Synthesis and reactions of 5-benzylidene-2-phenyl-4,5-dihydro-1,3-oxazol-4-ones

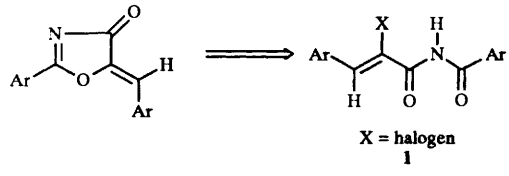
Yennu Santosh Laxmi and Divi Sarangapani Iyengar *
Organic Division-II, Indian Institute of Chemical Technology, Hyderabad 500007, India

5-Benzylidene-2-phenyl-4,5-dihydro-1,3-oxazol-4-one was prepared by the cyclization of *N*-benzoyl-2-bromo-3-phenylpropenamide in the presence of sodium hydride.

The chemistry of 4,5-dihydrooxazol-4-ones has attracted interest because of their varied biological activity and in the case of the 2-amino derivatives their pharmacological properties; the antibiotic indolmycin also contains this heterocyclic skeleton.[1] Since the chemistry of 5-arylidene-2-phenyl-4,5-dihydrooxazol-4-ones has been little explored we have now synthesized a number of these compounds for biological evaluation and here report our results.

Results and discussion

Since *N*-benzoylchloroacetamides undergo smooth cyclodehydrohalogenation to give 4,5-dihydro-1,3-oxazol-4-ones,[2] we thought it possible to synthesize the title compounds from the appropriate *N*-benzoyl-2-halogeno-3-phenylpropenamides **1** (see Scheme 1). Thus, sodium benzamide, generated *in situ* from



Scheme 1

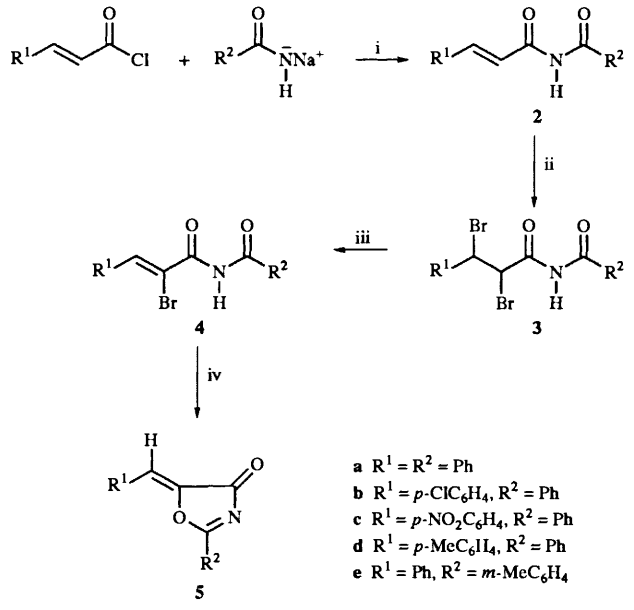
benzamide and sodium hydride, was treated with 3-phenylpropenoyl chloride in anhydrous tetrahydrofuran to give the *N*-benzoyl-3-phenylpropenamide **2**. Bromination of this with bromine in acetic acid then afforded the *N*-benzoyl-2,3-dibromo-3-phenylpropanamide **3**, subsequent treatment of which with triethylamine in chloroform effected smooth dehydrohalogenation to give the bromopropenamide intermediate **4** required for the synthesis of the title compound (Scheme 2).

The bromo bisamide **4** underwent cyclization when heated under reflux for 4 h with an equimolar quantity of sodium hydride in anhydrous glyme. The crude product was purified by column chromatography to give 5-benzylidene-2-phenyl-4,5-dihydrooxazol-4-one **5a** as a red crystalline solid, the spectral results for which were in accord with the assigned structure (see Experimental section).

Other 4,5-dihydrooxazol-4-ones **5b–e** were synthesized from the substituted benzamide or 3-arylpropenoic acids[3] (see Tables 1 and 2).

Hydrogenation of **5a** over Pd/C at atmospheric pressure resulted in the reduction of the azomethine linkage to give the oxazolidine **6** as a white crystalline compound. This was readily reoxidized to **5a** when a methanolic solution was exposed to air (Scheme 3).

The ring opening of the oxazolone **5a** was achieved under basic conditions and recyclization occurred in acidic media. This reversible cyclization in acid–base media is significant in not having been observed previously for this series. Thus,



Scheme 2 *Reagents and conditions:* i, −78 °C, THF; ii, Br_2, AcOH; iii, Et_3N, $CHCl_3$; iv, NaH, $(MeO)_2C_2H_4$, reflux, 4 h

treatment of **5a** with aq. sodium hydroxide gave the ring-opened product *N*-benzoylphenylpyruvamide **7**, probably formed by the initial addition of a hydroxide ion to the azomethine carbon of **5a**. The compound **7** on acidification with aq. HCl gave the starting material **5a**. Conversion of **7** into **5a** under acidic conditions could be visualized as intramolecular addition of the amide enol to the β-carbonyl and subsequent water loss from the hemiketal intermediate (see Scheme 3). In fact, compound **7**, prepared by an unambiguous method, gave the oxazolone **5a** on treatment with HCl (Scheme 3).

Experimental

All solvents were dried and distilled prior to use according to standard procedures. Melting points reported were determined in open capillaries with a Mettler FP-51 melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer in $CDCl_3$ unless otherwise specified. IR spectra were recorded on a Perkin-Elmer 221 spectrometer. Mass spectra were recorded on a VG micromass 7070H instrument at 70 eV.

Preparation of *N*-benzoyl-3-phenylpropenamide 2

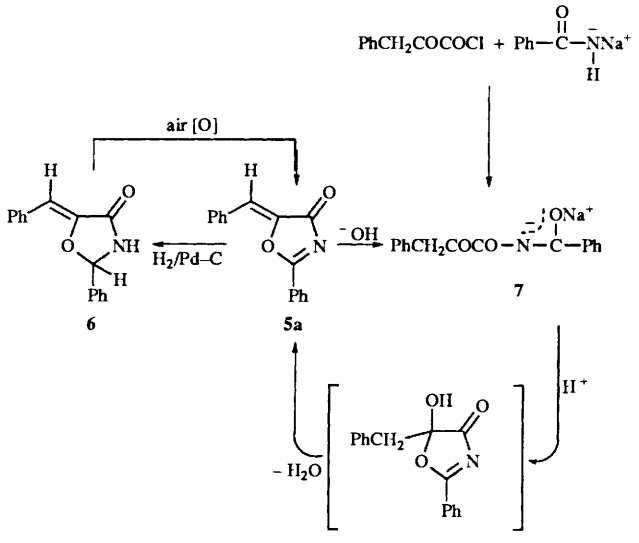
To a suspension of sodium hydride (50% suspension in mineral oil; 3.041 g, 62 mmol) in anhydrous THF (300 cm^3) at 0 °C was added a solution of benzamide (8.2 g, 67 mmol) in THF (50

Table 1 Physical and spectral data of **2a–d**

Compound	R^1	R^2	Mp (°C)	Spectroscopic data
2b	*p*-ClC_6H_4	Ph	179.1	δ_H 7.4–7.8 (11 H, m) and 9.18 (br s, NH) ν_{max} 3260 (NH), 1700 and 1650 (C=O) *m/z* 287 (M^+ + 2, 18), 285 (M^+, 55), 167 (30), 165 (90)
2c	*p*-$NO_2C_6H_4$	Ph	172.1	δ_H 7.3–8.2 (11 H, m) and 10.5 (br s, NH) ν_{max} 3220 (NH), 1705 and 1665 (C=O) *m/z* 296 (M^+, 20), 176 (20), 105 (100)
2d	*p*-MeC_6H_4	Ph	180.2	δ_H 2.4 (3 H, s, Me), 7.2–7.9 (11 H, m) and 8.5 (s, NH) ν_{max} 3200 (NH), 1690 and 1670 (C=O) *m/z* 265 (M^+, 40), 145 (75), 105 (100), 91 (45)
2e	Ph	*m*-MeC_6H_4	153.4	δ_H 2.4 (3 H, s, Me), 7.3–7.8 (11 H, m) and 8.5 (s, NH) ν_{max} 3260 (NH), 1695 and 1665 (C=O) *m/z* 265 (M^+, 25), 131 (80), 119 (100), 91 (65)

Table 2 Physical and spectral data of **5a–d**

Compound	R^1	R^2	Mp (°C)	Spectroscopic data
5b	*p*-ClC_6H_4	Ph	259.1	δ_H 7.2–8.1 (10 H, m) ν_{max} 1745 (C=O), 1690 (O–C=N) *m/z* 285 (M^+ + 2, 15), 283 (M^+, 45), 254 (45), 104 (100)
5c	*p*-$NO_2C_6H_4$	Ph	262.2	δ_H 7.4–8.5 (10 H, m) ν_{max} 1760 (C=O), 1705 (O–C=N) *m/z* 294 (M^+, 50), 265 (60), 163 (20), 104 (100)
5d	*p*-MeC_6H_4	Ph	218.8	δ_H 2.3 (3 H, s, Me), 7.1–7.5 (10 H, m) ν_{max} 1730 (C=O), 1690 (O–C=N) *m/z* 265 (M^+, 40), 234 (55), 130 (54), 104 (100)
5e	Ph	*m*-MeC_6H_4	217.1	δ_H 2.4 (3 H, s, Me), 7.2–7.4 (10 H, m) ν_{max} 1760 (C=O), 1690 (O–C=N) *m/z* 263 (M^+, 20), 234 (35), 165 (10), 118 (100)



Scheme 3

cm^3) under an inert atmosphere. The reaction mixture was stirred for 30 min, after which it was cooled to −78 °C and treated with 3-phenylpropenoyl chloride (10 g, 60 mmol) in THF (100 cm^3), added dropwise. The mixture was allowed to warm to room temperature and then concentrated under reduced pressure. Water (250 cm^3) was added to the residue, and the precipitate was filtered off and purified by column chromatography on silica gel (benzene–ethyl acetate 9:1) to afford **2** (10.15 g) as a pale yellow solid, mp 143.5 °C; ν_{max}(KBr)/cm^{-1} 3230, 1700 and 1655; δ_H 7.6–7.9 (12 H, m, Ph) and 8.6 (1 H, br, NH); *m/z* 251 (M^+, 43%), 131 (90) and 105 (100); HRMS (EI) (Found: M^+, 251.0949. Calc. for $C_{16}H_{13}NO_2$: *M*, 251.0946).

***N*-Benzoyl-2,3-dibromo-3-phenylpropanamide 3**

To a solution of **2** (4.0 g, 11 mmol) in acetic acid (20 cm^3), bromine (2 cm^3, 11 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4 h to give a precipitate which was filtered off and washed with benzene to afford the title product **3** (5.92 g) as a colourless solid, mp 153.6 °C; δ_H 5.52 (1 H, d, *J* = 12, PhC*H*Br), 6.46 (1 H, d, *J* = 12, COC*H*Br), 7.43–7.88 (10 H, m, Ph) and 9.06 (1 H, br, NH); *m/z* 331 (M^+ − HBr, 10), 329 (10), 250 (50) and 105 (100).

***N*-Benzoyl-2-bromo-3-phenylpropenamide 4**

To a solution of **3** (2.0 g, 4.8 mmol) in dichloromethane (20 cm^3), triethylamine (0.692 g, 48 mmol) was added. The mixture was stirred for 5 h after which it was diluted with chloroform (10 cm^3), washed with HCl (2 mol dm^{-3}; 2 × 10 cm^3) and water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to yield **4** (1.4 g) as a colourless solid, mp 92.6 °C; δ_H 7.4–7.78 (10 H, m, Ph), 8.42 (1 H, s, HC=) and 9.92 (1 H, br, NH); δ_C 164.7 (C=O), 159.7 (C=O), 141.1 (=Br*C*–CO), 133.2–127.6 (Ar–C) and 113.0 (=*C*HPh); *m/z* 250 (M^+ − HBr, 100), 105 (60), 104 (65) and 102 (35).

5-Benzylidene-2-phenyl-4,5-dihydrooxazol-4-one 5a

To a stirred suspension of sodium hydride (50% suspension in mineral oil; 0.140 g, 3 mmol) in anhydrous 1,2-dimethoxyethane (20 cm^3) was added **4** (1.0 g, 0.3 mmol) at 0 °C. The mixture was refluxed for 4 h after which it was concentrated under reduced pressure, suspended in water (10 cm^3), neutralized with concentrated aq. HCl and extracted with dichloromethane (3 × 25 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography (benzene–ethyl acetate, 8:2) and sublimed *in vacuo* to give **5a** (0.29 g) as a red crystalline solid, mp 186 °C; δ_H 7.20–7.70 (11 H, m, Ph); δ_C 161.4 (C=O), 159.8 (O–C=N) and 132.9–127.3 (Ar–C); ν_{max}(KBr)/cm^{-1} 1740 and 1695; *m/z* 249 (M^+, 90), 118 (40) and

104 (80); HRMS (EI) (Found: C, 77.0; H, 4.4; N, 5.6%; M^+ 249.0778. Calc. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62%; M^+, 249.0790).

Hydrogenation of 5a

To a solution of **5a** (0.1 g) in ethyl acetate (20 cm^3), palladium-carbon (5%; 5 mg) was added after the flask had been flushed with hydrogen. The reaction mixture was stirred under a hydrogen atmosphere for 5 h by which time the initial red colour of the mixture had disappeared. The reaction mixture was filtered and the filtrate was evaporated to give 5-benzylidene-2-phenyloxazolidin-4-one **6** (90 mg) as a colourless solid, mp 220 °C; δ_H([$^2H_6$]acetone) 5.50 (1 H, s, OHCN), 7.3–7.7 (11 H, m, Ph and –HC=) and 8.50 (1 H, br, NH); ν_{max}(KBr) cm^{-1} 3300 and 1680; *m/z* 251 (M^+, 25) (Found: C, 76.5; H, 5.2; N, 5.55. Calc. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.22; N, 5.57).

Action of alkali on 5a

To a suspension of **5a** (30 mg) in water (2 cm^3) was added dropwise aq. NaOH (2 mol dm^{-3}). The solution became blue initially and then finally pale yellow. Acidification of the alkaline solution gave back red crystalline **5a**; δ_C(NaOD–D_2O) 192.5 (H_2C–*C*=O) 174.9 (OC–*C*=O), 167.6 (N–C=O), 137.3–126.2 (ArC), 104.6 (Ph*C*H=CO) and 66.5 (Ph*C*H_2). These values indicate that keto–enol tautomers are present.

Synthesis of 5a *via* *N*-benzoyl-2-oxo-3-phenylpropanamide 7

To a suspension of sodium hydride (50% suspension in mineral oil; 0.489 g, 10 mmol) in anhydrous THF (50 cm^3) at 0 °C was added a solution of benzamide (1.47 g, 11 mmol) in THF (5 cm^3) under an inert atmosphere. The reaction mixture was stirred for 30 min and then cooled to −78 °C and treated dropwise with 2-oxo-3-phenylpropanoyl chloride[4] (2 g, 0.01 mol) in THF (10 cm^3). After the mixture had been allowed to warm to room temperature it was evaporated under reduced pressure, diluted with water (10 cm^3) and extracted with ethyl acetate (3 × 25 cm^3). The aqueous layer was acidified with conc. HCl and extracted with chloroform (3 × 25 cm^3). The organic extracts were dried (Na_2SO_4) and evaporated and the residue subjected to silica gel column chromatography (benzene–ethyl acetate, 9:1) to give **5a** (50 mg) as a red crystalline solid, mp 186 °C. The spectral data was superimposible with the data of **5a** obtained from **4**.

Acknowledgements

We are grateful to the CSIR for award of research fellowship (to Y. S. L.) and Dr A. V. Rama Rao for the use of facilities.

References

1 Y. Shyamsunder Rao and Robert Filler, *Chemistry of Heterocyclic Compounds*, John Wiley and Sons, Inc., 1986, p. 644.
2 (*a*) R. M. Roderhorst and T. H. Koch, *J. Am. Chem. Soc.*, 1975, **97**, 7298; (*b*) Y. Shyamsunder Rao and Robert Filler, *J. Chem. Soc., Chem. Commun.*, 1970, 1622; (*c*) T. H. Koch and R. M. Roderhorst, *Tetrahedron Lett.*, 1972, 4039.
3 J. Frederick, J. Dippy and J. E. Page, *J. Chem. Soc.*, 1938, 357.
4 Vogel, *Text Book of Practical Organic Chemistry* ELBS, 5th ed., 1989, p. 741 and 1155.

Paper 5/03680A
Received 8*th June* 1995
Accepted 11*th August* 1995