Synthesis of *N*1-Substituted 1,2,3,6-Tetrahydropyrimidin-2-ones via an Unexpected Reaction of Thiazolo[3,2-*a*]-pyrimidine Derivatives and Nitrile Oxide

Li, Xiaofang(李筱芳) Yi, Pinggui*(易平贵) Yu, Xianyong*(于贤勇)

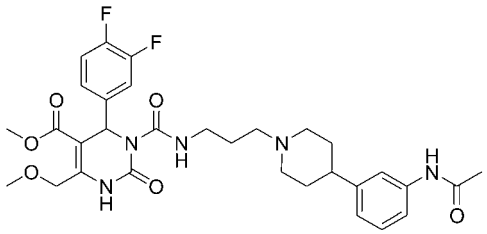
Key Laboratory of Theoretical Chemistry and Molecular Simulation of Ministry of Education, Hunan Province College Key Laboratory of QSAR/QSPR, School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan, Hunan 411201, China

A new class of *N*1-substituted 1,2,3,6-tetrahydropyrimidin-2-ones was prepared in moderate yields by the reaction of nitrile oxide with thiazolo[3,2-*a*]pyrimidine derivatives via a domino 1,3-dipolar cycloaddition/ring-opening/substitution process. The structures of the products were characterized thoroughly by IR, elemental analysis, MS, NMR together with X-ray crystallographic analysis.

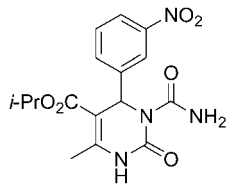
Keywords 1,2,3,6-tetrahydropyrimidin-2-one, cycloaddition, thiazolo[3,2-*a*]pyrimidine, nitrile oxide, synthesis

Introduction

Tetrahydropyrimidone (THPM) is an important type of heterocyclic compounds,[1] which have wide range biological responses and can be used as calcium channel modulators, antihypertensive agents, mitotic kinesin Eg5 inhibitors, and melanin concentrating hormone receptor (MCH1-R) as antagonists.[2-5] Some classical compounds among them are shown in Figure 1. On the other hand, the functionalization (acylation, alkoxycarbonylation, and alkylation) of *N*1 position of THPM is of considerable importance for the preparation of biologically important THPM.[6]



SNAP-7941
MCH1 receptor antagonist



SQ 32926
antihypertensive agent

Figure 1 Biologically active THPM.[3]

Spiro-compounds also are an important class of organic compounds because of their biological activities.[7,8] One of the most widely used methods for the synthesis of these compounds is via 1,3-dipolar cycloaddition reaction to exocyclic double bonds.[9,10] In the present work, we report the results of our attempt to apply the 1,3-dipolar cycloaddition reaction involving ethyl 2-[(methoxycarbonyl)methylidene]-2,3-dihydro-6-methyl-3-oxo-4-[(un)substituted phenyl]-5*H*-thiazolo-[3,2-*a*]pyrimidine-5-carboxylate (**1**) and nitrile oxide (**2**). Such an approach, however, resulted in a synthesis of various *N*1-substituted 1,2,3,6-tetrahydropyrimidin-2-ones **4** instead of the expected spiroisoxazoline **3**, as shown in Scheme 1.

What is more, substances containing isoxazole building blocks are frequently used in drug discovery as an important bioisostere to improve pharmacokinetic properties of drug candidates.[11,12] Therefore, we believe that our present results should be useful for the synthesizing bioactive complex *N*1-substituted 1,2,3,6-tetrahydropyrimidin-2-ones.

Experimental

Materials and instruments

1[13] and **2**[14] were prepared according to the reported procedures. All NMR spectra were recorded on a

* E-mail: fine_chem@163.com
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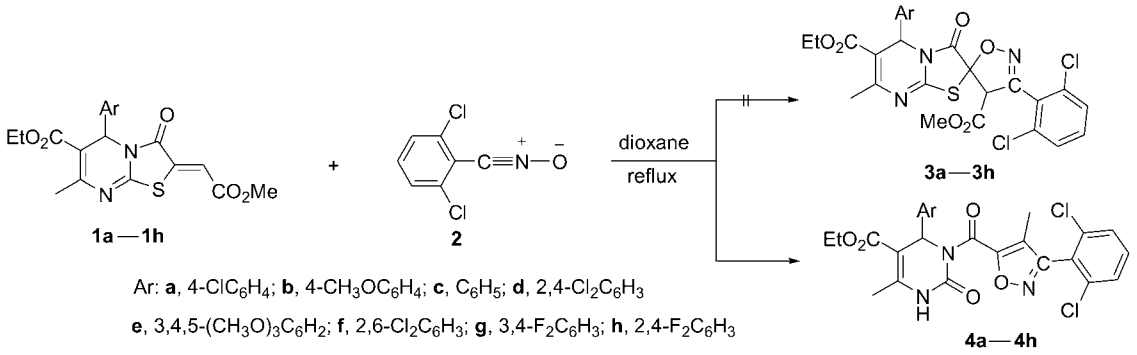
Scheme 1



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.

Crystal structure determination

Determination of the unit cell and data collection for methyl 3-(2,6-dichlorophenyl)-5-[6-(4-chlorophenyl)-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (**4a**) was performed on a Bruker SMART CCD diffractometer at 113 K. Crystal data and details of the data collection and refinement are collected in Table 1. The structure was solved using the direct method implemented in the program SHELXS97. All non-hydrogen atoms were refined using a full-matrix least-square procedure on F^2. Anisotropic displacement parameters were assigned to non-hydrogen atoms.

Table 1 Crystal data and structure refinement for compound **4a**

Empirical formula	$C_{27}H_{21}Cl_6N_3O_7$
Formula weight	712.17
Temperature	113 K
Wavelength	0.071073 nm
Crystal system, space group	triclinic, *P*-1
Unit cell dimensions,	
a/nm	0.81813(16)
b/nm	1.3847(3)
c/nm	1.4366(3)
α/(°)	95.29(3)
β/(°)	100.68(3)
γ/(°)	105.09(3)
Cell volume/nm^3	1.5272(5)
Z	2
Calculated density/(g•cm^{-3})	1.549
μ/mm^{-1}	0.613
Crystal size/mm^3	0.18×0.16×0.12
θ range for data collection/(°)	2.0−27.9
Limiting indices	−10≤*h*≤10, −18≤*k*≤18, −18≤*l*≤12
Reflections collected/unique	7128/4030 [*R*(int)=0.074]
Final *R* indices [$I>2\sigma(I_0)$]	R_1=0.057, wR_2=0.152
Largest diff. peak and hole/(e•nm^{-3})	620 and −500

General procedure for the synthesis of *N*1-substituted 1,2,3,6-tetrahydropyrimidin-2-ones

A mixture of **1** (1 mmol) and **2** (2 mmol) in dioxane (30 mL) were refluxed overnight. The solvent was evaporated in vacuum. The residue was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (5∶1, *V*∶*V*) as eluent to afford the corresponding **4a**—**4h**.

Methyl 3-(2,6-dichlorophenyl)-5-[6-(4-chlorophenyl)-5-(ethoxcabonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4a) White solid, yield 88%; m.p. 192—193 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.25 (t, *J*=7 Hz, 3H), 2.32 (s, 3H), 3.46 (s, 3H), 4.16—4.21 (m, 2H), 6.61 (s, 1H), 7.33 (d, *J*=8.5 Hz, 2H), 7.38—7.41 (m, 3H), 7.44 (d, *J*=8.5 Hz, 2H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.17, 18.16, 52.24, 54.68, 61.03, 105.14, 110.30, 126.15, 128.08, 128.88, 129.01, 131.70, 134.58, 135.25, 135.33, 136.80, 145.13, 150.74, 157.85, 159.54, 164.29, 166.82; IR (KBr) *v*: 3427.3, 1732.8, 1713.6, 1686.3, 1653.3, 1397.2, 1235.4, 1092.9, 784.0 cm^{-1}; ESI-MS *m*/*z*: 592 [M + H]$^+$. Anal. calcd for $C_{26}H_{20}Cl_3N_3O_7$: C 52.68, H 3.40, N 7.09; found C 52.59, H 3.36, N 7.18.

Methyl 3-(2,6-dichlorophenyl)-5-[6-(4-methoxyphenyl)-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4b) White solid, yield 68%; m.p. 195—196 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.24 (t, *J*=7 Hz, 3H), 2.33 (s, 3H), 3.44 (s, 3H), 3.80 (s, 3H), 4.16 (q, *J*=7 Hz, 2H), 6.61 (s, 1H), 6.87 (d, *J*=8.5 Hz, 2H), 7.36—7.39 (m, 3H), 7.42 (d, *J*=8.5 Hz, 2H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.17, 18.11, 52.16, 54.79,

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55.32, 60.85, 105.67, 110.01, 114.05, 126.25, 128.03, 128.81, 130.40, 131.60, 135.30, 135.39, 144.57, 150.79, 157.87, 159.58, 159.70, 164.49, 167.13; IR (KBr) *v*: 3416.1, 1740.1, 1731.7, 1709.3, 1685.6, 1662.3, 1606.8, 1513.9, 1391.3, 1246.7, 1095.1, 783.1 cm^{-1}; ESI-MS *m*/*z*: 588 $[M+H]^+$. Anal. calcd for $C_{27}H_{23}Cl_2N_3O_8$: C 55.11, H 3.94, N 7.14; found C 55.21, H 3.79, N 7.08.

Methyl 3-(2,6-dichlorophenyl)-5-[6-phenyl-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4c) White solid, yield 72%; m.p. 209—210 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.25 (t, J=5 Hz, 3H), 2.33 (s, 3H), 3.39 (s, 3H), 4.16—4.20 (m, 2H), 6.66 (s, 1H), 7.33—7.39 (m, 4H), 7.42—7.45 (m, 4H), 8.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.16, 18.14, 52.11, 55.23, 60.90, 105.49, 110.10, 126.20, 127.41, 128.03, 128.69, 128.84, 131.62, 135.28, 135.41, 138.35, 144.88, 150.80, 157.87, 159.54, 164.47, 167.05; IR (KBr) *v*: 3422.7, 1741.6, 1732.5, 1714.0, 1688.1, 1657.4, 1387.9, 1296.7, 1238.7, 1096.9, 782.0 cm^{-1}; ESI-MS *m*/*z*: 558 $[M+H]^+$. Anal. calcd for $C_{26}H_{21}Cl_2N_3O_7$: C 55.93, H 3.79, N 7.53; found C 55.88, H 3.82, N 7.51.

Methyl 3-(2,6-dichlorophenyl)-5-[6-(2,4-dichlorophenyl)-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4d) White solid, yield 78%; m.p. 210—211 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.25 (t, J=5 Hz, 3H), 2.30 (s, 3H), 3.44 (s, 3H), 4.13—4.17 (m, 2H), 6.73 (s, 1H), 7.25 (d, J=10 Hz, 1H), 7.36—7.43 (m, 4H), 7.49 (d, J=10 Hz, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.22, 18.33, 52.14, 55.46, 60.99, 103.43, 109.72, 126.20, 127.38, 128.02, 130.12, 131.62, 132.35, 134.26, 135.06, 135.19, 135.31, 144.09, 150.11, 157.74, 158.17, 159.57, 164.11, 167.09; IR (KBr) *v*: 3429.2, 1732.9, 1696.6, 1683.4, 1662.0, 1396.0, 1255.1, 1103.7, 786.2 cm^{-1}; ESI-MS *m*/*z*: 626 $[M+H]^+$. Anal. calcd for $C_{26}H_{19}Cl_4N_3O_7$: C 49.78, H 3.05, N 6.70; found C 49.74, H 3.02, N 6.62.

Methyl 3-(2,6-dichlorophenyl)-5-[6-(3,4,5-trimethoxyphenyl)-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4e) White solid, yield 71%; m.p. 207—208 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.27 (t, J=5 Hz, 3H), 2.34 (s, 3H), 3.47 (s, 3H), 3.82 (s, 3H), 3.84 (s, 6H), 4.18—4.24 (m, 2H), 6.63 (s, 1H), 6.66 (s, 2H), 7.37—7.42 (m, 3H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.27, 18.17, 52.16, 55.05, 56.19, 60.80, 66.97, 104.36, 105.40, 110.36, 126.22, 127.98, 128.04, 131.67, 133.73, 135.23, 135.36, 138.17, 144.89, 150.72, 153.32, 157.77, 157.86, 159.60, 164.52, 167.09; IR (KBr) *v*: 3431.6, 1729.6, 1709.3, 1689.2, 1652.8, 1607.1, 1583.4, 1392.3, 1246.3, 1091.2, 783.5 cm^{-1}; ESI MS *m*/*z*: 648 $[M+H]^+$. Anal. calcd for $C_{29}H_{27}Cl_2N_3O_{10}$: C 53.71, H 4.20, N 6.48; found C 53.68, H 4.18, N 6.43.

Methyl 3-(2,6-dichlorophenyl)-5-[6-(2,6-dichlorophenyl)-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4f) White solid, yield 69%; m.p. 225—226 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.14 (t, J=7 Hz, 3H), 2.23 (s, 3H), 3.48 (s, 3H), 4.16 (q, J=7 Hz, 2H), 7.04 (s, 1H), 7.18—7.21 (m, 1H), 7.34—7.41 (m, 5H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.18, 18.55, 52.08, 56.10, 60.63, 100.08, 109.05, 126.30, 127.94, 129.43, 129.59, 131.54, 133.17, 135.38, 144.07, 149.88, 157.70, 158.83, 159.65, 164.36, 167.49; IR (KBr) *v*: 3418.3, 1732.7, 1706.6, 1683.5, 1651.9, 1396.6, 1254.4, 1099.2, 783.7 cm^{-1}; ESI-MS *m*/*z*: 626 $[M+H]^+$. Anal. calcd for $C_{26}H_{19}Cl_4N_3O_7$: C 49.78, H 3.05, N 6.70; found C 49.70, H 3.12, N 6.63.

Methyl 3-(2,6-dichlorophenyl)-5-[6-(3,4-difluorophenyl)-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4g) White solid, yield 65%; m.p. 238—239 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.27 (t, J=5 Hz, 3H), 2.38 (s, 3H), 3.53 (s, 3H), 4.19—4.24 (m, 2H), 6.61 (s, 1H), 7.15—7.18 (m, 2H), 7.28—7.30 (m, 1H), 7.38—7.45 (m, 3H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.18, 18.29, 52.27, 54.16, 61.13, 104.99, 110.50, 116.56, 117.58, 123.59, 126.18, 128.03, 131.66, 135.30, 145.27, 150.14, 157.87, 159.55, 164.18, 166.63; IR (KBr) *v*: 3412.6, 1730.3, 1710.3, 1647.8, 1517.4, 1397.3, 1255.3, 1093.9, 786.8 cm^{-1}; ESI-MS *m*/*z*: 594 $[M+H]^+$. Anal. calcd for $C_{26}H_{19}Cl_2F_2N_3O_7$: C 52.54, H 3.22, N 7.07; found C 52.60, H 3.16, N 7.15.

Methyl 3-(2,6-dichlorophenyl)-5-[6-(2,4-difluorophenyl)-5-(ethoxycarbonyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1-carbonyl]isoxazole-4-carboxylate (4h) White solid, yield 72%; m.p. 229—230 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.25 (t, J=7 Hz, 3H), 2.29 (s, 3H), 3.44 (s, 3H), 4.15—4.17 (m, 2H), 6.60 (s, 1H), 6.82—6.90 (m, 2H), 7.35—7.42 (m, 3H), 7.50—7.55 (m, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.07, 18.25, 52.13, 52.98, 60.89, 102.80, 104.38, 109.89, 111.28, 122.18, 126.20, 128.00, 131.60, 135.30, 144.48, 150.15, 157.73, 157.98, 159.58, 164.21, 167.10; IR (KBr) *v*: 3428.1, 1742.3, 1732.3, 1699.0, 1683.3, 1662.3, 1504.8, 1396.7, 1257.4, 1102.3, 786.3 cm^{-1}; ESI-MS *m*/*z*: 594 $[M+H]^+$. Anal. calcd for $C_{26}H_{19}Cl_2F_2N_3O_7$: C 52.54, H 3.22, N 7.07; found C 52.44, H 3.26, N 7.01.

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 **4a** displayed $\nu_{C=O}$ at 1732.8, 1713.6 and 1686.3 cm^{-1}. The mass spectrum of **4a** showed a molecular ion peak at *m*/*z* 592 ($[M+H]^+$), which can exclude the existence of **3a**. The ^{1}H NMR spectrum of **4a** revealed a singlet at δ 2.32 resulting from methyl, a triplet at δ 1.25 for C**H**$_3$CH$_2$O protons, a multiplet in the range of δ 4.16—4.21 for CH$_3$C**H**$_2$O protons, a singlet at δ 3.46 for CH$_3$O protons, a singlet at δ 6.61 for benzylic proton, several multiplets in the range of δ 7.33—7.44 for aromatic protons and a singlet at δ 8.63 resulting from NH. On

the other hand, the structure was established to be **4** rather than **3** based on the characterized peaks on their ^{1}H NMR spectra. The absence of any signal between δ 4.5—6.5 that is assignable for the methine proton of **3** excluded the presence of product **3**.[15-17]

The ^{13}C NMR spectrum of the product **4a** exhibits the presence of methyl carbon at 18.16, ethyl carbons at δ 14.17 and 61.03, OCH_3 at δ 52.24, benzylic carbon at δ 54.68, and carbonyl carbons at δ 164.29 and 166.82. Further, the structure of the product was confirmed by X-ray diffraction analysis of **4a**, as shown in Figure 2.

Mechanistically, the 1,3-dipolar cycloaddition reaction of **1** with **2** results in the formation of intermediate **3**, which undergoes a subsequent ring-opening to the corresponding intermediate **3'** (or **3"**), finally, the S of **3'** (or **3"**) was substituted by O in the existence of nitrile oxide **2**,[18-19] which lead to the formation of title product **4**, shown in Scheme 2. What's more, when we increase the molar ratios of **1** and **2** (from 1∶2 to 1∶1, and 2∶1 finally), no other product except **1** and product **4** is observed.

Conclusion

A novel synthesis of *N*1-substituted 1,2,3,6-tetrahydropyrimidin-2-ones was accomplished by the reaction of nitrile oxide with thiazolo[3,2-*a*]pyrimidine derivatives in moderate yields. The domino 1,3-dipolar cycloaddition/ring-opening/substitution process offers an easy way to synthesize *N*1-substituted 1,2,3,6-tetrahydropyrimidin-2-ones. Therefore, we believe that our present results would enrich the chemistry of tetrahydropyrimidin-2-one.

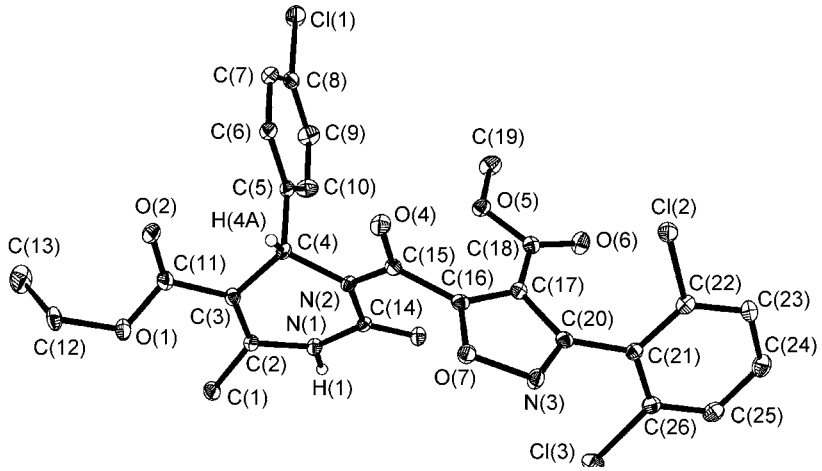
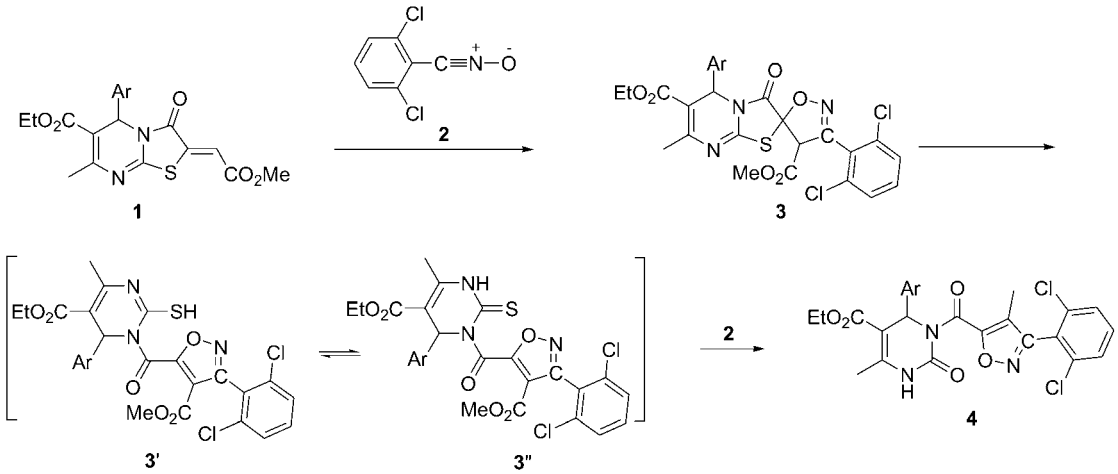


Figure 2 ORTEP diagram of **4a** (solvent and partial H atoms have been omitted for clarity).

Scheme 2



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