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common precursor<sup>†</sup>

Tuneable radical cyclisations: a tin-free approach towards tricyclic and spirocyclic heterocycles *via* a

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A novel common precursor approach towards both tricyclic and spirocyclic heterocycles is described. Cyclisations are based on thiyl radical/isocyanide methodology and avoid the use of tin.

Tricyclic heterocycles and their related spirocyclic congeners are attractive synthetic targets due to their occurrence in natural products and their frequent use as therapeutics.1 Nearly all members of these two distinct chemical series possess potent and widely differing biological activities and have attracted significant attention from both synthetic and medicinal chemists.1 In particular, martinelline 1 and martinellic acid 2 - isolated from the roots of Martinella iquitosensis, have featured frequently in the literature, due to their unique occurrence in nature and their antibiotic/antagonistic activity towards several G-protein coupled receptors (GPCR) systems including bradykinin and muscarinic receptors.<sup>2</sup> Amongst the non-natural product based compounds, the related tricyclic molecule - NVP-BEZ235 3, which is a dual inhibitor of PI3K/mTor pathway serves to highlight the anticancer potential of this class of compound.3 Related to their tricyclic counterparts, the spirooxindole heterocycles have also attracted significant attention, not least due to their structural complexity. This ranges from simple members such as horsfiline 4 and coerulescine 5,4 through to more substituted derivatives such as alstonisine 6 and spirotryprostatin A 7.5,6 There have been a significant number of synthetic efforts directed towards 7 and related derivatives due to its potent antinioplastic activity via inhibition of the cell cycle (Fig. 1).6

There have been several approaches to both these classes of compound using radical methodology as a result of the mild flexible and predictable conditions that can be used, preventing the need for protection/deprotection steps.<sup>7</sup> In particular

Takeda et al. have reported an attractive radical route to the core structure of Martinelline,7 whilst Beckwith and Storey have developed a route towards oxindoles via hydrogen atom abstraction using tributyltin hydride.8 Despite the large number of reports towards both classes of compound, many rely upon the use of organo-tin hydride reagents as a way of mediating these processes.7,8 An alternative method for the formation of nitrogen heterocycles that avoids the use of tin involves the addition of thiyl radicals to isocyanides, generating  $\alpha$ -imidoyl radicals which can undergo cyclisation onto a pendant alkene/ alkyne.9 However, there is no approach that allows for the synthesis of both chemical classes commencing from a common precursor. We now wish to disclose a novel tuneable approach to both tricyclic and spirocyclic heterocycles that is able to select for both classes via simple modification of the reaction conditions. The disconnection sequence towards both the pyrrologuinoline core 8 and the spirocyclic structure 9 from reaction of the precursor 11 is shown in detail (Scheme 1).

We envisaged that under suitable reaction conditions the intermediate  $\alpha$ -imidoyl radical derived from addition of a thiyl radical to the isocyanide **11**, would undergo either 6-*endo* or 5-*exo* cyclisation to generate either the tricyclic core **8**, or the spirocyclic structure **9** respectively. Our approach was inspired







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Scheme 1 Disconnection of the tricyclic and spirocyclic cores.

by the reports of Saegusa, Fukuyama and Rainier who had demonstrated precedent for 5-*exo* cyclisation, but there was limited evidence for successful obtention of the product of 6-*endo* cyclisation.<sup>9,10</sup> The synthesis of the cyclisation precursor **11** commenced with iodination of methyl-4-aminobenzoate **12** to give the palladium coupling precursor **13** in 80% yield.<sup>11</sup> Use of Suzuki–Miyaura conditions for the formation of amine **15** proved problematic with commercially available *N*-Boc-pyrrole-2-boronic acid **14**. However, switching to the use of freshly prepared **14** following the procedure of Martina,<sup>12</sup> amine **15** was obtained in 82% yield. Subsequent formylation with formic acetic anhydride,<sup>13</sup> followed by dehydration with phosphorus oxychloride and diisopropylamine proceeded smoothly, resulting in isocyanide **11** in 79% yield (Scheme 2).<sup>14</sup>

With the cyclisation precursor **11** in hand, investigation of a range of conditions were explored in order to select for either 6-*endo* or 5-*exo* cyclisation in a thermodynamic or kinetic manner respectively and the results are outlined below (Table 1).

Evaluation of the effects of reaction concentration (Table 1, entries 1–3) on the ratio of 8 and 9, showed that only the 6-*endo* product 8 was formed at higher concentrations, but under more dilute conditions (entries 3–4), the ratio of 8 : 9 changed to a more favorable 11 : 89 ratio of the two products. At this point, it was evident that the reaction was tunable and either the product of 5-*exo* or 6-*endo* addition could be readily selected. Simple variation of the amount of AIBN (Table 1, entries 4–8), whilst the amount of thiophenol and the reaction concentration were kept constant also insinuated that the radical cyclisation could be tuned easily. The kinetic 5-*exo* spirocycle was favoured at higher concentrations of AIBN, suggesting that the cyclised product is



Scheme 2 Synthesis of common cyclisation precursor 11.

Table 1 Optimisation of reaction conditions for obtention of both tricyclic and spirocyclic heterocycles 8 and 9 respectively<sup>a</sup>



Entry	Concentration (M)	AIBN (equiv.)	PhSH (equiv.)	Product ratio	
				6-endo ( <b>8</b> )	5-exo (9)
1	0.2	0.3	5	100	0
2	0.1	0.3	5	100	0
3	0.05	0.3	5	56	44
4	0.03	0.3	5	11	89
5	0.05	0.5	5	48	52
6	0.05	0.1	5	100	0
7	0.05	1.0	5	42	58
8	0.05	1.5	5	13	87
9	0.05	1.5	50	0	100
10	0.05	0.1	50	94	6

<sup>*a*</sup> Ratios of **8** and **9** were determined from the <sup>1</sup>H-NMR spectrum of the crude reaction mixture. All reactions were carried out at 80 °C in toluene for 2 hours by direct addition of reagents.

rapidly trapped and that the reaction itself is reversible. However, when the concentration of AIBN is low, the rate of cyclisation and subsequent reduction is slow and accordingly, the more stable thermodynamic 6-*endo* product predominates. To confirm the effects of the equivalents of AIBN on the reaction outcome, a large excess of thiophenol was used whilst varying the amount of AIBN (Table 1, entries 9 and 10). There was little difference on the reaction outcome when 50 equivalents of thiophenol were used, with selectivity easily tuned for either 5-*exo* or 6-*endo* addition.

With confirmation that the equivalents of AIBN and reaction concentration were critical, the reaction was carried out on a larger scale to fully isolate and characterise both products. As predicted, the tricyclic heterocycle **8** was obtained in 62% isolated yield when the reaction was carried out with 0.1 equivalents of AIBN. On repeating the reaction, but with conditions tuned for the synthesis of the spirocyclic product, compound **9** was isolated in 47% yield. A second product – **17** was also observed following purification, which corresponded to the double bond isomer, in 18% yield, from the parent compound **9**. On contact with silica, the double bond undergoes a 1,3-hydride shift to give **17** and both products in a combined yield of 64% (Scheme 3).

In summary, we have developed a novel approach towards the synthesis of pyrroloquinoline and spirocyclic heterocycles using tin-free radical methodology, starting from a common precursor. This short flexible reaction sequence will provide a rapid approach to structurally diverse compounds of significant interest and the application of this methodology is currently under active investigation using other heterocyclic motifs. Examination of their corresponding biological effects and the results obtained will be reported in due course.



Scheme 3 Selection for 6-endo or 5-exo cyclisation.

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## Notes and references

- (a) A. I. S. Almeida, A. M. S. Silva and J. A. S. Cavaleiro, Synlett, 2011, 2955; (b) Y. Hamada, Chem. Pharm. Bull., 2012, 60, 1; (c) H. Benakki, E. Colacino, C. André, F. Guenoun, J. Martinez and F. Lamaty, Tetrahedron, 2008, 64, 5949; (d) M. Nyerges, Heterocycles, 2004, 63, 1685; (e) M. L. Testa, L. Lamartina and F. Mingoia, Tetrahedron, 2004, 60, 5873; (f) T. Stalling and J. Martens, Synthesis, 2013, 355; (g) Q. Zhang, M. Ding, Z. Cao, J. Zhang, F. Ding and K. Ke, Neurochem. Res., 2013, 38, 1661; (h) T. Li, H. Yin, C. Yao, X. Wang, B. Jiang, S. Tu and G. Li, Chem. Commun., 2012, 48, 11996; (i) C. Marti and E. M. Carreira, Eur. J. Org. Chem., 2003, 2209.
- 2 (a) K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger and S. L. Varga, J. Am. Chem. Soc., 1995, 117, 6682; (b) M. K. Gurjar, S. Pal and A. V. R. Rao, Heterocycles, 1997, 45, 231; (c) B. B. Snider, Y. Ahn and B. M. Foxman, Tetrahedron Lett., 1999, 40, 3339; (d) C. J. Lovely and H. Mahmud, Tetrahedron Lett., 1999, 40, 2079; (e) O. Hara, K. Sugimoto and Y. Hamada, Tetrahedron, 2004, 60, 9381; (f) R. Le Goff, A. M. Lawson, A. Daïch and S. Comesse, Org. Biomol. Chem., 2013, 11, 1818; (g) M. Hadden, M. Nieuwenhuyzen, D. Osborne, P. J. Stevenson, N. Thompson and A. D. Walker, Tetrahedron, 2006, 62, 3977; (h) C. Xia, L. Heng and D. Ma, Tetrahedron Lett., 2002, 43, 9405.
- 3 F. D. R. Stauffer, S.-M. Maira, et al., Bioorg. Med. Chem. Lett., 2008, 18, 1027.
- 4 (a) S. Hong, M. Jung, Y. Park, M. W. Ha, C. Park, M. lee and H. Park, *Chem.-Eur. J.*, 2013, **19**, 9599; (b) E. Rajanarendar, S. Ramakrishna, K. G. Reddy, D. Nagaraju and Y. N. Reddy, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3954; (c) Y. Arun,

G. Bhaskar, C. Balachandran, S. Ignacimuthu and P. T. Perumal, *Bioorg. Med. Chem. Lett.*, 2013, 23, 1839; (d) J. A. Murphy, R. Tripoli, T. A. Khan and U. W. Mali, *Org. Lett.*, 2005, 7, 3287; (e) M. Görmen, R. Le Goff, A. M. Lawson, A. Daïch and S. Comesse, *Tetrahedron Lett.*, 2013, 54, 2174; (f) A. Jossang, P. Jossang, H. A. Hadi, T. Sévenet and B. Bodo, *J. Org. Chem.*, 1991, 56, 6527; (g) N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, I. Vit and R. I. Willing, *Phytochemistry*, 1998, 48, 437; (h) S. Bascop, J. Sapi, J. Laronze and J. Lévy, *Heterocycles*, 1994, 38, 725.

- 5 J. Yang, X. Z. Wearing, P. W. Le Quesne, J. R. Deschamps and J. M. Cook, *J. Nat. Prod.*, 2008, **71**, 1431.
- 6 (a) C. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, 52, 12651; (b) A. P. Antonchick, H. Schuster, H. Bruss, M. Schürmann, H. Preut, D. Rauh and H. Waldmann, *Tetrahedron*, 2011, 67, 10195; (c) M. Cheng, H. Wang and L. Gong, *Org. Lett.*, 2011, 13, 2418; (d) F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.*, 2004, 6, 4249; (e) T. Onishi, P. R. Sebahar and R. M. Williams, *Tetrahedron*, 2004, 60, 9503; (f) S. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino and N. Rosan, *J. Am. Chem. Soc.*, 1999, 121, 2147.
- 7 (a) S. T. Hilton, T. C. T. Ho, G. Pljevaljcic and K. Jones, Org. Lett., 2000, 2, 2639; (b) C. Escolano and K. Jones, Tetrahedron, 2002, 58, 1453; (c) O. Miyata, A. Shirai, S. Yoshino, T. Nakabayashi, Y. Takeda, T. Kiguchi, D. Fukumoto, M. Ueda and T. Naito, Tetrahedron, 2007, 63, 10092; (d) T. Naito, Pure Appl. Chem., 2008, 80, 717; (e) T. C. T. Ho and K. Jones, Tetrahedron, 1997, 53, 8287.
- 8 A. L. J. Beckwith and J. M. D. Storey, *J. Chem. Soc., Chem. Commun.*, 1995, 977.
- 9 (a) J. D. Rainier and A. R. Kennedy, J. Org. Chem., 2000, 65, 6213; (b) D. Nanni, G. Calestani, R. Leardini and G. Zanardi, Eur. J. Org. Chem., 2000, 707; (c) M. D. Bachi, A. Balanov and N. Bar-Ner, J. Org. Chem., 1994, 59, 7752; (d) K. C. Majumdar and P. Debnath, Tetrahedron, 2008, 64, 9799; (e) M. Lamberto and J. D. Kilburn, Tetrahedron Lett., 2008, 49, 6364; (f) M. Lamberto, D. F. Corbett and J. D. Kilburn, Tetrahedron Lett., 2004, 45, 8541.
- 10 (a) T. Fukuyama and G. Liu, *Pure Appl. Chem.*, 1997, **69**, 501;
  (b) H. Tokuyama, M. Watanabe, Y. Hayashi, T. Kurokawa,
  G. Peng and T. Fukuyama, *Synlett*, 2001, 1403; (c)
  T. Saegusa, S. Kobayashi and Y. Ito, *J. Org. Chem.*, 1970, 35, 2118.
- 11 A. G. Arvanitis, P. J. Gilligan, et al., J. Med. Chem., 1999, 42, 805.
- 12 S. Martina, V. Enkelmann, G. Wegner and A. Schlüter, *Synthesis*, 1991, 613.
- 13 T. G. Back, M. Parveez and J. E. Wulff, *J. Org. Chem.*, 2003, **68**, 2223.
- 14 R. Obrecht, R. Hermann and I. Ugi, Synthesis, 1985, 400.