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Solution phase synthesis of imidazo[1,2-b]pyrazol-2-one, an interesting 5,5-fused heterocyclic ring system

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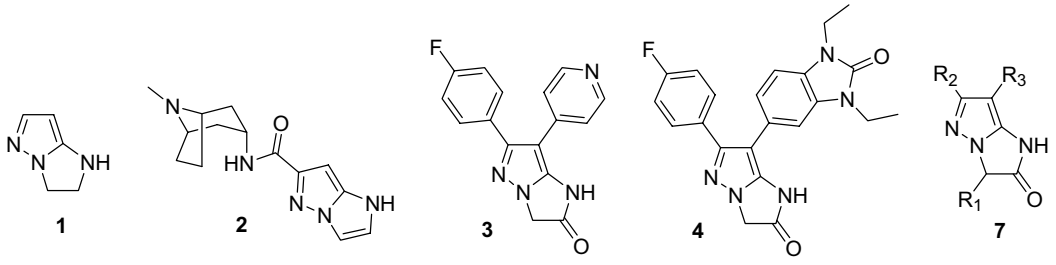
Abstract—The solution phase synthesis of a series of imidazo[1,2-b]pyrazol-2-ones, a fused 5,5-ring system, based on diverse set of hydrazino acids and malononitriles is described. The method involves formation of 5-aminopyrazoles followed by intra-molecular cyclodehydration.

The ability to generate large numbers of compounds rapidly in parallel processes, rather than by sequential reiteration of individual syntheses, is one of several factors that contribute to the appeal of combinatorial chemistry for drug discovery.[1] Solution phase organic chemistry and combinatorial chemistry have been widely used during the last few years in the continued search for biologically active compounds. The synthesis of vast libraries of structurally diverse compounds based on heterocyclic scaffolds, including imidazoles, benzodiazepines, diketopiperazines, oxazolidinones, and quinolones have been disclosed.[2] Our efforts in this area have led to an investigation of several types of heterocycles, including 1,2,3-triazoles,[3] and 1,2,4-triazin-6-ones.[4] Our continuing interest in this area has lead us to investigate the synthesis of imidazo[1,2-b]pyrazol-2-ones, an unusual 5,5-fused ring system.

A brief literature search revealed only a limited number of examples of 1H-imidazo[1,2-b]pyrazol-2-ones and related structures. 2,3-Dihydro-1H-imidazo[1,2-b]pyrazole (IMPY, **1**) has been found to reversibly inhibit DNA synthesis without significantly affecting RNA or protein synthesis. The antiviral and antitumor activities of many agents depend, at least in part, on their ability to inhibit DNA synthesis.[5] IMPY has been shown to be active against Herpes Simplex Virus type-1 (HSV-1).[6] Several derivatives of 1H-imidazo[1,2-b]pyrazoles, (e.g., *N*-(tropanyl)imidazo[1,2-b]pyrazolecarboxamide, **2**), have been shown to have potential as CNS agents.[7] Additionally, the pyrazolopyridine analog **3** has been shown to inhibit both interluekin-1 and tumor necrosis factor,[8] while the pyrazole benzimidazolone derivative **4** is a MAP kinase inhibitor with anti-inflammatory activity.[9] In an effort to further explore this interesting scaffold, we



Keywords: Pyrazole; Heterocycle; Imidazolone; Hydrazino acid; Aminopyrazole.
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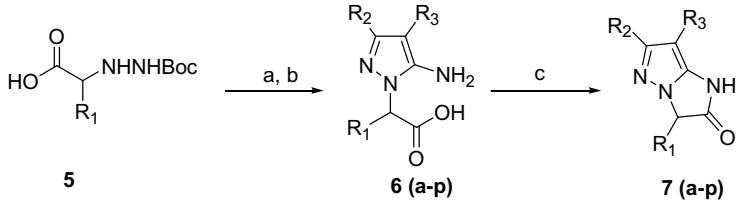
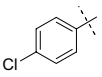
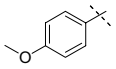
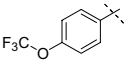
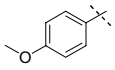
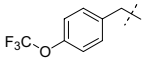
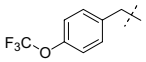


Scheme 1. Solution phase synthesis of 1H-imidazo[1,2-*b*]pyrazol-2-ones. Reagents and conditions: (a) 50% TFA–DCM, rt, 1 h; (b) R_2COCHR_3CN, MeOH, rt, 18 h; (c) EDCI·HCl, DCM, rt, 15–18 h.

Table 1. Representative examples of solution phase synthesis of bicyclic and tricyclic imidazopyrazolones (**7**)[11]

Entry	R_1	R_2	R_3	Yield (%)	Entry	R_1	R_2	R_3	Yield (%)
7a			H	55	**7i**	H		H	55
7b		*t*-Bu	H	81	**7j**	Bn	*t*-Bu	H	60
7c		Ph	H	60	**7k**	Bn	Ph	H	67
7d	Et	*t*-Bu	H	54	**7l**	Bn		H	69
7e	Et		H	55	**7m**		$-CH_2SCH_2-$		19
7f		*t*-Bu	H	55	**7n**	Et	$-CH_2SCH_2-$		22
7g		Ph	H	55	**7o**	H	$-CH_2SCH_2-$		16
7h	H	*t*-Bu	H	84	**7p**	Bn	$-CH_2SCH_2-$		18

have developed a simple synthesis of imidazo[1,2-b]pyrazol-2-ones from commercially available malononitriles and α-hydrazino acids.

As previously reported, a range of Boc-protected α-hydrazino acids (**5**) can be readily prepared from either the corresponding α-bromoacids or α-hydroxy-acids.[10] Standard Boc deprotection of the hydrazine with TFA in methylene chloride followed by condensation with commercially available malononitriles provided the desired amino pyrazoles (**6**). EDCI mediated intramolecular cyclodehydration was then achieved resulting in the formation of the desired 5,5-ring system, imidazo[1,2-b]pyrazol-2-ones (**7a**–**l**) in good to excellent yields (Scheme 1, Table 1). Interestingly, this chemistry was able to provide fused tricycles **7m**–**p**, although the yields were relatively low, most likely due to the highly strained nature of the 5,5,5-fused tricyclic system.

In conclusion, we have developed a simple process for the preparation of the 5,5 fused ring system, imidazo[1,2-b]pyrazol-2-one from readily available starting materials in good to excellent yield. In addition, we have extended the chemistry to the preparation of 5,5,5 fused tricyclic systems.

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11. Representative procedure (entry **7b**): Boc-protected hydrazine leucine (2.0 g) was deprotected under standard conditions (TFA–methylene chloride, 50%, 50 mL, 2 h, rt). 4,4-Dimethyl-3-oxopentane nitrile (100 mg, 0.80 mmol) and hydrazine leucine (128.5 mg, 0.88 mmol) were stirred in methanol for 18 h at room temperature to give the corresponding amino pyrazole (**6b**) in 32% yield, ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (dd, $J = 6.6$ Hz each, 6H, 1.31 (s, 9H, 1.92 (m, 1H), 2.09 (m, 2H), 5.42 (m, 1H), 5.65 (s, 1H). (M^+H) 254. The amino pyrazole **6b** (20 mg, 0.08 mmol) was then treated with EDCI (22.7 mg, 0.12 mmol) in methylene chloride at room temperature for 18 h to give the cyclized product **7b** (15 mg, 81%). Spectral data for Table 1: Entry **7a** ^{1}H NMR (300 MHz, CD_3OD): δ 0.96 (dd, $J = 6.50$ Hz each, 6H), 1.89 (m, 1H), 2.08 (m, 2H), 4.70 (t, $J = 6.5$ Hz, 1H), 6.06 (s, 1H), 7.37 (d, $J = 4.70$ Hz, 2H), 7.73 (d, $J = 4.70$ Hz, 2H). (M^+H) 290.76. Entry **7b** ^{1}H NMR (300 MHz, CD_3OD): δ 0.91 (d, $J = 6.42$ Hz, 3H), 0.99 (d, $J = 6.45$ Hz, 3H), 1.31 (s, 9H), 1.93 (m, 1H), 2.01 (m, 2H), 4.58 (t, $J = 6.1$ Hz, 1H), 5.62 (s, 1H). (M^+H) 236. Entry **7c** ^{1}H NMR (300 MHz, CD_3OD): δ 0.97 (dd, $J = 6.50$ Hz each, 6H), 1.92 (m, 1H), 2.03 (m, 2H), 4.72 (t, $J = 6.41$ Hz, 1H), 6.06 (s, 1H), 7.26–7.42 (m, 3H), 7.75 (d, $J = 5.21$ Hz, 2H). (M^+H) 256. Entry **7d** ^{1}H NMR (300 MHz, CD_3OD): δ 0.77 (t, $J = 7.40$ Hz, 3H), 1.32 (s, 9H), 2.08–2.19 (m, 2H), 4.63 (t, $J = 5.34$ Hz, 1H), 5.65 (s, 1H). (M^+H) 208. Entry **7e** ^{1}H NMR (300 MHz, CD_3OD): δ 0.86 (t, $J = 7.40$ Hz, 3H), 2.07–2.24 (m, 2H), 3.83 (s, 3H), 4.69 (t, $J = 5.15$ Hz, 1H), 6.0 (s, 1H), 6.96 (d, $J = 4.70$ Hz, 2H), 7.70 (d, $J = 4.70$ Hz, 2H). (M^+H) 258. Entry **7f** ^{1}H NMR (300 MHz, CD_3OD): δ 1.30 (s, 9H), 3.52 (d, $J = 4.90$ Hz, 1H), 3.57 (d, $J = 4.90$ Hz, 1H), 4.90 (t, $J = 3.07$ Hz, 1H), 5.40 (s, 1H), 6.84–7.01 (m, 4H). (M^+H) 354. Entry **7g** ^{1}H NMR (300 MHz, CD_3OD): δ 3.50 (d, $J = 4.76$ Hz, 1H), 3.55 (d, $J = 4.76$ Hz, 1H), 4.95 (t, $J = 4.60$ Hz, 1H), 5.82 (s, 1H), 6.93–7.03 (m, 4H), 7.24–7.34 (, 3H), 7.67 (d, $J = 7.06$ Hz, 2H). (M^+H) 374. Table **7h** ^{1}H NMR (300 MHz, CD_3OD): δ 1.30 (s, 9H), 4.60 (s, 2H). (M^+H) 180. Entry **7i** ^{1}H NMR (300 MHz, CD_3OD): δ 3.71 (s, 3H), 4.54 (s, 2H), 5.86 (s, 1H), 6.81 (d, $J = 4.92$ Hz, 2H), 7.54 (d, $J = 4.64$ Hz, 2H). (M^+H) 230. Entry **7j** ^{1}H NMR (300 MHz, CD_3OD): δ 1.33 (s, 9H), 3.52 (d, $J = 4.80$ Hz, 1H), 4.90 (t, $J = 3.2$ Hz, 1H), 6.94 (m, 3H), 7.10 (m, 2H). (M^+H) 270. Entry **7k** ^{1}H NMR (300 MHz, CD_3OD): δ 3.62 (dd, $J = 4.74$ Hz each, 2H), 5.06 (t, $J = 3.50$ Hz, 1H), 5.91 (s, 1H), 7.06 (m, 3H), 7.16 (m, 2H), 7.44 (m, 3H), 7.81 (d, $J = 7.0$ Hz, 2H). (M^+H) 290. Entry **7l** ^{1}H NMR (300 MHz, CD_3OD): δ 3.27 (m, 2H), 4.91 (t, 3.61 Hz, 1H), 6.05 (s, 1H), 6.90 (m, 3H), 7.0 (m, 2H), 7.19 (d, $J = 8.10$ Hz, 2H), 7.75 (d, $J = 6.7$ Hz, 2H). (M^+H) 374. Entry **7m** ^{1}H NMR (300 MHz, CD_3OD): δ 1.07 (dd, $J = 7.0$ Hz each, 6H), 2.30 (m, 1H), 3.75 (s, 2H), 3.87 (s, 2H), 4.74 (d, $J = 4.91$ Hz, 1H) (M^+H) 224. Entry **7n** ^{1}H NMR (300 MHz, CD_3OD): δ 0.91 (t, $J = 7.40$ Hz, 3H), 2.23 (m, 2H), 3.87 (s, 2H), 3.98 (s, 2H), 4.63 (m, 1H). (M^+H) 210. Entry **7o** ^{1}H NMR (300 MHz, CD_3OD): 3.80 (s, 2H), 3.85 (s, 2H), 4.62 (s, 2H). (M^+H) 182. Entry **7p** ^{1}H NMR (300 MHz, CD_3OD): δ 3.27 (m, 2H), 3.81 (s, 4H), 4.93 (m, 1H), 6.90–7.12 (m, 5H). (M^+H) 272.