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ORIGINAL PAPER

Efficient synthesis of novel imidazo[1,2-a]pyrimidine derivatives via one-pot three-component procedure

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Abstract Synthesis of novel derivatives of imidazo[1,2-a] pyrimidine from one-pot three-component reaction of aldehydes, 2-amino-benzimidazole, and α-tetralone in the presence of catalytic amount of *p*-toluene sulfonic acid under reflux condition in EtOH has been presented. The simplicity and safety of the process, high yields and short reaction times were the main advantages of this protocol.

Keywords Imidazo[12-a]pyrimidines · One-pot reaction · Multi-component reaction

Introduction

Multi-component reactions (MCRs) involving at least three starting materials in a one-pot reaction have gained much attention in modern organic chemistry. MCRs' outstanding features such as atom economy, efficiency, simplicity, environmental amiability, and cost-effectiveness in comparison to multi-step processes have made it a convenient tool for synthesis of various organic compounds [1–7].

Imidazo[1,2-a]pyrimidines have received much attention due to their physiological, anti-inflammatory [8], analgesic [9], antipyretic [10], bronchodilator, anxiolytic, and antifungal [11, 12] activities.

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To date, the synthesis of various derivatives of these compounds has been reported [13–18]. The most common synthetic methods reported for the preparation of imidazo[1,2-a]pyrimidine ring systems involve closure of the imidazole ring by the condensation of 2-aminopyrimidine and closure of the pyrimidine ring by the condensation of 2-aminoimidazole with appropriate electrophilic compounds.

Synthesis of imidazo[1,2-a]pyrimidines via condensation of 2-aminopyrimidine with α-halocarbonyl compounds has also been developed. The drawback of this method is difficulty in preparation, purification, toxicity, and lachrymatory property of α-halocarbonyl compounds which limit its reliability. Taking this fact into account, developing an efficient and simple route for synthesis of imidazo[1,2-a] pyrimidines is of great interest [19–24].

In our efforts to use MCRs in the synthesis of heterocycles [25–27], herein we present a multi-component and efficient route for the synthesis of novel imidazo[1,2-a] pyrimidines from the reaction of aldehydes, 2-amino-benzimidazole, and α-tetralone in the presence of catalytic amount of *p*-toluene sulfonic acid (Scheme 1).

Experimental procedures

A mixture of aldehydes (10 mmol), 2-amino-benzimidazole (10 mmol), and α-tetralone (10 mmol) with catalytic amount of *p*-toluene sulfonic acid (0.5 mol%) was refluxed in EtOH in appropriate reaction time. The progress of the reaction was monitored by TLC. At the end of reaction, the precipitated products were filtered and recrystallized from *n*-hexane: chloroform mixture (1.5:2).

Characterization was performed using ^{1}H and ^{13}C NMR, FTRI, and GC techniques.

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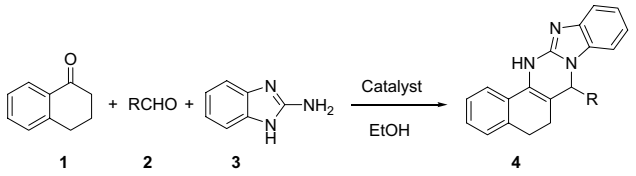


Scheme 1 Synthesis of imidazo[1,2-a]pyrimidines derivatives via one-pot three-component reaction of aldehydes, 2-amino-benzimidazole, and α-tetralone

Physical and spectral data

7-Phenyl-5,6,7,13-tetrahydro-7a,12,13-triaza-indeno[1,2-b]phenanthrenes (Entry 1) m.p.: 282 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.72 (s, 1H, NH), 6.87–8.70 (m, 13H, CH), 5.62 (s, 1H, CH), 2.97 (t, 2H, CH_2), 2.81 (t, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 21.40, 28.1, 66.60, 109.00, 114.00, 121.00, 123.30, 125.50, 126.80, 127.30, 127.60, 128.00, 128.40, 129.10, 129.00, 130.70, 131.60, 132.30, 140.00, 142.60, 145.00, 158.40; FT-IR: 3,426 (NH), 1,629 (C=N); MS: *m/z* 349[M^+].

7-(4-Chloro-phenyl)-5,6,7,13-tetrahydro-7a,12,13-triaza-indeno[1,2b]phenanthrenes (Entry 2) m.p.: 260 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.73 (s, 1H, NH), 7.10–8.75 (m, 12H, CH), 6.31 (s, 1H, CH), 2.98 (t, 2H, CH_2), 2.83 (t, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 23.80, 33.00, 67.40, 109.10, 115.10, 122.50, 125.50, 126.80, 127.10, 127.40, 127.70, 128.00, 129.30, 129.50, 129.00, 131.60, 132.80, 136.90, 140.00, 143.40, 144.90, 158.20; FT-IR: 3,421 (NH), 1,624 (C=N); MS: *m/z* 383[M^+].

7-(3-Chloro-phenyl)-5,6,7,13-tetrahydro-7a,12,13-triaza-indeno[1,2b]phenanthrenes (Entry 3) m.p.: 306 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.73 (s, 1H, NH), 7.03–8.72 (m, 12H, CH), 6.33 (s, 1H, CH), 2.98 (t, 2H, CH_2), 2.79 (t, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 23.70, 27.70, 67.40, 109.10, 113.70, 119.50, 121.10,125.50, 125.40, 126.80, 126.80, 127.00, 127.30, 127.50, 128.10, 128.60, 131.00, 131.60, 132.60, 135.60, 140.10, 143.00, 144.80, 158.10; FT-IR: 3,422 (NH), 1,627 (C=N); MS: *m/z* 383[M^+].

7-(4-Nitro-phenyl)-5,6,7,13-tetrahydro-7a,12,13-triaza-indeno[1,2-b]phenanthrenes (Entry 4) m.p.: 309 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.73 (s, 1H, NH), 6.98–8.72 (m, 12H, CH), 6.15 (s, 1H, CH), 3.01 (t, 2H, CH_2), 2.80 (t, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 24.00, 27.90, 67.40, 109.10, 113.10, 115.40, 120.30, 121.50, 124.20, 125.70, 125.80, 127.40, 127.70, 128.00, 131.40, 131.90, 132.60, 135.20, 139.80, 141.50, 149.10, 158.40; FT-IR: 3,444 (NH), 1,626 (C=N); MS: *m/z* 394[M^+].

7-(3-Nitro-phenyl)-5,6,7,13-tetrahydro-7a,12,13-triaza-indeno[1,2-b]phenanthrenes (Entry 5) m.p.: 316 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.72 (s, 1H, NH), 7.00–8.72 (m, 12H, CH), 6.17 (s, 1H, CH), 3.00 (t, 2H, CH_2), 2.80 (t, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 23.80, 28.00, 67.30, 109.10, 113.70, 119.50, 122.20, 125.50, 126.80, 126.40, 126.80, 127.80, 128.30, 128.50, 128.50, 129.60, 131.40, 131.70, 132.40, 135.50, 140.20, 143.00, 148.80, 158.50; FT-IR: 3,442 (NH), 1,625 (C=N); MS: *m/z* 394[M^+].

7-*p*-Tolyl-5,6,7,13-tetrahydro-7a,12,13-triaza-indeno[1,2-b]phenanthrenes (Entry 6) m.p.: 251 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.74 (s, 1H, NH), 6.99–8.723 (m, 12H, CH), 6.32 (s, 1H, CH), 2.98 (t, 2H, CH_2), 2.82 (t, 2H, CH_2), 2.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 21.70, 24.30, 28.00, 64.40, 109.10, 114.20, 115.40, 120.10, 121.30, 124.00, 125.50, 125.40, 126.40, 127.70, 127.80, 129.40, 130.90, 131.60, 134.20, 138.80, 140.50, 148.10, 157.40; FT-IR: 3,421 (NH), 1,622 (C=N); MS: *m/z* 363[M^+].

7-(4-Methoxy-phenyl)-5,6,7,13-tetrahydro-7a,12,13-triaza-indeno[1,2-b]phenanthrenes (Entry 7) m.p.: 270 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.71 (s, 1H, NH), 6.96–8.70 (m, 12H, CH), 6.35 (s, 1H, CH), 4.02 (s, 3H, CH_3), 2.95 (t, 2H, CH_2), 2.80 (t, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 23.80, 28.1, 55.5, 66.60, 109.00, 114.00, 120.80, 123.30, 125.30, 127.20, 127.40, 127.90, 129.30, 129.30, 128.40, 128.90, 130.10, 131.40, 133.00, 140.00, 144.70, 145.10, 158.420; FT-IR: 3,420 (NH), 1,600 (C=N); MS: *m/z* 379[M^+].

5,6,7,13-Tetrahydro-7a,12,13-triaza-indeno[1,2-b]phenanthrenes (Entry 8) m.p.: 185 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.60 (s, 1H, NH), 7.93–7.70 (m, 8H, CH), 4.42 (s, 2H, CH_2), 2.25 (t, 2H, CH_2), 2.20 (t, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 23.80, 28.1, 55.50, 109.00, 114.10, 115.15, 121.80, 123.21, 123.30, 126.80, 127.00, 127.30, 128.40, 128.90, 134.40, 138.30,

141.20, 152.80; FT-IR: 3,430 (NH), 1,610 (C=N); MS: *m/z* 273[M^+].

7- Methyl- 5,6,7,13-tetrahydro-7a,12,13-triaza-indeno [1,2-b]phenanthrenes (Entry 9) m.p.: 199 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.70 (s, 1H, NH), 7.97–7.73 (m, 8H, CH), 4.43 (s, 1H, CH), 2.26 (t, 2H, CH_2), 2.21 (t, 1H, CH), 2.20 (d, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 22.50, 23.80, 28.10, 45.50, 119.00, 114.10, 115.00, 121.83, 123.15, 123.30, 126.80, 127.20, 127.30, 128.40, 128.90, 134.40, 138.30, 141.20, 152.80; FT-IR: 3,440 (NH), 1,615 (C=N); MS: *m/z* 287[M^+].

7- Ethyl- 5,6,7,13-tetrahydro-7a,12,13-triaza-indeno [1,2-b]phenanthrenes (Entry 10) m.p.: 210 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.80 (s, 1H, NH), 7.97–7.73 (m, 8H, CH), 4.43 (s, 1H, CH), 2.26 (t, 2H, CH_2), 2.21 (t, 2H, CH_2), 1.65 (m, 2H, CH_2),1.00 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 12.50, 23.80, 24.1, 28.00, 53.50, 119.00, 114.10, 115.00, 121.80, 123.01, 123.30, 126.80, 127.12, 127.30, 128.40, 128.90, 134.40, 138.30, 141.20, 152.80; FT-IR: 3,440 (NH), 1,600 (C=N); MS: *m/z* 301[M^+].

7- Propyl- 5,6,7,13-tetrahydro-7a,12,13-triaza-indeno [1,2-b]phenanthrenes (Entry 11) m.p.: 225 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.78 (s, 1H, NH), 7.97–7.73 (m, 8H, CH), 4.43 (s, 1H, CH), 2.26 (t, 2H, CH_2), 2.21 (t, 2H, CH_2), 1.80 (t, 2H, CH_2), 1.40 (m, 2H, CH_2),1.00 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 14.20, 18.20, 22.50, 28.1, 36, 51.50, 119.00, 114.10, 115.00, 121.80, 122.80, 123.30, 126.80, 127.30, 128.40, 128.90, 134.40, 138.30, 141.20, 152.80; FT-IR: 3,448 (NH), 1,614 (C=N); MS: *m/z* 315[M^+].

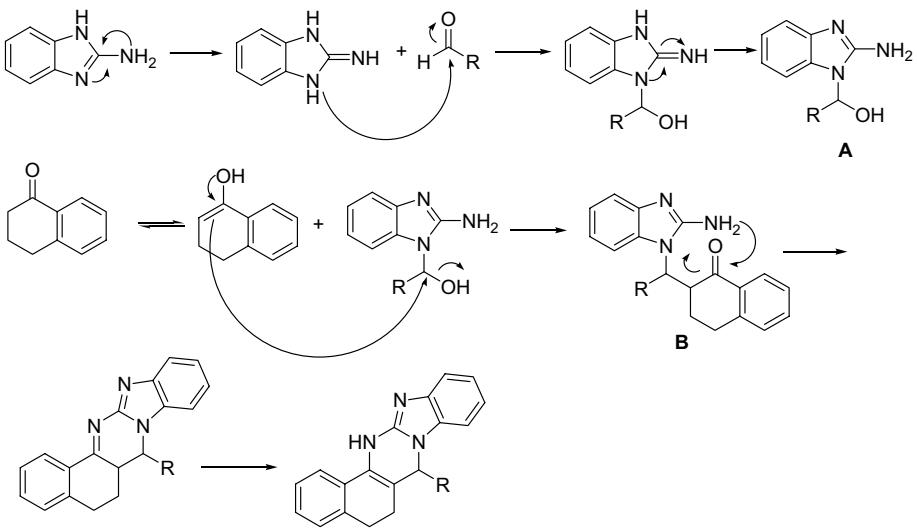
Table 1 Synthesis of imidazo[1,2-a]pyrimidines using *p*-toluene sulfonic acid under reflux condition in EtOH

Entry	R	Time (min)	Yield[a] (%)
1	Ph	10	95
2	4-Cl C_6H_4	15	98
3	3-Cl C_6H_4	20	97
4	4-NO_2 C_6H_4	35	94
5	3-NO_2 C_6H_4	25	96
6	4-Me C_6H_4	30	94
7	4-OMe C_6H_4	35	95
8	H	20	92
9	CH_3	35	88
10	CH_3CH_2	40	85
11	$CH_3CH_2CH_2$	45	82

[a] Isolated yields

Results and discussion

Imidazo[1,2-a]pyrimidines derivatives have been successfully obtained from the reaction of aldehydes, 2-aminobenzimidazole, and α-tetralone in the presence of catalytic amount of *p*-toluene sulfonic acid. The reliability of the process has been investigated by using various aliphatic and aromatic aldehydes and ketones (Table 1). The results showed that this reaction did not proceed in the presence of ketones. This observation was attributed to lower activities of ketones in comparison to aldehydes.



Scheme 2 The proposed mechanism of imidazo [1,2-a] pyrimidine derivatives formation

Table 2 Synthesis of compound **4** using various amounts of *p*-toluene sulfonic acid under reflux condition in EtOH

Entry	Amount of catalyst	Time (min)	Yield[a] (%)
1	2	30	95
2	1	30	95
3	0.5	35	94
4	0.25	50	90

[a] Isolated yields

As shown in Table 1, aromatic aldehydes with electron withdrawing groups on aromatic ring led to better yields than aliphatic ones.

It is worth mentioning that this procedure cannot be generalized to β-tetralone and no product was obtained in its presence.

Regarding the reaction mechanism, it has been proposed that condensation of aldehydes with 2-amino-benzimidazole produced intermediates **A** which successively reacted with α-tetralone and formed **B**. The cyclization of **B** gave the desired imidazo[1,2-a]pyrimidine derivatives (Scheme 2) [28].

To study and optimize the reaction condition, synthesis of derivative **4** (Table 1) was selected as the model reaction.

This reaction was performed under solvent-free and stirring condition in the presence and absence of catalyst.

The results showed that under both conditions, no product was obtained in the absence of catalyst even after a long reaction time of 12 h. Also, reflux condition was better than stirring, and higher yield and shorter reaction time were obtained under this condition. Therefore, all derivatives were synthesized using this protocol.

The optimum amount of catalyst was obtained by performing the model reaction in the presence of various amounts of catalyst (2, 1, 0.5, 0. 25 mol%). The results are summarized in Table 2. As shown in this table, the optimum amount of catalyst is 0.5 mol%.

Conclusion

In summary, we have developed a facile and efficient method for the synthesis of new derivatives of imidazo[1,2-a]pyrimidine from one-pot three-component reaction of aldehydes, 2-amino-benzimidazole, and α-tetralone in the presence of catalytic amount of *p*-toluene sulfonic acid under reflux condition in EtOH.

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