Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6809–6813

Ultrasonic assisted-silica mediated [3+2] cycloaddition of azomethine ylides—a facile multicomponent one-pot synthesis of novel dispiroheterocycles

A. R. Suresh Babu and R. Raghunathan*

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

Received 18 April 2007; revised 4 July 2007; accepted 12 July 2007
Available online 21 July 2007

Abstract—An efficient synthesis of dispiro-oxindolopyrrolizidine and dispirooxindolothienopyrrole derivatives has been expediently accomplished via a one-pot, three-component 1,3-dipolar cycloaddition reaction. High regioselectivity was achieved on ultrasonication in the presence of silica as a catalyst. X-ray diffraction studies of one of the cycloadducts proved the structure and regiochemistry of the cycloaddition.
© 2007 Elsevier Ltd. All rights reserved.

In recent years multicomponent reactions[1] (MCR's) leading to interesting heterocyclic scaffolds have emerged as powerful tools for delivering the molecular diversity needed in combinatorial approaches for the synthesis of bioactive compounds and creating diverse chemical libraries of drug-like molecules for biological screening.[2] 1,3-Dipolar cycloaddition reactions are efficient methods for the construction of heterocyclic units in a highly regio- and stereoselective manner.[3] In particular, the chemistry of azomethine ylides has gained significance in recent years as it serves as an expedient route for the construction of nitrogen-containing five-membered heterocycles, which constitute the central skeleton of numerous natural products.[4] Amongst various aza heterocycles, functionalized pyrrolizidines are a class of alkaloids with significant biological activity.[5] Spiro compounds represent an important class of naturally occurring substances characterized by their pronounced biological properties,[6–12] including potent aldose reductase inhibitions and polio and rhinovirus 3C-proteinase inhibitions. Hence, we have used 1,3-dipolar cycloaddition reactions for their synthesis. However, such reactions can be slow due to poor mass transfer and require vigorous reaction conditions, expensive catalysts and often lead to mixtures of products with poor regio- and stereoselection. Ultrasonication is an important technique in organic synthesis and has a profound impact on the way chemists approach organic and parallel synthesis. Reductions in reaction times, improved yields and suppression of side products, relative to traditional thermal heating, are benefits of this technology.[13] Although 1,3-dipolar cycloaddition reactions carried out on a solid support[14] by microwave irradiation have proved to be beneficial in terms of regio- and stereoselectivity, only a few reports are available on the use of ultrasonic irradiation in 1,3-dipolar cycloaddition reactions.[15,16]

In continuation of our research in the area of 1,3-dipolar cycloadditions,[17–19] we herein report for the first time, the use of ultrasonic irradiation in a three-component, one-pot synthesis of novel dispiro-oxindolopyrrolizidines through reaction of the azomethine ylides generated from isatin/ninhydrin and L-proline with various unusual dipolarophiles.

The multicomponent reaction was carried out by ultrasonication of a mixture of 1 equiv of isatin **2** with 1 equiv of L-proline **3** or (*R*)-thiazolidine-4-carboxylic acid **6** in 20 mL of acetonitrile followed by the addition of 1 equiv of dipolarophile **1a–e** and 200 mg of silica (100–200 mesh). The mixture was stirred until completion of the reaction as evidenced by TLC (Table 1).

The reaction proceeds through decarboxylative condensation of isatin **2** with L-proline **4** or (*R*)-thiazolidine-4-carboxylic acid **6** to generate an azomethine ylide. The generated 1,3-dipole subsequently undergoes 1,3-dipolar

* Corresponding author. Tel.: +91 044 09444333883; e-mail: ragharaghunathan@yahoo.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.085

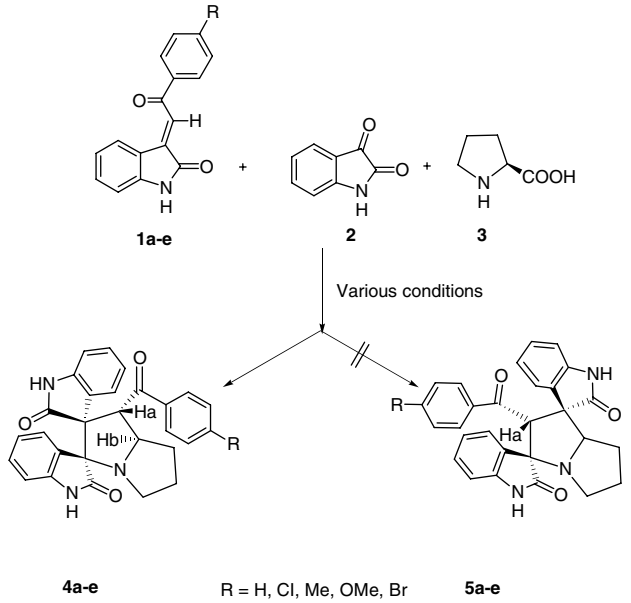
Table 1. Ultrasonic 1,3-dipolar cycloaddition reactions

Product	R	Method A		Method B		Method C		Method D	
		T (h)	*Y* (%)	*T* (h)	*Y* (%)	*T* (h)	*Y* (%)	*T* (h)	*Y* (%)
4a	H	8.1	45	3.2	79	2.9	83	3.0	87
4b	Cl	8.4	46	3.3	75	3.1	83	3.0	86
4c	Me	9.5	43	3.6	78	3.4	81	3.2	87
4d	OMe	9.5	42	3.6	79	3.4	84	3.2	87
4e	Br	9.3	48	3.0	85	2.7	88	2.8	92
7a	H	9.6	37	3.8	78	3.5	82	3.3	86
7b	Cl	8.8	47	3.1	77	2.9	84	2.9	88
7c	Me	8.9	45	3.2	76	2.8	81	3.0	85
7d	OMe	9.0	43	3.3	75	3.0	84	2.3	86
7e	Br	9.6	46	3.6	78	3.1	82	3.2	88
11a	H	8.7	42	3.0	75	2.7	81	2.8	86
11b	Cl	8.9	46	3.2	80	2.8	83	2.8	88
11c	Me	9.6	43	3.6	77	3.1	80	3.2	85
11d	OMe	9.6	35	3.7	80	3.3	85	3.2	87
11e	Br	9.8	30	4.0	76	3.4	80	3.7	85
13a	H	8.8	47	3.3	79	3.0	83	2.8	86
13b	Cl	9.0	46	3.6	77	3.1	85	3.0	87
13c	Me	8.9	40	3.8	74	3.2	80	3.3	85
13d	OMe	9.6	42	3.9	78	3.3	81	3.1	86
13e	Br	8.9	47	3.3	82	3.0	86	2.9	88

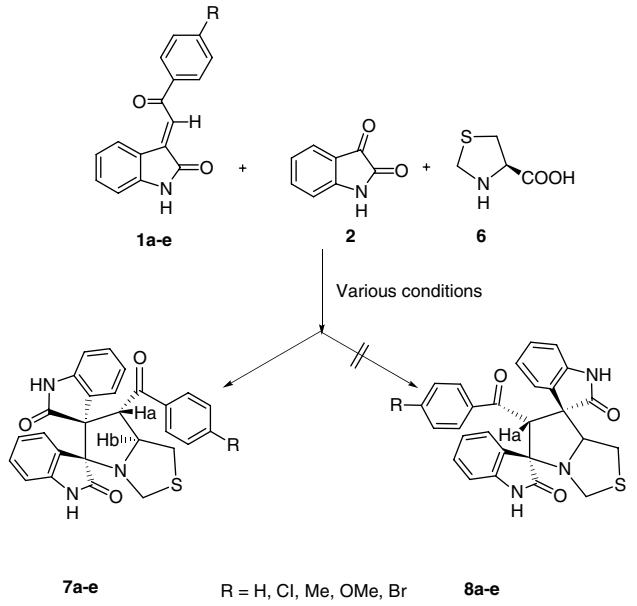
T (h) = time in hours; *Y* (%) = yield percent. Method A: methanol/ultrasonication. Method B: methanol–silica/ultrasonication. Method C: acetonitrile/ultrasonication. Method D: acetonitrile–silica/ultrasonication.

cycloaddition with the dipolarophile **1a**–**e** to afford novel dispiro-oxindolopyrrolizidines **4a**–**e** and **7a**–**e**, respectively (Schemes 1 and 2).

The products were characterized on the basis of their elemental analysis as well as IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The IR spectrum of **4a** showed peaks at 1710 and 1716 cm^{-1} due to the oxindole ring carbonyls whilst the benzoyl carbonyl appeared at 1678 cm^{-1}. In the ^{1}H NMR spectrum of **4a**, proton H_a appeared as a doublet at δ 5.34 ($J = 8.32$ Hz), which clearly showed the regiochemistry of the cycloaddition reaction. If the other possible regio-



Scheme 1.



Scheme 2.

isomer **5a** had been formed, the ^{1}H NMR spectrum would have shown a singlet for proton H_a instead. The NH protons of the two oxindoles appeared as two singlets at δ 9.91 and δ 10.39. The stereochemistries of cycloadducts **4a**–**e** were deduced on the basis of ^{1}H NOESY experiments. Irradiation of proton H_a at δ 5.34 did not cause any enhancement of the signal for the proton H_b, which appeared as a multiplet at δ 4.60–4.62.

The signals in the ^{13}C NMR spectrum of **4a** at δ 67.01 and δ 77.22 ppm correspond to the two-spiro carbons. The oxindole ring carbonyls resonated at δ 172.83 and

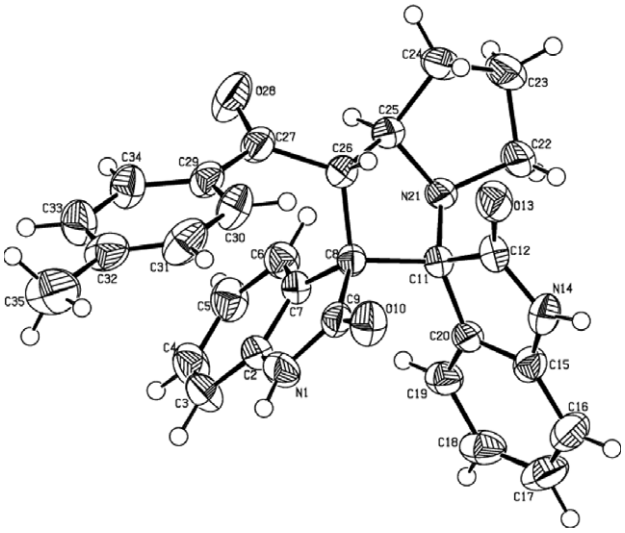
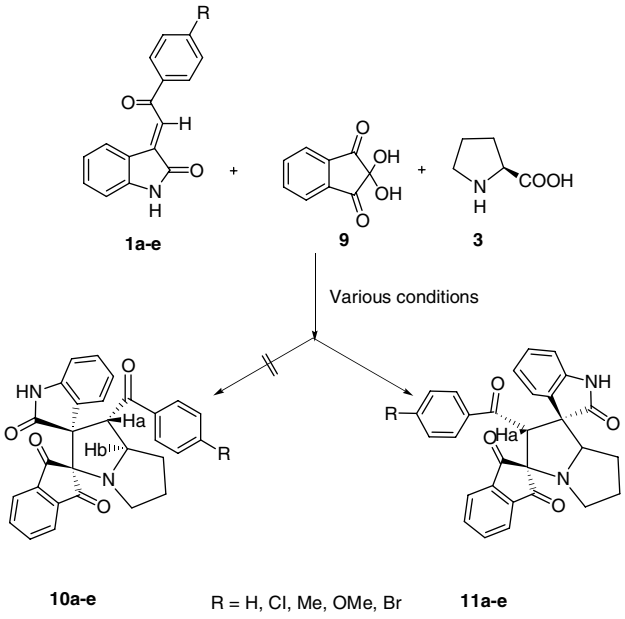


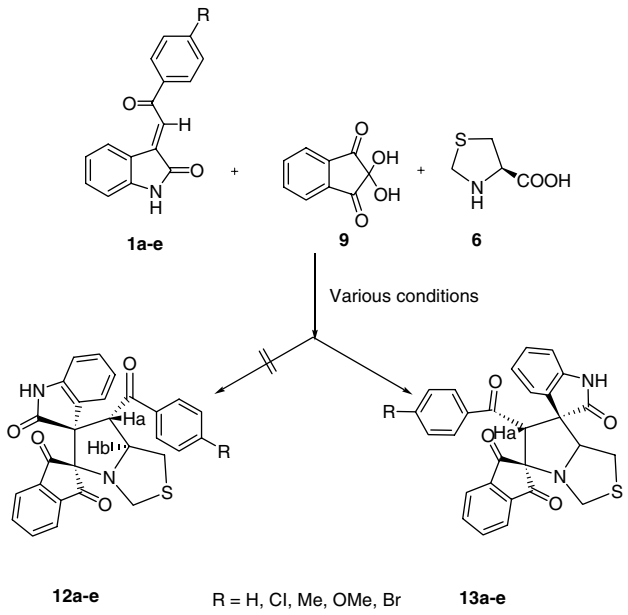
Figure 1. ORTEP diagram of **4c**.

177.46 ppm, respectively. The benzoyl carbonyl resonated at δ 197.18 ppm. Moreover, the presence of a molecular ion peak at m/z 449.5 (M^+) in the mass spectrum of **4a** confirmed the structure of the cycloadduct. The regio- and stereochemical outcome of the cycloaddition reaction was determined unambiguously by single crystal X-ray analysis of cycloadduct **4c** (Fig. 1).[20]

We have extended this methodology to azomethine ylides generated from ninhydrin **9** and L-proline **3** or (*R*)-thiazolidine-4-carboxylic acid **6** to prepare dispiropyrrolizidines **11a–e** and **13a–e** (Schemes 3 and 4). The IR spectrum of **11a** showed peaks at 1687 and 1717 cm^{-1} due to the benzoyl and oxindole ring carbonyls whereas the indanedione ring carbonyls resonated at 1730 and 1736 cm^{-1}. In the ^1H NMR spectrum of **11a**, proton H_a appeared as a singlet at δ 5.23, which



Scheme 3.



Scheme 4.

proved the regiochemistry of the cycloaddition reaction. If the other regioisomer **10a** had been formed then H_a would have appeared as a doublet or a doublet of doublets. The NH proton of the oxindole moiety occurred as a singlet at δ 10.67 whereas the pyrrolizidine –NCH– proton appeared as a multiplet in the region δ 4.36–4.37. The pyrrolizidine $-NCH_2$ protons appeared as multiplets in the region δ 1.56–2.47. The ^{13}C NMR spectrum of **11a** showed signals at δ 63.68 and 78.34 ppm corresponding to the two-spiro carbons. The benzoyl and oxindole ring carbonyls resonated at δ 199.36 and 181.04 ppm whereas the indanedione ring carbonyls resonated at δ 197.55 and 197.60 ppm, respectively. Moreover, the presence of a molecular ion peak at m/z 462.5 (M^+) in the mass spectrum of **11a** confirmed the structure of the cycloadduct. The regio- and stereochemical outcome of the cycloaddition reaction was determined unambiguously by single crystal X-ray analysis of cycloadduct **11a** (Fig. 2).[21] Comparable results were obtained with other derivatives of (*E*)-2-oxoindolino-3-ylidene acetophenones.

The structures and regiochemistries of the cycloadducts were confirmed from spectroscopic data. Ultrasonication in acetonitrile–silica was found to be an excellent medium in terms of conversion and reaction time. In fact, all the cycloadducts were obtained in high yields (85–92%) (Table 1). Furthermore, no aqueous work up was needed, the solvent was removed in vacuo and the reaction mixture was purified by column chromatography.[22]

In conclusion, for the first time, ultrasonic irradiation has been used for the 1,3-dipolar cycloaddition reactions of azomethine ylides in efficient three-component, one-pot syntheses of novel dispiro-oxindolopyrrolizidines and dispirooxindolothienopyrroles. This methodology offers several advantages including mild reaction conditions and short reaction times. The bioactivity of the

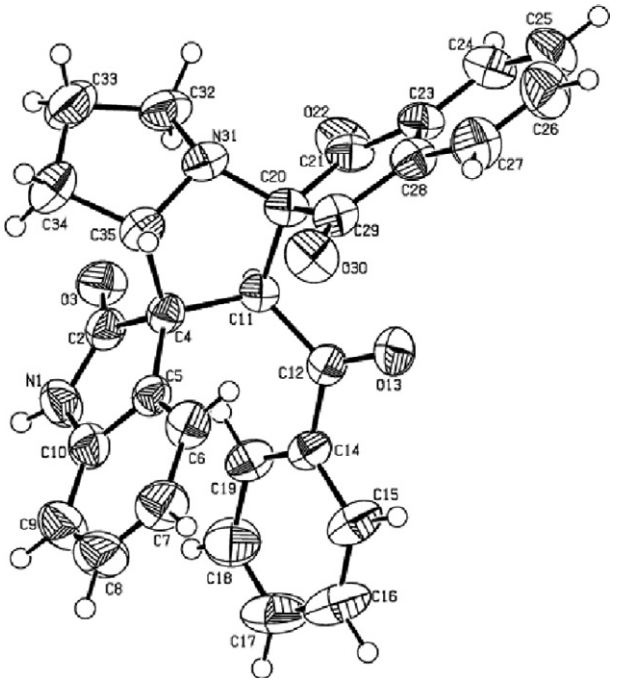


Figure 2. ORTEP diagram of **11a**.

newly synthesized dispiro-oxindolopyrrolizidine and dispirooxindolothienopyrrole derivatives will be published elsewhere.

Acknowledgements

A.R.S. thanks the Council of Scientific and Industrial Research (CSIR) for the award of senior research fellowship. R.R. thanks DST and DST-FIST, New Delhi, for financial assistance.

References and notes

1. For recent reviews, see: (a) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647–652; (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3324; (c) Ugi, J.; Heck, S. *Comb. Chem. High Throughput Screening* **2001**, *4*, 10–16; (d) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopala, L. *Acc. Chem. Res.* **2003**, *36*, 899–903.
2. (a) Weber, L. *Drug Discovery Today* **2002**, *7*, 143–147; (b) Domling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–309.
3. (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2; (b) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45; pp 231–252; (c) *Advances in Cycloaddition*; Grigg, R., Sridharan, V., Curran, D. P., Eds.; Jai Press: London, 1993; Vol. 3; pp 161–180.
4. (a) Liddel, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187–189, and 653–658; (b) Liddel, J. R. *Nat. Prod. Rep.* **1998**, *15*, 636–639.
5. (a) Hartmann, T.; Witte, L. Chemistry, Biology and Chemoecology of Pyrrolizidine Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press, 1995; Vol. 9; (b) Molineux, R. J. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Chapter 1.
6. (a) Del, A.; William, B. H.; Morris, H. R.; Smith, G. A.; Feeney, J.; Robert, G. C. K. *J. Am. Chem. Soc.* **1975**, *97*, 2497–2502; (b) Sapo, S.; Shiratori, O.; Katagiri, K. *J. Antibiot.* **1967**, *20*, 270–274; (c) Bailly, C.; Echepare, S.; Gago, F.; Waring, M. *Anti-Cancer. Drug Res.* **1999**, *15*, 291–295.
7. Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410–416.
8. Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603–4607.
9. De Amici, M.; De Michelli, C.; Sani, V. M. *Tetrahedron* **1990**, *46*, 1975–1986.
10. Cohen, V. L.; Kleinmann, E. E. PCT. Int. Appl. W.O. 24192; *Chem. Abstr.* **1995**, *123*, 296610t.
11. (a) Caroll, W. A.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 1164–1165; (b) Early, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785–3788; (c) Ban, Y.; Taga, N.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 736–739; (d) Ban, Y.; Seto, M.; Oishi, T. *Chem. Pharm. Bull.* **1975**, *23*, 2605–2607.
12. (a) Ban, Y.; Taga, N.; Oishi, T. *Tetrahedron Lett.* **1974**, 187–190; (b) Van Tamle, E. E.; Yardley, J. P.; Miyano, M., ; Hinshaw, W. B., Jr. *J. Am. Chem. Soc.* **1969**, *26*, 7333–7341.
13. Banerji, A.; Bandyopadhyay, T.; Prange, T.; Neuman, A. *Tetrahedron Lett.* **2005**, *46*, 2619–2622.
14. (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432; (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213–1234.
15. (a) Morrocchi, S.; Ricca, A.; Velo, L. *Tetrahedron Lett.* **1967**, 331–334; (b) Levna, I. S.; Morticova, E. I.; Kamernitzky, A. V. *Synthesis* **1972**, 562–566.
16. (a) Okuhawa, F.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, *41*, 113–115; (b) Misono, M. *Catal. Rev. Sci. Eng.* **1987**, *29*, 269–272; (c) Kozhevnikov, I. V. *Catal. Rev. Sci. Eng.* **1995**, *37*, 311–314.
17. (a) Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron* **2006**, *47*, 9221–9225; (b) Poornachandran, M.; Raghunathan, R. *Tetrahedron* **2005**, *46*, 7197–7208; (c) Arumugam, N.; Jayashankaran, J.; Rathnadurga, R.; Raghunathan, R. *Tetrahedron* **2005**, *61*, 8512–8516.
18. (a) Jayashankaran, J.; Rathnadurga, R.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303–7305; (b) Amalraj, A.; Raghunathan, R.; Sridevikumari, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407–412; (c) Subramaniyan, G.; Raghunathan, R.; Martin Castro, A. M. *Synthesis* **2002**, 2440–2443.
19. (a) Subramaniyan, G.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 2909–2913; (b) Amalraj, A.; Raghuanthan, R. *Tetrahedron* **2001**, *57*, 10293–10298; (c) Shanmugasundaram, M.; Raghunathan, R. *Tetrahedron* **2000**, *56*, 5241–5245.
20. Seshadri, P. R.; Selvanayagam, S.; Velmurugan, D.; Ravikumar, K.; Suresh Babu, A. R.; Raghunathan, R. *Acta Cryst. Sect. E* **2006**, *59*, o1458–o1460.
21. Seshadri, P. R.; Selvanayagam, S.; Velmurugan, D.; Ravikumar, K.; Suresh Babu, A. R.; Raghunathan, R. *Acta Cryst. Sect. E* **2006**, *59*, o1559–o1561.
22. *Representative procedure for the synthesis of dispiro-pyrrolizidines derivatives* **4a**–**e**: A mixture of isatin **2** (1 mmol), L-proline **3** (1 mmol) and (*E*)-2-oxoindolino-3-ylidene acetophenone **1a** (1 mmol) were stirred in acetonitrile (10 mL) containing silica (200 mg, 100–200 mesh). The mixture was then ultrasonicated until completion of the reaction as evidenced by TLC. The solvent was removed in vacuo and the crude product was subjected to column chromatography using petroleum ether:ethyl acetate (4:1) as eluent. The product was then recrystallized from

methanol. *Spectral data of* **4a**: *Spiro-[2.3′]-oxindole-spiro-[3.3′]-oxindole-4-benzoyl pyrrolizidine*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90–2.49 (m, 4H), 2.59–2.61 (m, 2H), 4.60–4.62 (m, 1H, H_b), 5.34 (d, $J = 8.32$ Hz, 1H, H_a), 6.16–7.15 (m, 13H), 9.91 (s, 1H, –NH), 10.39 (s, 1H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.07, 30.62, 46.74, 53.38, 65.50, 67.01, 77.22, 109.02, 109.12, 120.48, 120.93, 125.09, 125.26, 126.23, 127.66, 128.31, 128.93, 129.29, 135.65, 137.65, 137.79, 141.48, 142.52, 172.83, 177.46, 197.18; IR (KBr): 1678, 1710, 1716 cm^{-1}; mass *m*/*z*: 449.5 (M^+); Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.81; H, 5.15; N, 9.34. Found: C, 74.98; H, 5.30; N, 9.13. *Spectral data of* **11a**: *Spiro-[2.2′]-indan-1′,3′-dione-3-benzoyl-spiro-[4.3″]-oxindole-pyrrolizidine*. ^{1}H NMR (500 MHz, $CDCl_3$/DMSO-d_6): δ 1.56–1.58 (m, 2H), 1.83–1.85 (m, 2H), 2.46–2.47 (m, 2H), 4.36–4.37 (m, 1H, H_b), 5.23 (s, 1H, H_a), 6.37–8.10 (m, 13H), 10.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$/DMSO-d_6): δ 25.06, 26.53, 48.91, 63.68, 63.79, 74.07, 78.34, 109.46, 122.46, 124.32, 124.45, 125.33, 127.28, 128.65, 128.71, 133.55, 136.72, 181.04, 197.55, 197.60, 199.36; IR (KBr): 1687, 1717, 1730, 1736 cm^{-1}; mass *m*/*z*: 462.5 (M^+); Anal. Calcd for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.05. Found: C, 75.52; H, 4.56; N, 6.24.