Synthesis of [1,2,4]Oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-ones via 1,3-Dipolar Cycloaddition of Nitrile Oxide to Thiazolo[3,2-*a*]pyrimidin-3-one Derivatives

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A new class of [1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-one was prepared in moderate yields by the reaction of nitrile oxide with 2-arylmethylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-3-one. The reaction site of dipolarphile is the C=N of thiazolo[3,2-*a*]pyrimidin-3-one rather than the expected C=C of arylmethylidene. The structures of the products were characterized thoroughly by IR, elemental analysis, MS, and NMR analysis.

Keywords thiazolo[3,2-*a*]pyrimidine, 1,3-dipolar cycloaddition, nitrile oxide, [1,2,4]oxadiazolo[4,5-*a*]thiazolo-[2,3-*b*]pyrimidin-9(10*H*)-one

Introduction

Nitrile oxides are important intermediates as 1,3-dipoles in cycloaddition reaction.[1] Reaction of nitrile oxides with alkenes dipolarophiles can obtain isoxazolines which often have important bioactivities.[2-5] the C, N double bond of pyridine, quinoline, isoquinoline and 1,5-benzothiazepine as heterodipolarophile can also react with nitrile oxides to obtain oxadiazoles.[6,7] Oxadiazoles, the important bioisosters for esters and amides in drug discovery, have been reported to have muscarinic agonist, benzodiazepine receptor agonist, 5-HT agonist, and antirhinoviral activities.[8-11]

Thiazolo[3,2-*a*]pyrimidin-3-one derivatives are found to be associated with various biological activities such as antibacterial, antimicrobial and anticancer activities.[12-14]

The incorporation of isoxazoline (or oxadiazole) and thiazolo[3,2-*a*]pyrimidin-3-one into a triheterocyclic system, which we believe could be a useful framework with potential biological activities, has not been investigated yet. In the present work, we wish to report the preliminary results of our attempt to apply the 1,3-dipolar cycloaddition reaction involving nitrile oxide **2** and 2-arylmethylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-3-one **1**, which contain two possible dipolarophile sites (C=N and C=C). Our aim was not only to study the chemoselectivity of the reaction but also to develop a rapid access to new types of potentially bioactive triheterocyclic systems. Such an approach resulted in a synthesis of various [1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-ones **4** instead of the spiroisoxazoline **3**, as shown in Scheme 1.

Experimental

Materials and instruments

1[14] and **2**[15] were prepared according to the reported procedures. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C. TMS was used as an internal reference for ^{1}H and ^{13}C chemical shifts and $CDCl_3$ was as solvent. Elemental analysis was measured by an Elementar analyzer (varioEL II). MS was conducted by a Finnigan LCQ Advantage MAX mass spectrometer. IR spectra were recorded on a Perkin-Elmer spectrometer (Spectrum One). Melting points were measured by a Yanaco MP500 melting point apparatus and uncorrected.

General procedure for the synthesis of 3-(2,6-dichlorophenyl)-10-arylmethylidene-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-ones

A mixture of **1** (1 mmol) and **2** (0.19 g, 1 mmol) in dioxane (30 mL) were reflux for 24 h. The solvent was evaporated in vacuum. The residue was purified by

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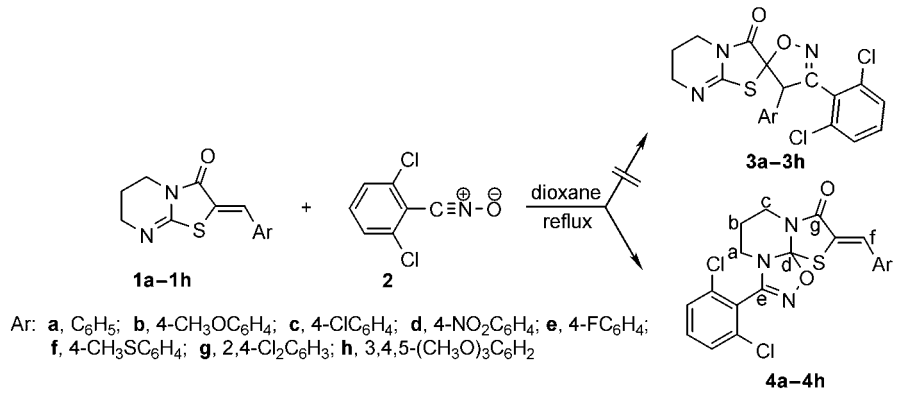
Scheme 1



column chromatography on silica gel using petroleum ether and ethyl acetate (V∶V=5∶1) as eluent to afford the corresponding **4a**—**4h**.

3-(2,6-Dichlorophenyl)-10-benzylidene-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-one (4a) White solid, yield 52%; m.p. 178—180 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.99—2.09 (m, 2H, H_b), 3.05 (ddd, J=1.7, 9.1, 15.4 Hz, 1H, H_a), 3.14 (ddd, J=1.7, 9.1, 15.4 Hz, 1H, H_a), 3.41 (ddd, J=1.4, 9.4, 14.2 Hz, 1H, H_c), 4.41 (ddd, J=1.4, 9.4, 14.2 Hz, 1H, H_c), 7.35—7.37 (m, 1H), 7.43—7.49 (m, 5H), 7.52—7.54 (m, 2H), 7.72 (s, 1H, H_f); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 23.03 (CH_2), 34.17 (CH_2), 36.45 (CH_2), 118.74 (C_d), 122.65 (C_f), 124.01, 128.11, 128.72, 128.81, 128.84, 129.05, 129.85, 132.90, 134.40, 136.18, 136.72, 152.35 (C=N), 163.91 (C=O); IR (KBr) v: 1693.7 (C=O) cm^{-1}; ESI MS m/z: 432 $[M+H]^+$. Anal. calcd for $C_{20}H_{15}Cl_2N_3O_2S$: C 55.56, H 3.50, N 9.72; found C 55.48, H 3.57, N 9.78.

3-(2,6-Dichlorophenyl)-10-(4-methoxybenzylidene)-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-one (4b) White solid, yield 58%; m.p. 221—223 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.96—2.02 (m, 1H, H_b), 2.04—2.10 (m, 1H, H_b), 3.05 (ddd, J=1.5, 9.1, 15.2 Hz, 1H, H_a), 3.13 (ddd, J=1.5, 9.1, 15.2 Hz, 1H, H_a), 3.40 (ddd, J=1.3, 9.4, 14.4 Hz, 1H, H_c), 3.85 (s, 3H, OCH_3), 4.40 (ddd, J=1.3, 9.4, 14.4 Hz, 1H, H_c), 6.96—6.98 (m, 2H), 7.43—7.50 (m, 5H), 7.67 (s, 1H, H_f); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 23.04 (CH_2), 34.11 (CH_2), 36.44 (CH_2), 55.38 (OCH_3), 118.76 (C_d), 122.70 (C_f), 127.10, 127.95, 128.71, 128.79, 131.58, 132.88, 136.17, 136.70, 152.31 (C=N), 164.14 (C=O); IR (KBr) v: 1693.3 (C=O) cm^{-1}; ESI MS m/z: 462 $[M+H]^+$. Anal. calcd for $C_{21}H_{17}Cl_2N_3O_3S$: C 54.55, H 3.71, N 9.09; found C 54.40, H 3.88, N 9.18.

3-(2,6-Dichlorophenyl)-10-(4-chlorobenzylidene)-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-one (4c) White solid, yield 55%; m.p. 182—183 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.97—2.09 (m, 2H, H_b), 3.05 (ddd, J=1.3, 9.4, 14.2 Hz, 1H, H_a), 3.16 (ddd, J=1.3, 9.4, 14.2 Hz, 1H, H_a), 3.40 (ddd, J=1.4, 9.4, 14.2 Hz, 1H, H_c), 4.40 (ddd, J=1.4, 9.4, 14.2 Hz, 1H, H_c), 7.40—7.48 (m, 7H), 7.65 (s, 1H, H_f); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.99 (CH_2), 34.26 (CH_2), 36.46 (CH_2), 118.80 (C_d), 122.55 (C_f), 124.74, 126.66, 128.73, 128.85, 129.08, 130.96, 132.96, 134.81, 136.17, 136.69, 152.39 (C=N), 163.68 (C=O); IR (KBr) v: 1698.8 (C=O) cm^{-1}; ESI MS m/z: 466 $[M+H]^+$. Anal. calcd for $C_{20}H_{14}Cl_3N_3O_2S$: C 51.46, H 3.02, N 9.00; found C 51.62, H 3.15, N 8.95.

3-(2,6-Dichlorophenyl)-10-(4-nitrobenzylidene)-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]-pyrimidin-9(10*H*)-one (4d) White solid, yield 55%; m.p. 217—219 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.99—2.04 (m, 1H, H_b), 2.10—2.15 (m, 1H, H_b), 3.07 (ddd, J=1.3, 9.1, 15.2 Hz, 1H, H_a), 3.18 (ddd, J=1.3, 9.1, 15.2 Hz, 1H, H_a), 3.42 (ddd, J=1.4, 9.2, 14.0 Hz, 1H, H_c), 4.43 (ddd, J=1.4, 9.2, 14.0 Hz, 1H, H_c), 7.46—7.50 (m, 3H), 7.67 (d, J=8.5 Hz, 2H), 7.73 (s, 1H, H_f), 8.29 (d, J=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.93 (CH_2), 34.49 (CH_2), 36.51 (CH_2), 118.96 (C_d), 122.39 (C_f), 124.09, 125.01, 128.77, 128.87, 129.11, 130.24, 133.07, 136.20, 136.72, 140.80, 147.05, 152.51 (C=N), 163.12 (C=O); IR (KBr) v: 1698.2 (C=O) cm^{-1}; ESI MS m/z: 477 $[M+H]^+$. Anal. calcd for $C_{20}H_{14}Cl_2N_4O_4S$: C 50.33, H 2.96, N 11.74; found C 50.55, H 3.11, N 11.63.

3-(2,6-Dichlorophenyl)-10-(4-fluorobenzylidene)-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-one (4e) White solid, yield 48%; m.p. 180—181 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.97—2.13 (m, 2H, H_b), 3.05 (ddd, J=1.5, 9.0, 15.3 Hz, 1H, H_a), 3.15 (ddd, J=1.5, 9.0, 15.3 Hz, 1H, H_a), 3.41 (ddd, J=1.25, 7.3, 14.2 Hz, 1H, H_c), 4.40 (ddd, J=1.3, 7.3, 14.2 Hz, 1H, H_c), 7.13 (t, J=8.5 Hz, 2H), 7.44—7.53 (m, 5H), 7.67 (s, 1H, H_f); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 23.00 (CH_2), 34.21 (CH_2), 36.46 (CH_2), 118.81 (C_d), 122.61 (C_f), 123.71, 123.73, 126.87, 128.73, 128.81, 131.75, 132.93, 136.19, 136.71, 152.37 (C=N), 163.78 (C=O); IR (KBr) v: 1703.7 (C=O) cm^{-1}; ESI MS m/z: 450 $[M+H]^+$. Anal. calcd for $C_{20}H_{14}Cl_2FN_3O_2S$: C 53.34, H 3.13, N 9.33; found C 53.20, H 3.29, N 9.24.

3-(2,6-Dichlorophenyl)-10-(4-methylthiobenzylidene)-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo-

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[2,3-*b*]pyrimidin-9(10*H*)-one (4f) White solid, yield 55%; m.p. 173—175 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.96—2.03 (m, 1H, H_b), 2.05—2.11 (m, 1H, H_b), 2.52 (s, 3H, SCH_3), 3.05 (ddd, J=1.5, 9.1, 15.2 Hz, 1H, H_a), 3.14 (ddd, J=1.5, 9.1, 15.2 Hz, 1H, H_a), 3.41 (ddd, J=1.3, 9.4, 14.4 Hz, 1H, H_c), 4.40 (ddd, J=1.3, 9.4, 14.4 Hz, 1H, H_c), 7.27—7.29 (m, 2H), 7.44—7.48 (m, 5H), 7.66 (s, 1H, H_f); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.17 (SCH_3), 23.04 (CH_2), 34.18 (CH_2), 36.47 (CH_2), 118.79 (C_d), 122.69 (C_f), 122.91, 125.94, 127.62, 128.72, 128.81, 130.21, 130.90, 132.89, 136.21, 136.75, 140.55, 152.34 (C=N), 164.00 (C=O); IR (KBr) v: 1693.9 (C=O) cm^{-1}; ESI MS m/z: 478 $[M+H]^+$. Anal. calcd for $C_{21}H_{17}Cl_2N_3O_2S_2$: C 52.72, H 3.58, N 8.78; found C 52.64, H 3.63, N 8.70.

3-(2,6-Dichlorophenyl)-10-(2,4-dichlorobenzylidene)-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo-[2,3-*b*]pyrimidin-9(10*H*)-one (4g) White solid, yield 50%; m.p. 214—215 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.96—2.12 (m, 2H, H_b), 3.05 (ddd, J=1.5, 9.4, 15.2 Hz, 1H, H_a), 3.16 (ddd, J=1.5, 9.4, 15.2 Hz, 1H, H_a), 3.41 (ddd, J=1.4, 9.4, 14.4 Hz, 1H, H_c), 4.42 (ddd, J=1.4, 9.4, 14.4 Hz, 1H, H_c), 7.31—7.34 (m, 1H), 7.44—7.50 (m, 4H), 7.55 (d, J=8.0Hz, 1H), 7.97 (s, 1H, H_f); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.98 (CH_2), 34.35 (CH_2), 36.50 (CH_2), 118.84 (C_d), 122.89 (C_f), 127.34, 127.68, 128.79, 128.86, 129.74, 129. 96, 131.41, 133.05, 135.04, 135.87, 116.19, 136.68, 152.46 (C=N), 163.19 (C=O); IR (KBr) v: 1700.2 (C=O) cm^{-1}; ESI MS m/z: 500 $[M+H]^+$. Anal. calcd for $C_{20}H_{13}Cl_4N_3O_2S$: C 47.93, H 2.61, N 8.38; found C 48.15, H 2.50, N 8.31.

3-(2,6-Dichlorophenyl)-10-(3,4,5-trimethoxybenzylidene)-6,7-dihydro-5*H*-[1,2,4]oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-one (4h) White solid, yield 53%; m.p. 186—188 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.89—2.10 (m, 2H, H_b), 3.06 (ddd, J=1.4, 9.1, 15.3 Hz, 1H, H_a), 3.15 (ddd, J=1.4, 9.1, 15.3 Hz, 1H, H_a), 3.41 (ddd, J=1.3, 9.4, 14.3 Hz, 1H, H_c), 3.89 (s, 3H, OCH_3), 3.92 (s, 6H, OCH_3), 4.41 (ddd, J=1.3, 9.4, 14.3 Hz, 1H, H_c), 6.78 (s, 2H), 7.44—7.49 (m, 3H), 7.64 (s, 1H, H_f); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 23.08 (CH_2), 34.17 (CH_2), 36.46 (CH_2), 56.16 (OCH_3), 56.21 (OCH_3), 60.97 (OCH_3), 118.91 (C_d), 122.58 (C_f), 123.12, 128.32, 128.80, 128.84, 130.00, 132.95, 136.21, 136.64, 138.84, 153.34 (C=N), 163.81 (C=O); IR (KBr) v: 1698.5 (C=O) cm^{-1}; ESI MS m/z: 522 $[M+H]^+$. Anal. calcd for $C_{23}H_{21}Cl_2N_3O_5S$: C 52.88, H 4.05, N 8.04; found C 52.94, H 3.95, N 7.91.

Results and discussion

The structures of compounds **4a**—**4h** were established by different spectroscopic techniques (IR, NMR, and MS) and elemental analysis. The IR spectrum of **4g** displayed $\nu_{C=O}$ at 1700.2 cm^{-1}. The mass spectrum of **4g** showed a molecular ion peak at m/z 500 ($[M+H]^+$) which indicates the addition of nitrile oxide to the 2-(2,4-dichlorobenzylidene)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-3-one. The ^{1}H NMR spectrum of **4g** revealed several multiplets in the range of δ 1.96—4.44 resulting from 1,4,5,6-tetrahydropyrimidine ring for the six protons of three methylenes, several multiplets in the range of δ 7.31—7.57 for aromatic protons. The existence of a singlet at δ 7.97 resulting from benzylidene proton indicates the C=C of benzylidene was not involved in the cycloaddition reaction. Furthermore, the absence of any singlet downfield of δ 6.5 that is assignable for the methine proton of **3g** excluded the presence of product **3g**.[2,3]

The ^{13}C NMR spectrum of the product **4g** exhibits the presence of three methylene carbons at δ 22.98, 34.35 and 36.50, carbonyl carbons at δ 163.19, benzylidene carbon at δ 122.89 (based on HMQC). The absence of any signal between δ 70—100 that is assignable for the methine and spiro carbon of **3g** excluded the presence of **3g**.[2] ^{1}H-^{13}C HMBC spectrum of **4g** adds conclusive support for the proposed structure. In the ^{1}H-^{13}C HMBC map of **4g** both H_a and H_c correlate with C_d (δ 118.84), H_c and benzylidene proton H_f correlate with a carbonyl carbon C_g (δ 163.1). The correlation of H_a and C_e (δ 152.46) indicates the carbon atom of nitrile oxide was connected with the nitrogen atom of C=N in 1,4,5,6-tetrahydropyrimidine ring (Figure 1). This kind of regioselectivity was general in the 1,3-dipolar cycloaddition reaction of nitrile oxide and C=N.[6,7]

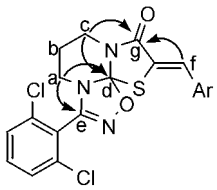

Figure 1 Part HMBC diagram of **4g**.

Conclusion

A novel series of heterocycle compounds, [1,2,4]-oxadiazolo[4,5-*a*]thiazolo[2,3-*b*]pyrimidin-9(10*H*)-ones, were synthesized by the reaction of nitrile oxide with the C=N of thiazolo[3,2-*a*]pyrimidine derivatives in moderate yields. The reaction shows high chemoselectivity which only the C=N involved in the cycloaddition and the C=C was inert. This chemoselectivity offers an easy way to synthesize new complicated heterocycles which is difficult to synthesize by common methods.

References

1 Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, Ed.: Padwa, A., Wiley, New York, **1984**, p. 291.

2 Li, X. F.; Yu, X. Y.; Feng, Y. Q. *Chin. J. Chem.* **2009**, *27*, 1531.

3 Li, X. F.; Feng, Y. Q.; Xu, M. *Acta Cryst. E* **2003**, *59*, 675.

4 Nicholas, G. M.; Eckman, L. L.; Newton, G. L. *Bioorg. Med. Chem.* **2003**, *11*, 601.
5 Patrizia, C.; Carmela, D.; Ernesto, F. *J. Nat. Prod.* **1999**, *62*, 590.
6 Caramella, P.; Bandiera, T.; Albini, F. M.; Gamba, A. Corsaro, A.; Perrini, G. *Tetrahedron* **1988**, *44*, 4917.
7 Baouid, A.; Elhazazi, S.; Hasnaoui, A.; Compain, P.; Lavergne, J.-P.; Huet, F. *New. J. Chem.* **2001**, *25*, 1479.
8 Sako, M.; Oda, S.; Ohara, S.; Hirota, K.; Maki, Y. *J. Org. Chem.* **1998**, *63*, 6947.
9 Macor, J. E.; Ordway, T.; Smith, R. L.; Verhoest, P. R.; Mack, R. A. *J. Org. Chem.* **1996**, *61*, 3228.
10 Romano, M. R.; Lograno, M. D. *Eur. J. Pharmacol.* **2009**, *608*, 48.
11 Quan, C.; Kurth, M. *J. Org. Chem.* **2004**, *69*, 1470.
12 Ashok, M.; Holla, B. S.; Kumari, N. S. *Eur. J. Med. Chem.* **2007**, *42*, 380.
13 Holla, B. S.; Rao, B. S.; Sarojini, B. K.; Akberali, P. M. *Eur. J. Med. Chem.* **2004**, *39*, 777.
14 Mohan, J.; Kumar, A. *Indian J. Heterocycl. Chem.* **2002**, *11*, 325.
15 Grundamann, C.; Dean, J. M. *J. Org. Chem.* **1965**, *30*, 2810.

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