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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.

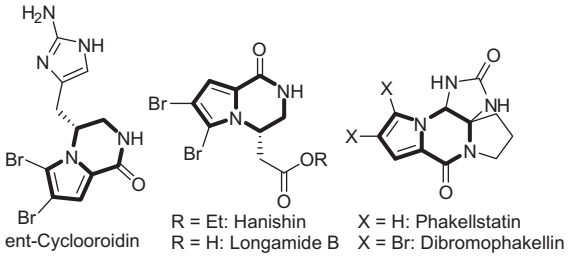

Figure 1. A few natural products containing 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine core.

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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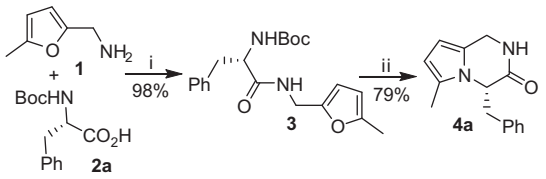
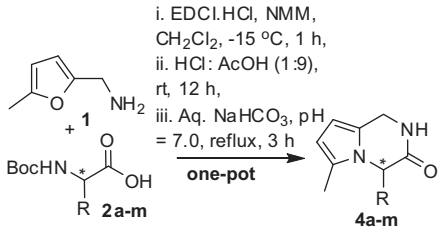


Scheme 1. Reagents and conditions- (i) EDCI.HCl (1.05 equiv), NMM (1.05 equiv), dry CH_2Cl_2, −15 °C, 1 h; (ii) (a) concd HCl: glacial acetic acid (1:9), rt, 12 h, (b) aq $NaHCO_3$, reflux, 3 h.

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



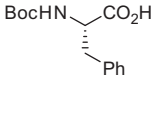
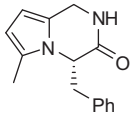
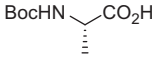
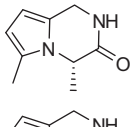
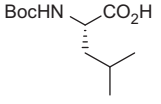
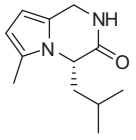
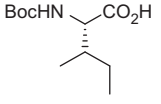
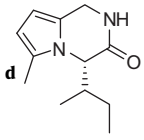
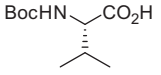
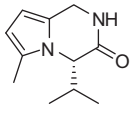
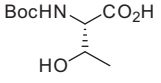
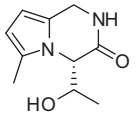
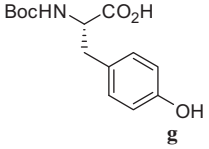
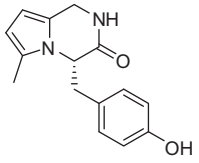
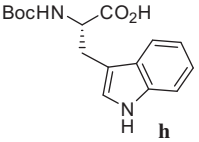
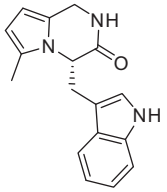
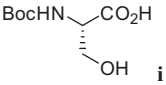
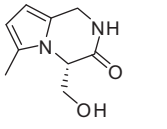
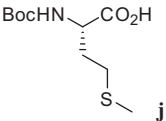
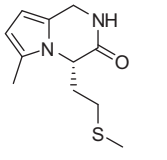
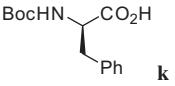
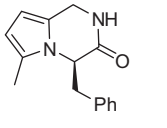
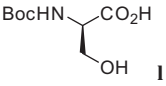
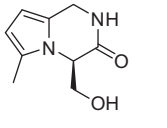
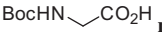
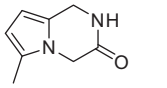
Entry	*N*-Boc amino acid (**2**)	Product (**4**)	Yield[a] (%)
1	 **a**	 **a**	85
2	 **b**	 **b**	89
3	 **c**	 **c**	92
4	 **d**	 **d**	91
5	 **e**	 **e**	90
6	 **f**	 **f**	83
7	 **g**	 **g**	88

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