An Efficient Synthesis of 3,3',4,4'-Tetrahydro-4,4'-bibenzo-[*e*][1,3]oxazine-2,2'-dione Derivatives with the Aid of Low-valent Titanium

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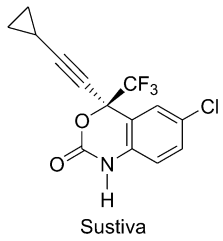
Synthesis of 3,3',4,4'-tetrahydro-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-diones via reaction of salicylidendphenylhydrazone and triphosgene with the aid of low-valent titanium reagent is described. This method has the advantages of accessible starting materials, good yields and short reaction time.

Keywords synthesis design, benzo[*e*][1,3]oxazine-2,2'-diones, low-valent titanium reagent, radical reactions

Introduction

Efavirenz (Sustiva) (Figure 1), a benzoxazinone derivative, is a nonnucleoside reverse transcriptase inhibitor that has been approved by the FDA (September 17, 1998) and is presently in clinical use for the treatment of AIDS. The fight against HIV, by developing more efficacious drugs than Efavirenz, has been the prime driving force for benzoxazinone derivatisation which has received considerable attention.[1-6]



Sustiva

Figure 1 Structure of Sustiva.

Partly due to the biological implications, much attention has been paid to the development of efficient methods for preparation of substituted benzoxazinones. They include such strategies as CO_2 incorporation reaction based upon three-component assembly by the use of arynes and imines,[7] salicylaldehyde-based mineral supported expeditious synthesis of benzoxazin-2-ones,[8,9] one-pot montmorillonite K-10 clay supported three-component reactions of substituted salicylaldehydes, ribosyl/deoxyribosylureas and ammonium acetate via cycloisomerisation of an aldimine intermediate under solvent-free irradiation conditions,[10] solution-phase parallel synthesis using complementary molecular reactivity and molecular recognition purification technology,[11] condensation of 1-menthone with salicylamide followed by isomerization of the adduct with 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU),[12] and salicylamideacetylene-dicarboxylate reactions as a route to benzoxazinones.[13] However, scarce general routes are known for the preparation of bibenzo[*e*][1,3]oxazine-2,2'-diones so far, therefore, a novel and general approach would be desirable and of high value.

Recent years we have witnessed a phenomenal growth in the application of low-valent titanium reagent.[14-16] The application of low-valent titanium reagent in organic synthesis provides some chemical processes with attributes such as enhanced reaction rates, higher yields of products and easier workup. Thus, this reagent should become popular.

Results and discussion

Considering the above reports and in pursuing our work on new reductive cyclization procedures,[17-21] we wanted to study the synthesis of compound **3a** using salicylidendphenylhydrazone (**1a**) and triphosgene **2** as starting materials. To our surprise, 1*H*,1'*H*-1,1'-binaphtho[1,2-*e*][1,3]oxazine-3,3'(2*H*,2'*H*)-dione (**4a**) was obtained as our final product (Scheme 1), while the expected product **3a**, was not detected.

The IR spectrum of **4a** showed intense peaks at 3233, 3148 cm^{-1} for secondary amine (NH) and 1733, 1705 cm^{-1} for carbonyl (C=O). ^1H NMR spectra of **4a** showed two singlets at δ 5.34 and 5.35 for the methyne proton. The structure of **4a** was confirmed by single-crystal X-ray analysis (Figure 2).[22] The crystallographic data are shown in Table 1.

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Received April 11, 2011; revised June 22, 2011; accepted July 12, 2011.
Project supported by the National Natural Science Foundation of China (No. 21072144) and the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 10KJA150049).

Scheme 1

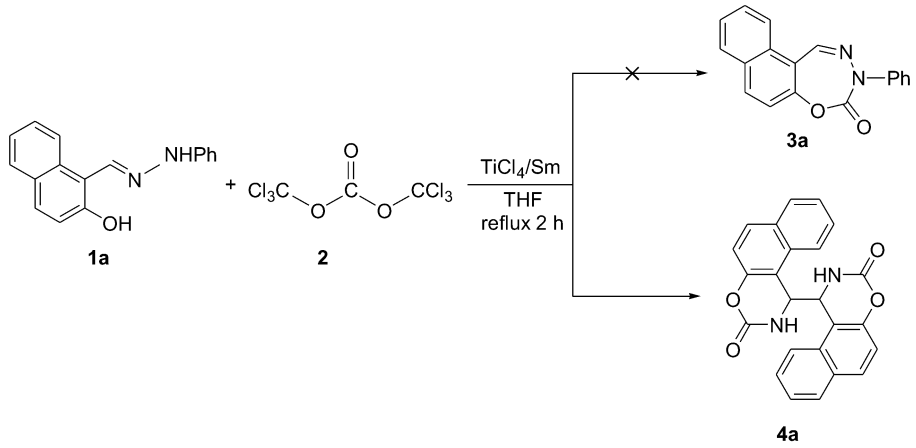


Table 1 Crystallographic data of compound **4a**

Empirical formula	$C_{24}H_{14}N_2O_4$
Formula weight	394.37
Temperature	223(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions	a=7.5307(15) Å, α=100.47(3)°
	b=11.066(2) Å, β=96.25(3)°
	c=12.088(2) Å, γ=105.58(3)°
Volume	940.9(3) Å^3
Z	2
Density (calculated)	1.392 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	408
Crystal size	0.45 mm×0.40 mm×0.20 mm
Theta range for data collection	3.40 to 27.50°
Limiting indices	$-9\leqslant h\leqslant 9$, $-11\leqslant k\leqslant 14$, $-15\leqslant l\leqslant 14$
Reflections collected	8440
Independent reflections	4070 [R(int)=0.0284]
Data/restraints/parameters	4070/0/272
Goodness-of-fit on F^2	1.270
Final R indices [$I>2\sigma(I)$]	R_1=0.0857, wR_2=0.2359
R indices (all data)	R_1=0.1140, wR_2=0.3151
Largest diff. peak and hole	0.677 and −0.647 e•Å^{-3}

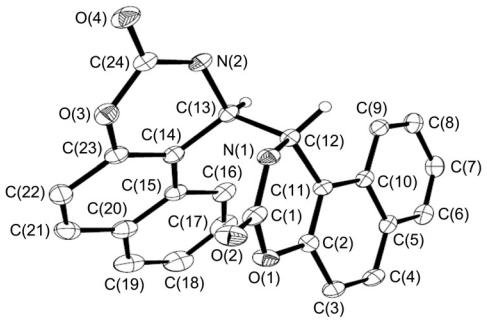
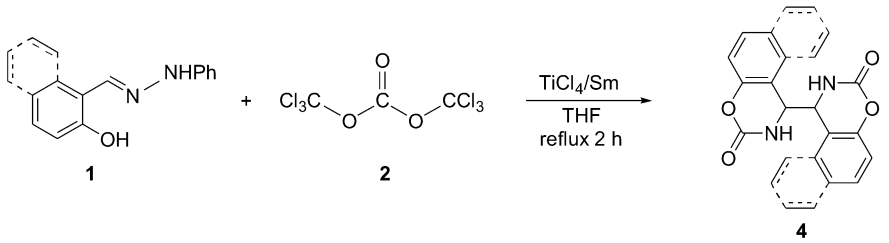


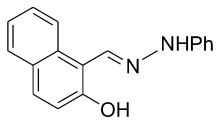
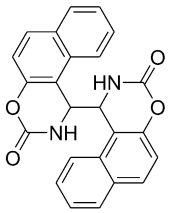
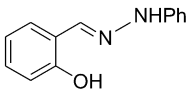
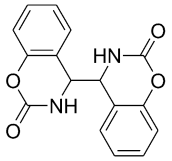
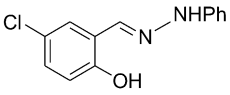
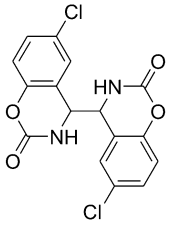
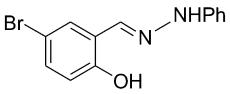
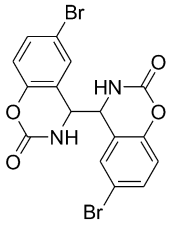
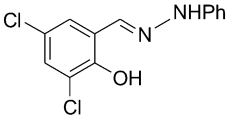
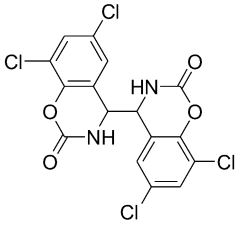
Figure 2 Molecular structure of product **4a**.

Then we performed the reaction of a variety of salicylidendphenylhydrazones **1** and triphosgene **2** via low-valent titanium reagent ($TiCl_4$/Sm) (Scheme 2). It was particularly noteworthy that the method could be applied to substituted salicylals with either electron-donating groups (such as alkyl, alkoxyl groups) or electron-withdrawing groups (such as halide groups), which highlighted the wide scope of the reaction. The results are summarized in Table 2.

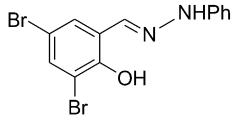
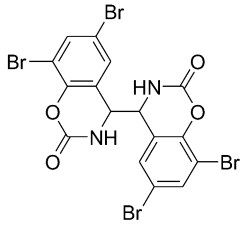
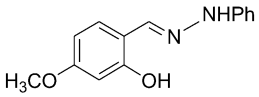
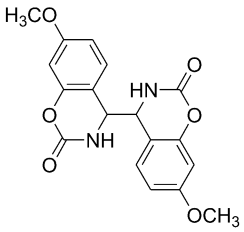
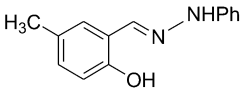
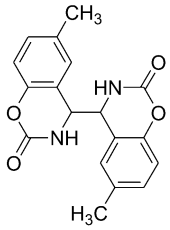
Considering atom economy, we then study the reactions of triphosgene **2** and salicylaldhydrazone under

Table 2 Synthesis of products **4**[a]



Entry	Salicylidendphenylhydrazone	Product	Yield/%
1		 **4a**	89
2		 **4b**	90
3		 **4c**	90
4		 **4d**	85
5		 **4e**	88

Continued

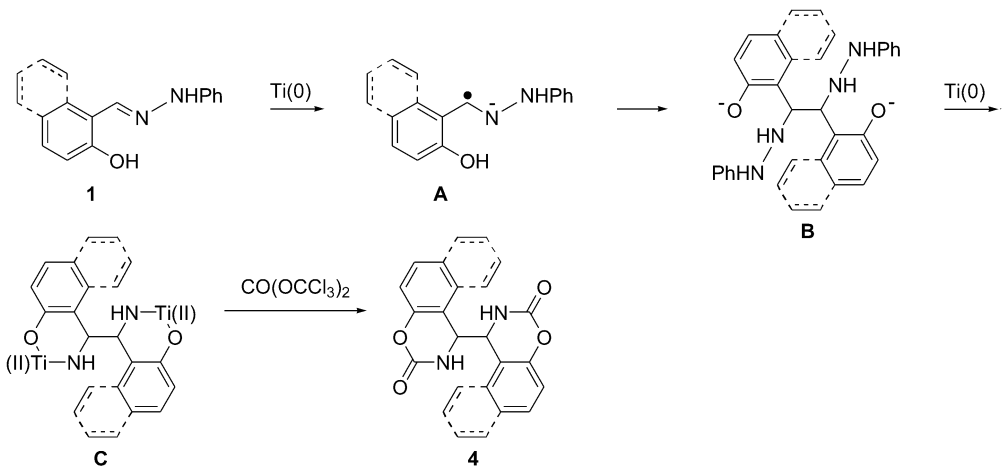
Entry	Salicylidendphenylhydrazone	Product	Yield/%
6		 **4f**	92
7		 **4g**	87
8		 **4g**	96

[a] All the products were characterized by ^{1}H NMR, IR spectra and HRMS.

the same conditions. However, the reactions were complex, only trace of the desired products were detected.

Although the mechanism of the reaction has not yet been established, a possible explanation is proposed in Scheme 2. $TiCl_4$ is reduced by Sm dust to give low-valent titanium species. First, an electron is transferred from low-valent titanium to salicylidendphenylhydrazone **1** to give a radical anion **A**. The two molecules of radical anion **A** couples each other to give **B**. Under the low-valent titanium reagent, N—N bond in **B** was cracked to form **C**. Then intermediate **C** cyclized to triphosgene to give the products **4**.

Scheme 2 Proposed mechanism



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In summary, the present method provides a useful preparation of 3,3',4,4'-tetrahydro-4,4'-bibenzo[*e*][1,3]-oxazine-2,2'-dione derivatives which cannot be prepared otherwise. A series of 3,3',4,4'-tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-diones were synthesized by the reaction of various salicylidendphenylhydrazones and triphosgene induced by low-valent titanium reagent ($TiCl_4$/Sm). A variety of substrates can participate in the process with good yields. Importantly, all the products we synthesized are new compounds. Our approach features the first successful reductive coupling of salicylidendphenylhydrazones and triphosgene, possessing the advantages of accessible starting materials, good yields and short reaction time. Thus, we developed a novel versatile method for the synthesis of 3,3',4,4'-tetrahydro-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-diones and hence offering easy access to a diverse array of *N*-heterocyclic compounds.

Experimental

THF was distilled from sodium-benzophenone immediately prior to use. All the reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 solution with TMS as internal standard. HRMS were obtained on a micromа GCT-TOF instrument. X-Ray diffractions were recorded on a Siemens P4 diffractometer.

General procedure for the synthesis of bibenzo[*e*]-[1,3]oxazine-2,2'-diones 4

$TiCl_4$ (0.5 mL, 4 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.6 g, 4 mmol) in freshly distilled anhydrous THF (10 mL) at room temperature under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to temperature and a solution of salicylidendphenylhydrazones (1 mmol) and triphosgene (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 2 h under N_2 atmosphere. After this period, the TLC analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (30 mL) and extracted with $ClCH_2CH_2Cl$ (50 mL × 3). The extracts were washed with water (50 mL × 3) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by recrystallization from 95% ethanol and DMF.

1*H*,1'*H*-1,1'-Binaphtho[1,2-*e*][1,3]oxazine-3,3'(2*H*,2'*H*)dione (**4a**): m.p. > 300 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 5.34 (s, 1H, CH), 5.35 (s, 1H, CH), 6.84 (d, J = 12.0 Hz, 2H, ArH), 7.08—7.09 (m, 4H, ArH), 7.36—7.39 (m, 2H, ArH), 7.82 (d, J = 8.0 Hz, 2H, ArH), 7.79 (d, J = 8.0 Hz, 2H, ArH), 8.77 (s, 1H, NH), 8.78 (s, 1H, NH); IR (KBr) ν: 3233, 3148, 2941, 1754, 1655, 1633, 1587, 1518, 1466, 1439, 1399, 1379, 1300, 1223, 1181, 1161, 1112, 994, 914, 808, 747 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{17}N_2O_4$ $[M+H]^+$ 311.1032, found 311.1040.

3,3',4,4'-Tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]-oxazine-2,2'-dione (**4b**): m.p. > 300 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 4.64 (s, 2H, 2×CH), 6.62 (d, J = 7.6 Hz, 1H, ArH), 6.82 (d, J = 8.4 Hz, 1H, ArH), 6.94 (d, J = 8.0 Hz, 1H, ArH), 7.03 (t, J = 7.6 Hz, 1H, ArH), 7.12—7.16 (m, 1H, ArH), 7.28—7.35 (m, 3H, ArH), 8.35 (s, 1H, NH), 8.47 (s, 1H, NH); IR (KBr) ν: 3243, 3144, 2940, 2360, 2341, 1733, 1618, 1594, 1460, 1406, 1317, 1250, 1225, 1190, 1099, 1030, 939, 911, 782, 750 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}N_2O_4Na$ $[M+Na]^+$ 319.0695, found 319.0697.

6,6'-Dichloro-3,3',4,4'-tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-dione (**4c**): m.p. > 300 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 4.68 (s, 2H, 2×CH), 6.72 (s, 1H, ArH), 6.98—7.02 (m, 2H, ArH), 7.39—7.40 (m, 2H, ArH), 7.56—7.57 (m, 1H, ArH), 8.27 (s, 1H, NH), 8.63 (s, 1H, NH); IR (KBr) ν: 3239, 3149, 3042, 2945, 1733, 1613, 1589, 1493, 1475, 1421, 1378, 1286, 1261, 1241, 1210, 1185, 1105, 1082, 933, 913, 905, 822, 761 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{10}Cl_2N_2O_4Na$ $[M+Na]^+$ 386.9916, found 386.9910.

6,6'-Dibromo-3,3',4,4'-tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-dione (**4d**): m.p. > 300 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 4.68 (s, 2H, 2×CH), 6.84 (s, 2H, ArH), 6.92—6.96 (m, 2H, ArH), 7.52—7.54 (m, 2H, ArH), 8.63 (s, 2H, 2×NH); IR (KBr) ν: 3244, 3151, 2942, 1717, 1652, 1613, 1585, 1558, 1490, 1463, 1381, 1285, 1265, 1244, 1223, 1184, 1125, 1098, 1073, 940, 904, 885, 823, 769 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{10}Br_2N_2O_4Na$ $[M+Na]^+$ 474.8905, found 474.8929.

6,6,8,8'-Tetrachloro-3,3'4,4'-tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-dione (**4e**): m.p. > 300 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 4.72 (s, 2H, 2×CH), 6.76 (s, 2H, ArH), 7.74—7.75 (m, 2H, ArH), 8.86 (s, 2H, 2×NH); IR (KBr) ν: 3264, 3160, 2929, 1755, 1735, 1670, 1458, 1376, 1320, 1292, 1206, 1183, 1088, 980, 939, 871, 837, 752 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_8Cl_4N_2O_4Na$ $[M+Na]^+$ 454.9136, found 454.9153.

6,6,8,8'-Tetrabromo-3,3'4,4'-tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-dione (**4f**): m.p. > 300 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 4.70 (s, 2H, 2×CH), 6.88 (s, 2H, ArH), 7.93 (s, 2H, ArH), 8.84 (s, 2H, 2×NH); IR (KBr) ν: 3245, 3160, 2949, 1717, 1607, 1418, 1381, 1285, 1223, 1125, 1088, 940, 909, 823, 769 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_8Br_4N_2O_4Na$ $[M+Na]^+$ 630.7116, found 630.7131.

7,7'-Dimethoxy-3,3',4,4'-tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-dione (**4g**): m.p. > 300 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: 3.58 (s, 6H, 2×CH_3O), 4.62 (s, 2H, 2×CH), 6.20 (s, 2H, ArH), 6.88 (s, 4H, ArH), 8.36 (s, 2H, 2×NH); IR (KBr) ν: 3233, 3142, 2938, 1734, 1629, 1596, 1515, 1444, 1403, 1302, 1187, 1158, 1131, 1113, 1030, 830, 798, 752 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}N_2O_6Na$ $[M+Na]^+$ 379.0906, found 379.0922.

6,6'-Dimethyl-3,3',4,4'-tetrahydro-2*H*,2'*H*-4,4'-bibenzo[*e*][1,3]oxazine-2,2'-dione (**4h**): m.p.＞300 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.14 (s, 6H, 2×CH_3), 4.54 (s, 1H, CH), 4.55 (s, 1H, CH), 6.36 (s, 2H, ArH), 6.81 (d, J=8.0 Hz, 2H, ArH), 7.12 (d, J=8.0 Hz, 2H, ArH), 8.40 (s, 1H, NH), 8.41 (s, 1H, NH); IR (KBr) v: 3238, 3151, 3029, 2945, 2920, 1723, 1618, 1605, 1504, 1478, 1377, 1304, 1268, 1255, 1157, 1120, 1098, 927, 842, 811, 766, 724 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}N_2O_4Na$ $[M+Na]^+$ 347.1008, found 347.1017.

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22 Crystallographic data for the structures of **4a** have been deposited at the Cambridge Crystallographic Data Centre, deposit number is CCDC-826853. Copies of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +441223 336 033; E-mail: deposit@ccdc.cam.ac.uk).

(E1104112 Zhao, C.; Zheng, G.)

