Indian Journal of Chemistry
Vol. 47B, July 2008, pp. 1117-1119

A facile synthesis of novel dispiroindano thiazolo[2,3-*b*]benzo[*h*]quinazoline pyrrolidines through 1,3-dipolar cycloaddition reaction

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Accepted 23 May 2008

(*E*)5*H*-2-(arylidine)-5-phenyl-6,7-di-hydrothiazolo[2,3-*b*]benzo[*h*]quinazolines undergo a regioselective 1,3-dipolar cycloaddition reaction with the azomethine ylide derived from ninhydrin and sarcosine to give a new class of complex dispiropyrrolidines in good yield. The structures of the synthesized cycloadducts have been elucidated by spectral methods.

Keywords: 1,3-Dipole, azomethine ylide, dispiropyrrolidines

The 1,3-dipolar cycloaddition has emerged as a powerful synthetic tool for the construction of highly functionalized O-, S-, and N-containing heterocycles[1-4]. Particularly, the 1,3-dipolar cycloaddition of azomethine ylide with olefinic dipolarophiles serves as a reliable approach for the synthesis of highly substituted pyrrolidine derivatives which are predominant in many natural products[5]. Since the pyrrolidine ring system is found in many bioactive substances, the development of more effective procedures for the synthesis of substituted pyrrolidines is of great importance. In addition to this, spiropyrrolidines have gained much attention in recent years due to their highly pronounced biological activities[6,7]. Molecules with thiazolidine nucleus have shown wide spectrum of bioactivities like anti-inflammatory and anti-hypertensive activities[8,9]. Apart from the well established pharmacological activities of thiazolone ring fused to cycloheptene system, the pyrimidine ring fused with carbocycles has shown anticancer and herbicidal activities[10,11].

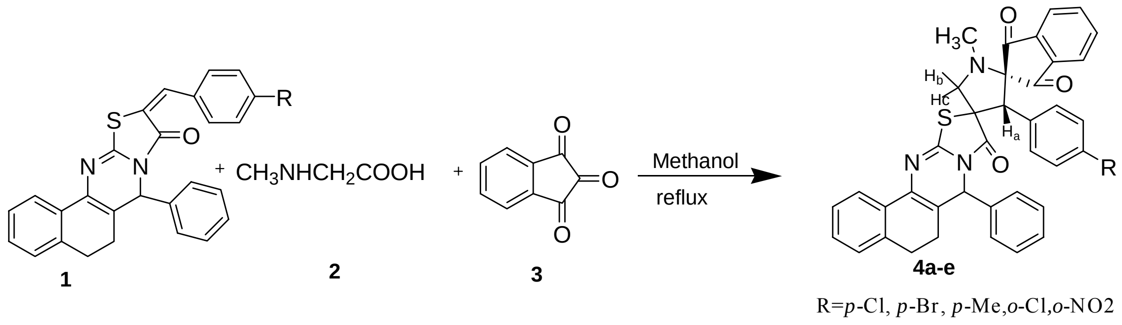
Since we have been involved in 3+2 cycloaddition chemistry in the construction of novel pyrrolidine derivatives[12,13] and also to study their biological applications, the reaction of the versatile 1,3-dipole azomethine ylide with (*E*)5*H*-2-(arylidine)-5-phenyl-6,7-di-hydrothiazolo[2,3-*b*]benzo[*h*]quinazolin-3(2*H*)-one as a dipolarophile has been studied.

Results and Discussion

In a one-pot cycloaddition, the azomethine ylide generated from ninhydrin **3** and sarcosine **2** was reacted with (*E*)5*H*-2-(arylidine)-5-phenyl-6,7-di-hydrothiazolo[2,3-*b*]benzo[*h*]quinazolin-3(2*H*)-one **1a-e** in refluxing methanol to afford a series of novel dispiropyrrolidines regioselectively in good yields. The structures of products **4a-e (Scheme I)** were confirmed by IR, ^{1}H and ^{13}C NMR, mass spectral studies, and elemental analysis. The IR spectrum of cycloadduct **4a** showed three characteristic peaks at 1738, 1712, and 1620 cm^{-1} corresponding to ninhydrin carbonyl and thiazolidine carbonyl groups. The ^{1}H NMR spectra of **4a** exhibited a singlet at δ 2.38 due to -NCH$_3$ of the pyrrolidine ring. The benzylic proton H$_a$ appeared as a singlet at δ 5.49. The H$_b$ and H$_c$ of the pyrrolidine -NCH$_2$ protons appeared as doublets at δ 3.14 and 3.16. Aromatic protons appeared as a multiplet in the region δ 7.03-7.82. The ^{13}C NMR signals at δ 174.47, 199.82 and 201.02 revealed the presence of thiozolone and ninhydrin ring carbonyl groups respectively. The two quaternary carbons appeared at δ 69.96 and 74.15. The mass spectrum showed a peak at *m/z* 641.69 (M$^+$).

Experimental Section

All melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR 8300 instrument. Mass spectra were recorded on a Jeol DX 303 HF spectrometer. ^{1}H and ^{13}C NMR were recorded in CDC1$_3$ using TMS as internal standard on a Bruker spectrometer at 300 and 75 MHz, respectively. Elemental analyses were carried out on a Perkin-Elmer 2400B instrument. The starting materials **3a-e** were prepared as per the literature procedure[14,15].



Scheme I

Table I — Physical data of compounds **4a-e**

Entry	Product	R	m.p. (°C)	Yield (%)	Reaction time (hr)
1	**4a**	*p*-Cl	184-86	74	5
2	**4b**	*p*-Br	102-04	85	6.5
3	**4c**	*p*-Me	112-14	71	5.5
4	**4d**	o-Cl	108-10	69	7
5	**4e**	*o*-NO_2	142-44	72	5

General procedure for the cycloaddition reaction of azomethine ylide generated from ninhydrin, 2 and sarcosine, 3 with (*E*)5*H*-2-(arylidine)-5-phenyl-6,7-di-hydrothiazolo[2,3-*b*]benzo[*h*]quinazolin-3(2*H*)-one, 3a-e

A mixture of ninhydrin **3** (1 mmole), sarcosine **2** (1 mmole), and (*E*)5*H*-2-(arylidine)-5-phenyl-6,7-dihydrothiazolo[2,3-*b*]benzo[*h*]quinazolin-3(2*H*)-one **1a-e** (1 mmole) was refluxed in methanol (25 mL) until the completion of the reaction as evidenced by TLC. After the reaction was over, the solvent was removed under reduced pressure, and the crude product was chromatographed over silica gel using hexane:ethyl acetate (8:2) to afford the cycloadducts **4a-e**. The reaction time and the chemical yield are indicated in **Table I**.

Synthesis of 1-*N*-methyl-3-(*p*-chloro-phenyl)spiro-(2,2')indandione spiro(4,2'')-5-phenyl-2,3,6,7-tetra-hydrothiazolo[2,3-*b*]benzo[*h*]quinazoline pyrrolidine, 4a

IR (KBr): 1738.7, 1712.4, 1620.8 cm^{-1}; ^1H NMR: δ 1.97 (t, 2H), 2.03 (t, 2H), 2.38 (s,3H), 2.98 (s,1H), 3.14 (d, 1H, H_b, $J = 6.9$ Hz), 3.16 (d, 1H, H_c, $J = 6.9$ Hz), 5.50 (s, 1H), 7.03-7.82 (m, 17H, ArH); ^{13}C NMR: δ 22.87, 24.95, 27.41, 29.42, 35.60, 41.66, 52.55, 60.76, 66.18, 69.46, 74.15, 114.93, 123.35, 123.75, 124.31, 126.61, 127.12, 127.68, 127.88, 127.97, 128.17, 128.66, 128.73, 128.82, 129.48, 130.02, 133.57, 135.14, 135.82, 137.18, 139.62, 174.47, 199.82, 201.02; MS: *m/z* 641.69 (M^+). Anal. Calcd. for $C_{38}H_{28}N_3O_3SCl$: C, 71.18; H, 4.39; N, 6.54. Found: C, 71.13; H, 4.50; N, 6.42%.

Synthesis of 1-*N*-methyl-3-(*p*-bromo-phenyl)spiro-(2,2')indandione spiro(4,2'')-5-phenyl-2,3,6,7-tetra-hydrothiazolo[2,3-*b*]benzo[*h*]quinazoline pyrrolidine, 4b

Dark Brown solid, IR (KBr): 1726.7, 1710.2, 1632.9 cm^{-1}; ^1H NMR: δ 2.04 (t, 2H), 2.24 (t, 2H), 2.36 (s,3H), 2.50 (s,1H), 2.83 (d, 1H, H_b, $J = 6.0$ Hz), 2.98 (d, 1H, H_c, $J = 6.0$ Hz), 5.70 (s, 1H), 7.32-8.04

(m, 17H, ArH); ^{13}C NMR: δ 22.63, 25.04, 27.43, 29.68, 31.57, 35.60, 39.81, 58.73, 60.10, 63.14, 74.15, 123.31, 123.43, 123.75, 124.21, 126.36, 126.73, 127.29, 127.88, 127.97, 128.17, 128.67, 128.83, 129.56, 131.12, 132.37, 135.23, 135.85, 136.35, 140.91, 141.64, 184.64, 199.95, 201.15; MS: *m/z* 686.43 (M^{+}). Anal. Calcd. for $C_{38}H_{28}N_3O_3SBr$: C, 66.47; H, 4.11; N, 6.12. Found: C, 66.23; H, 4.32; N, 6.21%.

Synthesis of 1-*N*-methyl-3-(*p*-methyl-phenyl)spiro-(2,2')indandione spiro(4,2'')-5-phenyl-2,3,6,7-tetrahydrothiazolo[2,3-*b*]benzo[*h*]quinazoline pyrrolidine, 4c

Brown solid, IR (KBr): 1739.7, 1712.4, 1634.8 cm^{-1}; ^{1}H NMR: δ 2.07 (t, 2H), 2.28 (t, 2H), 2.28 (s,3H), 2.42 (s,1H), 2.75 (d, 1H, H$_b$, *J* = 7.2 Hz), 2.87 (d, H$_c$, *J* = 7.2 Hz), 5.68 (s, 1H), 7.16-7.96 (m, 17H, ArH); ^{13}C NMR: δ 22.62, 24.33, 26.90, 27.55, 31.55, 35.59, 35.99, 39.79, 58.71, 63.12, 74.13, 123.43, 123.34, 123.74, 126.34, 127.25, 127.43, 127.53, 127.78, 128.15, 128.60, 128.81, 129.10, 129.86, 129.94, 131.77, 135.87, 136.38, 139.49, 140.89, 141.61, 174.15, 199.96, 201.15; MS: *m/z* 621.72 (M^{+}). Anal. Calcd. for $C_{39}H_{31}N_3O_3S$: C, 75.33; H, 5.02; N, 6.75. Found: C, 75.43; H, 4.99; N, 6.79%.

Synthesis of 1-*N*-methyl-3-(*o*-nitro-phenyl)spiro-(2,2')indandione spiro(4,2'')-5-phenyl-2,3,6,7-tetrahydrothiazolo[2,3-*b*]benzo[*h*]quinazoline pyrrolidine, 4d

Brown solid, IR (KBr): 1740.2, 1711.3, 1630.6 cm^{-1}; ^{1}H NMR: δ 2.04 (t, 2H), 2.26 (t, 2H), 2.37 (s,3H), 2.51 (s,1H), 2.74 (d, 1H, H$_b$, *J* = 9.0 Hz), 2.80 (d, 1H, H$_c$, *J* =9.0 Hz), 5.71 (s, 1H), 7.09-8.12 (m, 17H, ArH); ^{13}C NMR: δ 22.67, 25.01, 27.40, 29.34, 29.68, 35.61, 39.80, 58.72, 60.11, 63.15, 74.15, 123.25, 123.43, 125.48, 126.14, 126.70, 127.31, 127.91, 128.30, 128.89, 128.89, 128.98, 129.11, 130.12, 132.42, 133.68, 134.27, 135.24, 135.85, 136.36, 140.91, 175.31, 199.94, 201.14; MS: *m/z* 652.12 (M^{+}). Anal. Calcd. for $C_{38}H_{28}N_4O_5S$: C, 69.92; H, 4.32; N, 8.58. Found: C, 69.87; H, 4.28; N, 8.49%.

Synthesis of 1-*N*-methyl-3-(*o*-chloro-phenyl)spiro-(2,2')indandione spiro(4,2'')-5-phenyl-2,3,6,7-tetrahydrothiazolo[2,3-*b*]benzo[*h*]quinazoline pyrrolidine, 4e

Brown solid, IR (KBr): 1721.7, 1712.4, 1638.3 cm^{-1}; ^{1}H NMR: δ 2.04 (t, 2H), 2.17 (t, 2H), 2.36 (s,3H), 2.50 (s,1H), 2.85 (d, 1H, H$_b$, *J* =8.1 Hz), 2.96 (d, 1H, H$_c$, *J* = 8.1 Hz), 5.30 (s, 1H), 7.35-8.03 (m, 17H, ArH); ^{13}C NMR: δ 22.67, 24.34, 29.34, 29.68, 31.57, 35.60, 39.80, 53.42, 58.72, 63.14, 74.14, 123.43, 123.75, 124.31, 126.35, 126.78, 127.12, 127.34, 127.58, 127.94, 128.18, 128.65, 128.78, 129.56, 130.01, 132.42, 135.36, 135.85, 136.36, 140.91, 141.63, 173.52, 199.94, 201.14; MS: *m/z* 642.07 (M^{+}). Anal. Calcd. for $C_{38}H_{28}N_3O_3SCl$: C, 71.07; H, 4.39; N, 6.54. Found: C, 71.26; H, 4.32; N, 6.48%.

Conclusion

In conclusion, the syntheses of a series of novel dispiropyrrolidines have been achieved in a one pot three component cycloaddition reaction. It was observed that the nonstablized azomethine ylide generated has added regioselectively across the exocyclic double bonds of the diopolarophiles to give novel spiroheterocycles. The evaluation of biological activities of the synthesized compounds is in progress.

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