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

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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

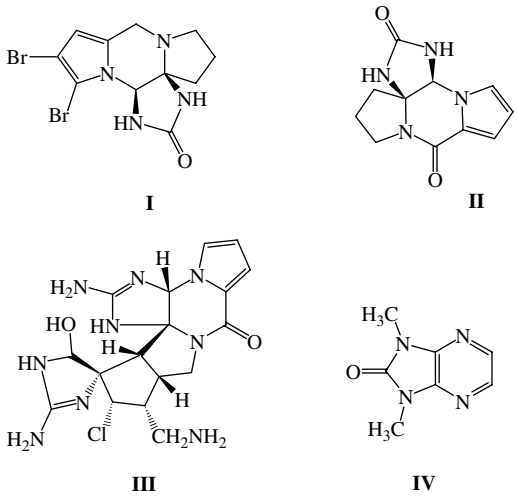

Figure 1. Structures of dibromophakellstatin **I**, phakellin **II** and palau'amine **III** and 1,3-dimethylimidazo[4,5-*b*]pyrazin-2-one **IV**.

Keywords: Imidazo[4,5-*b*]pyrazine; 2*H*-Pyran-2-ones; Ring transformation.
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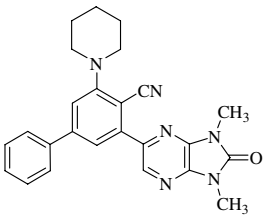
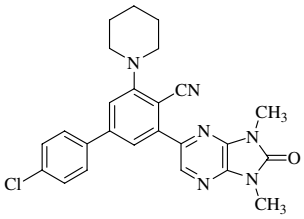
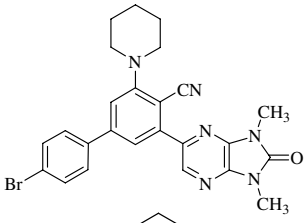
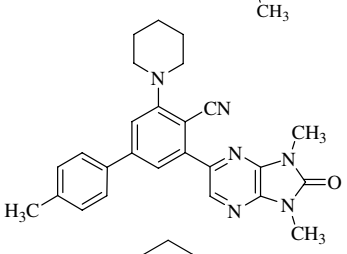
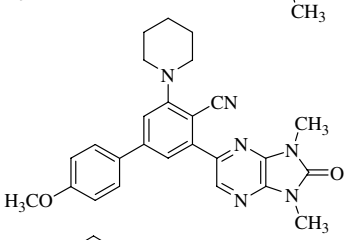
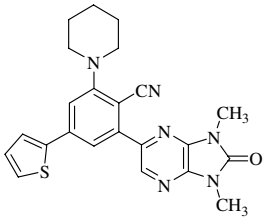
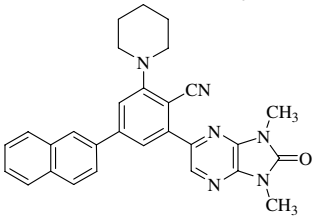
the condensation of a 4,5-diaminoimidazole nucleoside with 1,2-diketones.

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.

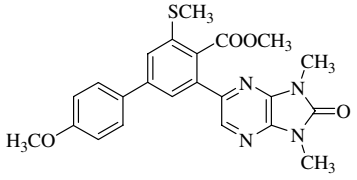
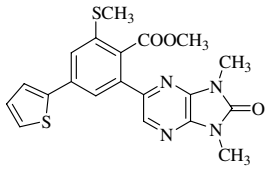
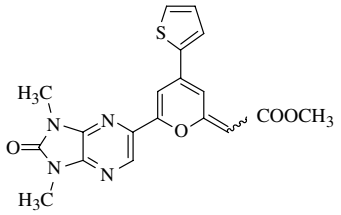
Table 1. Synthesis of imidazo[4,5-*b*]pyrazin-2-ones **4**

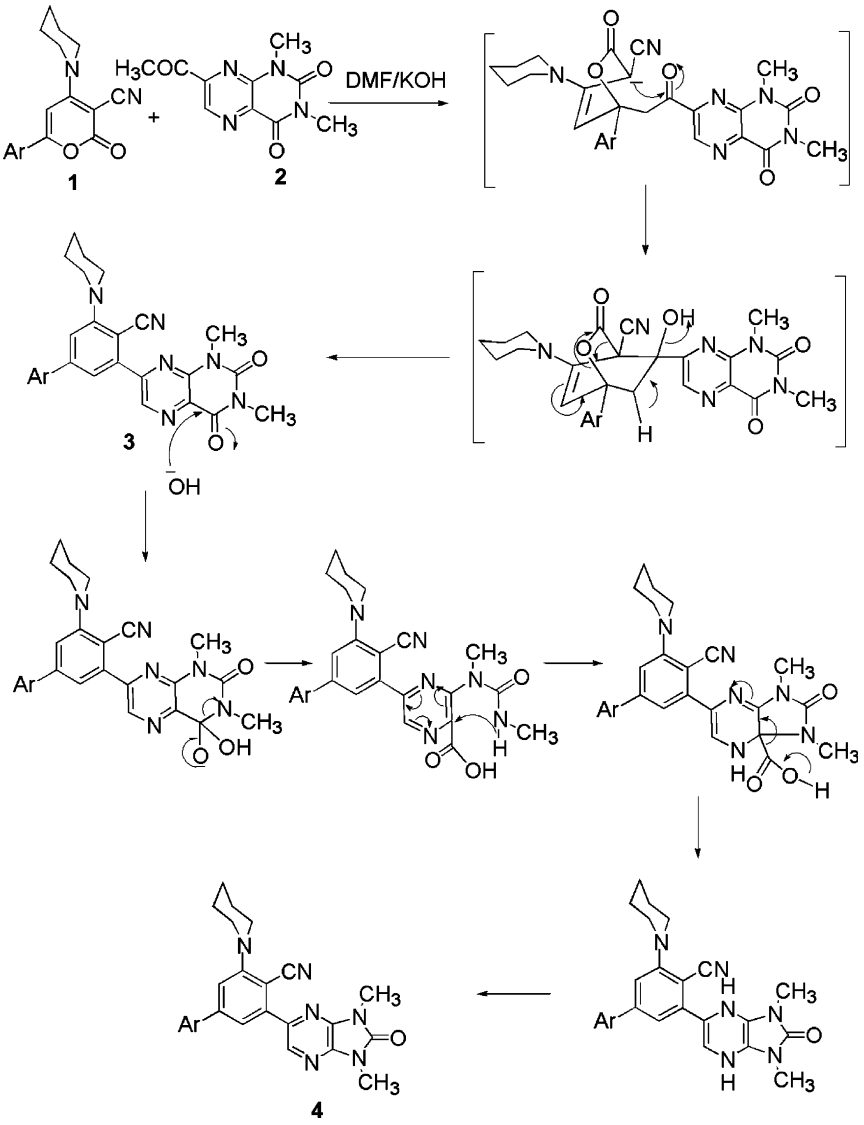
Compound	Structure	Time (h)	Yield (%)
4a		2	79
4b		2.5	81
4c		2.5	73
4d		2	83
4e		2.5	87
4f		2	75
4g		2	79

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



Scheme 1. A plausible mechanism for the formation of 6-aryl-1,3-dimethylimidazo[4,5-*b*]pyrazin-2-ones **4**.

yield 5-aryl-1,3-dimethylimidazo[4,5-*b*]pyrazin-2-ones **4** (Scheme 1).

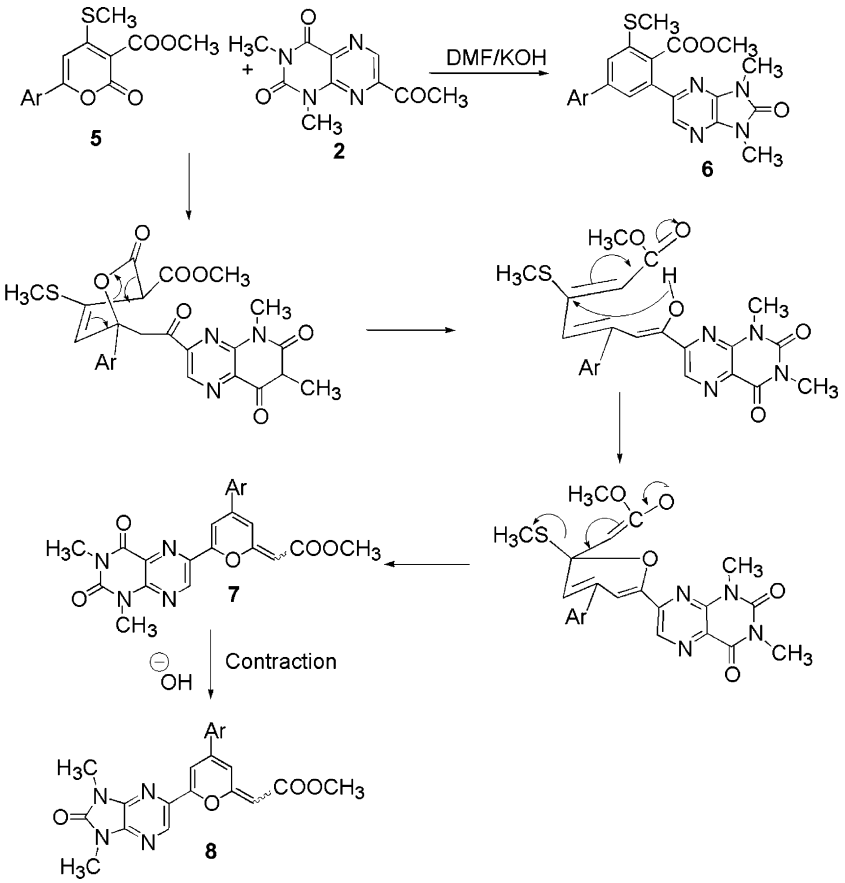
Several attempts were made to detect the proposed intermediate **3** from the reaction of **1** and **2** to ascertain the course of the reaction through real time proton NMR, but these failed.

Two other experiments with **1** and **2** were carried out in the presence of light and in the dark. In the former case, the reaction proceeded smoothly to provide **4** while in the dark, **2** decomposed completely leaving behind starting material **1**. From these experiments, it was concluded that light is essential for the activation and progress of the reaction. A plausible mechanism is depicted in Scheme 1.

The reaction was generalized further by reacting methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates **5** with **2** under analogous reaction conditions, to give 5-aryl-1,3-dimethylimidazo[4,5-*b*]pyrazin-2-ones **6** along with pyran **8**. Possibly, the weaker electron-withdrawing properties of –COOMe compared to CN at position 3 of the pyran ring facilitated the enolization followed by successive Michael addition and elimination of methyl mercaptan to yield **8** (Scheme 2 and Table 2). Separation of the products was difficult but we succeeded in separating the major constituent **6** through preparative TLC. The minor constituent **8** was unstable.

All the compounds were characterized by spectroscopic techniques.[18]

In summary, the reactions of suitably functionalized 2*H*-pyran-2-ones with 7-acetyl-1,3-dimethyllumazine result in the formation of 5-aryl-1,3-dimethylimidazo[4,5-*b*]-pyrazin-2-ones in fair to excellent yields. Our approach for the construction of this ring system is novel and opens a new avenue for the synthesis of this class of compounds within 2–3 h in high yields.



Scheme 2. A plausible mechanism for the formation of 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**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.021.

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18. *General procedure for the synthesis of 5-aryl-1,3-dimethyl-imidazo[4,5-b]pyrazin-2-ones* (**4**): An equimolar mixture

of 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitrile (0.5 mmol), 7-acetyl-1,3-dimethyllumazine (117 mg, 0.5 mmol) and KOH (34 mg, 0.6 mmol) in DMF (3.0 mL) was stirred under nitrogen for 2–2.5 h. Completion of the reaction was monitored by TLC, then excess DMF was removed under reduced pressure. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring, neutralized with 10% HCl (5.0 mL), and the precipitate obtained was filtered, washed with water, dried and purified by neutral alumina column chromatography, eluting with 20% hexane in chloroform.

5-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)-4′-methoxy-3-(piperidin-1-yl)-biphenyl-4-carbonitrile (**4e**): White powder; yield 87%; mp 194–196 °C; IR (KBr): 3010, 2926, 2862, 2367, 2340, 2201, 2143, 1722, 1658, 1586, 1553, 1452, 1353, 1266, 1090, 1010, 970, 825, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.63–1.65 (m, 2H, CH_2), 1.81–1.84 (m, 4H, CH_2), 3.27 (t, $J = 5.21$ Hz, 4H, CH_2NCH_2), 3.55 (s, 3H, NCH_3), 3.57 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 7.01 (d, $J = 8.72$ Hz, 2H, ArH), 7.20 (d, $J = 1.12$ Hz, 1H, ArH), 7.38 (d, $J = 1.24$ Hz, 1H, ArH), 7.56 (d, $J = 8.68$ Hz, 2H, ArH), 8.31 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.07, 25.93, 25.96, 26.19, 53.62, 55.42, 103.54, 114.02, 114.44, 116.58, 116.92, 117.97, 119.21, 120.71, 128.45, 132.09, 134.70, 138.65, 143.11, 143.37, 145.81, 153.97, 159.05, 160.19; MS (FAB): 455 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{26}H_{26}N_6O_2$ 454.21172 (M^+) found for *m*/*z* 454.21154.

General procedure for the synthesis of methyl (1,3-dimethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)-6-methylsulfanyl-4-arylbenzoate (**6**): This was prepared analogously by the reaction of methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates and 7-acetyl-1,3-dimethyllumazine. The mixture of two products obtained was separated by preparative TLC. The major products isolated in 35–39% yields were identified as methyl (1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyrazin-5-yl)-6-methylsulfanyl-4-arylbenzoates. The minor product could not be isolated due to instability at room temperature. In only one case, we did succeed in isolating the minor constituent from the reaction mixture as methyl [6-(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyrazin-5-yl)-4-thiophen-2-yl-pyran-2-ylidene]acetate (**8b**) in low yield.

Methyl 5-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]-pyrazin-5-yl)-4′-methoxy-3-methylsulfanyl-biphenyl-4-carboxylate (**6a**): Cream coloured solid; yield 39%; mp 180–182 °C; IR (KBr): 2945, 2364, 1730, 1661, 1602, 1512, 1453, 1336, 1283, 1251, 1184, 1058, 1022, 881, 836, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.55 (s, 3H, SCH_3), 3.51 (s, 3H, NCH_3), 3.54 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 7.00 (d, $J = 8.1$ Hz, 2H, ArH), 7.54–7.57 (m, 4H, ArH), 8.23 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 17.52, 25.76, 25.87, 52.04, 55.39, 114.43, 115.50, 121.27, 124.84, 126.15, 128.35, 131.32, 132.08, 133.37, 136.80, 138.26, 142.94, 144.31, 153.85, 159.90, 168.87; MS (FAB): 451 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{23}H_{22}N_4O_4S$ 450.13618 (M^+) found for *m*/*z* 450.13651.

Methyl [6-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]-pyrazin-5-yl)-4-thiophen-2-yl-pyran-2-ylidene]acetate (**8b**): Deep red solid; yield: 14%; mp: 157–159 °C; IR (KBr): 3084, 2366, 1724, 1677, 1586, 1551, 1494, 1455, 1421, 1371, 1286, 1226, 1142, 1092, 1007, 948, 919, 880, 810, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.59 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.78 (s, 3H, NCH_3), 5.13 (s, 1H, CH), 7.16 (dd, $J = 3.82$ and 3.86 Hz, 1H, ArH), 7.35 (d, $J = 1.7$ Hz, 1H, ArH), 7.47–7.55 (m, 3H, ArH), 8.26 (s, 1H, ArH); HRMS: (EI, 70 eV) calcd for $C_{19}H_{16}N_4O_4S$ 396.08923 (M^+) found for *m*/*z* 396.08955.