A facile pseudo three component reaction for the synthesis of benzo [4,5]imidazo[1,2-a]pyridine derivatives

Abstract

Background: Benzo[4,5]imidazo[1,2-a]pyridine derivatives were accessed through an efficient pseudo three component reaction between dialdehydes such as o-phthalaldehyde, glutaraldehyde, 2,3-thiophenedicarboxaldehyde and the active methylene 2-(1H-benzo[d]imidazol-2-yl)acetonitrile. The products were obtained in a one-pot manner with easy purification and further characterized by NMR, FT-IR and HRMS spectral data (Figure 1).

Results and discussions

We planned to perform a three component reaction with a 1,4-dielectrophilic substrate (I) and two carbon nucleophilic building blocks (II & III) to achieve the scaffold 1a (Figure 2).

Initially, a 3CR was carried out by adding sequentially
i. o-phthalaldehyde,
ii. Malononitrile
iii. 2-(1H-benzo[d]imidazol-2-yl)acetonitrile

In the presence of piperidine as the base in ethanol at room temperature (Figure 2). The resin like product was obtained which could not be purified and characterized. Then, the order of adding the reactants were changed to
a. o-phthalaldehyde,
b. 2-(1H-benzo[d]imidazol-2-yl) acetonitrile
c. Malononitrile (Figure 3)

Keywords: MCR, pseudo 3CR, isoquinoline, benzimidazole, one-pot synthesis
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A white precipitate formed in twenty minutes which was isolated by filtration, further purified and characterized by NMR to be scaffold B1 (Figure 3) as against the anticipated product A1. Then, the reaction was performed with other solvents and bases to check the feasibility, but no significant improvement in the yield was observed (Table 1). The reaction condition was optimized for ethanol as solvent and triethylamine as base (Table 1 - Entry 3).

Table 1 Optimization of reaction conditions for synthesis of B1

| Entry | Catalyst | Time | Solvent | Temp | Product yield (B1) |
|-------|----------|------|---------|------|--------------------|
| 1     | Piperidine | 1 h  | EtOH    | rt   | 75                 |
| 2     | EtN      | 1 h  | CH3CN   | rt   | 80                 |
| 3     | EtN      | 1 h  | EtOH    | rt   | 89                 |
| 4     | EtNC     | 2 h  | MeOH    | rt   | 75                 |
| 5     | K2CO3    | 24 h | CH3CN   | rt   | Nil                |
| 6     | DBU      | 2 h  | CH3CN   | rt   | 55                 |
| 7     | p-TsOH   | 24 h | H2O     | rt   | Nil                |

The lack of formation of isolable product in reaction Figure 4 may be due to high reactivity of 2, with possible formation of more than one unstable product (Figure 4). However when the sequence of addition of nucleophilic reagent is reversed the reaction might follow the path 1b shown in Figure 3.

The results reveal that 3 didn’t take part in the reaction instead the 2 itself reacted twice to form B1. The reaction was then carried out with all other active methylene groups like 2-[benz[d]imidazol-2-yl] acetonitril, 2-cyanoacetamide and ethyl 2-cyanoacetate along with 2 to check the possible outcome but, only one product (B1) was observed. The experiment can be considered as a competitive experiment performed between a dialdehyde and two carbon nucleophilic species. The results observed indicate that compound (2) selectively reacts with (1). The reaction is proposed to follow the mechanism shown in (Figure 5). Feng et al.,19 have also proposed a similar mechanism. The initial Knoevenagel condensation of 1 with 2 and the subsequent Michael addition of another 2 to the intermediate a would lead to c followed by tautomerisation to the desired product B1.

Encouraged by this result, we tried to explore this reaction with different dilaedaldehydes to check the feasibility of accessing skeletal diversity in one pseudo 3CR. The reaction resulted in good yield (80-89%) of the corresponding heterocyclic scaffold B1 Figure 6). The results also support the proposed mechanism. Thus we have established a facile pseudo three component reaction protocol for accessing skeletal diverse benzo [4,5]imidazo[1,2-a]pyridine derivatives derivatives with inherent provision for scaffold hopping.

Figure 4 Plausible unstable intermediates in reaction 1a.

Based on the results it’s understood that 3 didn’t take part in the reaction instead the 2 itself reacted twice to form B1. The reaction was then carried out with all other active methylene groups like 2-[benz[d]imidazol-2-yl] acetonitril, 2-cyanoacetamide and ethyl 2-cyanoacetate along with 2 to check the possible outcome but, only one product (B1) was observed. The experiment can be considered as a competitive experiment performed between a dialdehyde and two carbon nucleophilic species. The results observed indicate that compound (2) selectively reacts with (1). The reaction is proposed to follow the mechanism shown in (Figure 5). Feng et al.,19 have also proposed a similar mechanism. The initial Knoevenagel condensation of 1 with 2 and the subsequent Michael addition of another 2 to the intermediate a would lead to c followed by tautomerisation to the desired product B1.

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Experimental section

All reactions were performed under normal conditions at room temperature. All chemicals were purchased from Sigma Aldrich, Avra synthesis and were used as received. Deuterated solvents were purchased from Sigma Aldrich. IR spectra were recorded on a Perkin Elmer-FTIR spectrometer using solid samples as KBr plates. For compounds 1H NMR (400MHz, DMSO-d6) and 13C NMR (100MHz, DMSO-d6) spectra were recorded in DMSO-d6 on a Bruker 400MHz spectrometer using tetramethylsilane (TMS, δ=0) as an internal standard at room temperature. Mass spectra were recorded on Agilent 1200 LC/MS-6110 mass spectrometer (Supporting Information).

6-amino-7-(1H-benzo[d]imidazol-2-yl)-12-hydroxy-7a,12-dihydro-12aH-benzo[4,5]imidazo[1,2-a] indeno[2,1-c]pyridine-12a-carbonitrile (B1)

Into a round-bottomed flask was added 135mg (1mmol) of 1, 345.8 (2.2mmol) of 2, and trimethylamine (1mmol) in ethanol. This was stirred at room temperature for an hour. The resulting white precipitate was filtered and washed with methanol to yield 385mg of product. The yield (B1) was 76% (nearly 90%) of product. 1H NMR (400MHz, DMSO-d6) δ 13.08 (b, OH), 8.37 (s, NH), 8.03 (s, 1H), 7.71 (d, 1H), 7.54 (b, 2H), 7.4-7.3 (t, dd, 4H), 7.1 (s, 4H), 6.8 (d, 1H), 6.04 (s, 1H), 5.65 (s, 1H) ppm; δ 13C NMR (100MHz, DMSO-d6) δ 153.62, 145.24, 143.02, 142.88, 142.23, 141.19, 141.14, 133.65, 131.24, 129.72, 128.35, 125.48, 124.69, 123.96, 121.63, 121.45, 120.10, 117.67, 116.99, 114.30, 110.57, 79.76, 78.77, 56.06, 48.63, 48.38, 45.35, 15.88 ppm.

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IR (KBr, v, cm⁻¹) 3439, 3248, 2253, 1648, 1522. HRMS (ESI) Calcd for C₃₀H₂₅N₆O [M+H]+ 431.16amu, found 431.1621amu.

6-amino-5-(1H-benzo[d]imidazol-2-yl)-1-hydroxy-2,3,4,4a-tetrahydrobenzo[4,5]imidazo[2,1-a]isoquinoline-12b(1H)-carbonitrile (B2)

Into a round-bottomed flask was added glutaraldehyde 50% solution in water (1mmol), 345.8 (2.2mmol) of 2, and trimethylamine (1mmol) in ethanol. This was left to stir at room temperature for an hour. The resulting white precipitate was filtered and washed with methanol to yield 337mg (85%) of product. 1H NMR (400MHz, DMSO-d₆) δ 12.5 (b, OH), 7.54 (s, 4H), 7.2-7.1 (d, t, 4H), 5.52 (b, NH₂), 4.09 (b, 2H), 1.8 (dd, 2H), 1.7 (d, 1H), 1.6-1.5 (d, dd,3H), ppm; δ ¹³C NMR (100MHz, DMSO-d₆) δ 151.56, 121.58, 117.96, 72.43, 58.36, 31.42, 19.61ppm. IR (KBr, v, cm⁻¹) 3431, 3186, 2254, 1525.

5-amino-4-(1H-benzo[d]imidazol-2-yl)-12-hydroxy-3b,12-dihydro-11bH-benzo[4,5]imidazo[1,2-a]thieno[3',2':3,4]cyclopenta[1,2-c]pyridine-11b-carbonitrile (B3)

Into a round-bottomed flask was added 141mg of 2,3-thiophenedicarboxaldehyde (1mmol), 345.8 (2.2mmol) of 2, and trimethylamine (1mmol) in ethanol. This was left to stir at room temperature for an hour. The resulting white precipitate was filtered and washed with methanol to yield 354mg (81 %) of product. 1H NMR (400MHz, DMSO-d₆) δ 8.33 (s, 1H), 8.2 (s, 1H), 8.08 (d, 2H), 7.99 (d, 1H), 7.8(d, 2H), 7.7 (d, 1H), 6.76 (d, 1H), 7.57 (t,2H), 7.45-7.31 (m,6H), 7.22 (d, 1H) ppm; δ ¹³C NMR (100MHz, DMSO-d₆) δ 146.35, 145.98, 142.52, 142.47, 142.18, 138.64, 136.54, 134.48, 134.11, 133.5, 133.02, 130.46, 129.97, 126.36, 123.89, 123.75, 123.52, 119.52, 117.88, 117.77, 111. 44, 111.20, 104.63, 102.99, 73.15, 72.26ppm. IR (KBr, v, cm⁻¹) 3115, 2226, 1610, 1584, 1539.

Conclusion

In conclusion, we have developed an efficient one-pot synthesis of benzo [4,5]imidazo[1,2-a]pyridine derivatives using a pseudo three-component reaction. This method we have demonstrated rapid construction of a indene fused benzo[4,5]imidazo[1,2-a]pyridine and hydroisoquinoline fused benzimidazole derivatives in good yields from simple dialdehydes and 2-(1H-benzo[d]imidazol-2-yl) acetonitrile in EtOH under normal conditions in the presence of trimethylamine as a base. Thus we have established a facile pseudo three component reaction protocol for accessing skeletally diverse benzo [4,5]imidazo[1,2-a]pyridine derivatives dehydratives with inherent provision for scaffold hopping.

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Conflict of interest

Author declares that there is no conflict of interest.

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