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Solid-phase approach towards the synthesis of functionalized imidazo[1,2-*b*]pyrazol-2-ones

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Abstract—The solid-phase synthesis of a series of imidazo[1,2-*b*]pyrazol-2-ones, an interesting 5,5-fused ring system, based on diverse set of hydrazine acids and malanonitriles is described. The method involves formation of 5-aminopyrazoles on solid support and subsequent cyclizative cleavage off the resin. Compounds were obtained in acceptable to excellent yields and are suitable for biological evaluation without further purification.

Interest in solid-phase heterocyclic chemistry originated mainly in the pharmaceutical industry. Heterocycles not only enable the spatial fixation of a set of structural elements relevant to reversible binding to proteins, but can also have a strong influence on the solubility and properties of a compound. Because substituted heterocycles are often more easily prepared than the corresponding carbocycles, heterocyclic chemistry has played, and continues to play an important role in the development of new drugs.[1] Despite the growing interest for combinatorial chemistry and impressive achievements in the area of solid-phase organic chemistry (SPOC), the potential of solid-phase heterocyclic chemistry is rather unexplored.[2] Reports in the literature have indicated that, from certain intermediate structures grafted on the solid phase, it is possible to derive more than one type of heterocyclic compound library. Examples include the synthesis of pyrrolidines,[3] thiazolidines,[4] metathiazanones[4] and β-lactams[5] from immobilized aldimines, as well as the preparation of dioxopiperazines and dioxomorpholines from α-bromo-substituted dipeptides.[6] Additionally, both pyrazoles and isoxazoles can be generated from β-diketones.[7]

Our earlier efforts in this area have led to an investigation of several types of heterocycles, including 1,2,3-triazoles[8] and 1,2,4-triazin-6-ones.[9] As part of our ongoing efforts to develop scaffolds for the preparation of combinatorial libraries, we have recently reported a solution phase synthesis of a very interesting 5,5-ring system, imidazo [1,2-*b*]pyrazol-2-ones.[10] Compounds with a similar type of nucleus have shown potential as CNS,[11] antitumour,[12] antiviral[13] agents, and have also been shown to inhibit interleukin, tumour necrosis factor[14] and MAP kinases.[15] We wish to report herein the solid-phase synthesis of functionalized imidazo[1,2-*b*]-pyrazol-2-ones.

The previously described resin bound Boc protected α-hydrazino esters[16] **1** (Scheme 1) were deprotected under standard conditions (50% TFA in dichloromethane) and were treated with various malanonitriles in 10% acetic acid solution in ethanol at 70 °C to provide the requisite amino pyrazoles (**2**) on solid support. An examination of several reaction conditions revealed that both neutral and basic reaction conditions were not effective methods of promoting the desired cyclizative cleavage, yielding at best trace amounts of the desired products. Treatment of the resin with bis(trimethylsilyl) trifluoroacetamide (BSTFA) in 1,2-dichloroethane at 80 °C gave some encouraging results, providing a modest 12% yield of the desired cyclized product (**3**). The best results, however, were obtained with 25% acetic acid solution in toluene at 110 °C, which provided the desired products in good to moderate yield (Table 1). Interestingly, the chemistry was extendable to the

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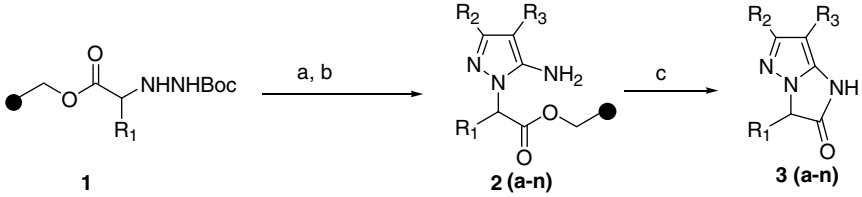
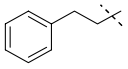
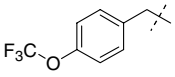
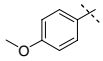
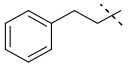
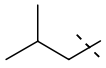
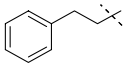
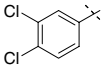
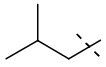
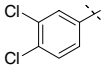
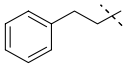
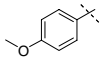
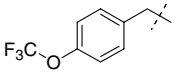
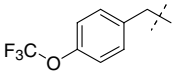
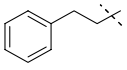
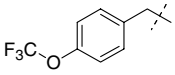
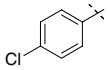
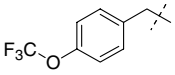


Scheme 1. Reagents and conditions: (a) (i) 50% TFA–CH_2Cl_2, rt, 1 h, (ii) 5% DIPEA–CH_2Cl_2, rt, 1/2 h; (b) R_2COCHR_3CN, 10% AcOH–EtOH, 70 °C, 15 h; (c) AcOH (25%), toluene, 110 °C, 24–48 h.

Table 1. Representative examples of the solid-phase synthesis of **3**[17]

Entry	R_1	R_2	R_3	Yield[a]	Entry	R_1	R_2	R_3	Yield[a]
3a		*t*-Bu	H	44	**3h**			H	40
3b		Ph	H	70	**3i**		*t*-Bu	H	28
3c			H	40	**3j**			H	21
3d			H	70	**3k**	Bn	*t*-Bu	H	40
3e		*t*-Bu	H	32	**3l**	Bn	Ph	H	23
3f		Ph	H	32	**3m**		$–CH_2SCH_2–$		39
3g			H	23	**3n**		$–CH_2SCH_2–$		27

[a] Yields are reported over three steps.

preparation of fused tricycles (**3m-n**), by application of the corresponding monocyclic malononitrile.

In summary, we have developed a simple and efficient solid-phase synthesis of functionalized imidazo[1,2-*b*]-pyrazol-2-ones. The products were easily purified by HPLC and obtained in acceptable yields.

References and notes

1. Dorwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH, 1999.
2. (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527–4554; (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643–5678.
3. Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029–7030.
4. Holmes, C. P.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328–7333.
5. Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253–254.
6. Scott, B. O.; Siegmund, A. C.; Marlowe, C. K.; Pei, Y.; Spear, K. L. *Mol. Diversity* **1996**, *1*, 125–134.
7. Marzinzik, A. L.; Felder, E. R. *Tetrahedron Lett.* **1996**, *37*, 1003–1006.
8. (a) Blass, B. E.; Coburn, K. R.; Faulkner, A. L.; Hunn, C. L.; Natchus, M. G.; Parker, M. S.; Portlock, D. E.; Tullis, J. S.; Wood, R. *Tetrahedron Lett.* **2002**, *43*, 4059–4061; (b) Blass, B. E.; Coburn, K. R.; Faulkner, A. L.; Seibel, W. L.; Srivastava, A. *Tetrahedron Lett.* **2003**, *44*, 2153–2155.
9. Blass, B. E.; Coburn, K. R.; Faulkner, A. L.; Liu, S.; Ogden, A.; Portlock, D. E.; Srivastava, A. *Tetrahedron Lett.* **2002**, *43*, 8165–8167.
10. Blass, B. E.; Srivastava, A.; Coburn, K. R.; Faulkner, A. L.; Janusz, J. J.; Ridgeway, J. M.; Seibel, W. L. *Tetrahedron Lett.* In press. doi:10.1016/j.tetlet.2003.10.177.
11. Vanotti, E.; Florentini, F.; Villa, M. *J. Het. Chem.* **1994**, *31*, 737–743.

12. Ennis, H. L.; Moller, L.; Wang, J. J.; Selawry, O. S. *Biochem. Pharmac.* **1971**, *20*, 2539–2546.
13. Pelling, J. C.; Shipman, C., Jr. *Biochem. Pharmac.* **1976**, *25*, 2377–2382.
14. Oku, T.; Kawai, Y.; Marusawa, H.; Yamazaki, H.; Abe, Y.; Tanaka, H. EP 531901, **1993**.
15. Dombroski, M. A.; Letavic, M. A.; McClure, K. F. WO 02072576, **2002**.
16. Wilson, L. J.; Li, M.; Portlock, D. E. *Tetrahedron Lett.* **1998**, *39*, 5135–5138.
17. Representative procedure: Resin bound Boc-protected hydrazine ester (5 g, loading 0.75 mmol/g) was treated with trifluoroacetic acid in methylene chloride (50%, 50 mL) for 1 h at room temperature. The resin was then filtered and washed successively with methylene chloride (three times), and methanol (three times). This was followed by neutralization of the salt with DIPEA in methylene chloride (5%, 50 mL, 30 min). The resin was then filtered, washed as previously described and dried under vacuum. Resin (700 mg, 0.52 mmol) was then placed in a 10 mL reaction vessel of a Quest™ 210. Benzoylacetonitrile (193.06 mg, 1.32 mmol) was added to the resin and the reagents were agitated for 15 h in 10% acetic acid solution in ethanol at 70 °C. The reaction was allowed to cool and the resin was filtered and washed successively with methylene chloride (three times) and methanol (three times). The resin was then dried under vacuum. Resin (100 mg, **2b**) was then treated with 25% solution of acetic acid in toluene (6 mL). After agitating at 110 °C for 48 h, the reaction was cooled, drained of the solvent and washed with methylene chloride (three times) and methanol (three times). The combined washings were evaporated to yield the product (**3b**, 70%). Spectral data for Table 1. Entry **3a**, ^{1}H NMR (300 MHz, CD_3OD): δ 1.33 (s, 9H), 2.43 (m, 2H), 2.60 (t, $J = 7.62$ Hz, 2H), 4.61 (t, $J = 5.0$ Hz, 1H), 5.51 (s, 1H), 7.15–7.25 (m, 5H). (M^+H) 284. Entry **3b**, ^{1}H NMR (300 MHz, CD_3OD): δ 2.37 (m, 2H), 2.56 (m, 2H), 4.61 (t, $J = 5.27$ Hz, 1H), 5.97 (s, 1H), 7.05–7.24 (m, 8H), 7.67 (d, $J = 8.10$ Hz, 2H). (M^+H) 304. Entry **3c**, ^{1}H NMR (300 MHz, CD_3OD): δ 2.36 (m, 2H), 2.57 (m, 2H), 4.60 (t, $J = 5.43$ Hz, 1H), 6.02 (s, 1H), 7.05–7.15 (m, 5H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.60 (d, $J = 6.40$ Hz, 1H), 7.84 (s, 1H). (M^+H) 372. Entry **3d**, ^{1}H NMR (300 MHz, CD_3OD): δ 2.36 (m, 2H), 2.58 (m, 2H), 3.73 (s, 3H), 4.60 (t, $J = 5.22$ Hz, 1H), 5.90 (s, 1H), 6.87 (d, $J = 6.81$ Hz, 2H), 7.07–7.12 (m, 5H), 7.59 (d, $J = 8.91$ Hz, 2H). (M^+H) 334. Entry **3e**, ^{1}H NMR (300 MHz, CD_3OD): δ 1.33 (s, 9H), 3.53 (dd, $J = 5.01$ Hz each, 2H), 4.91 (m, 1H), 5.41 (s, 1H), 6.10–7.05 (m, 4H). (M^+H) 354. Entry **3f**, ^{1}H NMR (300 MHz, CD_3OD): δ 3.33 (d, $J = 3.63$ Hz, 2H), 4.93 (t, $J = 4.65$ Hz, 1H), 5.81 (s, 1H), 6.92–7.02 (m, 4H), 7.23–7.33 (m, 3H), 7.77 (d, $J = 6.99$ Hz, 2H). (M^+H) 374. Entry **3g**, ^{1}H NMR (300 MHz, CD_3OD): δ 3.32 (d, $J = 3.72$ Hz, 2H), 4.93 (t, $J = 3.84$ Hz, 1H), 5.81 (s, 1H), 6.93–7.01 (m, 4H), 7.30 (d, $J = 6.72$ Hz, 2H), 7.66 (d, $J = 6.66$ Hz, 2H). (M^+H) 408. Entry **3h**, ^{1}H NMR (300 MHz, CD_3OD): δ 3.31 (d, $J = 3.60$ Hz, 2H), 3.73 (s, 3H), 4.92 (t, $J = 4.00$ Hz, 1H), 5.73 (s, 1H), 6.85–7.01 (m, 6H), 7.60 (d, $J = 8.70$ Hz, 2H). (M^+H) 404. Entry **3i**, ^{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 **3j**, ^{1}H NMR (300 MHz, CD_3OD): δ 0.97 (dd, $J = 6.69$ and 9.09 Hz, 6H), 1.96 (m, 1H), 2.13 (m, 2H), 4.73 (t, $J = 6.93$ Hz, 1H), 6.12 (s, 1H), 7.53 (d, $J = 8.38$ Hz, 1H), 7.69 (d, $J = 6.37$ Hz, 1H), 7.94 (s, 1H). (M^+H) 325. Entry **3k**, ^{1}H NMR (300 MHz, CD_3OD): δ 1.33 (s, 9H), 3.32 (m, 2H), 4.79 (m, 1H), 5.37 (s, 1H), 6.96–7.12 (m, 5H). (M^+H) 270. Entry **3l**, ^{1}H NMR (300 MHz, CD_3OD): δ 3.21 (m, 2H), 4.95 (m, 1H), 5.80 (s, 1H), 6.90–7.32 (m, 10H). (M^+H) 290. Entry **3m**, ^{1}H NMR (300 MHz, CD_3OD): δ 2.26 (m, 2H), 2.52 (m, 2H), 3.69 (s, 2H), 3.81 (s, 2H), 4.55 (t, $J = 5.31$ Hz, 1H), 7.06–7.16 (m, 5H). (M^+H) 286. Entry **3n**, ^{1}H NMR (300 MHz, CD_3OD): δ 3.27 (d, $J = 3.80$ Hz, 2H), 3.37 (s, 2H), 3.43 (s, 2H), 4.86 (t, $J = 4.21$ Hz, 1H), 6.99 (br s, 4H). (M^+H) 356.