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Expeditious synthesis of chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines ☆

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ABSTRACT

An expeditious one-pot two-step synthesis of chiral 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones via reaction between 5-methyl furfurylamine and *N*-Boc amino acids is described. $LiAlH_4$-mediated reduction of 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones affords respective chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines in excellent yields.

In order to meet the growing demand of the high throughput screening against the unexplored/newer molecular targets for the drug discovery process, chemical libraries of diverse small organic compounds of biological interest are sought. A set of such compounds can be either bought commercially or prepared by adopting different synthetic protocols. A synthetic protocol for obtaining novel compounds is considered productive if it employs cheap and readily available starting substrates, simple reaction conditions, atom-economy, generation of complexity in one-pot and cascade processes.

1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazine is considered to be a scaffold of significant interest as it is found in several natural products including cyclooroidin, hanishin, longamide B, and dibromophakellin (Fig. 1).[1] Besides, this class of molecules is endowed with a variety of bioactivities which include antiamnesic, antihypoxic,[2] antiarrhythmic,[3] psychotropic,[4] antihypersensitive,[5] and aldose reductase inhibition.[6] In addition, compounds incorporating this subunit are reported as potassium channel ligands,[7] serotonin and noradrenaline reuptake inhibitors,[8] and cannabinoid receptor agonists.[9] Given such significance, there is much interest in their synthesis. Some of the approaches to prepare 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines include selective hydrogenation or reduction of 3,4-dihydropyrrolo[1,2-*a*]pyrazines,[5,10] condensation of benzotriazole, 2-(pyrrol-1-yl)-1-ethylamine and formaldehyde[11], and chiral catalyst-mediated aza-Friedal–Crafts reaction of 2-(pyrrol-1-yl)-1-ethylamine with aldehyde.[12] Moreover, two different protocols for the synthesis of chiral pyrrole-pyrazine-oxazoles, which are precursors to this fused-system, starting from 2-pyrrolecarbaldehyde have been also disclosed.[13] We noticed that though a few of the reported methods lead to chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines, they either involve very expensive catalyst, formation of side-products or issues of diastereoselectivity during the reaction sequences.[12,13] As a consequence we became interested in developing a simpler straightforward approach to this scaffold. Herein in this preliminary report we disclose an efficient one-pot synthesis of chiral 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones which were smoothly reduced to 4-substituted-6-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines.

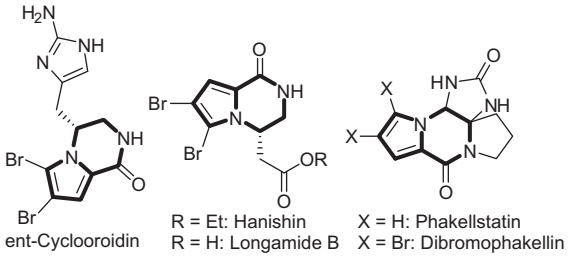

Figure 1. A few natural products containing 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine core.

The 2,5-disubstituted furan ring is susceptible to ring opening under oxidative conditions especially in the presence of acid to afford a 1,4-diketo system.[14] Employing this property, Butin and coworkers disclosed an acid-catalyzed synthesis of pyrrolo[1,2-*a*][1,4]benzodiazepines from *N*-(furfuryl)anthranilamides which

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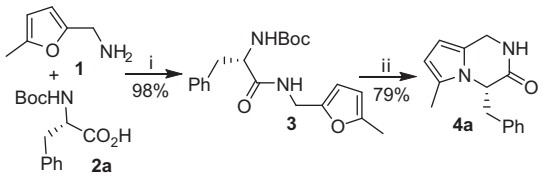
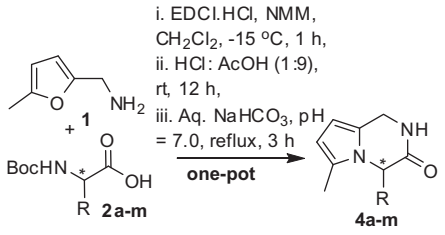


Scheme 1. Reagents and conditions- (i) EDCI.HCl (1.05 equiv), NMM (1.05 equiv), dry CH_2Cl_2, −15 °C, 1 h; (ii) (a) concd HCl: glacial acetic acid (1:9), rt, 12 h, (b) aq $NaHCO_3$, reflux, 3 h.

Table 1
Scope of the protocol for preparing diverse 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones via one pot reaction



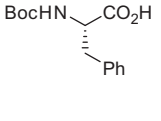
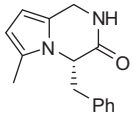
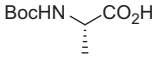
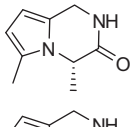
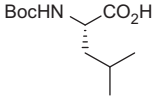
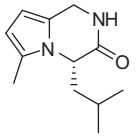
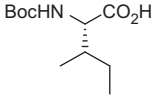
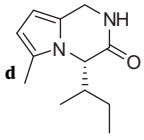
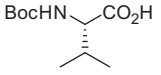
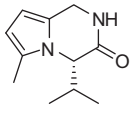
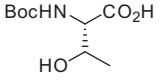
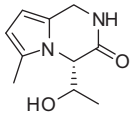
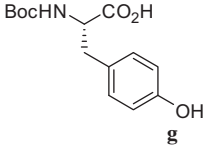
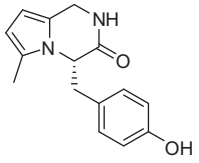
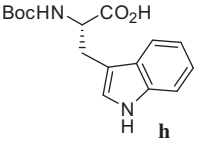
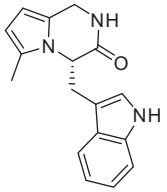
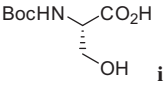
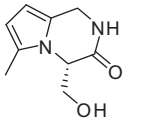
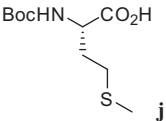
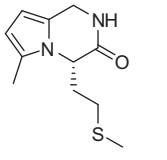
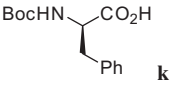
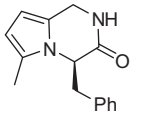
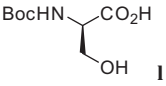
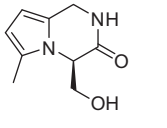
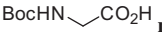
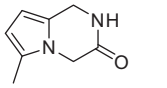
Entry	*N*-Boc amino acid (**2**)	Product (**4**)	Yield[a] (%)
1	 **a**	 **a**	85
2	 **b**	 **b**	89
3	 **c**	 **c**	92
4	 **d**	 **d**	91
5	 **e**	 **e**	90
6	 **f**	 **f**	83
7	 **g**	 **g**	88

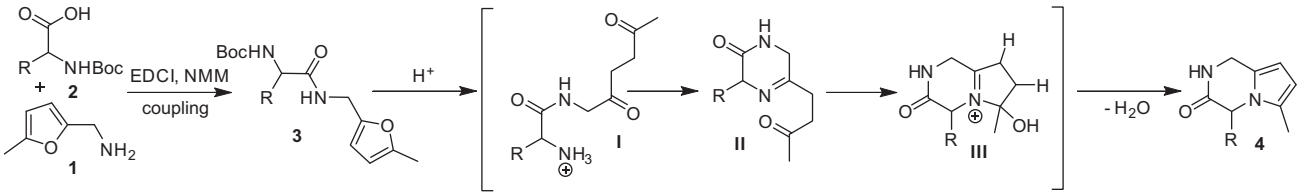
Table 1 (*continued*)

Entry	*N*-Boc amino acid (**2**)	Product (**4**)	Yield[a] (%)
8	 **h**	 **h**	89
9	 **i**	 **i**	77
10[b]	 **j**	 **j**	86
11	 **k**	 **k**	85
12	 **l**	 **l**	79
13	 **m**	 **m**	86

[a] Isolated yields.
[b] Product **4j** is an oil and hence isolated via column chromatography.

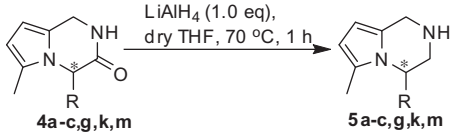
in turn were prepared from 2-amino aromatic and heteroaromatic acids.[15] They extended this methodology for the synthesis of pyrrolo[1,2-*a*][1,4]diazepine from furfurylamine and β-alanine.[16] Influenced by this work we reasoned that coupling of 5-methyl furfurylamine with *N*-Boc amino acids will lead to an amide derivative which upon acid-promoted simultaneous furan-ring opening and deprotection of the Boc-group would afford an intermediate which may cyclize intramolecularly to furnish chiral 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones.

Aiming at this objective, we initiated our study by performing a pilot reaction toward optimization with commercially available 5-methyl-furfuryl amine (**1**) and the *N*-Boc phenyl alanine (**2a**). The coupling reaction between the two was carried out in the presence of EDCI·HCl and NMM in methylene chloride as the reaction medium chilled in an ice-salt bath. The reaction was found to be complete in 1 h to furnish a product (98% yields) that was characterized to be the anticipated furfurylamide (**3**) (Scheme 1). Thereafter screening experiments to identify the most suitable condition for the furan-ring opening and subsequent intramolecular ring closing were carried out. We discovered that treating furfurylamide (**3**) with a HCl: AcOH (1:9, v/v) mixture for 12 h at room temperature followed by neutralization with aqueous $NaHCO_3$ to pH 7.0 and subsequently heating the mixture for 3 h gave a product (79%) which was identified as (*S*)-4-methylphenyl-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (**4a**). At this stage it occurred



Scheme 2. Plausible mechanism for the formation of the 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones from *N*-Boc amino acids in one-pot.

Table 2
Results of reduction of 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones to 4-substituted-6-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines



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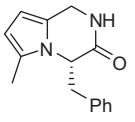
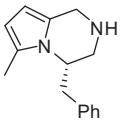
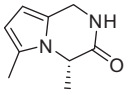
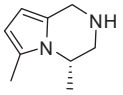
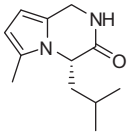
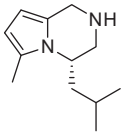
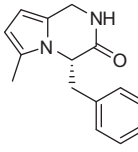
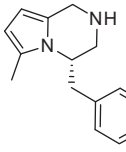
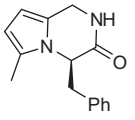
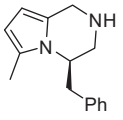
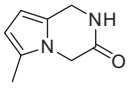
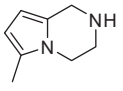
1	 **a**	 **a**	94
2	 **b**	 **b**	96
3	 **c**	 **c**	94
4	 **g**	 **g**	96
5	 **k**	 **k**	95
6	 **m**	 **m**	92

[a] Isolated yields.

to us that instead of isolating the furfurylamide we can perform the two step-process in one pot. To investigate this feasibility after pursuing the coupling reaction for 1 h, HCl: AcOH mixture was added to the same flask and the reaction was allowed to stir for 12 h. The contents were neutralized to pH 7.0 with aqueous $NaHCO_3$ and then heated to reflux for 2 h to afford the product as solid which was identical to the product isolated in two steps.[17] Since the yields were comparable in both processes, we considered to conduct the sequence as a one-pot process.

To investigate the scope of the protocol, in the next stage 5-methyl-furfurylamine was subjected to reactions with a variety of L and D *N*-Boc amino acids (**2a–m**). As illustrated in Table 1, it was gratifying to note that all amino acids afforded the corresponding 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones (**4a–m**) in excellent yields. It is worthwhile to mention that in most of the cases the major part of the total yields of products was isolated without any chromatographic purification.

A plausible mechanism for the formation of the product is illustrated in Scheme 2. The initial coupling reaction between **1** and **2** is followed by the acid-catalyzed ring opening of the furan ring and in situ deprotection of the *N*-Boc group of the amino acid in **3** to afford the free amine **I**. Subsequent sequential intramolecular cyclizations between the amino and the keto groups in **I** and **II** result in the intermediate **III** which undergoes dehydration to yield the observed product **4**. It may be noted that reaction was unsuccessful with furfurylamine indicating that substitution on the 5-position is necessary for the success of the reaction.

Finally some of the 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4*H*)-ones were transformed into their corresponding 4-substituted-6-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines via amide reduction. Treating compounds **4a–c**,**g**,**k**,**m** with $LiAlH_4$ in THF for 1 h at reflux temperature gave the reduced products **5a-c**,**g**,**k**,**m**, respectively (Table 2).[18]

In summary we have developed a facile approach for the synthesis of chiral substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines. The commercially available cheap starting materials, simple reaction conditions, excellent yields are some of the attractive features of this protocol. Further experiments for exploring the scope of this protocol and utility of the prepared 4-substituted-6-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines for synthesizing natural products are underway and will be subject of future communication.

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Supplementary data

Supplementary data (spectroscopic data and copies of ^1H and ^{13}C NMR data for all compounds is provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.067.

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17. *General procedure for the one pot synthesis of 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-ones as exemplified for* **4a**. To a stirred solution of *N*-Boc-L-Phenyl alanine **2a** (0.5 g, 1.89 mmol) in dry CH_2Cl_2 (20 mL) was added 5-methyl furfuryl amine (0.22 mL, 1.98 mmol) at −15 °C (chilled in an ice-salt mixture) followed by EDCI.HCl (0.38 g, 1.98 mmol) and *N*-methyl morpholine (0.22 mL, 1.98 mmol) and the reaction was allowed to continue at the same temperature. After 1 h when the entire amino acid was consumed, the reaction was treated with conc. HCl (3 mL) and glacial acetic acid (27 mL) at 0 °C and the reaction was continued at room temperature for 12 h. Thereafter the reaction mixture was poured into water (100 mL) and neutralized to pH ~7 with aq saturated $NaHCO_3$. The resulting aqueous solution was heated to reflux for 3 h and cooled to room temperature. Upon cooling, the product separates out as a precipitate which was filtered off, washed with water and air-dried (0.32 g). To recover additional product from the filtrate, it was extracted with EtOAc (2 × 20 mL), the organic layers were combined, washed with brine (25 mL) and subsequently dried over anhydrous Na_2SO_4. Evaporation of ethyl acetate in vacuo gave a residue which after purification via silica-gel column chromatography (hexane/EtOAc, 7:3) afforded the desired product, as a brown solid **4a** (0.06 g, total = 85%). *(S)-4-Benzyl-6-methyl-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-one*: mp = 122–124 °C; $[\alpha]_D$ = +135.3 (*c* 0.05, $CHCl_3$); R_f = 0.39 (hexanes/EtOAc, 60:40, v/v); ν_{max} (KBr) 1677 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.13 (s, 3H, CH_3), 3.20–3.33 (m, 3H, 2 × CH_2), 3.99 (dd, 1H, J_1 = 14.6 HZ, J_2 = 3.4 Hz, CH_2), 4.84 (s, 1H, CH), 5.72 (s, 1H, ArH), 5.92 (s, 1H, ArH), 6.63 (br s, 1H, NH), 6.81 (d, 3H, *J* = 7.0 HZ, ArH), 7.15–7.26 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.5, 39.1, 40.1, 58.5, 101.9, 107.9, 121.9, 126.3, 127.5, 128.4, 130.0, 135.0, 170.4; mass (ES+) *m*/*z* = 241.1(M^++1); ES-HRMS calcd. for $C_{15}H_{17}N_2O$ 241.1341, found 241.1339.
18. *General procedure for the synthesis of 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-ones from chiral 4-substituted-6-methyl 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines as exemplified for* **5c**. At 0 °C $LiAlH_4$ powder (0.02 g, 0.49 mmol) was added to a solution of 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one **4c** (0.1 g, 0.49 mmol) in dry THF (20 mL) and then the reaction mixture was heated to reflux. Upon consumption of starting material (as monitored by TLC) the reaction mixture was cooled to 0 °C and excess $LiAlH_4$ was quenched with ethyl acetate and water. The resulting white precipitate was filtered off and the filtrate was concentrated under reduced pressure to obtain the crude product which is purified by silica-gel column chromatography (hexane/EtOAc, 3:2) to afford 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4*H*)-ones as brown oil **5c** (0.08 g, 94%). *(S)-4-Isobutyl-6-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine*: $[\alpha]_D$ −44.0 (*c* 0.1 $CHCl_3$); R_f = 0.23 (hexanes/EtOAc, 50:50, v/v); ν_{max} (Neat) 3412 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.95 (d, 3H, *J* = 6.4 HZ, CH_3), 1.02 (d, 3H, *J* = 6.4 HZ, CH_3), 1.31–1.42 (m, 1H, CH), 1.80–1.89 (m, 1H, NH), 2.22 (s, 3H, CH_3), 3.08–3.25 (m, 2 H, CH_2), 3.92 (t, 1H, *J* = 11.1 Hz, CH), 4.00–4.13 (m, 2H, CH_2), 5.72 (s, 1H, ArH), 5.84 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.3, 21.5, 24.0, 25.3, 42.0, 43.9, 49.7, 60.5, 101.4, 106.1, 125.8, 126.0; mass (ES+) *m*/*z* = 193.1(M^++1); ES-HRMS calcd for $C_{12}H_{21}N_2$ 193.1705, found 193.1707.