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Synthesis of 2-indolylbenzimidazoles using Fischer's indole method

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Condensation of phenylhydrazine **5a** (*i.e.* **5**, R^2=H) with 2-acetylbenzimidazole **3** in the presence of catalytic amount of acetic acid in refluxing methanol gives phenylhydrazone derivative **6a** (R^2=H) of 2-acetylbenzimidazole, which on heating with the polyphosphoric acid (PPA) yields 2-(1*H*-2-indolyl)benzimidazole **7a** (*i.e.* **7**, R^2=H). **7** is alkylated using different alkylating agents under phase transfer catalyzed conditions using K_2CO_3 as a base and DMF as a solvent to give 2-(1*H*-indolyl)-1-substituted benzimidazoles **9**. The latter can also be prepared by alkylation of **3** giving **4**, followed by condensation with phenylhydrazine **5**, yielding **8** and the subsequent cyclization with PPA. Alternatively, **9** can also be prepared by treating indole-2-carboxylic acid **10** with *o*-phenylenediaminosulphate **1a**. H_2SO_4 (*i.e.* **1**, where R^1=H) in refluxing ethylene glycol yielding **7a**, followed by alkylation of the product under DMF/ K_2CO_3 /TEBAC conditions. Once again, treatment of N-substituted *o*-phenylenediaminosulphate **1b** (*i.e.* **1**, R^1=Me) with **10a/10b** in refluxing ethylene glycol results in the formation of **9a/9d**. **3** itself is obtained by acidic dichromate oxidation of 2-(α-hydroxy)ethylbenzimidazole **2**, which in turn is obtained from *o*-phenylenediamine **1a** (*i.e.* **1**, where R^1=H) and lactic acid under Phillip's conditions.

Keywords: Indoles, benzimidazoles, Philip's conditions, TEBAC, PTC

IPC: Int.Cl.[8] C07D

Indoles and their derivatives are found to possess pronounced biological activity[1]. Compounds in which the indole ring is fused with other heterocyclic rings have also been found to possess remarkable biological properties[2]. Many such derivatives are known in literature containing various heterocyclic moieties substituted at 2- and 3- position of indole. Juby and co-workers synthesized 3-tetrazolylmethylindoles by the reaction of 3-indolylacetonitrile with NaN_3 and these compounds were found to possess anti-inflammatory activity similar to that of indomethacin[3]. Tohru *et al*. synthesized 2-amino-4-scatylthiazoline by the reaction of α-chloromethyltryptamine with thiourea, which was found to be protective against radiation[4]. 3-piperidylethylindoles were prepared by Agarwal and co-workers by the reaction of indole with oxalylchloride followed by reduction and substitution with piperidine. These compounds are known to possess cardiovascular activity[5]. Cavrini and co-workers prepared 3-imidazolylmethylindoles by the reaction of 3-hydroxymethylindole with imidazole in the presence of *p*-TSA. These compounds were found to possess antifungal properties[6].

Benzimidazoles are known to possess pronounced but diverse biological activity[7]. The benzimidazole ring system represents an important pharmacophore in drug discovery, notable clinical examples being the antihistamine astemizole[8] and the proton pump inhibitor omeprazole[9]. Keeping in view the importance of indole and benzimidazole ring systems, it was considered desirable to synthesize compounds containing both these moieties. The present paper describes the synthesis of indolylbenzimidazoles using the Fischer's indole synthesis.

Results and Discussion

Treatment of *o*-phenylenediamine **1** with lactic acid under Phillip's conditions gave the previously reported[10] 2-α-hydroxyethylbenzimidazole **2**. The latter, on oxidation with acidic dichromate gave the well known[11] 2-acetylbenzimidazole **3**.

Condensation of **5a** (i.e. **5**, where R^2=H) with **3** in refluxing methanol containing a catalytic amount of acetic acid gave a product, which was found to be the corresponding phenylhydrazone derivative **6a** of 2-acetylbenzimidazole on the basis of its spectral and analytical data. Thus, its IR spectrum in KBr showed peaks at 3343 cm^{-1} (m, sharp, -NH stretching) and at 3056 cm^{-1} (very broad, m, tautomeric –NH) as diagnostic absorptions. Its ^1H NMR spectrum in

DMSO-d_6 showed signals at δ 2.4 (s, 3H, -N=C-CH_3), 6.8-7.8 (complex m, 9H, five protons of the phenylhydrazine ring and four protons of the aryl part of the benzimidazolyl ring), 9.7 (s, 1H, aryl –NH), ≅ 12.3 (broad s, 1H, tautomeric –NH of the benzimidazolyl ring.) Its CI mass spectrum showed molecular ion peak at *m/z* 251 corresponding to a molecular mass of 250.

6a on heating with polyphosphoric acid (PPA) at 140°C underwent Fischer's indolization reaction to yield 2-(1H-2-indolyl)benzimidazole **7a**. The structure of **7a** has been confirmed based on spectral and analytical data. Thus, its IR spectrum in KBr showed peaks at 3437 cm^{-1} (strong, sharp, -NH of indole ring system) and at ≅ 3055 cm^{-1} (very broad, m, -NH of benzimidazolyl ring system) as diagnostic absorptions. Its ^{1}H NMR in DMSO-d_6 showed signals at δ 6.9-7.8 (complex m, 9H, four protons of the aryl part of the indole ring system, one β-proton of the indole ring system and four protons of the aryl part of the benzimidazolyl ring system). The CI mass spectrum showed its molecular peak at *m/z* 234 in the Q+1 mode corresponding to a molecular mass of 233.

Reaction of 2-(1*H*-indolyl)benzimidazole **7a** with an alkylating agent such as dialkyl sulphate or benzyl chloride in the presence of K_2CO_3 as base and TEBAC as phase transfer catalyst in DMF gave the corresponding imidazole –NH- alkylated products **9**. Similarly **7b** was prepared by the condensation of **5b** with **3** yielding **6b**, followed by reaction with PPA (**Table I**).

Alternatively, the 1-substituted-2-acetylbenzimidazolephenylhydrazones **8** were prepared by the treatment of **3** with phenylhydrazine to give the corresponding phenylhydrazones **6**, which were then alkylated with different alkylating agents in CH_3CN in the presence of K_2CO_3 as a base and TEBAC as a phase transfer catalyst (**Table II**).

Table I — Characteristic data of 2-indolylbenzimidazoles **9** obtained from **7***

Starting Material	Reagent	Product	Yield (%)	m.p. (°C)
7a (R^2=H)	DMS	**9a** ($R^1 = CH_3$, R^2 = H)	80	225-27
7a (R^2=H)	DES	**9b** ($R^1 = C_2H_5$, R^2 = H)	83	188-90
7a (R^2=H)	$PhCH_2Cl$	**9c** ($R^1 = PhCH_2$, R^2 = H)	82	98-100
7b ($R^2=C_2H_5$)	DMS	**9e** ($R^1 = CH_3$, $R^2 = C_2H_5$)	79	198-200
7b ($R^2=C_2H_5$)	DES	**9f** ($R^1 = C_2H_5$, $R^2 = C_2H_5$)	78	98-102
7b ($R^2=C_2H_5$)	$PhCH_2Cl$	**9g** ($R^1 = PhCH_2$, $R^2 = C_2H_5$)	77	75-80

*All reactions were done in DMF at RT

Table II — Physical data of compounds **8** obtained from **6***

Starting Material	Reagent	Product	Yield (%)	m.p. (°C)
6a (R^2=H)	DMS	**8a** ($R^1=CH_3$, R^2=H)	83	203
6a (R^2=H)	DES	**8b** ($R^1=C_2H_5$, R^2=H)	80	128-30
6a (R^2=H)	$PhCH_2Cl$	**8c** ($R^1=PhCH_2$, R^2=H)	85	170-72
6b $R^2=C_2H_5$)	DMS	**8d** ($R^1=CH_3$, $R^2=C_2H_5$)	81	100-02
6b $R^2=C_2H_5$)	DES	**8e** ($R^1=C_2H_5$, $R^2=C_2H_5$)	79	114-16
6b $R^2=C_2H_5$)	$PhCH_2Cl$	**8f** ($R^1=PhCH_2$, $R^2=C_2H_5$)	78	120-25

*All reactions were done at RT

The compounds **8** thus obtained on treatment with PPA underwent Fischer indole cyclization to give **9**. The **9** obtained above were found to be identical with the corresponding derivatives prepared earlier in the route **6→7→ 9** in all respects.

Similarly, **8** were also prepared by the condensation of **4** with **5** in refluxing methanol containing catalytic amount of acetic acid (**Table III**).

The above compounds on treatment with PPA underwent Fischer indole cyclization to give **9** (**Table IV**).

It is obvious from the above discussion that the compounds **9** contained two heterocyclic rings, namely the benzimidazole ring and the indole ring. The above described reactions involved synthesis of **9** wherein the benzimidazole ring was precursor and the indole ring was built up by Fischer's method based on its condensation with phenylhydrazine. In an alternate approach, the synthesis of **9** was achieved starting from an indole derivative as precursor and its subsequent condensation with *o*-phenylenediaminosulphate derivative leading to synthesis of benzimidazole part of **9** similar to that in Phillips method.

Indole-2-carboxylic acid is an important precursor in the synthesis of 2-substituted derivatives. The same was used in the present work for condensation with *o*-phenylenediaminosulphate to build up the benzimidazole ring in 2 position of indole leading to the formation of **9**.

Table III — Physical data of compounds **8** obtained from **4***

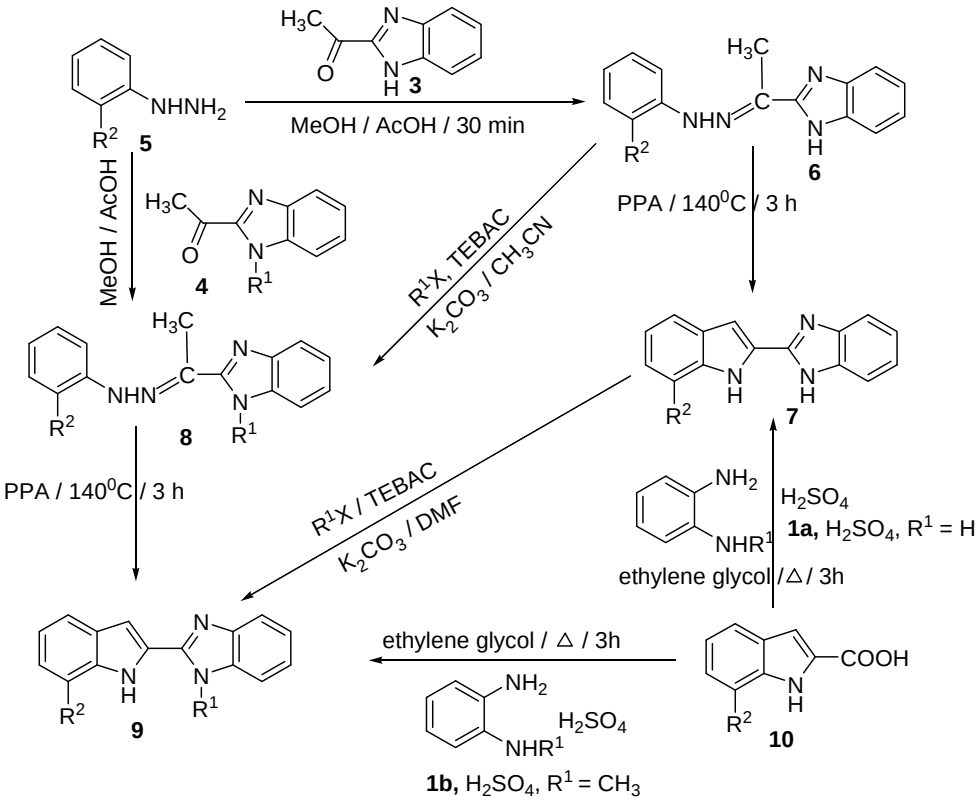
Starting Material	Reagent	Product	Yield (%)	m.p. (°C)
4a (R^1=CH_3)	**5a** (R^2=H)	**8a** (R^1=CH_3, R^2=H)	77	203
4b (R^1=C_2H_5)	**5a** (R^2=H)	**8b** (R^1=C_2H_5, R^2=H)	79	128-30
4c (R^1=$PhCH_2$)	**5a** (R^2=H)	**8c** (R^1=$PhCH_2$, R^2=H)	81	170-72
4a (R^1=CH_3)	**5b** (R^2=C_2H_5)	**8d** (R^1=CH_3, R^2=C_2H_5)	76	100-02
4b (R^1=C_2H_5)	**5b** (R^2=C_2H_5)	**8e** (R^1=C_2H_5, R^2=C_2H_5)	74	114-16
4c (R^1=$PhCH_2$)	**5b** (R^2=C_2H_5)	**8f** (R^1=$PhCH_2$, R^2=C_2H_5)	75	120-25

*All reactions were done in refluxing methanol

Table IV — Characteristic data of 2-indolylbenzimidazoles **9** obtained from **8***

Starting Material	Product	Yield (%)	m.p. (°C)
8a (R^1=CH_3, R^2=H)	**9a** (R^1 = CH_3, R^2 = H)	77	225-27
8b (R^1=C_2H_5, R^2=H)	**9b** (R^1 = C_2H_5, R^2 = H)	79	188-90
8c (R^1=$PhCH_2$, R^2=H)	**9c** (R^1 = $PhCH_2$, R^2 = H)	81	98-100
8d (R^1=CH_3, R^2=C_2H_5)	**9e** (R^1 = CH_3, R^2 = C_2H_5)	76	198-200
8e (R^1=C_2H_5, R^2=C_2H_5)	**9f** (R^1 = C_2H_5, R^2 = C_2H_5)	74	98-102
8f (R^1=$PhCH_2$, R^2=C_2H_5)	**9g** (R^1 = $PhCH_2$, R^2 = C_2H_5)	75	75-80

*All reactions were done in hot PPA at 140°C



Scheme I

Condensation of *o*-phenylenediaminosulphate salt **1a**. H_2SO_4 (where **1a** is **1**, R^1=H) with indole-2-carboxylic acid **10a** (i.e. **10**, R^2=H) in refluxing ethylene glycol for 3 hr gave a product which was found to be 2-(1H-indolyl)benzimidazole **7a**, prepared earlier in the route **5a + 3→6a→7a** on the basis of its m.p., m.m.p., co-TLC and superimposable IR. Similarly condensation of **1a**. H_2SO_4 (i.e. where **1a** is **1**, R^1=H) with **10b** (i.e. **10**, R^2=C_2H_5) led to the formation of **7b** (i.e. **7**, R^1=H,R^2=C_2H_5) identical in all respects (m.p., m.m.p., TLC and IR) with the product obtained in the route **5b + 3→6b→7b**. Alternatively, 1-substituted-2-(1H-indolyl)benzimidazoles **9** were prepared starting from N-substituted *o*-phenylenediamine sulphates. Thus, reaction of N-methyl-*o*-phenylenediaminosulphate **1b** (i.e. where **1b** is **1**, R^1=Me) and indole-2-carboxylic acid (i.e. **10**, R^2=H or C_2H_5) in refluxing ethylene glycol for 3 hr gave a product which was assigned the structure 1-methyl-2-(1H-indolyl)benzimidazole **9a** or **9d** depending R^2=H or C_2H_5. It was found to be similar in all respects with the compound obtained earlier. The above reaction was extended to other N-substituted *o*-phenylenediaminosulphates. All the reactions discussed above are summarized in **Scheme I**.

Experimental Section

Melting points are uncorrected and were obtained in open capillary tubes in sulfuric acid bath. TLC were run on glass plates coated with Silica Gel-G and visualization was by iodine vapors or UV light. IR spectra were recorded using Perkin Elmer model – 446 FTIR instrument in KBr pellets. ^{1}H NMR spectra were recorded on Gemini-2000 and AV-400 instruments operating at 200 MHz and 400 MHz respectively.

Preparation of 6 from 3: A mixture of **3** (3.2 g, 20 mmole), **5** (20 mmole), catalytic amount of acetic acid and methanol (25 mL) was refluxed for 2 hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered, washed with water and dried to get crude **6**, which on recrystallization from hot methanol gave pure **6**.

Preparation of 7 from 6: A mixture of PPA (10 mL) and **6** (10 mmole) in a 100 mL round bottomed flask was heated with occasional stirring at 140°C for 2 hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered. The filtered solid was resuspended in water and treated with a few drops of

Table V — Spectral data of the N-substituted phenylhydrazones **8**

Product	^{1}H NMR (DMSO d_6) δ (ppm)	APCI MS (M+1) *m/z*
8a	δ 2.51 (s, 3H, -N=C-CH_3), 4.14 (s, 3H, -N-CH_3), 6.80-7.70 (complex m, 9H, five protons of the phenyl hydrazine part, four protons of the aryl part of benzimidazolyl ring), 9.69 (s, 1H, -NH)	265
8b	δ 1.44 (t, 3H, -CH_3), 2.51 (s, 3H, -N=C-CH_3), 4.73 (q, 2H, -CH_2), 6.80-7.70 (complex m, 9H, five protons of the phenylhydrazine ring and four protons of the aryl part of the benzimidazolyl ring), 9.67 (s, 1H, -NH)	279
8c	δ 2.49 (s, 3H, -N=C-CH_3), 6.01 (s, 2H, -N-CH_2 of the benzylic part), 6.80-7.60 (complex m, 14H, five protons of the phenylhydrazine, four protons of the aryl part of the benzimidazolyl ring, five protons of the phenyl ring of the benzylic part)	341
8d	δ 1.35 (t, 3H, -CH_3), 2.58 (s, 3H, -C-CH_3), 2.75 (q, 2H, -CH_2), 4.20 (s, 3H, -NCH_3), 6.69-7.79 (complex m, 8H, four aryl protons of the phenylhydrazine ring, four aryl protons of the benzimidazolyl ring), 7.79 (s, 1H, -NH)	293
8e	δ 1.23 (t, 3H, -CH_3), 1.42 (t, 3H, -CH_3), 2.56 (s, 3H, -N=C-CH_3), 2.74 (q, 2H, -CH_2), 6.88-7.66 (complex m, 8H, four aryl protons of the phenylhydrazine ring and four aryl protons of the benzimidazolyl ring.	307
8f	δ 1.18 (t, 3H, CH_3), 2.58 (s, 3H, -N=C-CH_3), 2.68 (q, 2H, -CH_2), 6.02 (s, 2H, -CH_2 of the benzylic part), 6.77-7.72 (complex m, 13H, four aryl protons of the phenylhydrazine ring, four aryl protons of the benzimidazolyl ring and five aryl protons of the phenyl ring of the benzylic part)	369

Table VI — Spectral data of 2-indolylbenzimidazoles **9**

Product	^{1}H NMR (DMSO d_6) δ (ppm)	APCI MS (M+1) *m/z*
9a	δ 4.09 (s, 3H, -NCH_3), 6.95-7.70 (complex m, 9H, four aryl protons of the indole ring, one β proton of the indole ring and four aryl protons of the benzimidazolyl ring), 11.95 (s, 1H, -NH of the indole ring)	248
9b	δ 1.45 (t, 3H, -CH_3), 4.59 (q, 2H, -CH_2), 6.90-7.80 (complex m, 9H, four aryl protons of the indole ring, one β proton of the indole ring and four aryl protons of the benzimidazolyl ring), 11.93 (s, 1H, -NH)	262
9c	δ 5.86 (s, 2H, -NCH_2 of the benzylic part), 6.90-7.50 (complex m, 14H, four aryl protons of the indole ring, one β proton of the indole ring, four aryl protons of the benzimidazolyl ring and five phenyl protons of the benzylic part), 12.01 (s, 1H, -NH)	324
9d	δ 1.33 (t, 3H, -CH_3), 2.55 (s, 3H, -NCH_3), 4.12 (q, 2H, -CH_2), 7.06-7.82 (complex m, 8H, three aryl protons of the indole ring, one β proton of the indole ring and four aryl protons of the benzimidazolyl ring), 11.98 (s, 1H, -NH)	276
9e	δ 1.29 (t, 3H, -CH_3), 1.44 (t, 3H, -CH_3), 3.01 (q, 2H, -CH_2), 4.57 (q, 2H, -CH_2), 7.00-8.32 (complex m, 8H, three aryl protons of the indole ring, one β proton of the indole ring and four aryl protons of the benzimidazolyl ring), 11.85 (s, 1H, -NH)	290

aq. NH_3 solution for ~ 10-15 min. The resulting solid was filtered and dried to obtain crude **7**. The crude product obtained above was recrystallized from MeOH – DMF solution to obtain pure **7**.

General procedure for the preparation of 9 from 7: A mixture of **7** (1.2 g, 5 mmoles), K_2CO_3 (2.07 g, 15 mmoles), TEBAC (10 mg), CH_3CN (20 mL) and alkylating agent (7.5 mmoles) was stirred at RT for 3-4 hr. At the end of this period, the mixture was poured into ice-cold water. The separated solid was filtered and dried to obtain crude **9**, which on recrystallization from hot methanol gave pure **9** (**Table I**).

General procedure for the preparation of 8 from 6: A mixture of **6** (5 mmoles), K_2CO_3 (15 mmoles), TEBAC (10 mg), CH_3CN (20 mL) and appropriate alkylating agent (7.5 mmoles) was stirred at RT for 3-4 hr. At the end of this period, the mixture was poured into ice-cold water. The separated solid was filtered and dried to obtain crude **8**, which on recrystallization from hot methanol gave pure **8** (**Table II**).

General procedure for the preparation of 8 from 4: A mixture of **4** (20 mmoles), **5** (20 mmoles), catalytic amount of acetic acid and methanol (20 mL) was refluxed for 2 hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered, washed with water and dried to obtain crude **8**, which on recrystallization from hot methanol gave pure **8** (**Tables III** and **V**).

Table VII — Physical data of compounds **9a-g** prepared from **10***

Starting Material	Reagent	Product	Yield (%)	m.p. (°C)
10a (R^2 = H)	**1a** (R^1 = CH_3)	**9a** (R^2 = H)	76	225-27
10a (R^2 = H)	**1b** (R^1 = C_2H_5)	**9b** (R^2 = H)	75	188-90
10a (R^2 = H)	**1c** (R^1 = $PhCH_2$)	**9c** (R^2 = H)	79	98-100
10b (R^2 = C_2H_5)	**1** (R^1 = H)	**9d** (R^2 = C_2H_5)	76	187-90
10b (R^2 = C_2H_5)	**1a** (R^1 = CH_3)	**9e** (R^2 = C_2H_5)	79	198-200
10b (R^2 = C_2H_5)	**1b** (R^1 = C_2H_5)	**9f** (R^2 = C_2H_5)	74	98-102
10b (R^2 = C_2H_5)	**1c** (R^1 = $PhCH_2$)	**9g** (R^2 = C_2H_5)	78	75-80

*All reactions done in ethylene glycol under refluxing conditions

General procedure for the preparation of 9 from 8: A mixture of PPA (10 mL) and **8** (10 mmoles) in a 100 mL round bottomed flask was heated with occasional stirring at 140°C for 2 hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered. The filtered solid was resuspended in water and treated with few drops of aq. NH_3 solution for ~ 10-15 min. The resulting solid was filtered again and dried to obtain crude **9**, which on recrystallization from hot MeOH – DMF solution gave **9** (**Tables IV** and **VI**).

General procedure for the preparation of 9 from 10: A mixture of **10** (20 mmoles), ethylene glycol (20 mL) and appropriate *o*-phenylenediamino-sulfate (20 mmoles) was refluxed for 3 hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water. The separated solid was filtered. The filtered solid was resuspended in water (2 × 10 mL) and neutralized with aq. NH_3 solution to obtain crude **9**, which on recrystallization from hot MeOH – DMF gave pure **9** (**Table VII**).

Conclusion

In summary, herein is reported a convenient and useful methodology for the synthesis of indolyl-benzimidazoles by three alternative routes.

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