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A SIMPLE ONE-POT SYNTHESIS OF BENZOXAZINE- 2,4-DIONES AND BENZOTHIAZINE-2,4-DIONES †

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Abstract — A simple and efficient procedure has been developed for a one-pot synthesis of substituted benzoxazine-2,4-diones and benzothiazine-2,4-diones directly from salicylic acid (or thiosalicylic acid) and amines.

Synthetic chemists are becoming increasingly interested in the synthesis of substituted benzoxazine-2,4-diones due to their utility in pharmacology[1-4] and photography.[5] Hence, considerable effort has been devoted to the preparation of benzoxazine-2,4-diones by using a wide variety of synthetic approaches, including palladium-catalyzed cyclocarbonylation of *o*-iodophenols with heterocumulenes,[6] reaction of phenyl salicylate with isocyanates,[7] cyclization of salicylic acid with isothiocyanate in the presence of silver trifluoroacetate,[8] preparation from salicylamide[9] and other methods.[10] In this paper, we describe a new and efficient process for the synthesis of substituted benzoxazine-2,4-diones in one pot directly from salicylic acid and amines.

Initially, compound (**4a**) was prepared by cyclization of salicylamide with ethyl chloroformate according to the known procedure,[11] which took three steps from commercially available acetylsalicyloyl chloride. Scheme 1 illustrates this synthetic approach. Reaction of acetylsalicyloyl chloride with 3,4-

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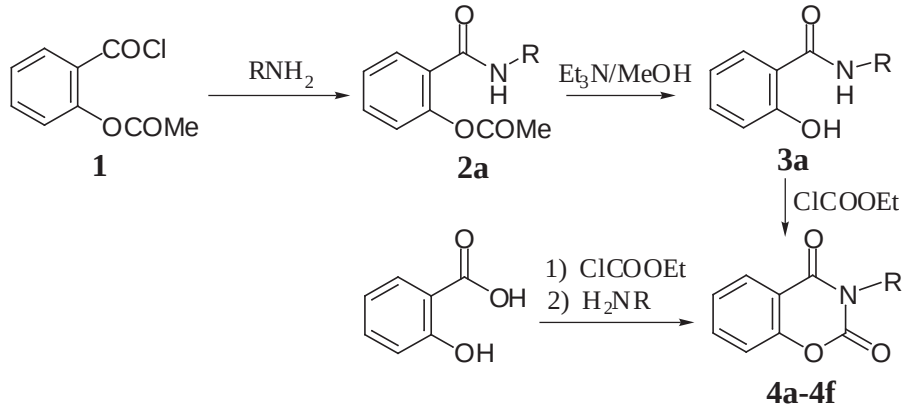
dimethoxyphenethylamine was carried out to give acetylsalicylamide (**2a**), and then compound (**2a**) was deacetylated with triethylamine/methanol to afford salicylamide (**3a**). Compound (**3a**) was cyclized with ethyl chloroformate to give compound (**4a**).

We realized that the existing methods include multi-step procedures, use of expensive catalyst or conversion of amine to isocyanates for synthesis of benzoxazine-2,4-dione derivatives, which provided us impetus to develop a simple and practical method to synthesize benzoxazine-2,4-dione derivatives. We found that benzoxazine-2,4-dione derivatives could be prepared in a one-pot reaction directly from salicylic acid and amines (Scheme 1). Salicylic acid was treated with ethyl chloroformate and the reaction mixture was evaporated at reduced pressure to remove unreacted ethyl chloroformate. Stirring the resulting residue with amines in the presence of triethylamine afforded the substituted benzoxazine-2,4-diones (**4a-4f**), whose structures have been confirmed by NMR and MS spectrometries.



a, R = 3,4-dimethoxyphenethyl b, R = benzyl c, R = 3,4-dimethylphenyl
d, R = 3-indolylethyl e, R = 2,6-dimethoxypyridin-3-yl f, R = 4-imidazolylethyl

Scheme 1

The mechanistic scheme for the one-pot synthesis of benzoxazine-2,4-dione is proposed in Scheme 2. Initially, we attempted to characterize the structures of intermediates produced by the reaction of salicylic acid with ethyl chloroformate. In this regard, salicylic acid was stirred with ethyl chloroformate in the presence of triethylamine at 0°C, the solvent then was evaporated under vacuum and the residue was extracted with ether and concentrated to obtain crude intermediate. The resulting liquid intermediate, however, proved hard to handle and we failed to acquire pure intermediate for further structure identification. We therefore modified the procedure to use 5-nitrosalicylic acid as the starting material for reaction with ethyl chloroformate in a dry ice-acetone bath. The resulting intermediate could be recrystallized from ether, and X-Ray crystallographic analysis (Figure 1) confirmed it to be anhydride (**6**). The results of the X-Ray study are illustrated in Figure 1. Most of the molecule is essentially planar. Excluding the 6 atoms in the O1 to C9 chain, the remainder of the molecule is planar (rms deviation of 0.21 Å for the 17 atoms). The O1 to C9 chain itself is planar (rms deviation of 0.05 Å) and is

approximately perpendicular to the plane through the rest of the molecule (the dihedral angle between the two planes is ~97 °). Both chains (O1 to C9 and C10 to C13) extend away from the aromatic ring with a dihedral angle of ~120 ° between the best planes through the two chains. There is one close intermolecular approach of 3.05 Å between C4 and O6 in a neighboring molecule (Tables 2, 3, 4, 5 and 6).

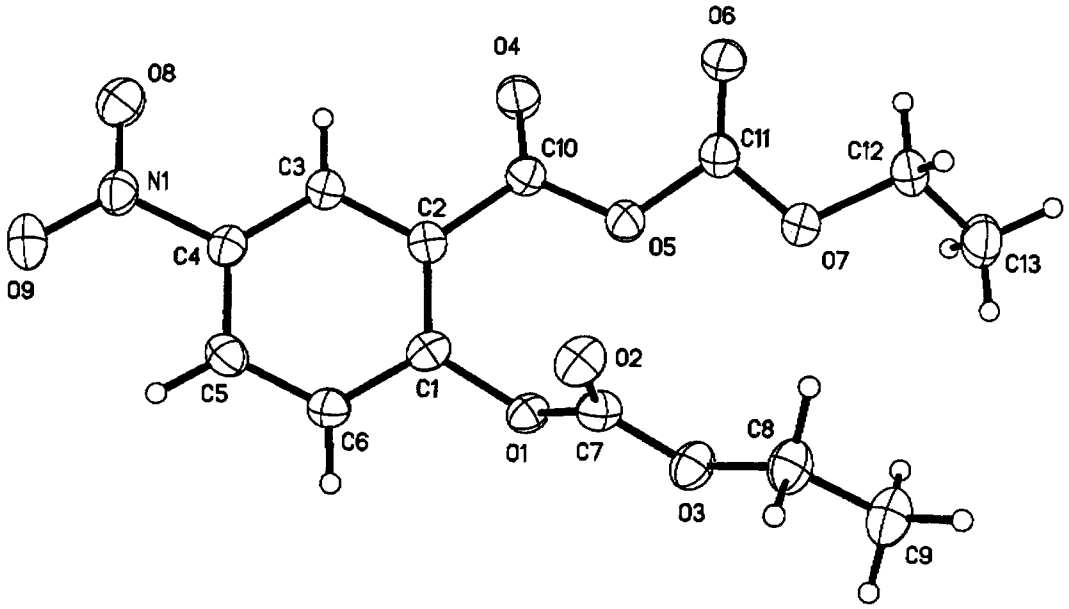
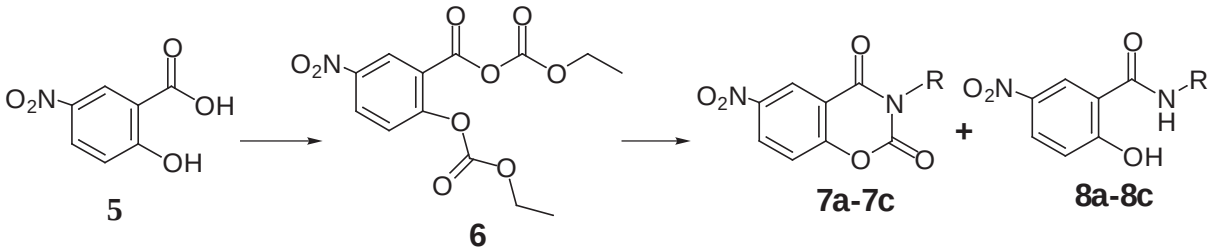


Figure 1, X-Ray structure of anhydride (**6**), drawn using experimentally determined coordinates with the thermal ellipsoids at the 20% probability level.

Depending on the nucleophilicity of the specific amines and reaction temperature, the reaction of anhydride (**6**) with amines may produce benzoxazine-2,4-diones (**7**) and/or salicylic amide (**8**) (Scheme 2 and Table 1). This results from nucleophilic attack on the anhydride or ethoxycarbonyl group in the intermediate (**6**) by amines.



a R = 3,4-dimethylphenyl, b R = 3,4-dimethoxyphenethyl, c R = *n*-butyl

Scheme 2

Table 1. Reaction of anhydride (**6**) with amines

Amine	Reaction temperature	**7**	**8**
3,4-Dimethylaniline	0°C to rt	69%	0%
3,4-Dimethoxyphenethylamine	0°C to rt	9%	63%
n-Butylamine	0°C	79%	0%

Table 2. Crystal data and structure refinement for Molecule (**6**).

Empirical formula	$C_{13}\,H_{13}\,N\,O_9$	
Formula weight	327.24	
Temperature	273(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.394(5) Å	α= 90°.
	b = 7.873(3) Å	β= 106.43(3)°.
	c = 15.588(5) Å	γ = 90°.
Volume	1459.0(9) $Å^3$	
Z	4	
Density (calculated)	1.490 Mg/m^3	
Absorption coefficient	1.120 mm^{-1}	
F(000)	680	
Crystal size	0.09 x 0.22 x 0.50 mm^3	
Theta range for data collection	3.72 to 66.83°.	
Index ranges	-13<=h<=14, -8<=k<=9, -14<=l<=17	
Reflections collected	6860	
Independent reflections	2449 [R(int) = 0.0427]	
Completeness to theta = 66.83°	94.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2449 / 53 / 417	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1298	
R indices (all data)	R1 = 0.0560, wR2 = 0.1443	
Extinction coefficient	0.0168(11)	
Largest diff. peak and hole	0.168 and -0.201 $e.Å^{-3}$	

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Molecule (**6**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5722(1)	713(1)	9462(1)	54(1)
C(1)	4809(1)	449(1)	8717(1)	51(1)
N(1)	1791(1)	-40(2)	6671(1)	70(1)
C(2)	4352(1)	-1165(2)	8498(1)	49(1)
O(2)	6949(1)	256(2)	8652(1)	71(1)
O(3)	7480(1)	665(2)	10149(1)	64(1)
C(3)	3356(1)	-1312(2)	7816(1)	54(1)
C(4)	2861(1)	134(2)	7380(1)	57(1)
O(4)	4286(1)	-4081(1)	8854(1)	75(1)
O(5)	5885(1)	-2645(1)	9490(1)	63(1)
C(5)	3330(1)	1736(2)	7576(1)	62(1)
O(6)	6435(1)	-5365(2)	9329(1)	69(1)
C(6)	4314(1)	1883(2)	8260(1)	60(1)
C(7)	6758(1)	524(2)	9349(1)	55(1)
O(7)	7337(1)	-3661(1)	10455(1)	71(1)
O(8)	1354(1)	-1411(2)	6522(1)	94(1)
C(8)	8643(1)	376(3)	10188(1)	76(1)
O(9)	1396(1)	1236(2)	6253(1)	98(1)
C(9)	9288(2)	310(4)	11151(1)	92(1)
C(10)	4804(1)	-2802(2)	8945(1)	55(1)
C(11)	6540(1)	-4074(2)	9730(1)	58(1)
C(12)	8168(2)	-4996(2)	10802(1)	83(1)
C(13)	8665(2)	-4730(3)	11762(1)	92(1)
O(1A)	5727(2)	-685(5)	9466(2)	82(2)
C(1A)	4816(2)	-437(2)	8718(3)	69(2)
N(1A)	1793(3)	-2(3)	6674(3)	97(4)
C(2A)	4352(3)	1172(2)	8495(3)	61(2)
O(2A)	6954(3)	-224(12)	8656(2)	113(3)
O(3A)	7482(2)	-618(9)	10154(2)	90(2)
C(3A)	3349(3)	1301(3)	7819(3)	69(2)
C(4A)	2861(3)	-153(3)	7387(3)	85(4)
O(4A)	4291(3)	4096(4)	8838(4)	103(2)
O(5A)	5881(2)	2653(3)	9489(3)	87(2)
C(5A)	3323(3)	-1756(3)	7603(4)	81(3)
O(6A)	6447(5)	5356(4)	9314(3)	98(3)
C(6A)	4312(4)	-1884(3)	8282(4)	86(3)
C(7A)	6765(2)	-548(12)	9348(2)	90(3)
O(7A)	7331(3)	3681(4)	10458(2)	98(2)
O(8A)	1294(4)	1324(4)	6569(5)	100(3)

C(8A)	8648(2)	-378(18)	10192(2)	115(5)
O(9A)	1389(6)	-1306(5)	6288(6)	177(6)
C(9A)	9299(4)	-360(30)	11154(3)	159(9)
C(10A)	4809(2)	2817(3)	8928(3)	79(2)
C(11A)	6534(3)	4085(4)	9731(3)	81(3)
C(12A)	8152(4)	5035(7)	10799(3)	155(6)
C(13A)	8728(9)	4694(15)	11740(4)	176(10)

Table 4. Bond lengths [Å] and angles [°] for Molecule (**6**)

O(1)-C(7)	1.3524(16)	O(1A)-C(7A)	1.353(2)
O(1)-C(1)	1.3886(16)	O(1A)-C(1A)	1.389(2)
C(1)-C(6)	1.3819(18)	C(1A)-C(6A)	1.382(2)
C(1)-C(2)	1.3941(17)	C(1A)-C(2A)	1.394(2)
N(1)-O(8)	1.2004(18)	N(1A)-O(8A)	1.201(3)
N(1)-O(9)	1.2224(18)	N(1A)-O(9A)	1.223(3)
N(1)-C(4)	1.4727(18)	N(1A)-C(4A)	1.473(2)
C(2)-C(3)	1.3874(18)	C(2A)-C(3A)	1.388(2)
C(2)-C(10)	1.4960(17)	C(2A)-C(10A)	1.496(2)
O(2)-C(7)	1.1944(18)	O(2A)-C(7A)	1.195(2)
O(3)-C(7)	1.3181(15)	O(3A)-C(7A)	1.319(2)
O(3)-C(8)	1.4433(19)	O(3A)-C(8A)	1.443(3)
C(3)-C(4)	1.3780(19)	C(3A)-C(4A)	1.378(2)
C(4)-C(5)	1.386(2)	C(4A)-C(5A)	1.387(3)
O(4)-C(10)	1.1813(16)	O(4A)-C(10A)	1.181(2)
O(5)-C(10)	1.3739(16)	O(5A)-C(10A)	1.375(2)
O(5)-C(11)	1.3763(16)	O(5A)-C(11A)	1.377(2)
C(5)-C(6)	1.379(2)	C(5A)-C(6A)	1.379(3)
O(6)-C(11)	1.1808(18)	O(6A)-C(11A)	1.182(3)
O(7)-C(11)	1.3149(17)	O(7A)-C(11A)	1.315(2)
O(7)-C(12)	1.464(2)	O(7A)-C(12A)	1.466(3)
C(8)-C(9)	1.489(2)	C(8A)-C(9A)	1.489(3)
C(12)-C(13)	1.464(3)	C(12A)-C(13A)	1.464(3)
C(7)-O(1)-C(1)	116.96(11)	C(1)-C(2)-C(10)	126.78(11)
C(6)-C(1)-O(1)	116.50(11)	C(7)-O(3)-C(8)	115.46(12)
C(6)-C(1)-C(2)	121.90(12)	C(4)-C(3)-C(2)	119.00(13)
O(1)-C(1)-C(2)	121.30(11)	C(3)-C(4)-C(5)	122.86(13)
O(8)-N(1)-O(9)	123.00(14)	C(3)-C(4)-N(1)	118.28(12)

O(8)-N(1)-C(4)	119.37(12)	C(5)-C(4)-N(1)	118.86(12)
O(9)-N(1)-C(4)	117.63(13)	C(10)-O(5)-C(11)	119.42(10)
C(3)-C(2)-C(1)	118.36(11)	C(6)-C(5)-C(4)	118.07(13)
C(3)-C(2)-C(10)	114.83(11)	C(5)-C(6)-C(1)	119.77(13)
O(2)-C(7)-O(3)	128.24(13)	C(1A)-C(2A)-C(10A)	126.7(2)
O(2)-C(7)-O(1)	125.30(12)	C(7A)-O(3A)-C(8A)	115.5(2)
O(3)-C(7)-O(1)	106.45(11)	C(4A)-C(3A)-C(2A)	119.0(2)
C(11)-O(7)-C(12)	114.76(12)	C(3A)-C(4A)-C(5A)	122.9(2)
O(3)-C(8)-C(9)	107.07(15)	C(3A)-C(4A)-N(1A)	118.5(2)
O(4)-C(10)-O(5)	123.60(11)	C(5A)-C(4A)-N(1A)	118.5(2)
O(4)-C(10)-C(2)	123.98(12)	C(10A)-O(5A)-C(11A)	119.0(2)
O(5)-C(10)-C(2)	112.41(10)	C(6A)-C(5A)-C(4A)	118.0(2)
O(6)-C(11)-O(7)	127.70(14)	C(5A)-C(6A)-C(1A)	119.8(2)
O(6)-C(11)-O(5)	126.29(13)	O(2A)-C(7A)-O(3A)	128.1(3)
O(7)-C(11)-O(5)	105.86(11)	O(2A)-C(7A)-O(1A)	125.2(3)
O(7)-C(12)-C(13)	108.87(17)	O(3A)-C(7A)-O(1A)	106.2(2)
C(7A)-O(1A)-C(1A)	117.0(2)	C(11A)-O(7A)-C(12A)	114.3(3)
C(6A)-C(1A)-O(1A)	116.4(2)	O(3A)-C(8A)-C(9A)	107.1(3)
C(6A)-C(1A)-C(2A)	122.0(2)	O(4A)-C(10A)-O(5A)	123.4(3)
O(1A)-C(1A)-C(2A)	121.1(2)	O(4A)-C(10A)-C(2A)	124.1(2)
O(8A)-N(1A)-O(9A)	122.7(3)	O(5A)-C(10A)-C(2A)	112.32(19)
O(8A)-N(1A)-C(4A)	119.4(3)	O(6A)-C(11A)-O(7A)	127.5(3)
O(9A)-N(1A)-C(4A)	117.3(3)	O(6A)-C(11A)-O(5A)	126.0(3)
C(3A)-C(2A)-C(1A)	118.24(18)	O(7A)-C(11A)-O(5A)	106.2(2)
C(3A)-C(2A)-C(10A)	115.04(18)	C(13A)-C(12A)-O(7A)	108.8(3)

Table 5. Anisotropic displacement parameters ($Å^2x\ 10^3$)for Molecule (**6**). The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	56(1)	58(1)	49(1)	-8(1)	17(1)	-6(1)
C(1)	56(1)	53(1)	47(1)	-3(1)	19(1)	0(1)
N(1)	58(1)	87(1)	61(1)	3(1)	7(1)	5(1)
C(2)	55(1)	49(1)	46(1)	1(1)	18(1)	0(1)
O(2)	72(1)	88(1)	60(1)	-8(1)	29(1)	-6(1)
O(3)	57(1)	77(1)	58(1)	-6(1)	15(1)	-2(1)
C(3)	57(1)	54(1)	53(1)	-2(1)	16(1)	-3(1)

C(4)	56(1)	67(1)	48(1)	0(1)	15(1)	9(1)
O(4)	65(1)	57(1)	96(1)	11(1)	10(1)	-9(1)
O(5)	59(1)	53(1)	67(1)	5(1)	5(1)	-2(1)
C(5)	74(1)	55(1)	57(1)	8(1)	20(1)	10(1)
O(6)	73(1)	66(1)	65(1)	-4(1)	15(1)	5(1)
C(6)	73(1)	48(1)	63(1)	0(1)	23(1)	-1(1)
C(7)	58(1)	53(1)	58(1)	-4(1)	22(1)	-5(1)
O(7)	65(1)	68(1)	69(1)	-5(1)	2(1)	5(1)
O(8)	68(1)	92(1)	103(1)	-5(1)	-7(1)	-5(1)
C(8)	58(1)	96(1)	78(1)	-1(1)	22(1)	2(1)
O(9)	92(1)	103(1)	82(1)	17(1)	0(1)	23(1)
C(9)	66(1)	121(2)	84(2)	-3(1)	10(1)	5(1)
C(10)	56(1)	54(1)	53(1)	1(1)	15(1)	-4(1)
C(11)	62(1)	57(1)	56(1)	5(1)	19(1)	0(1)
C(12)	64(1)	86(1)	87(2)	8(1)	2(1)	7(1)
C(13)	82(1)	98(1)	82(1)	3(1)	-2(1)	16(1)
O(1A)	75(3)	97(4)	69(3)	13(3)	14(3)	-3(3)
C(1A)	83(5)	65(5)	61(4)	1(4)	22(4)	10(4)
N(1A)	110(8)	87(7)	104(9)	-2(6)	45(7)	39(6)
C(2A)	70(5)	52(4)	61(4)	-15(3)	20(3)	-15(4)
O(2A)	108(6)	154(8)	87(6)	17(5)	44(4)	14(5)
O(3A)	72(4)	122(5)	74(4)	19(3)	16(3)	4(3)
C(3A)	75(5)	68(5)	67(5)	21(4)	27(4)	15(4)
C(4A)	81(7)	94(7)	81(7)	-18(5)	24(6)	-46(5)
O(4A)	77(4)	86(4)	137(5)	-25(4)	13(4)	3(3)
O(5A)	77(3)	81(3)	91(4)	-4(3)	1(3)	6(3)
C(5A)	87(6)	80(6)	70(6)	5(4)	11(4)	-19(5)
O(6A)	96(5)	95(6)	112(6)	24(4)	47(4)	13(4)
C(6A)	100(6)	64(5)	101(7)	0(4)	40(5)	-4(5)
C(7A)	67(5)	102(7)	100(7)	-3(5)	22(5)	8(5)
O(7A)	81(4)	106(4)	93(4)	-4(3)	1(3)	1(3)
O(8A)	86(5)	127(6)	77(5)	2(4)	5(4)	-4(4)
C(8A)	75(7)	155(13)	118(9)	-5(7)	33(6)	-4(7)
O(9A)	184(12)	182(11)	143(9)	-83(7)	10(8)	-29(9)
C(9A)	84(10)	240(20)	126(13)	-7(12)	-10(9)	-13(10)
C(10A)	77(5)	75(5)	83(5)	-10(4)	20(4)	-5(4)
C(11A)	79(5)	88(6)	69(5)	-5(4)	12(4)	-2(5)
C(12A)	170(11)	169(9)	91(7)	-74(6)	-21(7)	122(8)
C(13A)	190(20)	190(20)	150(16)	-14(12)	50(14)	-9(14)

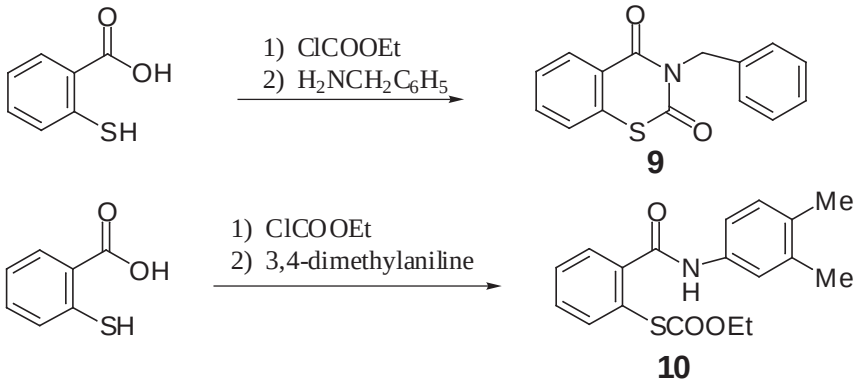
Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Molecule (**6**).

	x	y	z	U(eq)
H(3A)	3027	-2370	7656	65
H(5A)	2991	2685	7256	74
H(6A)	4644	2942	8414	72
H(8A)	8920	1290	9890	92
H(8B)	8721	-686	9896	92
H(9A)	10068	108	11204	139
H(9B)	9002	-592	11439	139
H(9C)	9211	1371	11431	139
H(12A)	8750	-4959	10497	100
H(12B)	7809	-6101	10698	100
H(13A)	9215	-5596	11995	139
H(13B)	8086	-4783	12061	139
H(13C)	9020	-3635	11861	139
H(3AA)	3011	2353	7659	83
H(5AA)	2975	-2714	7298	98
H(6AA)	4640	-2942	8446	103
H(8AA)	8746	685	9908	138
H(8AB)	8905	-1298	9884	138
H(9AA)	10083	-195	11206	239
H(9AB)	9197	-1415	11426	239
H(9AC)	9037	558	11450	239
H(12C)	8694	5073	10456	186
H(12D)	7773	6124	10741	186
H(13D)	9300	5536	11960	264
H(13E)	9067	3589	11796	264
H(13F)	8194	4736	12082	264

3,4-Dimethylaniline was reacted with intermediate (**6**), from 0°C to rt, to give the single product (**7a**). However, compound (**8b**), in addition to **7b**, was obtained as a major product when reaction of anhydride (**6**) with 3,4-dimethoxyphenethylamine was performed under the same conditions. Compared to 3,4-dimethoxyphenethylamine, butylamine, that possesses less steric hindrance and more nucleophilicity, when reacted with **6** at 0°C afforded only benzoxazine-2,4-dione (**7c**). The one-pot reactions shown in Scheme 1, gave benzoxazine-2,4-diones as a single product when the reaction was carried out from 0°C

to rt. If, however, the reaction was performed at rt or above, a small amount of salicylamide (**3a**), in addition to major product (**4a**)**,** also was obtained. Hence, the substituted group on the salicylic acid, the nucleophilicity of the amine and reaction temperature all play a key role in this reaction.

When this method was applied to thiosalicylic acid, benzothiazine-2,4-diones (**9**) was produced with benzylamine. However, thiosalicylamide ester (**10**) was obtained with 3,4-dimethylaniline (Scheme 3).



Scheme 3

In summary, the present procedure provides a simple, efficient and convenient one-pot synthesis for different kinds of benzoxazine-2,4-dione derivatives and benzyl substituted benzothiazine-2,4-dione derivatives. We believe that the described procedure will provide a better and more practical alternative to existing methods for synthesis of such derivatives.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer. MS spectra and HRMS were recorded on a VG 7070 mass spectrometer and Finnigan-1015D mass spectrometer. All exact mass measurements showed an error of less than 5 ppm. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

***N*-(3,4-Dimethoxyphenethyl)-2-acetoxybenzamide (2a)**: To an ice cold solution of 3,4-dimethoxyphenethylamine (0.26 mL, 1.5 mmol) and triethylamine (0.21 mL, 3.0 mmol) in $CHCl_3$ (20 mL), acetylsalicyloyl chloride (**1**) (300 mg, 1.5 mmol) was added, and the reaction mixture then was stirred at rt overnight. Thereafter, the solvent was removed, the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution and water, and dried over Na_2SO_4. Purification by column chromatography, using CH_2Cl_2/EtOAc (50:1) as an eluent, gave semi-solid compound (**2a**), which was recrystallized from ether to afford compound (**2a**) as white crystals (303 mg, 59%). mp 129°C; ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, J = 1.7 Hz, J = 7.7 Hz, 1H), 7.50-7.45 (m, 1H), 7.33 (dd, J = 1.1 Hz, J = 7.6 Hz, 1H), 7.09 (dd, J = 1.0 Hz, J = 8.1 Hz, 1H), 6.86-6.78 (m, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.69-3.63 (m, 2H), 2.88 (t, J = 6.8 Hz, 2H), 2.15 (s, 3H); MS (CI/CH_4) 343 $[M]^+$; HRMS m/z calcd for $C_{19}H_{21}NO_5$ 343.1420,

found 343.1431. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.34; H, 6.17; N, 4.03.

***N*-(3,4-Dimethoxyphenethyl)-2-hydroxybenzamide (3a)**: A solution of compound (**2a**) (32 mg, 0.093 mmol) in Et_3N/MeOH (1:1, 1 mL) was stirred at rt for one day. The solvent was evaporated under vacuum and recrystallized from ether to give compound (**3a**) (27 mg, 96%) as white crystals. mp 108°C; ^{1}H NMR ($CDCl_3$) δ 12.35 (s, 1H), 7.33-7.28 (m, 1H), 7.11 (dd, J = 1.5 Hz, J = 8.0 Hz, 1H), 6.90 (dd, J = 1.1 Hz, J = 8.4 Hz, 1H), 6.78-6.66 (m, 4H), 3.80 (s, 3H), 3.77 (s, 3H), 3.65-3.53 (m, 2H), 2.81 (t, J = 6.9 Hz, 2H); MS (CI/CH_4) 301 $[M]^+$; HRMS m/z calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1321. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.78; H, 6.44; N, 4.61.

3-(3,4-Dimethoxyphenethyl)benzoxazine-2,4-dione (4a): To an ice/salt cold solution of compound (**3a**) (27 mg, 0.090 mmol) and triethylamine (50 μL) in $CHCl_3$ (1 mL) was added ethyl chloroformate (17 μL, 0.18 mmol). The reaction mixture was allowed to rise to rt and stirring was continued at rt for one day. The solvent was removed under vacuum and the residue was applied to column chromatography (eluent: CH_2Cl_2) for purification and was recrystallized from ether to give compound (**4a**) (24 mg, 83%) as white crystals. mp 178°C; ^{1}H NMR ($CDCl_3$) δ 8.10 (dd, J = 1.5 Hz, J = 7.8 Hz, 1H), 7.90-7.70 (m, 1H), 7.43-7.34 (m, 1H), 7.31 (dd, J = 0.5 Hz, J = 8.3 Hz, 1H), 6.89-6.76 (m, 3H), 4.26 (t, J = 8.0 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.98 (t, J = 8.0 Hz, 2H). MS (CI/CH_4) m/z 327 $[M]^+$. Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.84; H, 5.40; N, 4.30.

General procedure for one-pot synthesis of compounds (4): To an ice/salt cold solution of salicylic acid **1** (139 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in chloroform (10 mL) was added ethyl chloroformate (0.22 mL, 2.2 mmol). The reaction mixture was allowed to rise to rt and was stirred for 3 h. The solvent was removed under vacuum to eliminate extra ethyl chloroformate, and the residue then was dissolved in $CHCl_3$ and cooled with ice. To the ice cold solution was added triethylamine (0.28 mL, 2mmol) and amine (1 mmol). The ice bath was removed and the reaction mixture was stirred at rt overnight. Thereafter, solvent was evaporated and the residue was applied to column chromatography (eluent: CH_2Cl_2/petroleum ether = 2) for purification and recrystallized from ether to give white crystals except indicated specifically.

3-Benzylbenzoxazine-2,4-dione (4b): yield 61%; mp 125°C (lit.,[12] 134°C); ^{1}H NMR ($CDCl_3$) δ 8.07 (dd, J = 1.5 Hz, J = 7.8 Hz, 1H), 7.68-7.67 (m, 1H), 7.53-7.50 (m, 2H), 7.37-7.26 (m, 5H), 5.19 (s, 2H); MS (CI/CH_4) m/z 253 $[M]^+$.

3-(3,4-Dimethylphenyl)benzoxazine-2,4-dione (4c): yield 63%; mp 209°C; ^{1}H NMR ($CDCl_3$) δ 8.15 (dd, J = 1.6 Hz, J = 7.9 Hz, 1H), 7.80-7.74 (m, 1H), 7.45-7.33 (m, 3H), 7.10-7.05 (m, 2H), 2.34 (s, 3H), 2.33 (s, 3H); MS (CI/CH_4) m/z 267 $[M]^+$; HRMS m/z calcd for $C_{16}H_{13}NO_3$ 267.0895, found 267.0885. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.61; H, 4.96; N, 5.22.

3-(3-Indolylethyl)benzoxazine-2,4-dione (4d): The precipitate was collected by filtration, washed with cold $CHCl_3$ and recrystallized from EtOAc to give **4d** as white crystals in the yield of 63%; mp 222°C; ^{1}H NMR (DMSO-d_6) δ 10.89 (s, 1H), 7.99 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.84-7.78 (m, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.46-7.41 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.11 (s, 1H), 7.09-6.96 (m, 2H), 4.11 (t, J = 8.1 Hz, 2H), 2.99 (t, J = 8.1 Hz, 2H); HRMS m/z calcd for $C_{18}H_{14}N_2O_3$ 306.1004, found 306.1017. Anal. Calcd for $C_{18}H_{14}N_2O_3 \cdot 0.25H_2O$: C, 69.56; H, 4.70; N, 9.01. Found: C, 69.51; H, 4.60; N, 9.00.

3-(2,6-Dimethoxypyridin-3-yl)benzoxazine-2,4-dione (4e): yield 51%; mp 214°C; ^{1}H NMR ($CDCl_3$) δ 8.15 (dd, J = 1.6 Hz, J = 7.8 Hz, 1H), 7.80-7.74 (m, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.42-7.35 (m, 2H), 6.46 (d, J = 8.3 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H); MS (CI/CH_4) m/z 300 $[M]^+$; HRMS m/z calcd for $C_{15}H_{12}N_2O_5$ 300.0746, found 300.0739. Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.10; H, 3.98; N, 9.34.

3-(4-Imidazolylethyl)benzoxazine-2,4-dione (4f): The precipitate was collected by filtration, washed with H_2O and recrystallized from MeOH/Et_2O to give **4f** as white crystals in the yield of 56%; mp 237°C; ^{1}H NMR (DMSO-d_6) δ 8.06 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.93-7.86 (m, 1H), 7.59-7.50 (m, 3 H), 6.99-6.96 (m, 1H), 4.18 (t, J = 7.7 Hz, 2H), 2.92 (br, 2H); MS (CI/CH_4) m/z 257 $[M]^+$.

Preparation of intermediate (6): To a dry ice/acetone cold solution of 5-nitrosalicylic acid (**5**) (183 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in $CHCl_3$ (10 mL) was added ethyl chloroformate (0.22 mL, 2.2 mmol) over a period of 30 min. The reaction mixture was stirred for 5 h in the dry ice/acetone bath, and then allowed to rise to rt and stirring was continued at rt overnight. The solvent was removed under vacuum and the residue was extracted with ether. The ether solution was concentrated to a small volume and allowed to stand in a refrigerator overnight to afford intermediate (**6**) as colorless crystals.

General procedure for the reaction of intermediate (6) with amine: To an ice cold solution of intermediate (**6**) (1 mmol) and triethylamine (0.42 mL, 3 mmol) in $CHCl_3$ (5 mL) was added amine (1 mmol). The reaction mixture was stirred at 0°C and allowed to rise to rt. The solvent was evaporated, the residue was applied to column chromatography (eluent: CH_2Cl_2) for purification and was recrystallized from ether to give white crystals.

3-(3,4-Dimethylphenyl)-6-nitrobenzoxazine-2,4-dione (7a): yield 69%; mp 195°C; ^{1}H NMR ($CDCl_3$) δ 8.99 (d, J = 2.7 Hz, 1H), 8.58 (dd, J = 2.7 Hz, J = 9.1, 1H), 7.51 (d, J = 9.1 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.05-7.01 (m, 2 H), 2.31 (s, 3H), 2.30 (s, 3H); MS (EI) m/z 312 $[M]^+$.

3-(3,4-Dimethoxylphenethyl)-6-nitrobenzoxazine-2,4-dione (7b): yield 9%; mp 206°C; ^{1}H NMR ($CDCl_3$) δ 8.95 (d, J = 2.7 Hz, 1H), 8.54 (dd, J = 2.7 Hz, J = 9.1 Hz, 1H), 7.44 (d, J =9.1 Hz, 1H), 6.75-

6.74 (m, 3H), 4.23-4.17 (m, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 2.94-2.89 (m, 2H); HRMS m/z calcd for $C_{18}H_{16}N_2O_7$ 372.0958, found 372.0945.

***N*-(3,4-Dimethoxyphenethyl)-2-hydroxy-5-nitrobenzamide (8b)**: yield 63%; mp 165-166°C; ^{1}H NMR ($CDCl_3$) δ 13.31 (s, 1H), 8.28-8.23 (m, 2H), 7.06 (d, J = 8.9 Hz, 1H), 6.90-6.75 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75-3.69 (m, 2H), 2.91 (t, J = 6.9 Hz, 2H); HRMS m/z calcd for $C_{17}H_{18}N_2O_6$ 346.1165, found 346.1169.

3-Butyl-6-nitrobenzoxazine-2,4-dione (7c): yield 79%; mp 94-95°C; ^{1}H NMR ($CDCl_3$) δ 8.94 (d, J = 2.7 Hz, 1H), 8.52 (dd, J = 2.7 Hz, J = 9.1 Hz, 1H), 4.04 (t, J = 7.5 Hz, 2H), 1.71-1.66 (m, 2H), 1.43-1.36 (m, 2H), 0.95 (q, J = 7.3 Hz, 3H); MS (EI) m/z 264 $[M]^+$.

General procedure for the preparation of compounds (9) and (10): To an ice/salt cold solution of thiosalicylic acid (154 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in chloroform (10 mL) was added ethyl chloroformate (0.22 mL, 2.2 mmol). The reaction mixture was allowed to rise to rt and was stirred at rt for 3 h. The solvent was removed under vacuum to eliminate any remaining ethyl chloroformate, and the residue then was dissolved in $CHCl_3$ and cooled with ice. To the ice cold solution was added triethylamine (0.28 mL, 2 mmol) and amine (1 mmol). The ice bath was removed and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was applied to column chromatography (eluent: CH_2Cl_2) for purification and recrystallized from ether.

3-Benzylbenzothiazine-2,4-dione (9): yield 66%; mp 107-108°C; ^{1}H NMR (acetone-d_6) δ 8.36-8.33 (m, 1H), 7.80-7.72 (m, 1H), 7.56-7.51 (m, 2H), 7.42-7.40 (m, 2H), 7.34-7.25 (m, 3H), 5.31 (s, 2H); MS (EI) m/z 269 $[M]^+$. Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20. Found: C, 66.79; H, 4.21; N, 5.07.

***N*-(3,4-Dimethylphenyl)-2-ethoxycarbonylthiobenzamide (10)**: yield 62%; mp 94°C; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.73- 7.65 (m, 2H), 7.60-7.53 (m, 2H), 7.45-7.44 (m, 1H), 7.32 (dd, J = 2.2 Hz, J = 8.1 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); MS (EI) m/z 329 $[M]^+$. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.39; H, 5.83; N, 4.28.

Single crystal X-Ray analysis of (6). Data for compound (**6**) were collected on a Bruker SMART 6K CCD system mounted on a 6Kw Cu rotating anode using Gobels mirrors to focus the beam. 6860 reflections were measured of which 2449 were unique (Rint = 0.043). The clear colorless (0.09 x 0.22 x 0.50 mm) crystal was monoclinic in space group $P2_1/c$ with a = 12.394(5)(1), b = 7.873(3), c = 15.588(5) Å and β = 106.43(3)°. The structures was solved by direct methods and refined by full-matrix least-squares on F^2 values using programs in the SHELXTL-PLUS package.[13] The parameters refined included the coordinates and anisotropic thermal parameters for all non-hydrogen atoms hydrogen atoms included using a riding model in which the coordinate shifts of their covalently bonded atoms were applied to the

attached hydrogens with C-H = 0.96 Å. H angles were idealized and Uiso(H) set at fixed ratios of Uiso values of bonded atoms. Final R-factors were 0.048 for the 1974 observed reflections and 0.056 for all 2449 data. The structure exhibited a full molecule disorder that refined to an occupancy of ~20%. The two components were constrained to have essentially the same bond lengths and angles. Adding the disorder to the structure reduced the R-factor from 0.147 to 0.048. A full molecule disorder is highly unusual and it could well be that the crystal is twinned but no twin law could be found that would fit the experimental data. Coordinates have been deposited with the Cambridge Crystallographic Database.[14]

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