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

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Abstract—An efficient synthesis of dispiroindenoquinoxaline pyrrolizidine derivatives has been expediently accomplished by a one-pot four component 1,3-dipolar cycloaddition reaction. High regioselectivity was achieved using heteropolyacid $H_4[Si(W_3O_{10})_3]$–silica as a catalyst. X-ray diffraction studies of one of the cycloadducts proved the structure and regiochemistry of the cycloadduct.

In recent years multicomponent reactions[1] (MCRs) 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 thereby 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] Among various aza heterocycles, functionalised pyrrolizidines are a class of alkaloids with significant biological activity.[5]

Substituted quinoxaline derivatives are pharmacologically important compounds. Although rare in Nature, examples such as leromycin and actinomycin possess a quinoxaline ring and are known to inhibit the growth of gram-positive bacteria and are also active against various transplantable tumors.[6] Spiro compounds represent an important class of naturally occurring substances characterized by their pronounced biological properties[7–11] such as potent aldose reductase inhibitors, polio and rhinovirus 3C-proteinase inhibitors. Hence, with renewed interest in such complex fascinating heterocycles, we have used the 1,3-dipolar cycloaddition reaction for their synthesis. However, such reactions sometimes lead to mixtures of products with poor regio- and stereoselection.[12] Although 1,3-dipolar cycloaddition reactions carried out on a solid support[13] have proved to be beneficial in terms of regio- and stereoselectivity, only a few reports are available on the use of Lewis acids in 1,3-dipolar cycloaddition reactions.[14] Thus an acid catalyst that has high catalytic activity, low toxicity, is moisture and air tolerant and economical is desirable.

Heteropolyacids are remarkable catalysts that are used under both homogenous and heterogenous conditions.[15] In this connection and in continuation of our research in the area of 1,3-dipolar cycloaddition,[16–18] we introduce the heteropolyacid $H_4[Si(W_3O_{10})_3]$, as a mild and efficient catalyst for the four-component, one-pot synthesis of novel dispironol indenoquinoxaline pyrrolizidines through 1,3-dipolar cycloaddition of an azomethine ylide generated from 1,2-phenylenediamine, ninhydrin and proline with various unusual dipolarophiles (Scheme 1).

The multicomponent reaction was carried out by stirring a mixture of 1 equiv of ninhydrin **2** and 1 equiv of 1,2-phenylenediamine **3** for 10 min in 10 mL of acetonitrile followed by addition of 1 equiv of L-proline **4**. This mixture was then added to a solution of 1 equiv of the 2-arylidene-1,3-indanedione **1a–f** containing the heteropolyacid (20 mol %) in 10 ml of acetonitrile. The

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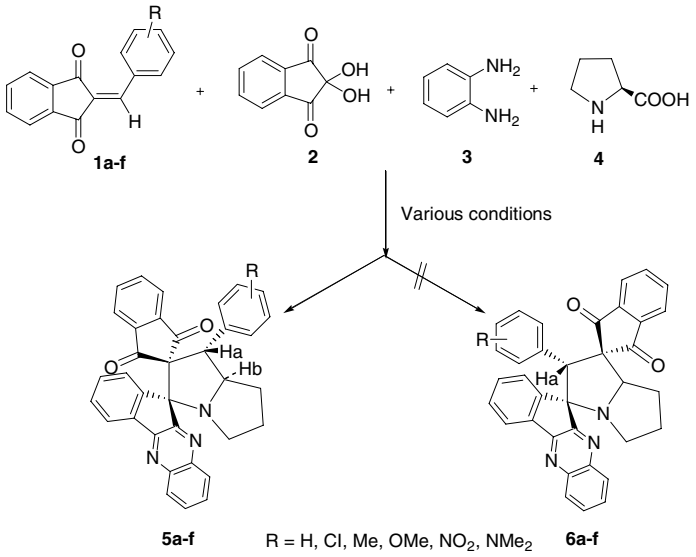
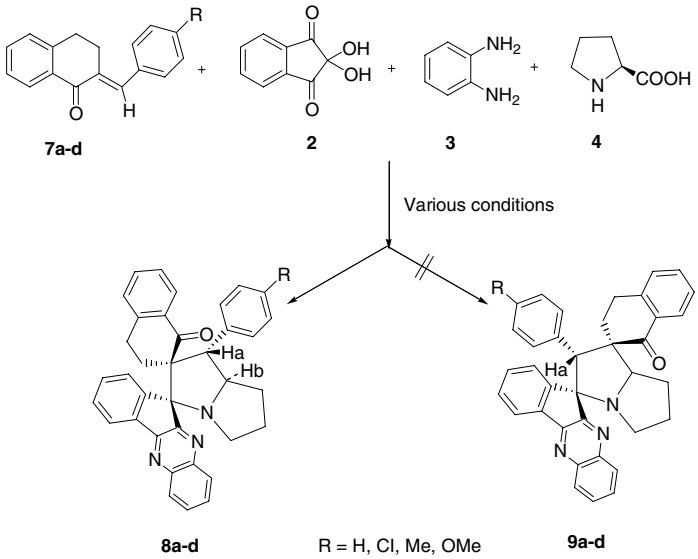


Scheme 1.

reaction mixture was then refluxed until completion of the reaction as evidenced by TLC.

The reaction proceeds through condensation of ninhydrin **2** and 1,2-phenylenediamine **3** to give an indenoquinoxaline-11-one which then generates an azomethine ylide with L-proline **4**. The 1,3-dipole subsequently undergoes a cycloaddition reaction with the dipolarophile 2-arylidene-1,3-indanedione **1a**–**f** to afford a series of novel dispiroindenoquinoxaline pyrrolizidines **5a**–**f**.

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 **5a** showed peaks at 1730 and 1736 cm^{-1} due to the indanedione ring carbonyls. In the ^{1}H NMR spectrum of **5a**, the benzylic proton H_a appeared as a doublet at δ 5.31 ($J = 9.38$ Hz) which clearly showed the regiochemistry of the cycloaddition reaction. If the other regioisomer **6a** had formed, then the ^{1}H NMR spectrum would have shown a singlet for the benzylic proton. The stereochemistry of the cycloadducts **5a**–**f** was deduced on the basis of ^{1}H NOESY. Irradiation of proton H_a at δ 5.31 did not cause any enhancement of the signal for the proton H_b which appeared as a multiplet at δ 5.02–5.08. The signals in the ^{13}C NMR spectrum of **5a** at 76.02 and 77.96 ppm correspond to the two spiro carbons. The indanedione ring carbonyls resonated at 196.62 and 198.37 ppm, respectively. Moreover, the presence of a molecular ion peak at m/z 519.6 (M^+) in the mass spectrum of **5a** confirming the structure of the cycloadduct. The regio- and stereochemical outcome of the cycloaddition reaction was determined by single crystal X-ray analysis of the cycloadduct **5a**.[19] Identical results were obtained with other derivatives of 2-arylidene-1,3-indanediones.

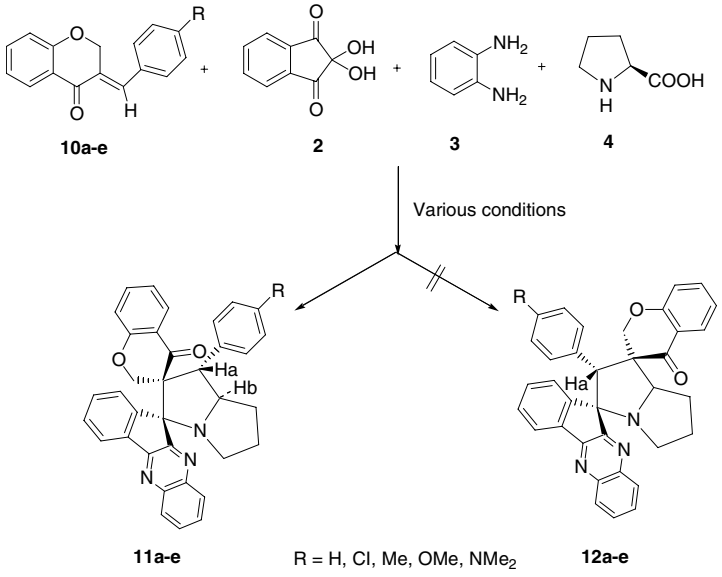


Scheme 2.

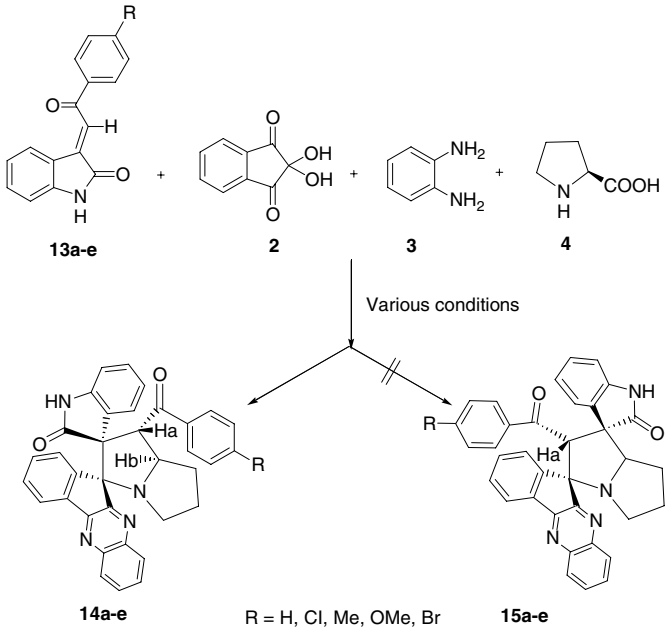
We have extended this methodology to other dipolarophiles including (*E*)-2-arylidene-tetrahydronaphthalene-1-ones, (*E*)-3-arylidene-4-chromanones and (*E*)-2-oxo-indolino-3-ylidene acetophenones (Schemes 2–4).

The structures and regiochemistries of the cycloadducts were similar to those obtained from 2-arylidene-1,3-indanediones and were confirmed from spectroscopic data. The catalytic activity of the heteropolyacid $H_4[Si(W_3O_{10})_3]$ and the yield of the cycloadducts, were found to vary with the concentration of the catalyst (Table 1). The optimum amount of catalyst was found to be 20 mol %. Heteropolyacid–silica (1:1) in acetonitrile was found to be an excellent catalyst in terms of conversion and reaction time. In fact, all the cycloadducts were obtained in high yields (85–92%). Furthermore, no aqueous work up was needed after completion of the reaction. The solvent was removed in vacuo and the reaction mixture was purified through column chromatography.[20]

In conclusion, $H_4[Si(W_3O_{10})_3]$ was used as an efficient catalyst in the 1,3-dipolar cycloaddition reaction of azomethine ylides for the efficient four-component, one-pot synthesis of a series of novel dispiroindeno-quinoxaline pyrrolizidines in one-pot. This catalyst offers several advantages including mild reaction conditions, cleaner reaction profiles, shorter reaction times



Scheme 3.



Scheme 4.

Table 1. $H_4[Si(W_3O_{10})_3]$ catalyzed cycloaddition reactions

Product	R	Method A		Method B		Method C		Method D	
		T (h)	*Y* (%)	*T* (h)	*Y* (%)	*T* (h)	*Y* (%)	*T* (h)	*Y* (%)
5a	H	8.1	45	3.2	79	2.9	83	3.0	87
5b	*p*-CI	8.4	46	3.3	75	3.1	83	3.0	86
5c	*p*-Me	9.5	43	3.6	78	3.4	81	3.2	87
5d	*p*-OMe	9.5	42	3.6	79	3.4	84	3.2	87
5e	*p*-NO_2	9.3	48	3.0	85	2.7	88	2.8	92
5f	*p*-NMe_2	9.6	37	3.8	78	3.5	82	3.3	86
8a	H	8.8	47	3.1	77	2.9	84	2.9	88
8b	*p*-CI	8.9	45	3.2	76	2.8	81	3.0	85
8c	*p*-Me	9.0	43	3.3	75	3.0	84	2.3	86
8d	*p*-OMe	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	*p*-CI	8.9	46	3.2	80	2.8	83	2.8	88
11c	*p*-Me	9.6	43	3.6	77	3.1	80	3.2	85
11d	*p*-OMe	9.6	35	3.7	80	3.3	85	3.2	87
11e	*p*-NMe_2	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	*p*-CI	9.0	46	3.6	77	3.1	85	3.0	87
13c	*p*-Me	8.9	40	3.8	74	3.2	80	3.3	85
13d	*p*-OMe	9.6	42	3.9	78	3.3	81	3.1	86
13e	*p*-Br	8.9	47	3.3	82	3.0	86	2.9	88

T (h) = time in hours; *Y* (%) = yield percent.
Method A: toluene/reflux.
Method B: $H_4[Si(W_3O_{10})_3]$/methanol/reflux.
Method C: $H_4[Si(W_3O_{10})_3]$/acetonitrile/reflux.
Method D: $H_4[Si(W_3O_{10})_3]$–silica/acetonitrile/reflux.

and better yields with high degrees of regio- and stereoselectivities. The bioactivity of the newly synthesized dispiroindenoquinoxaline pyrrolizidines derivatives will be published elsewhere.

Acknowledgements

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20. *Representative procedure for the synthesis of dispiroindenoquinoxaline pyrrolizidines derivatives* **5a**–**f** *using the heteropolyacid* $H_4[Si(W_3O_{10})_3]$ *as catalyst*. A mixture of ninhydrin **2** (1 mmol) and 1,2-phenylenediamine **3** (1 mmol) was stirred for 10 min in 10 mL of acetonitrile followed by the addition of L-proline (1 mmol). To this mixture, a solution of 2-benzylidene-1,3-indanedione **1a** (1 mmol) in 10 ml of acetonitrile and the heteropolyacid (20 mol %) were added. The mixture was then refluxed 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 using methanol as solvent.

Spectral data of **5a**: *spiro-[2.11′]-indeno-[1,2-b]quinoxaline-spiro-[3.2′]indane-1′,3′-dione-4-phenyl-pyrrolizidine.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10–2.22 (m, 3H), 2.34–2.42 (m, 2H), 2.68–2.72 (m, 1H), 5.02–5.08 (m, 1H, H_b), 5.32 (d, $J = 9.38$ Hz, 1H, H_a), 7.04–8.26 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.20, 31.12, 46.62, 52.62, 76.02, 77.96, 122.02, 122.60, 122.72, 126.51, 128.40, 128.98, 129.06, 129.60, 129.80, 130.10, 130.34, 131.08, 132.87, 134.70, 135.21, 135.57, 136.70, 140.82, 141.38, 142.50, 145.79, 153.03, 161.18, 196.62, 198.37; IR (KBr): 1730 cm^{-1}; Mass *m*/*z*: 519.6 (M^+); Anal. Calcd for $C_{35}H_{25}N_3O_2$: C, 80.90; H, 4.84; N, 8.08. Found: C, 81.12; H, 4.63; N, 8.22.

Spectral data of **8a**: *spiro-[2.11′]-indeno-[1,2-b]quinoxaline-spiro-[3.2′]-tetrahydronaphthalene-4-phenyl-pyrrolizidine.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.40 (m, 2H), 1.54–1.62 (m, 1H), 1.71–1.82 (m, 1H), 1.83–1.91 (m, 1H), 2.02–2.11 (m, 3H), 2.36–2.44 (m, 1H), 2.92–3.12 (m, 1H), 4.90 (d, $J = 10.7$ Hz, 1H, H_b), 5.16 (d, $J = 8.4$ Hz, 1H, H_a), 6.36–8.07 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.96, 27.27, 28.77, 29.54, 46.36, 54.27, 66.98, 67.92, 75.39, 76.92, 122.58, 126.07, 127.10, 128.53, 128.82, 129.74, 129.97, 130.37, 130.76, 131.65, 132.58, 132.70, 136.72, 136.89, 137.30, 140.89, 141.91, 142.68, 143.17, 149.37, 153.36, 163.10, 199.45; IR (KBr): 1736, 1668 cm^{-1}; Mass *m*/*z*: 519.6 (M^+); Anal. Calcd for $C_{36}H_{29}N_3O$: C, 83.20; H, 5.62; N, 8.08. Found: C, 83.4; H, 5.34; N, 8.44.

Spectral data of **11a**: *spiro-[2.11′]-indeno-[1,2-b]quinoxaline-spiro-[3.3′]-chroman-4′-one-4-phenyl-pyrrolizidine.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.82 (m, 1H), 1.90–2.10 (m, 3H), 2.48–2.54 (m, 1H), 3.09–3.12 (m, 1H), 3.35 (d, $J = 12.2$ Hz, 1H), 4.84 (d,$J = 12.2$ Hz, 1H), 5.18–5.24 (m, 1H, H_b), 6.04 (d, $J = 7.68$ Hz, 1H, H_a), 6.60–8.26 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.26, 28.18, 46.41, 55.31, 67.72, 71.77, 74.28, 76.83, 77.26, 114.31, 116.52, 120.56, 121.81, 127.86, 128.56, 128.91, 129.37, 129.93, 130.65, 132.51, 134.43, 137.34, 138.11, 140.66, 142.99, 144.71, 145.44, 158.74, 159.36, 160.23, 163.57, 193.21; IR (KBr): 1687 cm^{-1}; Mass *m*/*z*: 521.6 (M^+); Anal. Calcd for $C_{35}H_{27}N_3O_2$: C, 80.59; H, 5.21; N, 8.05. Found: C, 80.30; H, 5.52; N, 8.37.

Spectral data of **14a**: *spiro-[2.11′]-indeno-[1,2-b]quinoxaline-spiro-[3.3′]-oxindole-4-benzoyl-pyrrolizidine.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.34 (m, 4H), 2.63–2.85 (m, 2H), 4.96–5.02 (m, 1H, H_b), 5.91 (d, $J = 8.32$ Hz, 1H, H_a), 6.95–8.26 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.84, 31.06, 46.55, 56.08, 66.73, 69.33, 79.08, 109.37, 121.85, 122.08, 126.92, 128.07, 128.33, 128.92, 128.97, 129.09, 129.24, 129.83, 129.88, 130.21, 130.56, 132.82, 137.76, 140.52, 142.52, 145.19, 154.12, 163.17, 174.14, 199.31; IR (KBr): 1684, 1711 cm^{-1}; Mass *m*/*z*: 534.6 (M^+); Anal. Calcd for $C_{35}H_{26}N_4O_2$: C, 78.63; H, 4.90; N, 10.48. Found: C, 78.94; H, 4.58; N, 10.83.