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A novel entry into 1-methyl- and 1-aryl-octahydropyrrolo[3,4-*b*]pyrroles and their N-1–C-2 fused derivatives: stereoselective synthesis via an intramolecular azomethine ylide cycloaddition reaction

Mahalingam Poornachandran and Raghavachary Raghunathan*

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India

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Abstract—Synthesis of some novel pyrrolo[3,4-*b*]pyrrole derivatives has been accomplished in good yields by the intramolecular azomethine ylide cycloaddition reaction of a strategically situated unactivated alkenyl aldehyde with various secondary amino acids. A cis fused cycloadduct was formed in all cases.

The synthesis of polysubstituted and fused pyrrolidines, pyrrolizidines, indazolidines, pyranoquinolines and pyrrolo β-carboline ring systems has received synthetic chemists' attention over the years since these heterocycles form the structural subunits of biologically important alkaloids[1] and pharmaceutically important compounds.[2] Specifically, pyrrolo[3,4-*b*]pyrrole and its derivatives are used as adenosine kinase inhibitors[3] and serve as prime intermediates in the synthesis of 4-quinolone carboxylic acid and uracil-based antibacterials, which selectively inhibit DNA polymerase III C and type II bacterial topoisomerase.[4]

The wide range of bioactivities of these systems prompted us to devise a synthetic route to these heterocycles. In considering possible synthetic schemes, we decided that a [3+2] cycloaddition reaction would afford the most concise approach. A review of inter- and intramolecular versions of azomethine ylide cycloaddition revealed the versatility of intramolecular [3+2] cycloaddition for the synthesis of complex molecules.[5] The intramolecular [3+2] mode of cycloaddition has resulted in elegant syntheses of stereochemically defined heterocycles[6,7] since it is capable of annulating a proline moiety with high regio- and stereocontrol to even unactivated internal olefins, which do not react intermolecularly.[8] This powerful methodology has been extensively applied for the synthesis of complex molecules including heterocycles with removable and fixed chiral auxiliaries.[9–11] Though the intramolecular cycloaddition of azomethine ylides generated by the decarboxylative condensation of amino acids with strategically positioned alkenyl aldehydes and alkynyl aldehydes has been studied in several systems, to the best of our knowledge there has been no report on the cycloaddition of a simple *N*-tethered alkenyl aldehyde with acyclic or cyclic amino acids resulting in the formation of pyrrolo[3,4-*b*]pyrroles. Hence, herein we report our synthetic approach for the convergent synthesis of 1-methyl, 1-aryl-octahydro-5-tosylpyrrolo[3,4-*b*]pyrrole and its N-1–C-2 fused analogues.

The requisite olefinic aldehyde **5** was synthesized in four steps in excellent yield. Tosylation of allylamine **1** under standard reaction conditions gave sulfonamide **2** which was treated with ethyl bromo-/chloroacetate to afford *N*-allyl-*N*-(ethoxycarbonylmethyl)toluene-4-sulfonamide **3** in 85% yield. Reduction of the ester with LAH gave alcohol **4**. The oxidation of **4** to **5** with routine oxidizing agents like PCC, PDC, active MnO_2 and Cr_2O_3 under different reaction conditions did not give the expected results. However, the oxidation could be accomplished

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* Corresponding author. Tel.: +91 44 24746655; fax: +91 44 22352494; e-mail: ragharaghunathan@yahoo.com

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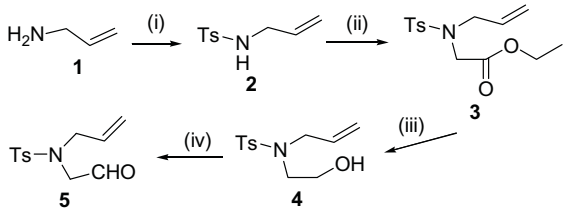


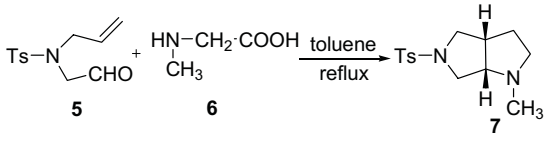
Scheme 1. Reagents and conditions: (i) TBAF, 10% NaOH/benzene, tosyl chloride, 0 °C–rt; 8 h, 90%; (ii) ethyl bromo-/chloroacetate, K_2CO_3/acetone, 5 h, 85%; (iii) $LiAlH_4$/THF, 65 °C, 4 h, 90%; (iv) iodoxybenzoic acid, DMSO, 4 h, 94%.

successfully with iodoxybenzoic acid (IBX) in DMSO to yield the key aldehyde **5**, *N*-allyl-*N*-(2-oxo-ethyl)toluene-4-sulfonamide in excellent yield. Though a synthetic pathway for the aldehyde **5** was reported in the literature,[12] the present reaction protocol is advantageous since it gives the key aldehyde in excellent overall yield (Scheme 1).

With aldehydes **5** in hand, the cycloaddition reactions were carried out with the formation of unstabilized azomethine ylides generated by decarboxylative condensation with various secondary amino acids.[13–16] Condensation of **5** with sarcosine **6** in refluxing toluene under Dean–Stark reaction conditions, generated the azomethine ylide which cyclized to yield the cis adduct, 1-methyl-octahydro-5-tosylpyrrolo[3-4-*b*]pyrrole, **7** as a brownish oil in 78% yield in 3 h (Scheme 2) (Table 1, entry 1).

The same reaction was carried out with various *N*-aryl glycines **8a–e** to obtain cis fused cycloadducts **9a–e** in good yields (Scheme 3) (Table 1, entries 2–6). Among the solvents used, toluene was found to be the best.

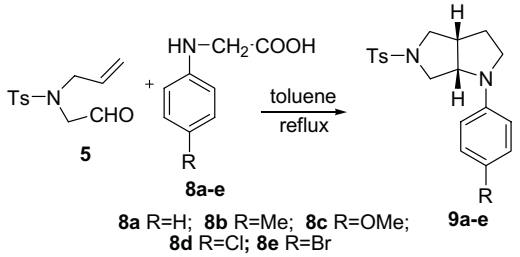
The assignment of cis stereochemistry to the ring junctions of all cycloadducts was initially made by analogy



Scheme 2.

Table 1. Intramolecular azomethine cycloadditions of compound **5** with secondary amino acids

Entry	Amino acid	Time (h)	Product	Yield (%)
1	**6**	3	**7**	78
2	**8a**	4	**9a**	76
3	**8b**	3	**9b**	79
4	**8c**	2.5	**9c**	81
5	**8d**	2	**9d**	80
6	**8e**	3.5	**9e**	79
7	**10a**	4	**11a**	83
8	**10b**	5	**11b**	74
9	**12**	3	**13**	68
10	**14**	3.5	**15**	65



Scheme 3.

with the stereochemistry observed for conventional azomethine ylide cycloaddition in similar systems.[10,17] The stereochemistry of a representative bicyclic compound **9e**,[18] was determined on the basis of ^{1}H NMR-COSY experiments. The coupling constant between H-3a and H-6a was 2.4 Hz, which is consistent only with a cis ring fusion. The stereochemistry of the cycloadduct **9e**, was further unambiguously corroborated by an X-ray crystallographic analysis (Fig. 1).[19]

In order to extend the scope of this reaction to the synthesis of N-1–C-2 fused derivatives of pyrrolo[3,4-*b*]-pyrroles, the alkenyl aldehyde **5** was reacted with proline **10a** and thiaproline **10b** to afford the tricyclic

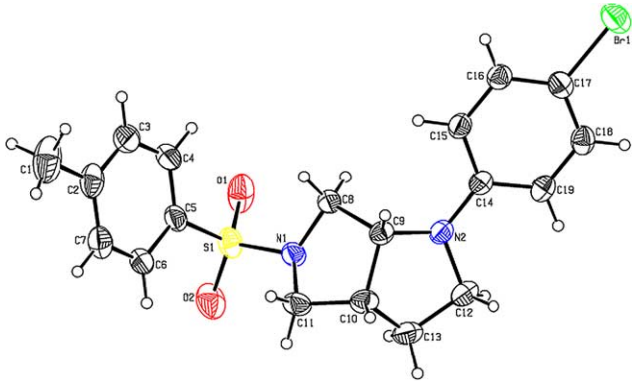
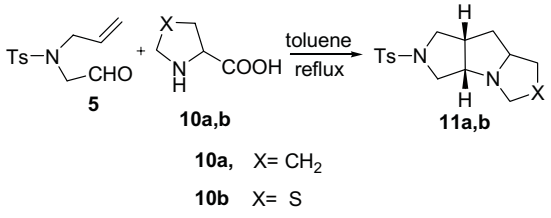
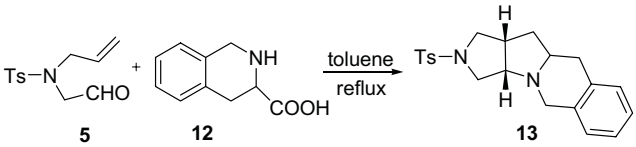


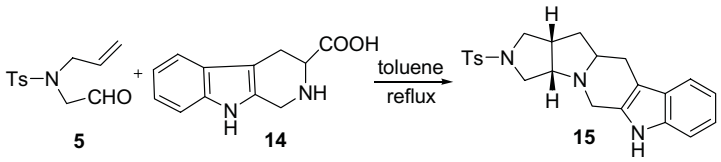
Figure 1. X-ray crystal structure of compound **9e**.



Scheme 4.



Scheme 5.



Scheme 6.

compounds **11a**,**b** in good yields (Scheme 4) (Table 1, entries 7 and 8).

Pyrido[3,4-*b*]indoles have been proved to be depressants of the central nervous system[20] and potent antiulcer agents.[21] In anticipation of enhancing bioactivity, we have synthesized pyrrolo[3,4-*b*]pyrroles **13**, **15** fused with tetrahydroisoquinoline and tetrahydropyridoindole units by the reaction of **5** with 1,2,3,4-tetrahydro isoquinoline-2-carboxylic acid **12** and 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **14** (Schemes 5 and 6) (Table 1, entries 9 and 10). In all cases, the cycloaddition took place in a cis fashion on the basis of 2D NMR experiments, where the coupling constants of hydrogen atoms on the ring junctions corresponded closely to those of **9e**.

In conclusion, we have accomplished the synthesis of some novel pyrrolo[3,4-*b*]pyrrole derivatives of biological interest with high stereoselectivity by tandem ylide generation followed by intramolecular trapping by an *N*-tethered alkenyl group. Further work is in progress for the screening of the biological activities of the synthesized molecules and the synthesis of bis-pyrrolo[3,4-*b*]pyrrole derivatives.

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References and notes

1. (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1999; Vol. 13, pp 1–161; (b) Daly, J. W. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, pp 141–169; (c) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, p 183; (d) Wrobel, J. T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 327; (e) Takahata, A.; Momose, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, p 189; (f) Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413–418; (g) Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187–193; (h) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 535–552.
2. (a) Patvardhan, S. P.; Joshi, K. S.; Vadlamudi, R. V. S. V.; Desphande, S. G. *Ind. J. Pharm. Sci.* **1998**, *60*, 384–387; (b) Gupta, P.; Butler, P.; Shepperson, N. B.; McHarg, A. *Eur. J. Pharmacol.* **2000**, *398*, 73–81; (c) Sternsfeld, F.; Guibin, A. R.; Jelly, R. A.; Matassa, V. G.; Reeve, A. J.; Hunt, P. A.; Beer, M. S.; Heald, A.; Stanton, J. A.; Sohal, B.; Watt, A. P.; Street, L. J. *J. Med. Chem.* **1999**, *42*, 677–690.
3. Bauser, M.; Delapierre, G.; Hauswald, M.; Flessner, T.; D'Urso, D.; Hermann, A.; Beyreuther, B.; De Vry, J.; Spreyer, P.; Reissmuller, E.; Meier, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1997–2000.
4. Petersen, U.; Schenke, T.; Krebs, A.; Grohe, K.; Scheriewer, M.; Haller, I.; Mezger, K. G.; Endermann, R.; Zeiler, H. J. U.S. Patent, 5,416,096, 1996; *Chem. Abstr.* **1996**, *124*, 289280c.
5. For some recent examples, see: (a) Vedejs, E.; Piotrowski, D. W.; Tucci, F. C. *J. Org. Chem.* **2000**, *65*, 5498–5505; (b) Pandey, G.; Sahoo, A. K.; Bagul, T. D. *Org. Lett.* **2000**, *2*, 2299–2301; (c) Vedejs, E.; Klapers, A.; Naidu, B. N.; Piotrowski, D. W.; Tucci, F. C. *J. Am. Chem. Soc.* **2000**, *122*, 5401–5402; (d) Coldham, I.; Crapnell, K. M.; Moseley, J. D.; Rabot, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1758–1763; (e) Novikov, M. S.; Khlebnikov, A. F.; Besidina, O. V.; Kastikov, R. R. *Tetrahedron Lett.* **2001**, *42*, 533–535.
6. (a) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123–180; (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10–23.
7. Jacobi, P. A.; Martinelli, M. J.; Polane, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594–5598.
8. (a) Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1983**, *48*, 2994–2997; (b) Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175–7178; (c) Mahmud, H.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2001**, *57*, 4095–4105; (d) Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554–1555; (e) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309–2315.
9. Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 452–456, and references cited therein.
10. Russel, M. G. N.; Beer, M. S.; Stanton, J. A.; Sohal, B.; Mortishire Smith, R. J.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2491–2496.
11. Pedrosa, R.; Andrés, C.; Heras, L.; Nieto, J. *Org. Lett.* **2002**, *4*, 2513–2516, and references cited therein.
12. Suritami, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709–2711.
13. (a) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 47–49; (b) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49–51; (c) Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin. Trans. 1* **1988**, 2703–2713.
14. For examples, of intramolecular 1,3-dipolar cycloadditions of azomethine ylides generated by the decarboxylation, see: (a) Grigg, R.; Savic, V.; Thronton-Pett, M. *Tetrahedron* **1997**, *53*, 10633–10642; (b) Harling, J. D.; Orlek, B. S. *Tetrahedron* **1998**, *54*, 14905–14912; (c) Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett.* **1999**, *40*, 3339–3342; (d) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217–4220.

15. Nyerges, M.; Balázs, L.; Kádas, I.; Bitter, I.; Kövesdhi, I.; Töke, L. *Tetrahedron* **1995**, *51*, 6783–6788.
16. (a) Manikandan, S.; Raghunathan, R. *Synth. Commun.* **2002**, *32*, 3587–3594; (b) Amalraj, A.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 10293–10298; (c) Subramaiyan, G.; Raghunathan, R.; Nethaji, M. *Tetrahedron* **2002**, *58*, 9075–9079.
17. (a) Armstrong, P.; Grigg, R.; Jordan, M. W.; Malone, J. F. *Tetrahedron* **1985**, *41*, 3547–3558; (b) Grigg, R.; Duffy, L. M.; Dorrity, M. J.; Malone, J. F.; Rajviroongit, S.; Thornton-Pett, M. *Tetrahedron* **1990**, *46*, 2213–2230.
18. All new compounds were characterized by spectroscopic data. A typical experimental procedure for the synthesis and characterization of cycloadduct **9e**: A mixture of 2.0 mmol of *N*-allyl-*N*-(2-oxo-ethyl)toluene-4-sulfonamide **5**, 3.0 mmol of *N*-(*p*-bromo)phenyl glycine **8e** in 30 mL of dry toluene was refluxed under Dean–Stark conditions till the completion of the reaction (3.5 h). The reaction mixture was then concentrated under reduced pressure. The concentrate was then extracted with dichloromethane (2×20 mL) and water (2×20 mL). The organic layer was washed with brine solution (2×20 mL), dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was then subjected to column chromatography (silica gel, 100–200 mesh) with hexane–ethyl acetate (8:2) to obtain the cycloadduct **9e**, 1-(4-bromophenyl)-octahydro-5-pyrrolo[3,4-*b*]pyrrole.
White powder, 79% (0.33 g); mp: 210 °C IR (KBr): 1338, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (δ): 1.81–1.86 (m, 1H); 2.03–2.08 (m, 1H); 2.35 (s, 3H); 2.85–2.89 (m, 1H); 3.06–3.14 (m, 4H); 3.20–3.29 (m, 2H); 3.92–3.96 (dt, 1H, $J_1 = 2.4$, $J_2 = 6.8$ Hz); 6.21–6.24 (d, 2H, $J = 9.1$ Hz); 7.18–7.22 (m, 4H); 7.55–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.54, 29.54, 42.36, 48.30, 52.42, 53.10, 62.57, 108.90, 114.14, 127.84. *m*/*z*, M^+ 421.60 (25%). Anal. Calcd for $C_{19}H_{21}N_2O_2SBr$; C, 54.16; H, 5.02; N, 6.64. Found: C, 54.28; H, 5.12; N, 6.54. The spectral data of all other cycloadducts were consistent with their structures.
19. Selvanayagam, S.; Velmurugan, D.; Ravikumar, K.; Poornachandran, M.; Raghunathan, R. *Acta Crystallogr.* **2005**, *E61*, 2493–2495.
20. Saxena, A. K.; Jain, P. C.; Anand, N. *J. Med. Chem.* **1973**, *16*, 560–564.
21. Tripathi, R. C.; Patnaik, G. K.; Saxena, A. K. *Indian J. Chem.* **1989**, *28B*, 333–337.