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$ZrOCl_2 \cdot 8H_2O$ mediated microwave induced [3+2] cycloaddition of azomethine ylides—a facile one-pot synthesis of novel dispiroheterocycles

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Abstract—An efficient microwave-assisted, $ZrOCl_2 \cdot 8H_2O$ mediated, synthesis of novel dispiro-oxindolopyrrolidines and -pyrrolizidines was accomplished through [3+2] cycloaddition reaction of azomethine ylides derived from acenaphthenequinone and sarcosine/L-proline with (*E*)-2-oxoindolino-3-ylidene acetophenones in good yields.

1,3-Dipolar cycloaddition reactions of azomethine ylides with olefinic and acetylenic dipolarophiles had resulted in a number of novel heterocyclic scaffolds which are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening.[1–3] Functionalized pyrrolidines and pyrrolizidines with spirooxindole ring systems are the central skeletons for numerous alkaloids and pharmacologically important compounds.[4]

Gelesmine, pseudotabersonine, formosanine, isoformosanine, morroniside and mitraphylline are some of the alkaloids containing spirooxindole ring systems.[5] Of particular interest, spiropyrrolidinyloxindole ring systems are also found in a number of alkaloids such as horsifiline, spirotryprostatine A and B, and elacomine etc.[6] Derivatives of spirooxindole find very wide biological applications as anti-microbials, anti-inflammatory, antitumourals, antibiotic agents and inhibitors of human NK-1 receptors.[7] They are also found to be potent aldose reductase inhibitors (ARIs) which help to treat and prevent diabetic complications arising from elevated levels of sorbitol.[8] Spirooxindoles have been reported to behave as poliovirus and rhinovirus 3C-proteinase inhibitors.[9] Hence, there has been renewed interest in the synthesis of these interesting compounds.

1,3-Dipolar cycloaddition reactions are well documented in the literature but most suffer from cumbersome experimental procedures, low yields and poor stereo- and regio-selectivities often leading to mixtures of products. Recently Nair et al., have reported synthesis of spiropyrrolidines involving sarcosine, 1,2-diones such as isatin, acenaphthenequinone and cyclobutene-1,2-diones.[10a–f] Hence the search for new methodology for achieving high stereo- and regio-selectivity is necessary. In this connection, it is found that zirconium(IV) salts are efficient Lewis acid catalyst[11] for novel organic transformations.

In continuation of our studies in the area of cycloaddition reaction,[12–15] we report herein the use of zirconium oxychloride octahydrate and Ball clay supported with zirconium oxychloride octahydrate as efficient catalysts for the regioselective synthesis of spiro-oxindolopyrrolidines and -pyrrolizidines through 1,3-dipolar cycloaddition reaction of azomethine ylides.

In this reaction we used (*E*)-2-oxoindolino-3-ylidene acetophenones as unusual dipolarophiles for spirooxindoles with potential biological significance. We observed that when the dipolarophiles **1a–e**, were subjected to 1,3-dipolar cycloaddition with the azomethine ylide generated by decarboxylation condensation of acenaphthenequinone **2** and proline **3** in methanol, a mixture of cycloadducts **4a–e** and **5a–e** was obtained (Scheme 1). Changing the solvent from methanol to acetonitrile and toluene had little effect on the regioselectivity of

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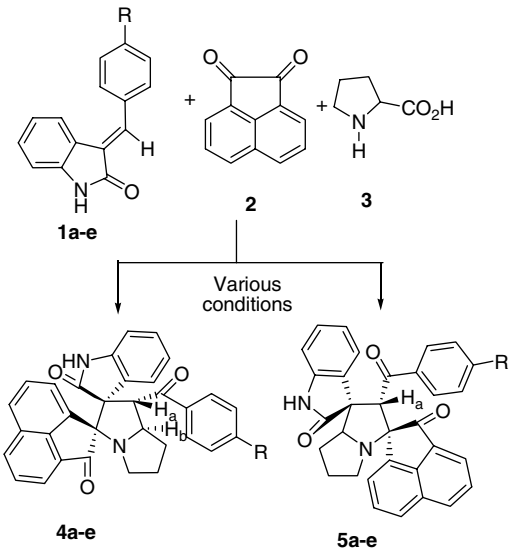


Scheme 1.

the reaction (Table 1). A neat reaction carried out using Ball clay, a rare mineral composed of 20–80% Kaolinite, 10–25% mica and 6–65% quartz, as a solid support by simply grinding the dipolarophiles **1a**–**e** with 1 mmol of acenaphthenequinone **2** and 1 mmol of L-proline **3**, led to cycloadducts **4a**–**e** as the major products and **5a**–**e** as the minor products. $ZrOCl_2{\cdot}8H_2O$ as the catalyst in aqueous methanol, acetonitrile and toluene afforded the cycloadducts **4a**–**e** as the major product with trace amounts of **5a**–**e** (Table 2).

Attempts were also made to carry the reaction using Ball clay supported $ZrOCl_2{\cdot}8H_2O$ as catalyst and we found that in all the cases, cycloadducts **4a**–**e** were obtained in excellent yields in shorter times. No trace of the other regioisomer **5a**–**e** was obtained. A similar trend was observed for all the derivatives when we replaced L-proline **3** with sarcosine **6** for generating the azomethine ylide (Scheme 2). The formation of the cycloadducts was confirmed by spectroscopic techniques.

The IR spectrum of pyrrolizidinoxindole derivative **4d** showed peaks at 1683 and 1710 cm^{-1} due to the benzoyl and oxindole ring carbonyls. A peak at 1720 cm^{-1} was observed due to acenaphthenequinone ring carbonyl. The ^1H NMR spectrum of **4d** demonstrated a singlet at δ 3.33 due to the –OMe group. The $-NCH_2$ protons of the pyrrolizidine ring appeared as multiplets in the region δ 1.96–2.55. The –NCH-proton appeared as multiplet in the region δ 4.75–4.77. The –CH proton attached to the benzoyl group appeared as doublet at δ 5.23 (d, $J = 8.05$). The oxindole –NH proton appeared as singlet at δ 9.76. The ^{13}C spectrum of **4d** demonstrated signals at δ 173.76, 195.98 and 208.23 due to oxindole, benzoyl and acenaphthenequinone ring carbonyls. The two spiro carbons resonated at δ 69.38 and 80.70 ppm. The mass spectrum of **4d** showed a molecular ion peak at 514.5 (M^+).

The IR spectrum of pyrrolizidinoxindole derivative **5d** showed absorptions at 1688 and 1706 cm^{-1} due to the benzoyl and oxindole ring carbonyls. A peak at 1716 cm^{-1} was observed due to acenaphthenequinone ring carbonyl. The ^1H NMR spectrum of **5d** demonstrated a singlet at δ 3.34 due to the –OMe group. The $-NCH_2$ protons of the pyrrolizidine ring appeared as a multiplet in the region δ 1.59–2.47. The –NCH-proton appeared as a doublet of doublets at δ 3.73 (dd, $J = 10.3$, 7.4 Hz). The –CH proton attached to the benzoyl group appeared as a singlet at δ 5.42. whilst the oxindole –NH proton appeared as a singlet at δ 10.66.

The ^{13}C spectrum of **5d** demonstrated resonances at δ 181.47, 197.72 and 202.32 due to the oxindole, benzoyl and acenaphthenequinone ring carbonyls. The two spiro carbons resonated at δ 76.46 and 76.85 ppm. The mass spectrum of **5d** showed a molecular ion peak at 514.5 (M^+).

Table 1. Effect of solvent on the cycloaddition reaction

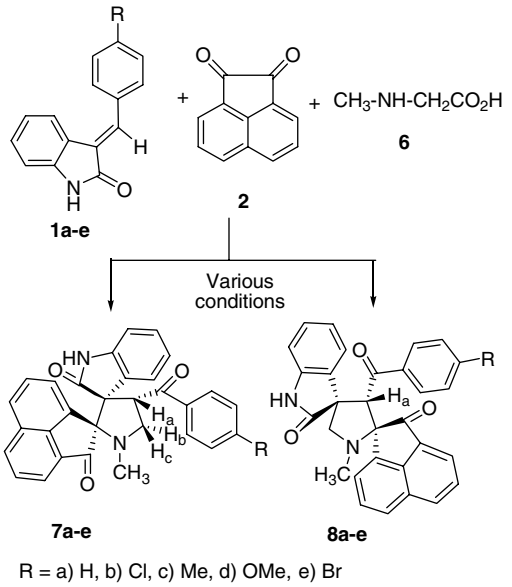
Entry	R	Method A			Method B			Method C		
		T (h)	*Y* (%)		*T* (h)	*Y* (%)		*T* (h)	*Y* (%)	
			4	**5**		**4**	**5**		**4**	**5**
a	H	7.7	45	21	6.3	60	30	6.0	63	30
b	*p*-CI	7.8	48	24	6.0	63	33	5.8	68	32
c	*p*-Me	8.2	47	23	6.5	64	30	6.6	67	32
d	*p*-OMe	8.6	43	28	7.2	61	31	7.0	62	36
e	*p*-Br	8.1	50	22	6.1	63	33	5.9	65	33
			7	**8**		**7**	**8**		**7**	**8**
a	H	7.5	50	24	6.8	61	33	6.4	66	33
b	*p*-CI	7.3	43	27	6.3	65	31	5.9	63	37
c	*p*-Me	8.3	45	22	6.0	63	36	5.5	68	32
d	*p*-OMe	7.9	47	24	6.8	67	32	6.1	64	31
e	*p*-Br	7.8	48	21	6.0	64	33	5.7	69	30

T (h) = time in hours; *Y* (%) = yield in %.
Method A: toluene/reflux.
Method B: methanol/reflux.
Method C: acetonitrile/reflux.

Table 2. Effect of $ZrOCl_2 \cdot 8H_2O$ on the cycloaddition reaction

Entry	R	Method A			Method B			Method C		
		T (min)	*Y* (%)		*T* (h)	*Y* (%)		*T* (min)	*Y* (%)	
			4	**5**		**4**	**5**		**4**	**5**
a	H	7.5	76	20	6.7	87	6	6.9	87	—
b	*p*-CI	7.8	79	20	6.0	85	—	6.5	85	—
c	*p*-Me	8.2	76	18	6.1	86	5	7.0	86	—
d	*p*-OMe	8.4	78	20	7.2	84	—	7.2	84	—
e	*p*-Br	7.5	75	15	6.6	86	6	6.6	86	—
			7	**8**		**7**	**8**		**7**	**8**
a	H	7.8	77	23	7.0	86	—	6.6	83	—
b	*p*-CI	8.0	73	20	6.8	80	—	7.0	86	—
c	*p*-Me	8.2	74	23	7.3	83	4	7.2	82	—
d	*p*-OMe	7.7	72	20	6.8	80	—	6.7	84	—
e	*p*-Br	6.9	75	20	6.6	85	6	6.8	81	—

T (h) = time in hours; *T* (min) = time in minutes; *Y* (%) = yield in %.
Method A: ball clay/MW.
Method B: $ZrOCl_2 \cdot 8H_2O$/MeOH/reflux.
Method C: $ZrOCl_2 \cdot 8H_2O$-Ball clay/MW (600 W).



Scheme 2.

The formation of the cycloadducts was confirmed by elemental analysis. Finally, the regio- and stereochemical outcomes of the cycloadditions were determined by single crystal X-ray analysis of the cycloadducts **4d** and **5e**, respectively.[16a,b]

Similarly, the structures of the cycloadducts **7a**–**e** and **8a**–**e** were confirmed by spectroscopic techniques. The regio- and stereochemical outcomes of the cycloaddition reaction were confirmed by single crystal X-ray analysis of **7d**.[16c]

Representative procedures[17] and spectroscopic data[18] for the spirooxindolopyrrolizidines are given.

In conclusion, we report the use of a rare mineral Ball-clay as a solid support and zirconium oxychloride octahydrate as a catalyst for 1,3-dipolar cycloaddition reactions. The Ball-clay supported zirconium oxychloride octahydrate catalyst proved to be efficient, having several advantages including mild reaction conditions, cleaner reaction profiles, shorter reaction times and better yields with high degree of regio and stereoselectivities. The bioactivities of the newly synthesized spirooxindolopyrrolidines and spirooxindolopyrrolizidines derivatives will be published elsewhere.

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References and notes

1. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2.
2. Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45, p 231.
3. Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: London, 1993; Vol. 3, p 161.
4. (a) Daly, J. W.; Spande, T. W.; Whittaker, N.; Highet, R. J.; Feigl, D.; Noshimori, N.; Tokuyama, T.; Meyers, C. W. *J. Nat. Prod.* **1986**, *46*, 210; (b) Molineux, R. J. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York, 1987, Chapter 1; (c) Fujimori, S. Jap. Pat. Appl. 88-2912; *Chem. Abstr.*, **1990**, *112*, 98409; (d) Waldmann, H. *Synlett* **1995**, 133; (e) Daly, J. W. R. In *Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, pp 141–169.
5. (a) Carroll, W. A.; Grieco, P. *J. Am. Chem. Soc.* **1993**, *115*, 1164; (b) Early, W. G.; Oh, T.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3785; (c) Ban, Y.; Taga, N.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 736; (d) Ban, Y.; Seto, M.; Oishi, T. *Chem. Pharm. Bull.* **1975**, *23*, 2605; (e) Ban, Y.; Taga, N.; Oishi, T. *Tetrahedron Lett.* **1974**, *2*, 187.
6. Hilton, S. T.; Ho, T. C.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639.

7. (a) Okita, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 11143; (b) Rosenmond, P.; Hosseini-Merescht, M.; Bub, C. *Leibigs Ann. Chem.* **1994**, *2*, 151; (c) Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892.
8. Rajeswaran, W. G.; Labroo, R. B.; Cohen, E. A. *J. Org. Chem.* **1999**, *64*, 1369.
9. Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277.
10. (a) Banerji, A.; Bandyopadhyay, T.; Prange, T.; Neuman, A. *Tetrahedron Lett.* **2005**, *46*, 2619; (b) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* **1999**, p 319 and 321; (c) Chary, K. P.; Mohan, G. H.; Iyengar, D. S. *Chem. Lett.* **1999**, *22*, 1336; (d) Chary, K. P.; Mohan, G. H.; Iyengar, D. S. *Synlett* **2000**, 683; (e) Karimi, B.; Seradji, H. *Synlett* **2000**, 805; (f) Nair, V.; Sheela, C. K.; Nigam, P. R.; Gunter, K. E. *Tetrahedron Lett.* **2000**, *41*, 6217.
11. Lenarsic, R.; Kocevar, M.; Polanc, S. *J. Org. Chem.* **1999**, *64*, 2558.
12. (a) Jayashankaran, J.; Rathnadurga, R.; Venketesan, R.; Raghunathan, R. *Tetrahedron* **2005**, *61*, 5595; (b) Arumugam, N.; Jayashankaran, J.; Rathnadurga, R.; Raghunathan, R. *Tetrahedron* **2005**, *61*, 8512; (c) Poornachandran, M.; Raghunathan, R. *Tetrahedron* **2005**, *46*, 7197.
13. (a) Jayashankaran, J.; Rathnadurga, R.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303; (b) Amalraj, A.; Raghunathan, R.; Sridevikumari, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407–419.
14. (a) Subramaniyan, G.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 2909; (b) Amalraj, A.; Raghuanthan, R. *Tetrahedron* **2001**, *57*, 10293; (c) Subramaniyan, G.; Raghunathan, R.; Martin Castro, A. M. *Synthesis* **2002**, 2440.
15. (a) Shanmugasundaram, M.; Raghunathan, R. *Tetrahedron* **2000**, *56*, 5241; (b) Subramaniyan, G.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 2909.
16. (a) Govind, M. M.; Selvanayagam, V.; Velmurugan, D.; Ravikumar, K.; Suresh Babu, A. R.; Raghunathan, R. *Acta Crystallogr., Sect. E* **2004**, *60*, o873–o875; (b) Govind, M. M.; Selvanayagam, V.; Velmurugan, D.; Ravikumar, K.; Suresh Babu, A. R.; Raghunathan, R. *Acta Crystallogr., Sect. E* **2004**, *60*, o604–o606; (c) Govind, M. M.; Selvanayagam, V.; Velmurugan, D.; Ravikumar, K.; Suresh Babu, A. R.; Raghunathan, R. *Acta Crystallogr., Sect. E* **2004**, *60*, o1003–o1005.
17. *Representative procedure for the synthesis of dispiropyrrolidizine derivatives* **4a** and **5a**. *Method A*: A mixture of (*E*)-phenacylideneoxindole **1a** (1 mmol), acenaphthenequinone **2** (1 mmol) and L-proline (1 mmol) was ground in a pestle with Ball clay (1 g) and subjected to microwave irradiation (Table 2). After completion of the reaction as evidenced by TLC analysis, the crude products were subjected to column chromatography using petroleum ether/EtOAc (9:1) as eluent. The cycloadducts were recrystallized using methanol as solvent. *Method B*: A mixture of (*E*)-phenacylideneoxindole **1a** (1 mmol), acenaphthene quinone **2** (1 mmol), L-proline (1 mmol), and $ZrOCI_2{\cdot}8H_2O$ (200 mg) in methanol (20 ml) was refluxed (Table 2). After completion of the reaction as evidenced by TLC analysis, the crude product was subjected to column chromatography using petroleum ether/EtOAc (9:1) as eluent. The cycloadduct was recrystallized using methanol as solvent. *Method C*: A mixture of (*E*)-phenacylideneoxindole **1a** (1 mmol), acenaphthenequinone **2** (1 mmol), L-proline (1 mmol), Ball clay (1 g) and $ZrOCl_2{\cdot}8H_2O$ (200 mg) was ground in a pestle and subjected to microwave irradiation (Table 2). After completion of the reaction as evidenced by TLC analysis, the crude product was subjected to column chromatography using petroleum ether/EtOAc (8:2) as eluent. The cycloadduct **4a** was obtained exclusively.
18. *Spectral data of* **4d**: *Spiro-[2.2′]-acenaphthene-1′-one-spiro-[3.3″]-oxindole-4-(4-methoxybenzoyl) pyrrolizidine*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96–2.55 (m, 6H), 3.33 (s, 3H), 4.75–4.77 (m, 1H), 5.23 (d, $J = 8.05$ Hz, 1H), 6.31–8.12 (m, 14H), 9.76 (s, 1H); ^{13}C NMR: δ 30.61, 31.02, 46.64, 54.08, 55.26, 66.61, 69.38, 80.70, 97.65, 109.13, 113.23, 119.92, 122.12, 122.37, 124.93, 127.10, 127.86, 127.98, 128.79, 129.61, 130.20, 130.77, 131.08, 132.23, 135.69, 139.93, 141.38, 163.29, 173.76, 195.98, 208.23; IR (KBr): 1683, 1710, 1720 cm^{-1}; Mass *m*/*z*: 514.5 (M^+). Anal. Calcd for $C_{33}H_{26}N_2O_4$: C, 77.02; H, 5.09; N, 5.44. Found: C, 77.40; H, 5.25; N, 5.31.
Spectral data of **5d**: *Spiro-[2.2′]-acenaphthene-1′-one-3-(4-methoxybenzoyl)-spiro-[4.3″]-oxindole-pyrrolizidine*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59–1.94 (m, 4H), 2.46–2.47 (m, 2H), 3.34 (s, 3H), 3.73 (dd, $J = 10.3$, 7.4 Hz, 1H), 5.42 (s, 1H), 6.43–8.21 (m, 14H), 10.66 (s, 1H); ^{13}C NMR: δ 21.50, 24.95, 27.20, 50.53, 64.52, 65.95, 76.46, 76.85, 109.26, 122.06, 122.36, 122.68, 125.97, 126.20, 127.70, 128.46, 129.03, 129.13, 129.22, 130.62, 130.78, 131.42, 133.45, 134.43, 137.88, 141.00, 141.76, 143.78, 181.47, 197.72, 202.32; IR (KBr): 1688, 1706, 1716 cm^{-1}; Mass *m*/*z*: 514.5 (M^+). Anal. Calcd for $C_{33}H_{26}N_2O_4$: C, 77.02; H, 5.09; N, 5.44. Found: C, 77.34; H, 5.23; N, 5.32.
Spectral data of **7d**: *Spiro-[2.2′]-acenaphthene-1′-one-spiro-[3.3″]-oxindole-4-(4-methoxybenzoyl) pyrrolidine*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.59 (s, 3H), 3.88 (dd, $J = 8.4$, 6.1 Hz, 1H), 5.43 (dd, $J = 9.9$, 8.4 Hz, 1H), 6.13 (dd, $J = 9.9$, 6.1 Hz, 1H), 7.03–7.95 (m, 14H), 8.26 (s, 1H); ^{13}C NMR: δ 35.01, 50.82, 54.77, 55.31, 63.41, 81.70, 108.92, 113.31, 113.44, 120.15, 122.12, 122.58, 123.12, 124.31, 125.59, 127.89, 128.18, 128.44, 128.60, 129.34, 130.15, 130.53, 131.25, 131.29, 131.71, 140.30, 142.40, 179.98, 195.21, 203.47; IR (KBr): 1684, 1712, 1720 cm^{-1}; Mass *m*/*z*: 488.4 (M^+). Anal. Calcd for $C_{31}H_{24}N_2O_4$: C, 76.21; H, 4.95; N, 5.73. Found: C, 76.48; H, 4.56; N, 5.91. *Spectral data of* **8d**: *Spiro-[2.2′]-acenaphthene-1′-one-3-(4-methoxybenzoyl)-spiro-[4.3″]-oxindole-pyrrolidine*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.62 (s, 3H), 3.94 (d, $J = 8.4$ Hz, 1H), 4.01 (d, $J = 8.4$ Hz, 1H), 5.54 (s, 1H), 7.06–7.98 (m, 14H), 10.04 (s, 1H); ^{13}C NMR: δ 35.18, 50.48, 54.36, 55.84, 63.78, 81.76, 108.90, 120.26, 121.34, 122.12, 123.28, 124.67, 125.06, 125.88, 128.58,129.06, 130.08, 131.82, 133.80, 135.06, 135.18, 142.06, 177.28, 192.59, 202.72; IR (KBr): 1688, 1714, 1718 cm^{-1}; Mass *m*/*z*: 488.4 (M^+). Anal. Calcd for $C_{31}H_{24}N_2O_4$: C, 76.21; H, 4.95; N, 5.73. Found: C, 76.57; H, 4.73; N, 5.96.