nitrogen is protected with nitrosyl or arylsulfonyl is 8–9 Hz, whereas that of *trans* isomer is < 4 Hz. The less coupling constant (1.8 Hz) in **5a–e** is perhaps due to π–π interaction between N-acetyl and C_2-aryl groups, thus significantly altering the C_2–H/C_3–H dihedral angle.[13]

The probable mechanism involves the ketalisation of **4** with TMOF in presence of either $HClO_4$ or H_2SO_4 to afford intermediate enol ether **7**. The electrophilic attack of HTIB on the double bond of enol ether **7** furnished the iodine (III) complex, **8**. Reductive elimination of iodobenzene from **8** with simultaneous migration of aryl residue from C_4 to C_3 position gave intermediate carbocation **9** which on hydrolysis afforded the ring contracted product **5** alongwith **6.** The migration of aryl residue is preferred over C_2 aryl ring probably because of greater stability of the carbocation formed. Compound **5** was formed by ring contraction of compound **4** under the reaction conditions while side product **6** was formed probably due to condensation of methanol and *p*-toluenesulfonic acid formed *in situ*.

The present approach for the synthesis of *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates is simple. This method avoids the use of toxic thallium salts for a similar type of reaction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones (**4**) that results in a mixture of *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates (**5**) and 4-methoxy-2-arylquinolines.[14] It should be noted that compound **4a** has also been reported to produce 3-phenylquinoline using HTIB under microwave irradiation instead of a ring contracted product.[15]

Experimental

FTIR spectra were obtained in KBr/neat film on Perkin Elmer Spectrum RX1 instruments and are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz and 100 MHz NMR Spectrometer, respectively in $CDCl_3$; shifts are expressed as ppm with respect to TMS. Elemental analysis was carried out on Perkin Elmer 2400 instrument. 2-Aminochalcone, 2-aryl-1,2,3,4-tetrahydro-4-quinolones, N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones were synthesised using known methods.[14,16]

General procedure

To a solution of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones (**4**, 2 mmol) in freshly distilled trimethylorthoformate (15 ml), was added 1–2 drops of either $HClO_4$ (70%) or conc. H_2SO_4 and stirred for 15–30 min. at room temperature (30°C). HTIB (753 mg, 2.2 mmol) was added in small amounts and the resulting solution was further stirred for 1 h. After completion of the reaction, as monitored by TLC, the reaction mixture was extracted with dichloromethane (3 x 15 ml), washed with saturated aq. sodium bicarbonate solution followed by water. The combined extract was dried over anhydrous Na_2SO_4. Removal of excess of solvent afforded gummy mass which was chromatographed over a neutral alumina column using hexane: ethyl acetate (9:1) as eluent to afford **5a–e** and **6**.

Compound **5a** (Ar = Ph): Oil,[14] yield 68%. IR: 2953 (C–H), 1738 (C=O), 1652 (C=O), 1494, 1385, 1280, 1265, 1029, 756 cm^{-1}. NMR: δ_H 2.05 (s, 3H, $COCH_3$), 3.76 (s, 3H, $COOCH_3$), 3.97 (d, 1H, J = 1.8 Hz, C_3–H), 5.85 (brs, 1H, C_2–H), 7.06–7.10 (m, 1H, C_5–H), 7.17–7.19 (m, 2H, C_4–H and C_6–H), 7.25–7.37 (m, 5H, C_6H_5), 8.34 (1H, d, J = 7.88 Hz, C_7–H); δ_C 24.1, 52.8, 55.7, 65.6, 117.2, 124.1, 125.0, 125.8, 126.0, 128.2, 129.3, 129.4, 141.3, 142.9, 169.5, 171.1.

Compound **5b** (Ar =C_6H_5Br-*p*): Oil, yield 73%. IR: 2923 (C–H), 1736 (C=O), 1661 (C=O), 1504, 1392, 1277, 1026, 759 cm^{-1}. NMR: δ_H 2.03 (s, 3H, $COCH_3$), 3.70 (s, 3H, $COOCH_3$), 3.85 (brs, 1H, C_3–H), 5.74 (brs, 1H, C_2–H), 7.00–7.04 (m, 3H, C_4–H, C_5–H and C_6–H), 7.28 (d, 2H, J = 7.70 Hz, $C_{2'}$–H and $C_{6'}$–H), 7.37 (d, 2H, J = 7.70 Hz, $C_{3'}$–H and $C_{5'}$–H), 8.24 (d, 1H, J = 7.60 Hz, C_7–H); δ_C 24.2, 53.0, 55.6, 65.0, 117.3, 122.2, 124.4, 125.7, 125.9, 126.9, 129.5, 132.5, 140.4, 142.8, 169.3, 171.0. Anal. Calcd. for $C_{18}H_{16}BrNO_3$: C, 57.8; H, 4.3; N, 3.7. Found: C, 57.9; H, 4.21; N, 3.6.

Compound **5c** (Ar =C_6H_5OMe-*p*): Oil,[14] yield 65%. IR: 2970 (C–H), 1735 (C=O), 1650 (C=O), 1501, 1369, 1095, 1122, 1033, 753 cm^{-1}. NMR: δ_H 2.37 (s, 3H, $COCH_3$), 3.66 (s, 6H, $COOCH_3$ and OCH_3), 3.79 (brs, 1H, C_3–H), 5.73 (brs, 1H, C_2–H), 6.88 (d, 2H, J = 7.80 Hz, $C_{3'}$–H and $C_{5'}$–H) 7.01–7.10 (m, 3H, C_4–H, C_5–H, and C_6–H), 7.49 (d, 2H, J = 7.80 Hz, $C_{2'}$ –H and $C_{6'}$–H), 8.29 (1H, d, J = 8.28 Hz, C_7–H).

Compound **5d** (Ar =$C_6H_5NO_2$-*p*): Oil, yield 71%. IR: 2950 (C–H), 1739 (C=O), 1660 (C=O), 1597, 1538, 1480, 1390, 1210, 867, 760 cm^{-1}. NMR: δ_H ($CDCl_3$) 2.04 (s, 3H, $COCH_3$), 3.82 (s, 3H, $COOCH_3$), 3.95 (brs, 1H, C_3–H), 5.99 (brs, 1H, C_2–H), 7.11 (m, 1H, C_5–H), 7.36–7.41 (m, 4H, C_4–H, C_6–H, $C_{3'}$–H and $C_{5'}$–H), 8.19 (d, 2H, J = 7.84 Hz, $C_{2'}$–H and $C_{6'}$–H), 8.32 (d, 1H, J = 7.16 Hz, C_7–H); δ_C 24.1, 53.1, 55.3, 64.9, 117.3, 124.6, 125.2, 126.0, 126.2, 129.7, 132.5, 142.5, 147.7, 148.3, 168.9, 170.0. Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.7; N, 8.2. Found: C, 63.7; H, 4.65; N, 8.1.

Compound **5e** (Ar =C_6H_5Cl-*p*): White solid, m.p. 52–53°C (lit.,[14] m.p. 52–53°C), yield 72%. IR: 2950 (C–H), 1735 (C=O), 1651 (C=O), 1492, 1387, 1280, 1260, 1032, 760, 557 cm^{-1}. NMR: δ_H 2.05 (s, 3H, $COCH_3$), 3.76 (s, 3H, $COOCH_3$), 3.97 (d, 1H, J = 1.8 Hz, C_3–H), 5.81 (brs, 1H, C_2–H), 7.05–7.11 (m, 3H, $C_{2'}$–H, $C_{6'}$–H and C_5–H), 7.26–7.41 (m, 4H, $C_{3'}$–H, $C_{5'}$–H, C_4–H and C_6–H), 8.43 (1H, d, J = 8.10 Hz, C_7–H).

Compound **6**: Oil (lit.,[11] m.p. 25–28°C), IR:2921 (C–H), 1529, 1369, 1195, 1038, 771, 680, 563 cm^{-1}. NMR: δ_H 2.45 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 7.35 (dd, 2H, J = 8.44 and 0.40 Hz, C_3–H and C_5–H), 7.77 (dd, 2H, J = 8.44 and 1.70 Hz, C_2–H and C_6–H); δ_C 21.6,

56.2, 128.0, 129.8, 132.0, 144.9. Anal. Calcd. for $C_8H_{10}O_3S$: C, 51.6; H, 5.41. Found: C, 51.7; H, 5.3.

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