One-pot regioselective synthesis of 2,9-disubstituted imidazo[1,2-*a*] benzimidazoles from 2-aminobenzimidazole and α-tosyloxy ketones

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One-pot regioselective synthesis in high yields of 2,9-disubstituted imidazo[1,2-*a*]benzimidazoles from 2-amino-benzimidazole and α-tosyloxy ketones is described.

Keywords: fused imidazoles, benzimidazoles, 2-aminobenzimidazole, α-tosyloxy ketones

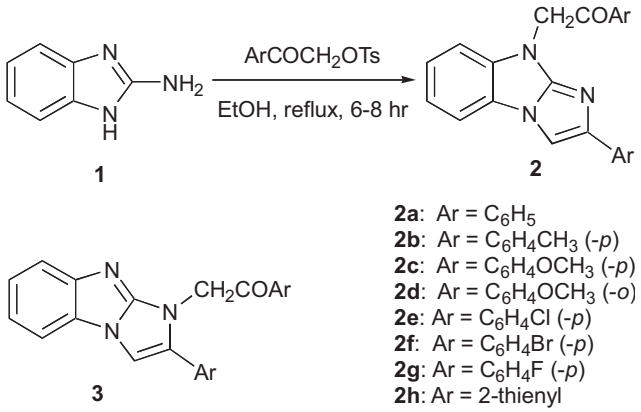
Imidazo[1,2-*a*]benzimidazoles are versatile compounds useful as analgesics,[1] anxiolytics and anticonvulsants,[2] and as corticotropin-releasing factor 1 receptor angonists[3]. The dihydro and tetrahydro imidazo[1,2-*a*]benzimidazoles derivatives have been shown to exhibit antihypertensive,[4] antihistamine[5] and antiproliferative activity[6]. The synthesis of imidazo[1,2-*a*]benz imidazoles has been reported utilising thermal rearrangement of 3-(*o*-aminophenyl)-2-imino-4-phenyl-4-thiazoline,[7] gas phase pyrolysis of 1-(2-azidophenyl)imidazole[8] and condensation of 2-amino-benzimidazole and α-bromoketones[1] or hydrazonoyl bromides[9] involving a number of steps.

α-Tosyloxy ketones are versatile intermediate for the synthesis of a variety of heterocycles.[10] [Hydoxy(tosyloxy) iodo]benzene (HTIB, Koser's reagent) and poly[4-(hydroxy (tosyloxy)iodo)]styrene are key reagents for the synthesis of α-tosyloxy ketones from enolisable ketones.[11-13] The value of α-tosyloxy ketones lies in replacing α-halo ketones, which are highly lachrymatory. Herein, we report the regioselective synthesis of 2,9-disubstituted imidazo[1,2-*a*]benzimidazol es by the reaction of 2-aminobenzimidazole with different α-tosyloxy ketones in high yields.

Results and discussion

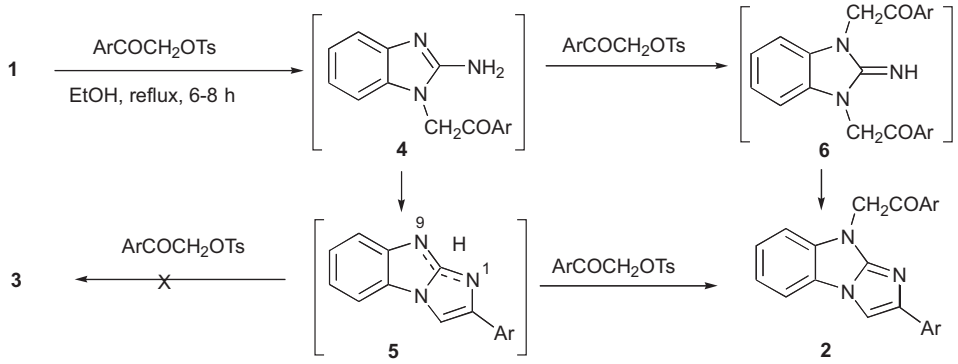
We investigated the reaction of 2-aminobenzimidazole (**1**) with α-tosyloxy ketones and found the formation of 2,9-disubstituted imidazo[1,2-*a*]benzimidazoles (**2**) regioselectively in ethanol under reflux (Scheme 1). The isomeric compound **3** could not be detected even in traces. Further, there was no product formation on stirring **1** and α-tosyloxy ketones at room temperature. However, with one equivalent each of **1** and α-tosyloxy ketone in refluxing ethanol, some amount of **1** was left unreacted along with formation of **2**. The reaction could be optimised by taking two equivalents of the α-tosyloxy ketone.

The structure of **2** was established through physical and analytical data. The carbonyl stretching frequency band in **2** appeared at 1685±5 cm^{-1} (see experimental). The isomeric compound **3** was ruled out on the basis of NMR (^1H and ^{13}C) study. The structure assignment of **2** finds further support from comparison with the published NMR (^1H and ^{13}C) data of 9-methylimidazo[1,2-*a*]benzimidazole.[14] These authors also synthesised the 1-methylimidazo[1,2-*a*]benzimidazole in addition to the 9-methyl compound and the structure comparison was based on rigorous NMR (^1H and ^{13}C) analysis which clearly established the structure as **2** instead of **3**.[14] The mass spectral fragmentation of **2** proceeds with elimination of the aroyl moiety at position 9 to generate the stable fragment ion as base peak.



Scheme 1

The mechanism involves the nucleophilic attack of NH of **1** on methylene of α-tosyloxy ketones to generate **4** by displacement of tosylate group that may cyclise to give **5** after dehydration. The recent study of the tautomerism of imidazo [1,2-*a*]benzimidazoles showed that the tautomeric proton is on N-9. *Ab initio* calculations confirm the greater stability of 9*H*-over 1*H*-imidazo[1,2-*a*]benzimidazole.[12] The reaction of **5**



Scheme 2

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produces **2** regioselectively instead of **3**. Alternatively, **4** may react with another molecule of α-tosyloxy ketone to afford **6** that may cyclise to give **2** after dehydration (Scheme 2).

The present approach for the synthesis of 2,9-disubstituted imidazo[1,2-*a*]benzimidazoles (**2**) is significant because it utilises α-tosyloxy ketones, that are easy to prepare from enolisable ketones and HTIB/poly[4-hydroxy(tosyloxy)iodo] styrene, instead of the lachrymatory α-bromo ketones. Further, it is a one-pot regioselective instead of a multistep synthesis and no chromatography is required for purification/separation of the product.

Experimental

FTIR spectra were obtained in KBr on a Perkin Elmer Spectrum RX1 instrument. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ + DMSO-d_6; shifts are expressed as ppm with respect to TMS. Elemental analysis was carried out on a Perkin Elmer 2400 instrument. HRMS were measured in EI mode on a Kratos MS-50 spectrometer.

α-Tosyloxy ketones were obtained by the reaction of enolisable ketones either with HTIB or poly-[4-hydroxy(tosyloxy)iodo]styrene in acetonitrile and were used without further purification.[11-13]

2-Aryl-9-(aroylmethyl)imidazo[1,2-a]benzimidazoles (**2–2h**)*: general procedure*

The α-tosyloxy ketone (4 mmol) was added to 2-aminobenzimidazole (**1**, 266 mg, 2 mmol) in dry ethanol (20 ml) and 3–4 drops of glacial acetic acid were added. The reaction mixture was refluxed for 6–8 h. The excess of ethanol was distilled off and the residue was cooled to room temperature. Water was added to precipitate the product, which was filtered off, washed with water, aqueous sodium bicarbonate, again with water, and dried to afford **2**, which was crystallised from aqueous ethanol.

Compound **2a** (Ar = Ph): M.p. 217–218°C (lit.[1] M.p. 218°C), yield 76%. IR: 3069, 1688, 1620, 1540, 1498, 1450, 1354, 1321, 1233, 1161 cm^{-1}. NMR: δ_H 5.75 (s, 2H, CH_2), 7.19–7.29 (m, 4H), 7.35–7.39 (m, 2H), 7.55–7.62 (m, 3H), 7.69 (t, 1H, *J* = 7.0, 7.3 Hz), 7.75 (s, 1H), 7.83 (d, 1H, *J* = 7.4 Hz), 8.11 (d, 1H, *J* = 7.4 Hz); δ_C 48.8, 102.2, 110.7, 120.0, 122.8, 124.1, 124.4, 126.2, 127.8, 128.0, 128.3, 128.4, 133.6, 134.0, 134.4, 135.6, 143.2, 149.4, 191.9. MS: Calcd. for $C_{23}H_{17}N_3O$: 351.1372, found 351.1361 (54); 246.1036 (100), 233.0941 (11), 105.0342 (16), 77.0390 (20).

Compound **2b** (Ar = $C_6H_4CH_3$-*p*): M.p.168–170°C, yield 71%. IR: 2916, 1693, 1603, 1497, 1408, 1347, 1232, 1131, 1060, 973, 811, 735 cm^{-1}. NMR: δ_C 2.35 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 5.71 (s, 2H, CH_2), 7.16–7.25 (m, 5H), 7.35 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 1H, *J* = 7.5 Hz), 7.70 (d, 2H, *J* = 8.0 Hz), 7.72 (s, 1H), 7.98 (d, 2H, *J* = 8.2 Hz); δ_C 21.3, 21.8, 49.2, 101.7, 110.0, 111.0, 120.6, 123.3, 124.9, 125.1, 128.4, 128.7, 129.3, 129.6, 132.0, 135.9, 136.6, 144.5, 145.2, 149.9, 191.5. MS: Calcd. for $C_{25}H_{21}N_3O$: 379.1685, found 379.1679 (69); 260.1199 (100), 119.0495 (40), 91.05441 (19). Anal. Calcd. for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.07. Found: C, 79.10; H, 5.48; N, 11.39%.

Compound **2c** (Ar = C_6H_4OMe-*p*): M.p.124–25°C, yield 72%. IR: 2942, 1683, 1602, 1493, 1450, 1308, 1236, 1169, 1027, 978, 827, 740 cm^{-1}. NMR: δ_H 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.59 (s, 2H, CH_2), 6.91 (d, 2H, *J* = 8.8 Hz), 6.95 (d, 2H, *J* = 8.4 Hz), 7.10 (d, 1H, *J* = 7.9 Hz), 7.17–7.22 (m, 2H), 7.50 (d, 1H, *J* = 7.3 Hz), 7.53 (s, 1H), 7.74 (d, 2H, *J* = 8.7 Hz), 8.04 (d, 2H, *J* = 8.8 Hz); δ_C 49.0, 55.3, 55.6, 101.1, 110.1, 110.9, 114.1, 120.6, 123.2, 125.0, 126.5, 127.5, 127.7, 130.6, 135.9, 144.3, 149.9, 158.8, 164.2, 190.3. MS: Calcd. for $C_{25}H_{21}N_3O_3$: 411.1583, found 411.1587 (73); 276.1139 (44), 135.0446 (100). Anal. Calcd. for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 72.54; H, 5.23; N, 10.01%.

Compound **2d** (Ar = C_6H_4OMe-*o*): M.p.172–174°C, yield 63%. IR: 2926, 1688, 1610, 1501, 1452, 1310, 1218, 1183, 1032, 981, 825, 742 cm^{-1}. NMR: δ_H 4.01 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 5.63 (s, 2H, CH_2), 7.01 (d, 1H, *J* = 7.3 Hz), 7.04–7.14 (m, 3H), 7.15–7.31 (m, 4H), 7.53–7.58 (m, 2H), 7.94 (t, 1H, *J* = 7.8, 8.5 Hz), 7.99 (s, 1H), 8.21 (dd, 1H, *J* = 1.5, 7.7 Hz); δ_C 53.7, 55.4, 55.7, 106.6, 109.9, 110.6, 111.0, 111.6, 120.3, 120.9, 121.1, 123.0, 123.6, 124.7, 125.1, 127.2, 128.1, 131.4, 135.2, 136.4, 139.7, 156.1, 159.7, 192.8. Anal. Calcd. for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 73.14; H, 5.20; N, 10.01%.

Compound **2e** (Ar = C_6H_4Cl-*p*)**:** M.p. 238–240°C (Lit.[1] 240-242°C), yield 74%. IR: 3118, 1688, 1604, 1534, 1445, 1342, 1219, 1102, 948, 850 cm^{-1}. NMR: δ_H 5.78 (s, 2H, CH_2), 7.24–7.30 (m, 3H), 7.34 (d, 2H, *J* = 8.5 Hz), 7.55 (d, 2H, *J* = 7.6 Hz), 7.65 (d, 1H, *J* = 7.6 Hz), 7.78 (dd, 2H, *J* = 7.7, 1.8 Hz), 7.83 (s, 1H), 8.09 (dd, 2H, *J* = 1.8, 6.7 Hz); δ_C 49.3, 102.5, 110.0, 111.2, 121.0, 123.7, 124.9, 126.4, 128.8, 129.4, 129.7, 132.6, 133.2, 135.0, 135.8, 140.9, 190.8. MS: Calcd. for $C_{23}H_{15}Cl_2N_3O$: 419.0592, found 419.0599 (44); 421.0156 (30), 423.0544 (6), 282.0615 (33), 280.0640 (100), 139.0019 (15), 110.9927 (11).

Compound **2f** (Ar = C_6H_4Br-*p*): M.p. 206–207°C (Lit.[1] 208–209°C), yield 75%. IR: 3121, 1679, 1595, 1528, 1448, 1336, 1224, 1107, 950, 853 cm^{-1}. NMR: δ_H 5.74 (s, 2H, CH_2), 7.21–7.28 (m, 3H), 7.48 (d, 2H, *J* = 8.5 Hz), 7.64 (d, 1H, *J* = 7.8 Hz), 7.72 (m, 4H), 7.81 (s, 1H), 8.01 (d, 2H, *J* = 8.6 Hz). MS: Calcd. for $C_{23}H_{15}Br_2N_3O$: 506.9582. Found: 506.9581 (35), 508.9563 (71), 510.9553 (36), 324.0111 (99), 324.0130 (100), 184.9425 (14), 156.9491 (8).

Compound **2g** (Ar = C_6H_4F-*p*): M.p. 182°C, yield 75%. IR: 3130, 1665, 1587, 1525, 1459, 1330, 1219, 1097, 976, 848 cm^{-1}. NMR: 5.66 (s, 2H, CH_2), 7.04–7.13 (m, 3H), 7.17–7.28 (m, 4H), 7.54 (d, 1H, *J* = 7.3 Hz),7.58 (s, 1H), 7.69–7.78 (m, 2H), 8.10–8.14 (m, 2H); δ_C 49.2, 102.0, 110.0, 111.2, 115.4, 115.6, 116.2. 116.4, 121.0, 123.6, 124.9, 126.9, 127.0, 131.0, 131.1, 135.8, 143.4, 149.8, 190.3. Anal. Calcd. for $C_{23}H_{15}F_2N_3O$: C, 71.31; H, 3.90; N, 10.85. Found: C, 71.10; H, 3.96; N, 10.74%.

Compound **2h** (Ar = 2-thienyl): M.p. 202–205°C, yield 63%. IR: 2921, 1671, 1499, 1446, 1408, 1349, 1239, 1188, 1152, 1040, 1006, 919, 854 cm^{-1}. NMR: δ_H 5.77 (s, 2H, CH_2), 7.01–7.04 (m, 1H), 7.19–7.38 (m, 5H), 7.68 (d, 1H, *J* = 7.5 Hz),7.84 (s, 1H), 7.93 (d, 1H, *J* = 4.5 Hz), 8.20 (d, 1H, *J* = 3.2 Hz). Anal. Calcd. for $C_{19}H_{13}N_3OS_2$: C, 62.79; H, 3.61; N, 11.56. Found: C, 62.68; H, 3.68; N, 11.32%.

The authors are thankful to CSIR and UGC, New Delhi for financial support and Mr. Avtar Singh, SAIF, Panjab University, Chandigarh for recording NMR data.

Received 14 June 2007; accepted 6 September 2007
Paper 07/4700 doi: 10.3184/030823407X244850

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