Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1281–1285

A novel synthesis of aryl tethered imidazo[4,5-*b*]pyrazin-2-ones through in situ ring construction and contraction☆

Ramendra Pratap,[a] Abhijeet Deb Roy,[b] Raja Roy[b] and Vishnu Ji Ram[a,*]

[a]*Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India*
[b]*Division of SAIF, Central Drug Research Institute, Lucknow 226 001, India*

Received 28 August 2006; revised 29 November 2006; accepted 7 December 2006

This Letter is dedicated to Professor Wolfgang Pfleiderer, University of Konstanz Germany, on the occasion of his 80th birthday

Abstract—An innovative synthesis of aryl tethered 1,3-dimethylimidazo[4,5-*b*]pyrazin-2-ones **4** and **6** has been delineated through base catalyzed ring transformation of 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles **1** and methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates **5** with 7-acetyl-1,3-dimethyllumazine **2** with subsequent ring contraction of the fused pyrimidine to an imidazole ring. An additional product, methyl [6-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyrazin-5-yl)-4-thiophen-2-ylpyran-2-ylidene]acetate **8b**, was also isolated from the reaction of **5** and **2**, as a minor constituent.

The imidazo[4,5-*b*]pyrazine ring system is present as a substructure in several marine natural products such as dibromophakellstatin[1] **I**, phakellin[2] **II** and palau'amine[3] **III** with diverse pharmacological activities, including antibacterial,[4] immunosuppressant,[5] antineoplastic,[6] antifungal,[7] antihypertensive,[8] diuretic, bronchodilatory,[9] cardiac-stimulatory[9] and pesticidal[10] (Fig. 1).

A comprehensive literature survey showed that the chemistry of the imidazo[4,5-*b*]pyrazine ring system has not been explored extensively. It was first prepared[11] through the condensation of 2,3-diaminopyrazine with an acid chloride or by fusion with urea. Acylation of the diamine followed by ring closure in hot diphenyl ether or heating 2,3-diaminopyrazine with an acid are other methods which has also been reported.[10] A Curtius reaction of 3-aminopyrazine-2-carboxylic acid azide proved to be a versatile route[9] for the synthesis of 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-ones. An alternative route has also been developed[12] through the condensation–cyclization of 2-amino-3-pyrazinecarboxylic acid with hydroxylamine in moderate yield. This ring system has also been prepared from the reaction of 2,5-diamino-3,6-dicyanopyrazine with alkyl isocyanate, but in poor yield.[13] Further, nucleosides of this class of compounds have been prepared[14] through

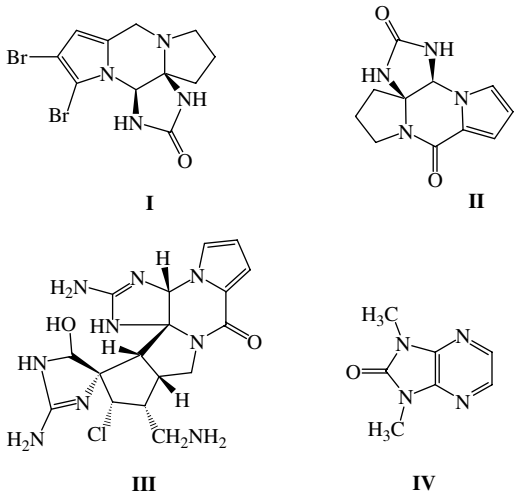


Figure 1. Structures of dibromophakellstatin **I**, phakellin **II** and palau'amine **III** and 1,3-dimethylimidazo[4,5-*b*]pyrazin-2-one **IV**.

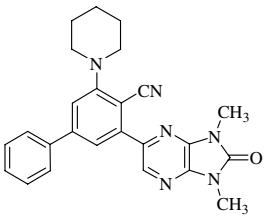
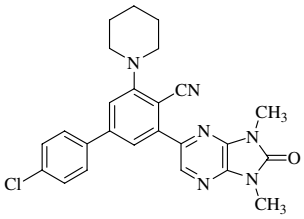
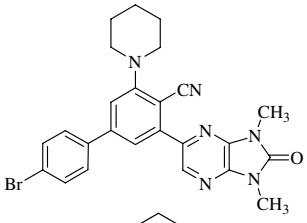
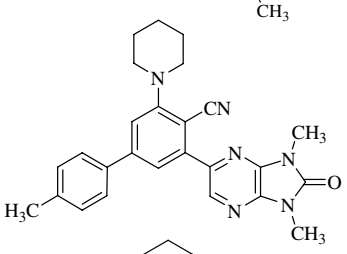
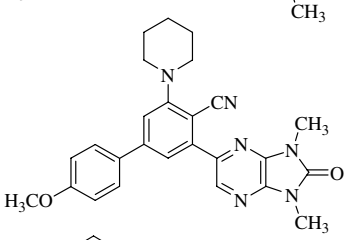
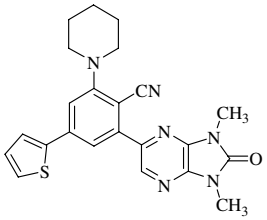
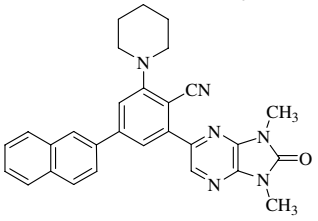
Keywords: Imidazo[4,5-*b*]pyrazine; 2*H*-Pyran-2-ones; Ring transformation.
☆CDRI Communication No. 7067.
*Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405; e-mail: vjiram@yahoo.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.021

the condensation of a 4,5-diaminoimidazole nucleoside with 1,2-diketones.

We report here a concise synthesis of 5-aryl-1,3-dimethylimidazo[4,5-*b*]pyrazin-2-ones **4** and **6** through the base catalyzed ring transformation of **1** and **5** with 7-acetyl-1,3-dimethyllumazine **2** with subsequent contraction of the pyrimidine to an imidazole ring.

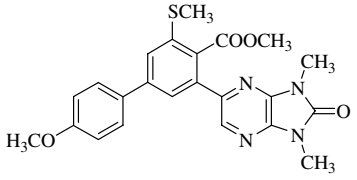
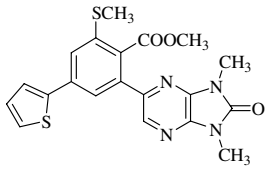
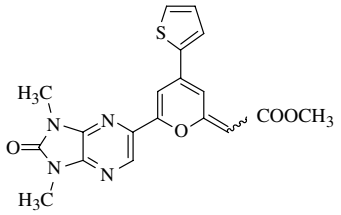
Table 1. Synthesis of imidazo[4,5-*b*]pyrazin-2-ones **4**

Compound	Structure	Time (h)	Yield (%)
4a		2	79
4b		2.5	81
4c		2.5	73
4d		2	83
4e		2.5	87
4f		2	75
4g		2	79

6-Aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles **1** and methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates **5** were used for the ring transformation with 7-acetyl-1,3-dimethyllumazine **2**. The former were obtained[15] in two steps by stirring an equimolar mixture of aryl methyl ketones and methyl 2-cyano-3,3-dimethylthioacrylate in the presence of powdered KOH in DMSO, followed by amination with piperidine in ethanol at reflux. Lactones **5** were prepared[15] analogously from the reaction of aryl methyl ketones and methyl 2-carbomethoxy-3,3-dimethylthioacrylate. 7-Acetyl-1,3-dimethyllumazine **2** was prepared by acylation of 1,3-dimethyllumazine.[16]

The reaction of 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles **1** with 7-acetyl-1,3-dimethyllumazine **2** in the presence of powdered KOH in dry DMF afforded 5-aryl-1,3-dimethylimidazo[4,5-*b*]pyrazin-2-ones **4** in good yields. Analogously, the reaction of **5** with 7-acetyl-1,3-dimethyllumazine under identical reaction conditions produced a mixture of two products, 5-biaryl-1,3-dimethylimidazo[4,5-*b*]pyrazin-2-ones **6** and methyl 4-aryl-[6-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyrazin-5-yl)pyran-2-ylidene]acetate **8**. The yields and reaction conditions for these reactions are presented in Tables 1 and 2. The structures of the final compounds **4**, **6** and **8b** were established unequivocally using one- and two-dimensional NMR experiments (see Supplementary data). Possibly, the first stage of the reaction is the conversion of the acetyl to a biaryl[17] to form 7-biaryl-1,3-dimethyllumazine **3** as an intermediate with subsequent ring contraction in a second step to

Table 2. Synthesis of imidazo[4,5-*b*]pyrazin-2-ones **6** and **8b**

Compound	Structure	Time (min)	Yield (%)
6a		45	39
6b		50	35
8b		50	14