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# A novel heterotricyclic assembly through intramolecular imino Diels–Alder reaction: synthesis of pyrrolo[3,4-*b*]quinolines

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ABSTRACT

The synthesis of a series of hexahydropyrrolo[3,4-*b*]quinolines has been achieved in excellent yields by the reaction of aldimines derived from aromatic amines and N-prenylated aliphatic aldehydes in acetonitrile with $InCl_3$ as a catalyst in a short duration of time.



Quinoline- and pyrrole-based structural scaffolds have been established as the essential part of many natural products. Synthetic compounds having these moieties exhibited a wide range of biological activities. Tetrahydroquinolines have shown biological activities,[1–4] such as psychotropic,[5] antiallergenic,[6] antiinflammatory,[7] and estrogenic activities.[8] Pyrrolidines and their fused derivatives have shown a wide spectrum of biological activities.[9,10] Hexahydro pyrrolo quinolines are considered to be the prime candidates in the construction of bacterial topoimerase inhibitors.[11] In particular, the substitution of these bicycloamines attached at the C-7 position of quinolines has led to the synthesis of various antibacterial agents like moxifloxacin.[12,13]

It is therefore not surprising that many synthetic methods have been developed and much interest has been paid to the synthesis of tetrahydroquinoline derivatives in recent years.[14,15] Among the methods available for the construction of nitrogen containing six-membered heterocycles, the imino Diels–Alder reaction provides a rapid means of constructing such molecules with control of regio-and stereo- selectivities. Imines which are readily prepared from the corresponding aldehydes and ketones allow a variety of imine dienophiles accessible for this reaction.[16–18]

Both inter- and intramolecular versions of imino Diels–Alder reactions are well known in the literature and they have been catalyzed by various catalysts[19–21] $InCl_3$ has been found to be one of the best catalysts, since it is a mild and water-tolerant Lewis acid imparting high regio- and chemoselectivities.[22,23]

Unlike the intermolecular aza Diels–Alder reaction of aza dienes generated from the reactions of arylaldehydes with arylamines, there are only a few reports available for the IMDA of dienes generated from allyl tethered aliphatic aldehyde with arylamines.[24]

In continuation of our research interest in the area of the imino Diels–Alder reaction,[25,26] we herein describe the synthesis of hexahydropyrrolo[3,4-*b*]quinolines from aromatic amines and *N*-allyl derivatives of aliphatic aldehydes via intramolecular [4+2] cyclization of imines catalyzed by $InCl_3$.

The electron-rich alkenyl aldehyde precursors required for the intramolecular cyclization reaction were synthesized by a series of chemical transformations from an amino alcohol **1**. Accordingly, ethanolamine **1a** was N-tosylated by tosyl chloride **2** under standard PTC reaction conditions to give the corresponding sulphonamide derivative **3a** which on N-prenylation under mild basic conditions afforded 2-(*N*-(3-methylbut-2-enyl)-*N*-tosylamino)ethanol **4a**. The *N*-prenyl tethered amino alcohol **4a** was then oxidized to the *N*-prenyl aldehyde **5a** in IBX in DMSO solvent in excellent yield. The structures of the synthesized aldehyde and alcohol were established on the basis of their spectroscopic data. A similar reaction sequence was adopted for the synthesis of alkenyl aldehyde **5b** starting from 2-amino butanol **1b** (Scheme 1).

The aldehydes so prepared (**5a** and **5b**) were then subjected to the intramolecular imino Diel's–Alder reaction. A 20 mol % of indium trichloride was added to the reaction mixture containing alkenyl aldehyde **5a** and aniline **6a** in acetonitrile solvent to generate the imine which was trapped by an N-tethered prenyl moiety and intramolecularly cyclized to give the cycloadducts. It was noticed that the reaction was complete in 20 min after effective stirring at room temperature and afforded a 36:64 mixture of

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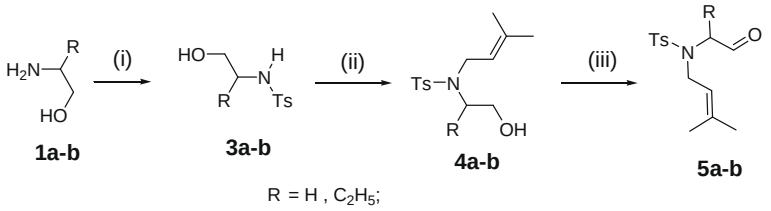
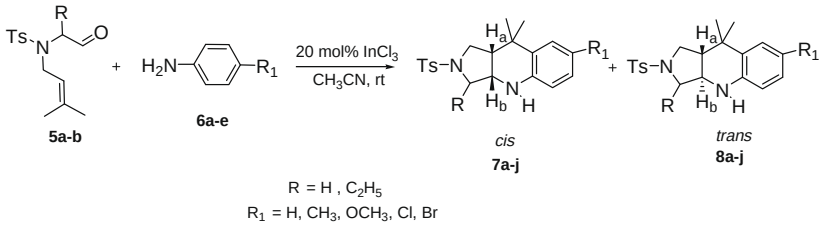



**Scheme 1.** Reagents and conditions: (i) TBAB, 10% NaOH/benzene, tosyl chloride **2**, 0 °C-RT; 8 h, 90%; (ii) prenyl bromide $K_2CO_3$/acetone, 12 h, 90%; (iii) iodoxybenzoic acid, DMSO, 2 h, 98%.




**Scheme 2.**

**Table 1**
$InCl_3$-catalyzed synthesis of hexahydropyrrolo[3,4-*b*]quinoline derivatives

| Entry | R | $R_1$ | Products | | Ratio cis:trans | Time (min) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | H | H | **7a** | **8a** | 36:64 | 20 | 92 |
| 2 | H | $OCH_3$ | **7b** | **8b** | 35:65 | 25 | 93 |
| 3 | H | $CH_3$ | **7c** | **8c** | 38:62 | 30 | 86 |
| 4 | H | Cl | **7d** | **8d** | 39:61 | 20 | 94 |
| 5 | H | Br | **7e** | **8e** | 40:60 | 20 | 96 |
| 6 | Et | H | **7f** | **8f** | 30:70 | 25 | 94 |
| 7 | Et | $OCH_3$ | **7g** | **8g** | 35:65 | 30 | 91 |
| 8 | Et | $CH_3$ | **7h** | **8h** | 31:69 | 25 | 89 |
| 9 | Et | Cl | **7i** | **8i** | 25:75 | 20 | 96 |
| 10 | Et | Br | **7j** | **8j** | 23:77 | 20 | 97 |

cis–trans isomers of hexahydropyrrolo[3,4-*b*]quinolines **7a** and **8a** in 92% yield (Scheme 2, Table 1). The formation of the cycloadducts was confirmed by their spectral data.[27] Thus, the $^1$H NMR spectrum of compound **8d** exhibited a broad singlet at $\delta$ 4.12 for the NH proton of the quinoline ring. The two geminal dimethyl protons were observed at $\delta$ 1.07 and 1.25 as singlets and the aromatic methyl group exhibited a singlet at $\delta$ 2.41. The two $NCH_2$ protons of the pyrrolidine ring were observed as doublets of doublets in the range $\delta$2.99–3.34. Particularly diagnostic were the protons $H_a$ and $H_b$ ring situated at the ring junctions, showing doublets of triplets at $\delta$ 1.92 ($J$ = 8.0, 12 Hz) and $\delta$ 3.28 ($J$ = 12.0, 12.0 Hz), respectively. The trans fusion at the ring junction was discerned by the high value of the coupling constant (12 Hz). On the other hand, the $^1$H NMR spectrum of **7d** exhibited two doublets of triplets at $\delta$ *2.16* ($J$ = 8.0, 10.8 Hz) and $\delta$ *3.48* ($J$ = 4.0, 10.8) for the $H_a$ and $H_b$ protons. The small value for the coupling constant of (4 Hz) between $H_a$ and $H_b$ in 7 d indicated the cis fusion at the ring junctions.

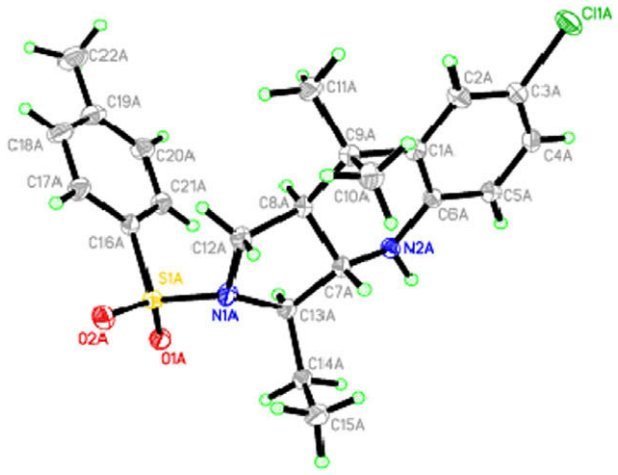



**Figure 1.** ORTEP diagram of **8i**.

The cis- and trans stereochemistries of the products were assigned on the basis of the coupling constants of the protons at the ring junctions in analogy to similar systems.[28–31]cis-Fusion at the ring junction was further confirmed by a strong NOE between $H_a$ and $H_b$. The intramolecular imino Diel's–Alder reaction was further extended with the alkenyl aldehydes **5a–b** and aromatic amines **6a–e** to obtain a series of hexahydropyrrolo[3,4-*b*]quinoline derivatives **7a–j** and **8a–j**. Further, the structure and the stereochemistry of the cycloadduct **8i** was confirmed by single crystal X-ray diffraction analysis (Fig. 1).[32]

In conclusion, an intramolecular imino Diel's–Alder reaction between various substituted *N*-alkenyl aliphatic aldehydes and aryl amines were carried out in the presence of an Indium chloride catalyst for the synthesis of hitherto unreported hexahydro pyrrolo[3,4-*b*]quinolines.

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27. *General experimental procedure*: $InCl_3$ (0.6 mmol, 206 mg) was added to a mixture of (*N*-(3-methylbut-2-enyl)-*N*-tosylamino) acetaldehyde **5** (3 mmol, 500 mg) and arylamine **6** (1 equiv, 200 mg) in acetonitrile (20 mL). The reaction mixture was stirred at room temperature for 30 min. On completion of the reaction as indicated by TLC, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over $Na_2SO_4$. The solvent was evaporated in vacuo, and the crude product was chromatographed on silica gel (EtOAc–hexane mixture) to afford pure diastereoisomers in good yield. *Representative spectral data of the products*: Compound 7**d**: yellow colored liquid; IR (KBr) 3398.3 (NH), 1339.5, 1156.2 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.15 (s, 3H), 1.24 (s, 3H), 2.16 (dt, $H_a$, $J$ = 8.0, 10.8 Hz), 2.43 (s, 3H), 2.73 (dd, 1H, $J$ = 8.0,10.8 Hz), 3.31 (dd, 1H $J$ = 10.8, 4.0 Hz), 3.46–3.48 (m, 1H, $H_b$, $J$ = 4.0, 10.8 Hz), 3.85(t, 1H, $J$ = 4.0 Hz), 4.12 (br s, NH), 6.79–7.63 (Ar-7H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 21.50, 26.97, 32.54, 33.27, 48.71, 49.02, 50.91, 56.49, 114.34, 121.47, 125.54, 126.60, 127.33, 129.09, 129.67, 134.00, 138.99, 143.36; MS (*m*/*z*) 390.19 ($M^+$); Anal. Calcd for $C_{20}H_{23}N_2O_2SCl$; C, 61.45, H, 5.93, N, 7.17. Found: C, 61.33, H, 6.07, N, 7.05.Compound **8d**: yellow colored liquid; IR (KBr) 3379.1 (NH), 1339.5, 1160.1 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.07 (s, 3H), 1.25 (s, 3H), 1.92 (dt, $H_a$, $J$ = 8.0,12.0 Hz), 2.41 (s, 3H), 3.00 (t, 1H, $J$ = 12.0 Hz), 3.21 (dd, 1H, $J$ = 12.0, 12.0 Hz), 3.28 (distorted dt, $H_b$, $J$ = 12.0, 12.0 Hz), 3.55 (dd, 1H, $J$ = 8.0, 8.0 Hz), 3.81(dd, 1H, $J$ = 12, 8.0 Hz), 4.12 (br s, NH), 6.40–7.74 (Ar-7H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 21.52, 26.74, 28.55, 34.62, 46.87, 50.09, 50.62, 53.18, 116.97, 123.54, 126.62, 126.97, 127.29, 132.80, 134.07, 141.68, 143.71; MS (*m*/*z*) 390.52 ($M^+$); Anal. Calcd For $C_{20}H_{23}N_2O_2SCl$; C, 61.45, H, 5.93, N, 7.17. Found: C, 61.36, H, 5.83, N, 7.26.
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