A General Method for the Synthesis of 3-Phenyl-2*H*-1,4-benzoxazines and 3-Phenyl-2*H*-3,4-dihydro-1,4-benzoxazines

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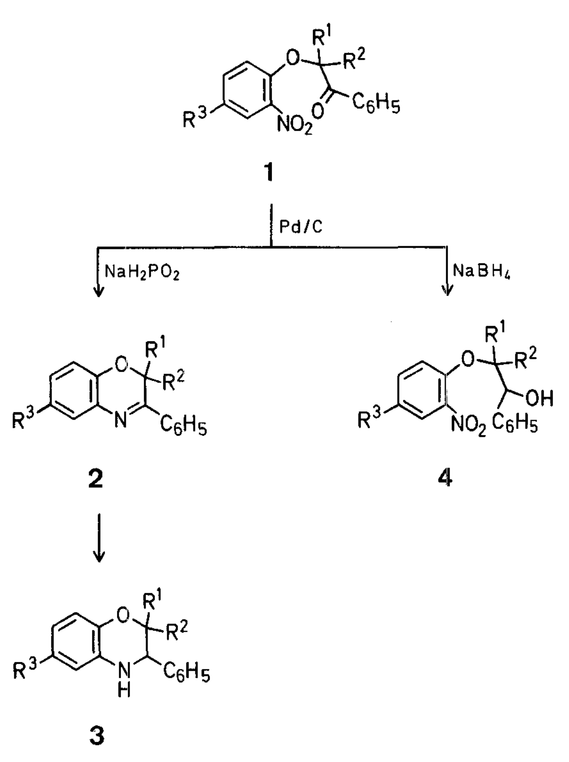
Nitroarenes with suitably substituted side-chains in the position *ortho* to the nitro group are known to undergo intramolecular cyclisation to yield heterocycles[1]. Reduction of 4-methyl-2-nitrophenoxyacetone with hydrogen over Raney nickel under high pressure (115–122 atm) gives mainly 3,6-dimethyl-2*H*-3,4-dihydro-1,4-benzoxazine[2]. Similar *o*-nitrophenoxyalkyl ketones on treatment with hydrogen over Raney nickel at lower pressures (4 atm) are also reported to give 2*H*-3,4-dihydro-1,4-benzoxazines[3] in high yield.

Nitro ketones of the type **1** react with zinc dust in ethanol to give 3-phenyl-2*H*-1,4-benzoxazine *N*-oxides[4]. However, the most convenient synthesis of 3-phenyl-2*H*-1,4-benzoxazine derivatives reported to date seems to be the alkali-induced intramolecular condensation of 2-acetylaminophenoxyacetophenones[5,6]. In an attempt to avoid this often laborious procedure we have studied the reductive cyclisation of 2-nitrophenoxyacetophenones **1**. Use of sodium borohydride with 5 % palladium on carbon as reducing agent resulted in reduction of the carbonyl group only[7,8] to give **4**, whereas systems such as zinc/acetic acid or iron/hydrochloric acid were highly unsatisfactory[9].

We now report a rapid, selective procedure for the synthesis of the biologically important[10] 1,4-benzoxazine system using sodium phosphinite as hydrogen donor and 5 % palladium on carbon as catalyst in a two phase system of water/tetrahydrofuran[11]. Depending on the amount of catalyst used and the reaction time, compounds **2** or **3** can be obtained as main products from **1**.

The absence of side products is probably due to the rapid reduction of the initially formed nitrones to the imino derivatives **2a–f** by the phosphorus(III) species[12]. ^{1}H-N.M.R. monitoring of the reaction mixture reveals the gradual disappearance of the peak at $\delta = 5.45$ or 5.35 ppm of the keto compounds **1a**, **d** and the corresponding appearance of a peak at $\delta = 5.0$ or 5.05 ppm for the products **2a**, **d**. The formation of the amines **3a**, **d** is seen by the appearance of a peak at $\delta = 7.25$–7.35 ppm corresponding to the phenyl group in the position 3 of the benzoxazine ring. The more complex situation by products **b**, **c**, **e**, and **f** renders ^{1}H-N.M.R. monitoring unsatisfactory, however the reaction can be conveniently followed by T.L.C. analysis in these cases (see experimental).



	R^1	R^2	R^3
a	H	H	H
b	CH_3	CH_3	H
c	CH_3	H	H
d	H	H	CH_3
e	CH_3	CH_3	CH_3
f	CH_3	H	CH_3

Table 1. 3-Phenyl-2*H*-1,4-benzoxazines **2a–f**

Product	Yield [%]	m.p.	Molecular formula[a] or Lit. m.p.	I.R. (nujol) $\nu_{C=N}$ [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]	M.S. *m/e* ($M^{+\cdot}$)
2a	80	100–102°	100–102°[9]	1620	5.0 (s, 2H)	209
2b	85	86–87°	$C_{16}H_{15}NO$ (237.3)	1610	1.57 (s, 6H, 2CH_3)	237
2c	65	92–93°	$C_{15}H_{13}NO$ (223.3)	1610	5.10 (q, 1H, $J = 8$ Hz); 1.45 (d, 3H, CH_3, $J = 8$ Hz)	223
2d	85	69–70°	$C_{15}H_{13}NO$ (223.3)	1615	5.05 (s, 2H); 2.35 (s, 3H, CH_3)	223
2e	90	86–88°	$C_{17}H_{17}NO$ (251.3)	1620	2.33 (s, 3H, CH_3); 1.55 (s, 6H, 2CH_3)	251
2f	75	73–75°	$C_{16}H_{15}NO$ (237.3)	1610	5.05 (q, 1H, $J = 7$ Hz); 2.25 (s, 3H, CH_3); 1.45 (d, 3H, CH_3, $J = 7$ Hz)	237

[a] All new compounds had satisfactory microanalyses (C ±0.25, H ±0.16, N ±0.22).

3-Phenyl-2*H*-1,4-benzoxazines 2a–f:

To a stirred mixture of sodium phosphinite (2 g) in water (20 ml) and tetrahydrofuran (20 ml) containing the ketone[13] **1a–f** (1 g) is added commercial grade 5 % palladium on carbon catalyst (0.05 g). The reduction is monitored by ^{1}H-N.M.R. (see text) or

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Table 2. 3-Phenyl-3,4-dihydro-1,4-benzoxazines **3a–f**

Product	Yield [%]	m.p.	Molecular formula[a]	I.R. (nujol) ν_{NH} [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]	M.S. m/e ($M^{+\cdot}$)
3a	98	oil	$C_{14}H_{13}NO$ (211.3)	3360	7.25 (s, 5H_{arom}); 3.65 (br. s, NH); 3.7–4.5 (m, 3H)	211
3b	97	145–147°	$C_{16}H_{17}NO$ (239.3)	3330	7.35 (s, 5H_{arom}); 4.18 (br. s, NH); 3.95 (s, 1H); 1.28 (s, 3H, CH_3); 1.15 (s, 3H, CH_3)	239
3c	98	oil	$C_{15}H_{15}NO$ (225.3)	3370	7.35 (s, 5H_{arom}); 4.50 (m, 2H); 4.05 (br. s, NH); 1.10 (d, 3H, CH_3, $J=6$ Hz)	225
3d	98	oil	$C_{15}H_{15}NO$ (225.3)	3330	7.30 (s, 5H_{arom}); 3.70–4.40 (m, 3H); 3.75 (br. s, NH); 2.17 (s, 3H, CH_3)	225
3e	95	oil	$C_{17}H_{19}NO$ (253.3)	3360	7.35 (s, 5H_{arom}); 4.14 (s, 1H); 3.85 (br. s, NH); 2.21 (s, 3H, CH_3); 1.25 (s, 3H, CH_3); 1.13 (s, 3H, CH_3)	253
3f	94	oil	$C_{16}H_{17}NO$ (239.3)	3360	7.22 (s, 5H_{arom}); 4.2 (m, 2H); 3.68 (br. s, NH); 2.15 (s, 3H, CH_3); 1.0 (d, 3H, $J=6$ Hz, CH_3)	239

[a] All products had satisfactory microanalyses (C ±0.24, H ±0.19, N ±0.24).

by T.L.C. on SiO_2 plates using 1 : 4 benzene/cyclohexane as eluent. Ketones **1** have an R_f of 0.5, amines **3** appear at the solvent front, and imines **2** show a spot in an intermediate position. When traces of the amino compound **3** are first detected, the catalyst is filtered off, the two phase solution is diluted with water (100 ml), and extracted with ether. The ether extracts are concentrated under reduced pressure and the residue is subjected to column chromatography on SiO_2 using 1 : 4 benzene/cyclohexane as eluent to give the imine **2**; yield: 65–80% (see Table 1). Unreacted ketone **1** can be recovered by elution with benzene.

3-Phenyl-2*H*-3,4-dihydro-1,4-benzoxazines 3a–f:

To a stirred mixture of sodium phosphinite (5 g) in water (20 ml) and tetrahydrofuran (20 ml) containing the nitro ketone **1a–f** (1 g) is added 5% palladium on carbon catalyst (0.2 g). The reduction is completed within about 4 h. The amines are obtained by the previous procedure and purified by column chromatography on SiO_2 using 1 : 4 benzene/cyclohexane as eluent; yield: 93–98% (see Table 2).

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