Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 829–832

A novel entry to dispiropyrrolo-bicyclo[2.2.1]heptanes through sequential 1,3-dipolar and Diels–Alder cycloaddition reactions

Rathna Durga R. S. Manian, Jayadevan Jayashankaran, S. Selva Kumar and Raghavachary Raghunathan*

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

Received 3 May 2005; revised 3 November 2005; accepted 11 November 2005
Available online 2 December 2005

Abstract—The synthesis of novel dispiroheterocycles containing a bicyclo[2.2.1]heptane ring system through sequential [3+2] and [4+2] cycloadditions is described.

The 1,3-dipolar cycloaddition reaction has long been an important reaction for the synthesis of five-membered heterocyclic compounds such as pyrrolidines, pyrrolines, and pyrroles.[1–3] The synthesis of functionalized pyrrolidine templates is a good entry point for the synthesis of peptidomimetic libraries.[4] Spiropyrrolidines have received considerable attention as a result of their biological activity, a number of which display interesting antimicrobial, antitumoral, and antibiotic properties. In addition, they also act as inhibitors of human NK-I receptor activity.[5]

The Diels–Alder reaction is a standard method for preparing six-membered ring derivatives, which are versatile building blocks for the synthesis of numerous natural products. The reaction is useful for the construction of carbocycles and heterocycles and allows the creation of two bonds simultaneously with a high level of regio- and stereoselectivity.[6,7] Furans have been used as electron-rich diene partners in the Diels–Alder reactions to prepare rigid oxygenated bicyclic systems en route to various natural products.

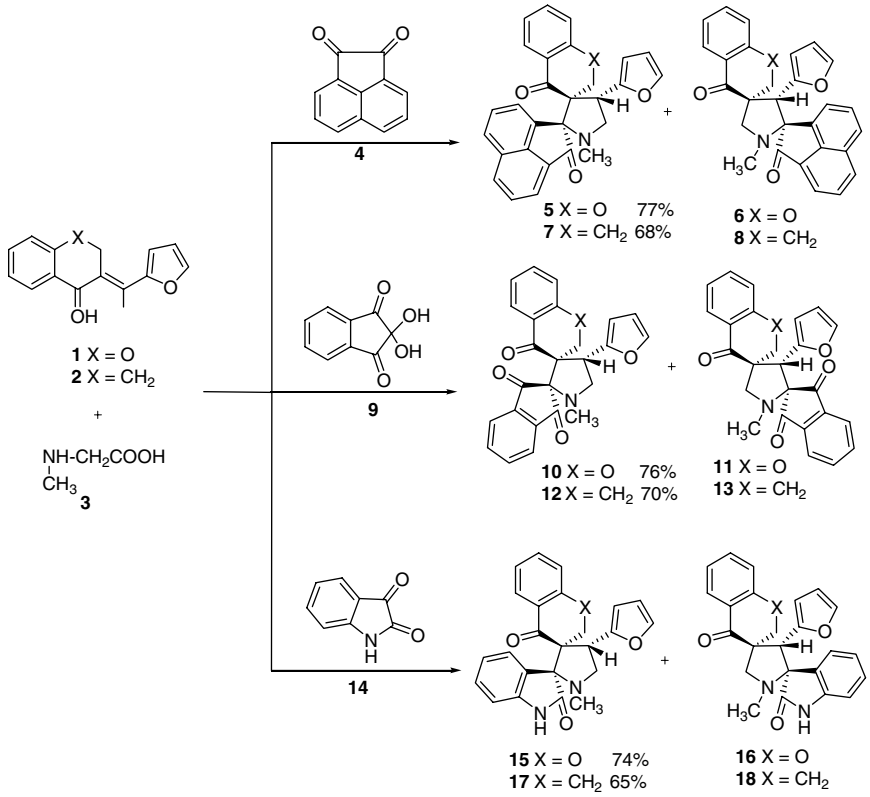
As part of our ongoing research program[8–10] directed toward the synthesis of complex nitrogen heterocycles using the versatile 1,3-dipole, we were interested in developing a route to spiropyrrolo-bicyclo[2.2.1]heptane derivatives via 1,3-dipolar and intermolecular Diels–Alder cycloaddition in a sequential manner.

In this letter, we describe the 1,3-dipolar cycloaddition of the azomethine ylide generated by reaction of the amino acid sarcosine with the ketones, isatin, ninhydrin, and acenaphthequinone, with (*E*)-3-furfurylidene-4-chromanone/(*E*)-2-furfurylidene-1-tetralone containing exocyclic double bond for our studies (Scheme 1). (*E*)-3-Furfurylidene-4-chromanone **1** and (*E*)-2-furfurylidene-1-tetralone **2** were prepared according to the literature report.[11,12] The azomethine ylide generated by the reaction of sarcosine with acenaphthaquinone in boiling aqueous methanol readily reacted with **2** to give a single regioisomer as evidenced by spectral analysis.[13] The reaction afforded novel dispiroheterocyclic 1′,2′,3′,4′-tetrahydro-1′-onespiro[2′.3]*N*-methyl-(4-furfuryl)pyrrolidinespiro[2.2″]acenaphthen-1″-one **7** in 68% yield containing acenaphthenone, chromanone, and furan ring systems by regio- and stereocontrolled cycloaddition. The structure and the regiochemistry of the product was confirmed by spectral[14] and X-ray diffraction studies.

The ^{1}H NMR spectrum of **7** showed multiplets in the region δ 1.63–2.34 for the tetralone ring protons. The NCH protons of the pyrrolidine ring demonstrated a doublet of doublets at δ 3.68 ($J = 8.8$, 10.7 Hz) and at δ 4.05 ($J = 9.8$, 10.7 Hz). The benzylic proton exhibited a doublet of doublets at δ 5.17 ($J = 8.8$, 9.8 Hz). If the

* Corresponding author. Tel.: +91 44 2351269x228; fax: +91 44 2352494; e-mail: ragharaghunathan@yahoo.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.089



Scheme 1.

other regioisomer **8** was formed then the ^{1}H NMR spectrum would give a singlet for the benzylic proton. This clearly demonstrates the regiochemistry of the reaction. The H_a and H_c protons of the furan moiety resonated as doublets at δ 6.42 ($J = 6.8$ Hz) and at δ 6.61 ($J = 2.9$ Hz), respectively. The H_b proton of the furan ring system showed a doublet of doublets at δ 6.53 ($J = 2.9$, 6.8 Hz). In the ^{13}C NMR spectrum of **7**, the signals at δ 196.5 and 207.9 ppm manifests the presence of tetralone and acenaphthequinone ring carbonyls, respectively. The IR spectrum of **7** showed two peaks corresponding to tetralone and acenaphthenequinone ring carbonyls at 1681.8 and 1705.0 cm^{-1}, respectively.

Also the structure of the product was confirmed through mass, spectral, and elemental analysis. The structure of the dispirocyclo adduct **7** was finally confirmed through X-ray diffraction studies (Fig. 1). Similar results were obtained with other spiropyrrolidine derivatives **5**, **10**, **12**, **15**, and **17** synthesized by the cycloaddition of the azomethine ylide generated from isatin, ninhydrin, and acenaphthequinone across the exocyclic double bond of (*E*)-3-furfurylidene-4-chromanone **1** and (*E*)-2-furfurylidene-1-tetralone **2**.

Having developed a simple and efficient synthetic route for the synthesis of spiropyrrolidine ring systems with furyl substituents, we turned our attention to explore the 4π system of furan being used as a diene in Diels–Alder reactions to yield bicyclo[2.2.1]heptane systems (Scheme 2).[15] Thus, dispiroheterocycles **5**, **7**, **10**, **12**, **15**, and **17**, when subjected to intermolecular Diels–Alder reactions with dimethylacetylene dicarboxylate (DMAD) in refluxing toluene for 12–15 h under a nitrogen atmosphere, underwent [4+2] cycloaddition readily to afford the corresponding bicyclo derivatives.

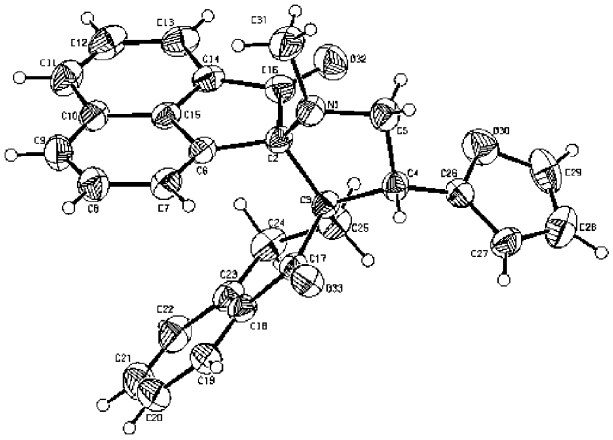
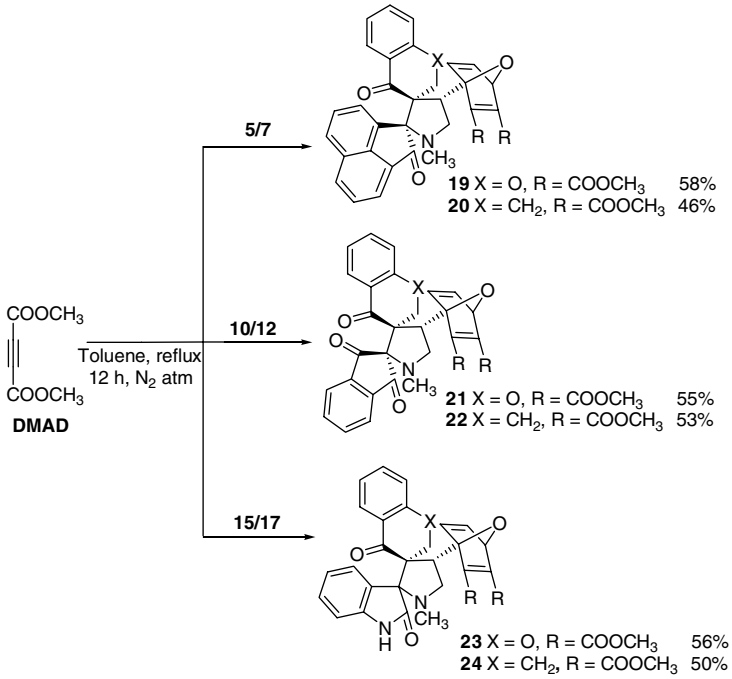


Figure 1. ORTEP diagram of **7**.

The reaction of the dispiroheterocycle **7** with DMAD in refluxing toluene gave the bicyclo derivative 1′,2′,3′,4′-tetrahydro-1′-onespiro[2′.3]-*N*-methyl-[4-(7-oxa-bicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid dimethyl ester)] pyrrolidinespiro[2.2″]acenaphthen-1″-one **20** in 46% yield. The structure of the bicyclo derivative **20** was



Scheme 2.

confirmed through spectral analysis. The ^{1}H NMR spectrum of **20** exhibited doublet of doublets at δ 3.54 ($J = 8.6$, 10.8 Hz) and δ 4.20 ($J = 9.7$, 10.8 Hz) for the protons of the pyrrolidine ring and a doublet of doublets at δ 5.09 ($J = 8.6$, 9.7 Hz) due to C-4 benzylic proton of the pyrrolidine moiety. The H_a and H_c protons of the bicyclo[2.2.1]heptane system resonated as doublets at δ 6.21 ($J = 5.0$ Hz) and at δ 6.60 ($J = 1.8$ Hz), respectively. The H_b proton showed a doublet of doublets at δ 6.42 ($J = 1.8$, 5.0 Hz). The ^{13}C NMR spectrum of **20** showed signals at δ 164.1, 189.8, and 205.6 ppm for the ester carbonyl, tetralone carbonyl, and acenaphthenone carbonyl groups, respectively. Similar results were obtained for the other bicyclo[2.2.1]heptane derivatives.[16]

In conclusion, this letter describes a simple and efficient synthetic approach to spiropyrrolo-bicyclo[2.2.1]heptanes. The synthetic route involves 1,3-dipolar cycloaddition reaction of the azomethine ylide generated from di- and tri-ketones and sarcosine with (*E*)-3-furfurylidene-4-chromanone and (*E*)-2-furfurylidene-1-tetralone in a regio- and stereocontrolled fashion followed by intermolecular Diels–Alder cycloaddition of the spiropyrrolidines obtained with dimethylacetylene dicarboxylate. This two-step synthetic sequence is very efficient and yielded the dispiro heterocyclic compounds in good yields.

Acknowledgements

We thank CSIR, New Delhi, for the financial support. R.D. and J.J. (SRF) thank CSIR, New Delhi, for fellowships.

References and notes

1. Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45, p 231.
2. Padwa, A. Intramolecular 1,3-Dipolar Cycloaddition. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991.
3. Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: London, 1993; Vol. 3, p 161.
4. (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869; (b) Dessimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651; (c) Guan, Y.; Green, M. A.; Bergstrom, D. E. *J. Comb. Chem.* **2000**, *2*, 297, and Refs. 2–9 cited therein; (d) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171; (e) Feng, Z.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1181.
5. (a) Okita, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 11143; (b) Rosenmond, P.; Hosseini-Merescht, M.; Bub, C. *Liebigs Ann. Chem.* **1994**, *2*, 151; (c) Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892.
6. (a) Oppolzer, W. Combining C–C Bonds. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, Chapter 4.1; (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1–120; (c) Hayashi, Y.; Jørgensen, K. A.; Kobayashi, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH, 2001, Chapters 1, 4, and 5.
7. (a) Willis, M. C. Enantioselective Cycloaddition Reactions. In *Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: UK, 2001, Chapter 8; (b) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction*; John Wiley and Sons: Chichester, UK, 2002; (c) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.
8. (a) Manikandan, S.; Shanmugasundaram, M.; Raghunathan, R.; Malar, E. J. P. *Heterocycles* **2000**, *53*, 579; (b) Manikandan, S.; Ashraf, M. M.; Raghunathan, R. *Synth. Commun.* **2001**, *31*, 3593; (c) Manikandan, S.; Raghunathan, R. *J. Chem. Res. (S)* **2001**, 424.

9. (a) Manikandan, S.; Jayashankaran, J.; Raghunathan, R. *Synth. Commun.* **2003**, *33*, 4059; (b) Subramaniyan, G.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 2909.
10. (a) Amalraj, A.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 10293; (b) Subramaniyan, G.; Raghunathan, R.; Martin Castro, A. M. *Synthesis* **2002**, 2440; (c) Jayashankaran, J.; Rathna Durga, R. S. M.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303.
11. Albercht, R.; Kessler, H. J.; Schroeder, E. *Bull. Groupe. Fr. Argiles* **1969**, *21*(1), 71–78; *Chem. Abstr.* **1970**, *76*, 59493.
12. Mitsui, S.; Senda, Y.; Saito, H. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 694.
13. **Representative procedure for the preparation of dispiropyrrolidine cycloadducts**: A solution of sarcosine (1 mmol), acenaphthaquinone/ninhydrin/isatin (1 mmol), and 3-furfurylidene-4-chromanone/2-furfurylidene-1-tetralone (1 mmol) were refluxed in aqueous methanol. Completion of the reaction was evidenced by TLC analysis. The solvent was then removed in vacuo and the crude subjected to column chromatography using petroleum ether–ethyl acetate as eluent.
14. **1′,2′,3′,4′-Tetrahydro-1′-onespiro[2′.3]-*N*-methyl-(4-furfuryl)-pyrrolidinespiro[2.2″]indane-1″,3″-one 12**: Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03–2.50 (m, 4H), 2.28 (s, 3H), 3.52 (dd, $J = 8.8$, 12.0 Hz, 1H), 3.78 (dd, $J = 9.3$, 12.0 Hz, 1H), 4.90 (dd, $J = 9.3$, 8.8 Hz, 1H), 5.88 (d, $J = 4.3$ Hz, $1H_a$), 6.11 (dd, $J = 2.9$, 4.3 Hz, $1H_b$), 6.18 (dd, $J = 2.9$ Hz, $1H_c$), 6.63–8.03 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 25.9, 35.7, 43.7, 55.3, 64.2, 80.7, 108.4, 110.4, 122.5, 122.8, 126.4, 127.8, 128.0, 132.7, 133.4, 135.5, 136.4, 140.9, 141.6, 141.7, 142.8, 196.0, 196.7, 200.4 ppm. Mass *m*/*z*: 411 (M^+). Anal. Calcd for $C_{26}H_{21}NO_4$: C, 75.91; H, 5.11; N, 3.41. Found: C, 76.21; H, 5.29; N, 3.20.
Chroman-4′-onespiro[3′.3]-*N*-methyl-(4-furfuryl)pyrrolidinespiro[2.3″]oxindole 15: Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.47 (d, $J = 12.2$ Hz, 1H), 3.69 (dd, $J = 7.8$, 9.0 Hz, 1H), 3.84 (dd, $J = 9.0$, 10.8 Hz, 1H), 4.50 (dd, $J = 10.8$, 7.8 Hz, 1H), 4.74 (d, $J = 12.2$ Hz, 1H), 6.36 (d, $J = 5.0$ Hz, $1H_a$), 6.59 (dd, $J = 5.0$, 2.6 Hz, $1H_b$), 6.62 (d, $J = 2.6$ Hz, 1H), 6.78–7.80 (m, 8H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.8, 42.0, 56.3, 61.4, 70.4, 74.3, 114.4, 115.1, 119.2, 120.8, 122.0, 123.4, 127.6, 127.5, 129.1, 129.8, 136.6, 141.6, 176.0, 192.0 ppm. Mass *m*/*z*: 400 (M^+). Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 72.00; H, 5.00; N, 7.00. Found: C, 72.29; H, 5.18; N, 6.85.
15. **Representative procedure for the preparation of spiropyrrolo-bicyclo[2.2.1]heptane cycloadducts**: A solution of dispiroheterocycle (1 mmol) obtained in the previous step was refluxed in toluene with dimethylacetylene dicarboxylate (1.2 mmol) under a nitrogen atmosphere until the completion of the reaction as evidenced by TLC analysis. The solvent was then removed in vacuo. The crude was then subjected to column chromatography using petroleum ether–ethyl acetate as eluent.
16. **1′,2′,3′,4′-Tetrahydro-1′-onespiro[2′.3]-*N*-methyl-[4-(7-oxa-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid dimethyl ester)]pyrrolidinespiro[2.2″]indane-1″,3″-one 22**: Yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03–2.32 (m, 4H), 2.20 (s, 3H), 3.60 (dd, $J = 8.8$, 11.0 Hz, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 3.74 (dd, $J = 9.8$, 11.0 Hz, 1H), 4.67 (dd, $J = 8.8$, 9.8 Hz, 1H), 6.49 (d, $J = 4.6$ Hz, $1H_a$), 6.55 (dd, $J = 2.3$, 4.6 Hz, $1H_b$), 6.70 (d, $J = 2.3$ Hz, $1H_c$), 6.75–8.05 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 26.1, 36.1, 44.5, 56.8, 58.9, 69.9, 70.6, 70.8, 71.0, 72.7, 112.1, 114.5, 115.8, 122.1, 124.8, 125.1, 126.1, 126.1, 126.7, 127.0, 127.4, 129.7, 137.1, 142.5, 162.8, 190.7, 200.0, 212.7 ppm. Mass *m*/*z*: 553 (M^+).
Chroman-4′-onespiro[3′.3]-*N*-methyl-[4-(7-oxa-bicyclo[2.2.1]-hepta-2,5-diene-2,3-dicarboxylic acid dimethyl ester)]pyrrolidinespiro[2.3″]oxindole 23: Yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H), 3.43 (d, $J = 12.2$ Hz, 1H), 3.74 (dd, $J = 7.8$, 8.8 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.99 (dd, $J = 8.8$, 10.7 Hz, 1H), 4.48 (dd, $J = 7.8$, 10.7 Hz, 1H), 4.60 (d, $J = 12.2$ Hz, 1H), 6.51 (d, $J = 4.8$ Hz, $1H_a$), 6.55 (dd, $J = 2.0$, 4.8 Hz, $1H_b$), 6.71 (d, $J = 2.0$ Hz, $1H_c$), 6.89–7.61 (m, 8H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.8, 45.6, 59.2, 59.6, 66.6, 68.1, 69.6, 71.7, 73.7, 116.5, 120.9, 21.1, 122.2, 125.9, 126.9, 127.6, 127.9, 128.7, 129.2, 135.1, 141.2, 160.9, 177.3, 191.6 ppm. Mass *m*/*z*: 542 (M^+).