SHORT PAPER

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A novel reduction of *o*-nitrophenoxy compounds promoted by low-valent titanium: an access to 2H-1,4-benzoxazine derivatives†

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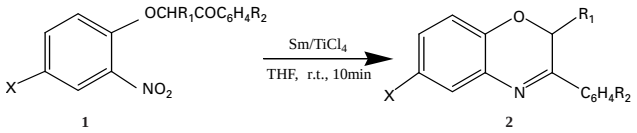
The intramolecular reductive cyclizations of *o*-nitrophenoxyacetophenones, *o*-nitrophenoxyacetate and *o*-nitrophenoxyacetonitrile induced by the Sm/$TiCl_4$ system were studied; 2H-1,4-benzoxazines are obtained in high yields under room temperature conditions.

Nitroarenes with suitably substituted side-chains in the position *ortho* to the nitro group are known to undergo intramolecular cyclization to yield heterocycles.[1] Reduction of *o*-nitro-phenoxyalkyl ketones on treatment with hydrogen over Raney nickel at low pressures (4 atm) are reported to give 2H-3,4-dihydro-1,4-benzoxazines[2] in high yields. Battistoni[3] has reported the reductive cyclization of *o*-nitrophenoxyacetophenones using sodium phosphinite as hydrogen donor and 5% palladium-on-carbon as catalyst. However, this method requires prior isolation of the intermediate *o*-nitrophenoxyacetophenones. Furthermore, it has also been reported that 3,4-dihydrobenzoxazines instead of 3-aryl-2H-1,4- benzoxazines can be obtained from the above reaction when it is carried out for longer periods using excess catalyst. Alternatively, 3-aryl-2H-1,4- benzoxazines can be also prepared *via* the electrochemical reduction of *o*-nitrophenoxyacetophenone.[4]

Also, some groups obtained the compounds **2** from intramolecular and intermolecular condensation of ketones with amine groups. For example, base-catalysed intramolecular condensation of *o*-aminophenoxyacetophenones generated *in situ* from the previously prepared *o*-acetylaminophenoxyacetophenones using ethanolic potassium hydroxide were reported[5–7] for the synthesis of the compounds **2**. This method involves isolation of the intermediate 2-acetylamino-phenoxyacetophenones, which is often laborious and tedious. Shridhar *et al*.[8] have reported one-step synthesis for the compounds **2** by the reaction of readily available *o*-aminophenols with the appropriate phenacyl bromide. But it needs several hours to complete the reaction, and the yields are low. Alternatively, condensations of *o*-aminophenols with phenacyl bromide under phase-transfer catalysis conditions afforded the compounds **2** were also reported.[9]

The low-valent titanium reagent has an exceedingly high ability in promoting reductive coupling of carbonyl compound and is attracting increasing interest in organic synthesis. A lot of other functional groups can also be coupled by this reagent.[10] Recently, we have reported a reductive cleavage reaction of Se–Se bonds, Te–Te bonds and reductive coupling of nitriles with nitro compounds using the $TiCl_4$/Sm/THF system.[11] Here, we wish to report reductive cyclizations of *o*-nitrophenoxyacetophenones promoted by the $TiCl_4$/Sm system in anhydrous THF.

When *o*-nitrophenoxyacetophenones **1** were treated with low-valent titanium, prepared from titanium tetrachloride and samarium powder in anhydrous THF, the biologically active[12]



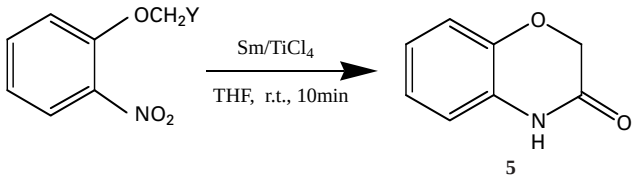
1 **2**

Scheme 1

3-aryl-2H-1,4-benzoxazines are obtained in high yield (Scheme 1). The results are summarized in Table 1.

Moreover, when we substituted methyl *o*-nitrophenoxyacetate **3** or *o*-nitrophenoxyacetonitrile **4** for *o*-nitrophenoxyacetophenone **1** in the Sm/$TiCl_4$ system, the 3,4-dihydro-3-oxo-2H-1,4-benzoxazine **5** was obtained in good yield (Scheme 2).

Compared with ref. 9, the pre-preparation of the low-valent titanium reagent and the work-up of the reaction mixture appear to be more complicated, but the reaction of o-nitrophenoxyacetophenones induced by the reagent is rapid and mild and the yield is satisfactory. So the present study provides a new access to 2H-1,4-benxoxazine derivatives.



5

3 Y=$COOCH_3$ Yield (%)
4 Y=CN 75
70

Scheme 2

Experimental

General. Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a dinitrogen atmosphere. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker AC 80 spectrometer as $CDCl_3$ solutions. Chemical shifts were expressed in ppm downfield from internal standard tetramethylsilane.

Synthesis of the o-nitrophenoxy compounds: o-Nitrophenoxyacetophenone **1** and *o*-nitrophenoxyacetonitrile **4** were prepared from sodium *o*-nitrophenoxide: reaction with bromoacetophenone led to **1**.[13] and reaction with chloroacetonitrile led to **4**.[14] Methyl *o*-nitropenoxyacetate **3** was obtained by reaction of 2-nitrophenol with α-bromo methyl acetate.[15]

Synthesis of 3-aryl-2H-1,4-benzoxazines 2a–h and 3,4-dihydro-3-oxo-2H-1,4-benoxazine **5**.-$TiCl_4$ (0.22 ml, 2 mmol) was added dropwise using a syringe to a stirred suspension of Sm powder (0.3 g, 2 mmol) in freshly distilled dry THF (15 ml) at room temperature under dinitrogen. After the completion of the addition, the

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

Table 1 The synthesis of 3-aryl-2H-1,4-benzoxazines promoted by low-valent titanium

Product	X	R^1	R^2	Yield (%)*	M.p. (°C) Lit. M.p. (°C)	ν_{max} (cm^{-1})	δH (ppm)
2a	H	H	H	87	109–111 (113[8])	1605	4.90(s,2H), 6.75–8.00(m,9H)
2b	H	H	*p*-Cl	80	159–161 (159[8])	1605	5.10(s,2H), 6.90–8.00 (m,8H)
2c	H	H	*p*-Br	85	160–162 (162[9])	1610	5.10(s,2H), 7.00–8.00(m,8H)
2d	H	CH_3	H	85	90–92 (92-93[3])	1610	1.50(d,3H,*J*=7.5Hz),5.10(q,1H,*J*=8Hz), 6.75–7.95(m,8H)
2e	Cl	H	H	89	93–95 (95[8])	1605	5.00(s,2H), 6.80–8.05(m, 8H)
2f	Cl	H	*p*-Cl	92	129–131 (130[8])	1605	4.90(s,2H), 6.80–8.00(m,7H)
2g	Cl	H	*p*-Br	90	123–125 (1268)	1610	4.95(s,2H), 6.85–8.00(m,7H)
2h	Cl	H	*p*-CH3	82	117–119 (120[8])	1605	2.40(s,3H),4.95(s,2H),6.80–7.95(m,7H)

*Isolated yield

mixture was refluxed for 2h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of *o*-nitrophenoxyacetophenones **1a–h** or methyl *o*-nitrophenoxy acetate **3** or *o*-nitrophenoxyacetonitrile **4** (1 mmol) in anhydrous THF (3 ml) was added. The mixture was stirred for 10 minutes at room temperature under dinitrogen (the reaction was monitored by TLC). Then the reaction mixture was quenched with 0.1N HCl (3 ml) and extracted with diethyl ether (3×15 ml). The combined extracts were washed with a saturated solution of $Na_2S_2O_3$ (15 ml), a saturated solution of NaCl (15 ml), dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products **2a–h** were purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:8) as eluent and the product **5** was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:4) as eluent.

3,4-Dihydro-3-oxo-2H-1,4-benoxazine **5:** m.p. 170–172°C (lit[4] 174°C). δ_H (ppm) 4.5 (s, 2H, CH_2), 6.9 (m, 4H, C_6H_4), 9.6 (br s, 1H, NH). n_{max} (cm^{-1}) 3160, 1700.

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