SHORT PAPER

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Synthesis and X-ray crystallographic analysis of 4,4′-disubstituted *N*–(2-hydroxypropyl)azetidin-2-one from benzil and (±)-2-amino-1-methylethanol[†]

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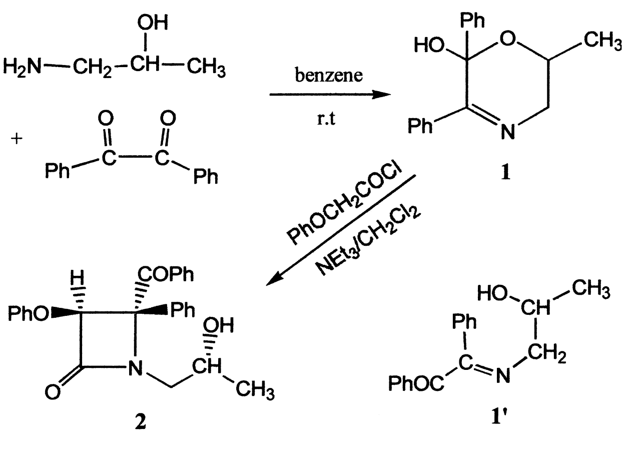
5,6-Dihydro-2-hydroxy-6-methyl-2,3-diphenyl-2*H*-1,4-oxazine **1**, derived from benzil and (±)-2-amino-1-methylethanol, reacts with phenoxyacetyl chloride in the presence of triethylamine to give a single isomer of a 4,4′-disubstituted azetidin-2-one **2**, whose structure has been unambiguously confirmed by X-ray crystallographic analysis.

Keywords: benzil, (±)-2-amino-1-methylethanol, azetidin-2-ones

There is continuing interest in the modification of the β-lactam ring which is endowed with broad-spectrum antibiotic activity. Numerous research groups have directed their efforts to synthesize diversely substituted β-lactams. The synthesis of 4,4′-disubstituted β–lactams starting from benzil has been previously reported from our laboratory in which N-methyl[1] and N-amino[2] substituents are present. Two stereoisomers were obtained and the stereochemistry of the C3 and C4 groups was tentatively assigned on the basis of ^{1}H NMR spectra. In the present work, the synthesis of a *N*-(2-hydroxypropyl)-4,4′-disubstituted β-lactam is described, and the stereochemistry of the groups has been confirmed by X-ray crystallographic analysis. It is noteworthy that only a single isomer was obtained in this reaction.

Reaction of benzil with (±)-2-amino-1-methylethanol was carried out in benzene at room temperature and furnished a cyclic compound (**1**) instead of the expected open chain imine (**1′**)**.** The product was confirmed to be 5,6-dihydro-2-hydroxy-6-methyl-2,3-diphenyl-2*H*-1,4-oxazine **1** by systematic spectral analysis. The IR spectrum of **1** indicated the presence of the O-H and C=N groups at 3200 and 1640 cm^{-1}. No carbonyl band was observed. Alcaide and coworkers reported similar results regarding the formation of cyclic imine by varying the reaction conditions (catalyst, solvent, temperature) and also reported the existence of the ring-chain tautomerism in solution between the cyclic imine **1** and the related open-chain α-imino ketone **1′**.[3,4]



Scheme 1 Azetidinone 2 formation from cyclic imine 1.

The reaction of **1** with phenoxyacetyl chloride in the presence of triethylamine in dichloromethane at 0°C followed by stirring at r.t afforded a single isomer of the 4,4′-disubstituted azetidin-2-one **2** in 73% yield (Scheme 1). The structure of **2** was confirmed by elemental and spectral (IR and ^{1}H NMR) analysis. IR spectrum showed the presence of β-lactam carbonyl group at 1770 cm^{-1} and the 300MHz ^{1}H NMR spectrum revealed the C3 hydrogen at δ 5.46.

The X-ray-crystal structure analysis[5] confirmed the cis-orientation between the C2-hydrogen and the C3 benzoyl group (Fig.1). In the diastereomeric mixture (space group $P1^-$) of **2**, the relative configuration at C2, C3 and C5 are *S*, *R* and *R* respectively. An interesting feature is observed in the crystal structure of **2**; the O–H moiety of the hydroxypropyl side chain participates in a strong intramolecular hydrogen bond involving the carbonyl oxygen of the β-lactam ring [O(1)...H2(A) = 2.305 Å, O(2)-H2(A)…O(1) = 138.0°].

Experimental

5,6-Dihydro-2-hydroxy-6-methyl-2,3-diphenyl-2H-1,4-oxazine **(1):** Benzil (10 mmol) and 2-amino-1-methylethanol (10mmol) were dissolved in benzene (30ml) and stirred at r.t for 12 hours. The white solid was filtered and used as such for the next step, yield: 83%; m.p: 153–155°C; IR (KBr): 3200,1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 1.15 (d, *J* = 6.3 Hz, 3H, CH$_3$); 3.49 (m, 2H, CH$_2$); 3.56 (br.s, 1H, OH); 4.02 (m, 1H, CH); 7.05-7.89 (m, 10H, Ar-H).

4-Benzoyl-1-(2-hydroxypropyl)-3-phenoxy-4-phenylazetidinone **(2):** The cyclic imine **1** (1.9 g, 7.1 mmol) was suspended in dry dichloromethane (40 ml) and triethylamine (3.9 ml, 28.4 mmol) was added at 0°C. Phenoxyacetyl chloride (1.2 g, 7.1 mmol) in dry dichloromethane (20 ml) was added dropwise over 45 minutes at the same temperature. The ice-bath was removed and the mixture was stirred at r.t. for 2 hours; the reaction mixture became homogeneous by this time. It was stirred for a further 19 hours. The organic layer was washed with water (2 × 50 ml), 5% NaHCO$_3$ solution (1 × 30 ml) and brine solution (2 × 30 ml) and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent furnished the crude product, which was purified by column chromatography over neutral alumina (eluent: 30% EtOAc : petroleum ether). Yield: 73%, m.p. 125°C; IR (KBr): 3540, 1770, 1710 cm^{-1}; ^{1}H NMR (300MHz, CDCl$_3$): δ 1.15 (d, *J* = 6.4 Hz, 3H, CH$_3$); 3.18 (d, *J* = 6.7 Hz, 2H, NCH$_2$); 4.14 (m, 1H, C$\underline{H}$OH); 4.37 (br. s, 1H, OH); 5.46 (s, 1H, C$_3$-H); 7.03- 7.53 (m, 13H, Ar-H); 7.92(m, 2H, Ar-H); Anal: calc. for C$_{25}$H$_{23}$NO$_4$: C, 74.81; H, 5.73; N, 3.49; found: C, 74.63; H, 5.68; N, 3.54.

Crystal data for **2:** C$_{25}$H$_{23}$NO$_4$, M$_r$ = 401.44, F(000) = 424, Triclinic, *a* = 8.124(1), *b* = 9.657(1), *c* = 14.246(1)Å, α = 89.46(1)°, β = 83.30(1)°, γ = 71.04(1)°, *V* = 1049.31(18) Å^3, space group $P\bar{1}$, Z = 2, D$_x$ = 1.271 mg/m^3, μ(M$_o$K$_\alpha$) = 0.086 mm^{-1}. The experimental data were collected at 293(2) K on a Siemens P4 diffractometer using a graphite monochromator with M$_o$K$_\alpha$ radiation (λ = 0.71073 Å). The structure was solved and refined by Shelxl 97.[5] The final R value was 0.0539, (R$_w$ = 0.1418) for 2909 reflections [*I* > 2δ(*I*)].

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

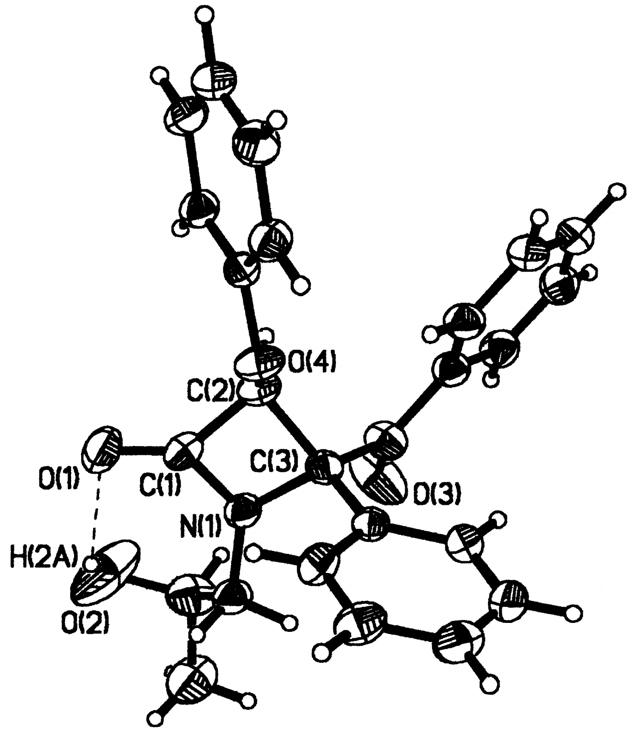

Fig. 1 A perspective "ORTEP" view of **2**. The intramolecular hydrogen bond is shown with dotted lines.

Table 1 Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for **2**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor

	x	*y*	*z*	U(eq)
O(1)	107(3)	4312(2)	8800(2)	84(1)
O(2)	–3170(4)	5924(5)	10017(2)	208(2)
O(3)	–1113(3)	9441(2)	8714(2)	112(1)
O(4)	2413(2)	5151(2)	7027(1)	60(1)
N(1)	–1174(2)	6705(2)	8330(1)	52(1)
C(1)	112(3)	5427(3)	8413(2)	57(1)
C(2)	1491(3)	5975(2)	7845(2)	54(1)
C(3)	–112(3)	7373(2)	7671(2)	49(1)
C(4)	–3061(3)	7167(3)	8591(2)	61(1)
C(5)	–3635(4)	7310(4)	9616(2)	84(1)
C(6)	–5592(4)	7937(5)	9831(3)	107(1)
C(7)	–708(2)	7537(2)	6692(2)	47(1)
C(8)	–1027(3)	8841(3)	6217(2)	63(1)
C(9)	–1613(3)	8962(3)	5336(2)	76(1)
C(10)	–1902(3)	7811(3)	4924(2)	73(1)
C(11)	–1614(3)	6520(3)	5390(2)	70(1)
C(12)	–1028(3)	6387(2)	6265(2)	59(1)
C(13)	0(3)	8787(3)	8092(2)	61(1)
C(14)	1483(3)	9322(2)	7751(2)	53(1)
C(15)	2786(3)	8599(3)	7033(2)	58(1)
C(16)	4134(3)	9151(3)	6749(2)	66(1)
C(17)	4185(3)	10412(3)	7173(2)	71(1)
C(18)	2901(4)	11130(3)	7878(2)	72(1)
C(19)	1546(3)	10594(3)	8169(2)	63(1)
C(20)	4196(2)	4413(2)	7004(2)	47(1)
C(21)	5064(3)	4065(2)	7787(2)	56(1)
C(22)	6860(3)	3333(3)	7659(2)	66(1)
C(23)	7752(3)	2932(3)	6775(2)	68(1)
C(24)	6856(3)	3256(3)	6005(2)	70(1)
C(25)	5077(3)	3995(3)	6112(2)	60(1)

Table 2 Bond lengths [Å] and angles [°] for **2**

O(1)–C(1)	1.207(3)	O(2)–C(5)	1.403(5)
O(3)–C(13)	1.206(3)	O(4)–C(20)	1.388(2)
O(4)–C(2)	1.407(3)	N(1)–C(1)	1.348(3)
N(1)–C(4)	1.454(3)	N(1)–C(3)	1.484(3)
C(1)–C(2)	1.534(3)	C(2)–C(3)	1.583(3)
C(3 –C(7)	1.520(3)	C(3)–C(13)	1.530(3)
C(4)–C(5)	1.475(4)	C(5)–C(6)	1.501(4)
C(7)–C(12)	1.382(3)	C(7)–C(8)	1.387(3)
C(8)–C(9)	1.383(4)	C(9)–C(10)	1.360(4)
C(10)–C(11)	1.371(4)	C(11)–C(12)	1.376(3)
C(13)–C(14)	1.490(3)	C(14)–C(19)	1.388(3)
C(14)–C(15)	1.390(3)	C(15)–C(16)	1.385(3)
C(16)–C(17)	1.379(4)	C(17)–C(18)	1.369(4)
C(18)–C(19)	1.383(4)	C(20)–C(21)	1.370(3)
C(20)–C(25)	1.379(3)	C(21)–C(22)	1.390(3)
C(22)–C(23)	1.370(4)	C(23)–C(24)	1.365(4)
C(24)–C(25)	1.379(3)		
C(20)–O(4)–C(2)	119.15(16)	C(1)–N(1)–C(4)	132.5(2)
C(1)–N(1)–C(3)	96.41(17)	C(4)–N(1)–C(3)	129.61(17)
O(1)–C(1)–N(1)	131.9(2)	O(1)–C(1)–C(2)	136.0(2)
N(1)–C(1)–C(2)	92.19(18)	O(4)–C(2)–C(1)	116.88(19)
O(4)–C(2)–C(3)	115.36(17)	C(1)–C(2)–C(3)	85.34(15)
N(1)–C(3)–C(7)	111.85(17)	N(1)–C(3)–C(13)	111.74(17)
C(7)–C(3)–C(13)	113.85(18)	N(1)–C(3)–C(2)	85.37(15)
C(7)–C(3)–C(2)	117.68(16)	C(13)–C(3)–C(2)	113.07(18)
N(1)–C(4)–C(5)	115.1(2)	O(2)–C(5)–C(4)	110.0(3)
O(2)–C(5)–C(6)	105.5(3)	C(4)–C(5)–C(6)	112.0(3)
C(12)–C(7)–C(8)	117.8(2)	C(12)–C(7)–C(3)	119.99(18)
C(8)–C(7)–C(3)	122.2(2)	C(9)–C(8)–C(7)	120.6(2)
C(10)–C(9)–C(8)	120.7(2)	C(9)–C(10)–C(11)	119.5(2)
C(10)–C(11)–C(12)	120.3(3)	C(11)–C(12)–C(7)	121.2(2)
O(3)–C(13)–C(14)	120.9(2)	O(3)–C(13)–C(3)	118.8(2)
C(14)–C(13)–C(3)	120.27(18)	C(19)–C(14)–C(15)	119.5(2)
C(19)–C(14)–C(13)	118.1(2)	C(15)–C(14)–C(13)	122.4(2)
C(16)–C(15)–C(14)	119.6(2)	C(17)–C(16)–C(15)	120.3(2)
C(18)–C(17)–C(16)	120.2(2)	C(17)–C(18)–C(19)	120.1(2)
C(18)–C(19)–C(14)	120.2(2)	C(21)–C(20)–C(25)	120.52(19)
C(21)–C(20)–O(4)	124.67(19)	C(25)–C(20)–O(4)	114.79(19)
C(20)–C(21)–C(22)	118.6(2)	C(23)–C(22)–C(21)	121.3(2)
C(24)–C(23)–C(22)	119.2(2)	C(23)–C(24)–C(25)	120.6(2)
C(20)–C(25)–C(24)	119.7(2)		

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