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Tetrahedron Letters 44 (2003) 7617–7621

TETRAHEDRON LETTERS

Investigation of the selective reduction of isatin derivatives. Synthesis of α-hydroxyacetophenone derivatives and ethyl *spiro*-3,3-(ethylenedioxy)-2-hydroxyindoline carboxylates

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Received 5 June 2003; revised 7 August 2003; accepted 15 August 2003

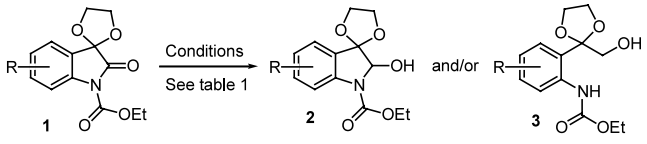
Abstract—The product from the reduction of ethyl *spiro*-3,3-(ethylenedioxy)-2-oxindole carboxylates (**1**) using borohydride salts has been found to be dependant upon both solvent and metal ion. With polar solvents and lithium bromide/sodium borohydride, *spiro*-3,3-(ethylenedioxy)-2-hydroxyindole carboxylates (**2**) are obtained in high yields whilst [2-(2-hydroxymethyl-[1,3]dioxolan-2-yl)-phenyl]-carbamic acid ethyl esters (**3**) are obtained using sodium borohydride in less polar solvents.

Isatin and its derivatives have proved to be versatile starting materials for the synthesis of heterocyclic, and non-cyclic, natural products, and analogues, as well as for the synthesis of potentially important compounds with biological activity.[1] We have been interested in the reduction of isatin derivatives as a means for the synthesis of indoles, as isatin can be considered to be an umpoled indole equivalent. We have shown that acylisatins are reduced to the *N*-alkylindoles,[2] 3,3-difluoro-2-oxindoles are reduced to 3-fluoroindoles,[3] and isatin Aldol adducts are reduced to tryptophols in excellent yields using THF solutions of BH_3·THF.[4]

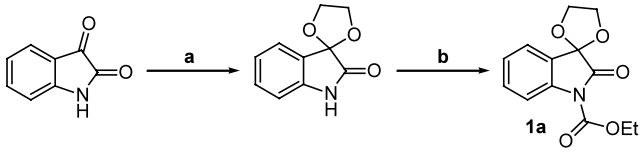
In this present study, we have investigated the reduction of ethyl *spiro*-3,3-(ethylenedioxy)-2-oxindole carboxylates (**1**) under various conditions. This study has resulted in the determination of methodology for the selective preparation of either ethyl *spiro*-3,3-(ethylenedioxy)-2-hydroxyindole carbamates (**2**) or [2-(2-hydroxymethyl-[1,3]dioxolan-2-yl)-phenyl]-carbamic acid ethyl esters (**3**) (Scheme 1).

Compounds **2** are potentially useful intermediates for the synthesis of *N*-acyliminium ions and subsequent reactions with nucleophilic species[5–8] whilst α-hydroxyacetophenones (of which **3** are derivatives) are potential intermediates for the synthesis of 1,2-diols, 1,2-aminoalcohols, phenethylalcohols, or phenethylamines, many of which posses important biological activities or are used as, or in the preparation of, asymmetric ligands.[9–15]

Our study began with the preparation of **1a** by reaction of isatin with ethylene glycol mixed with toluene and a catalytic quantity of H_2SO_4, under conditions of azeotropic removal of water using a Dean–Stark apparatus. Compound **4** was subsequently treated with a mixture of Et_3N and ethyl chloroformate in CH_2Cl_2 to give **1a** in 88% yield after workup (Scheme 2). The



Scheme 1. Reduction of compounds **1**.



Scheme 2. Synthesis of compound **1a**. *Reagents*: **a** $(CH_2OH)_2$, toluene, cat. H_2SO_4; **b** CH_2Cl_2, Et_3N, $ClCO_2Et$.

Keywords: hydroxylactam; α-hydroxyacetophenone; isatin; reduction; *N*-acyliminium precursor.

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doi:10.1016/j.tetlet.2003.08.058

Table 1. Reduction of compound **1a** with metal borohydrides in solvents with different polarities

Table entry	$NaBH_4$ +additive[a]	Solvent[b]	Ratio of **2a**:**3a**[c]	Mass balance (%)	Table entry	$NaBH_4$ +additive[a]	Solvent[b]	Ratio of **2a**:**3a**[c]	Mass balance (%)
1		MeOH	94:6	79	10	LiBr	EtOH	23:77	90
2		EtOH	20:80	76	11	LiBr	THF	42:58	73
3		Et_2O	12:88	83	12	LiBr	CH_3CN	100:0	80
4		THF	12:88	87	13	$CaCl_2$	MeOH	90:10	72
5		CH_3CN	75:25	76	14	$CaCl_2$	EtOH	38:62	90
6	1 mol. equiv.	CH_3CN	93:7	72	15	$CaCl_2$	THF, reflux	91:9	70
7	Li_2CO_3	EtOH	40:60	76	16	$ZnCl_2$	MeOH	28:72	82
8	Li_2CO_3	THF	40:60	82	17	$ZnCl_2$	EtOH	19:81	84
9	LiBr	MeOH	75:25	83	18	$ZnCl_2$	THF, reflux	99:1	69

[a] General experimental procedure: $NaBH_4$ (2.0 mmol) was added to the respective solvent (20 ml) containing additive (2.0 mmol) whilst being cooled on an ice water bath. After a few minutes the substrate (1.0 mmol) was added and the ice bath was removed. The reactions were allowed to warm to room temperature and after two hours were hydrolysed with a small quantity of sat. aqueous NH_4Cl, concentrated to remove the volatile organic solvent and the residue extracted with ethyl acetate and sat. aqueous NaCl solution. The organic extract was dried over Na_2SO_4, filtered and evaporated under reduced pressure.

[b] Room temperature unless otherwise stated.

[c] Ratios were determined by GC and GC–MS analysis of the crude products.

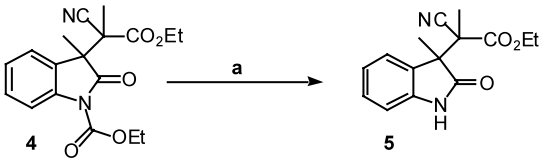
reduction of **1a** was investigated using a number of borohydride salts in various solvents. Table 1 details these results.

A first analysis of the results presented in Table 1 reveals a reversal in reaction selectivity on changing the solvent from methanol to ethanol (Table 1 entries 1/2, 9/10 and 13/14), with the exception of the use of $ZnCl_2$ (Table 1 entries 16 and 17). Changing the solvent from MeOH to acetonitrile continued the observed trend, with respect to increasing the solvent polarity, and greater yields of ring-closed product **2a** were obtained. The yield of **2a** could be increased by decreasing the number of mole equivalents of $NaBH_4$ when using acetonitrile as solvent (Table 1 entries 5 and 6). In the case of LiBr, as an additive in acetonitrile, compound **2a** was obtained exclusively (entry 12). It is also seen that the use of less polar solvents (THF and Et_2O) generally had little effect upon the ratio of **2a**:**3a** (compare Table 1 entries: 2, 3, and 4, as well as 7 and 8, and, 10 and 11) with the exception of the use of $ZnCl_2$, or $CaCl_2$, where a greater yield of ring closed product **2a** was observed (Table 1 entries 15 and 18). It should be noted that the use of $ZnCl_2$ or $CaCl_2$ in THF required that the reaction be refluxed in order to observe consumption of the starting material.

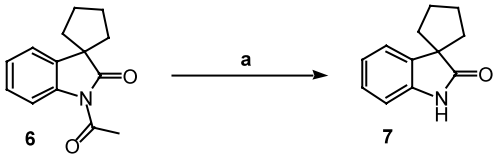
So far as we are aware there is no reported systematic survey of solvent or metal ion effects on the reduction of cyclic imides.[5,16] There are however, various reports that suggest that certain solvents, or methods, are better than others for the obtention of the α-hydroxylactams, precursors for the synthesis of *N*-acyliminium ions.

Speckamp and co-workers reported the use of EtOH with portion wise addition of HCl as a means for the selective preparation of hydroxylactams.[17] Altmann and co-workers observed ring opening on treating a hydroxypyroglutarimide derivative with $NaBH_4$ in EtOH in the presence of HCl, standard conditions for the synthesis of α-hydroxylactams.[18] Chamberlin, in studies of cationic cyclizations, reported that the use of MeOH as solvent for the preparation of hydroxylactams was superior to the $EtOH/H_2SO_4$ procedure.[19] The addition of various metal salt additives, but not lithium salts, to the reduction of cyclic *N*-imidotryptamines in EtOH using $NaBH_4$ has been reported and the authors highlighted the use of $CuCl_2$, $CoCl_2$ and $HgCl_2$ for the obtention of tryptamine hydroxylactam derivatives.[20] Evans and co-workers, as part of a synthesis of histrionicotoxin, found that the use of CH_2Cl_2 as solvent for the Grignard addition to the magnesate of glutarimide gave a quantitative yield of the hydroxyamide on workup. In the absence of CH_2Cl_2 and using Et_2O as solvent they obtained a 1:1 mixture of the hydroxylactam and the ring opened ketoamide.[21] Quirion and co-workers as part of work aimed at the synthesis of bicyclic lactams also found the $NaBH_4$/EtOH/HCl methodology to be unsatisfactory whilst the use of the $NaBH_4$/MeOH method gave the desired product in good yield.[22]

The reduction of **1a** is found to be highly regioselective with the reduction of the *endo* carbonyl group to give **2a** and **3a**. This regioselectivity may be attributed to the presence of the Lewis basic oxygen atoms of the *spiro*-1,3-dioxolane ring which provide a unique co-ordinating environment for Lewis acidic cations. Thus, the coordination of a Lewis acidic species to the endocyclic amide carbonyl, facilitated by the neighbouring 1,3-dioxolane ring, would serve to activate this carbonyl group for regioselective reduction. This hypothesis was tested in two separate reactions (Schemes 3 and 4). The addition of compound **4** to a solution of $NaBH_4$ in EtOH resulted in a quantitative yield of **5** (Scheme 3).[23] Similarly, with compound **6**,[24] reduction with $NaBH_4$ and LiBr in acetonitrile resulted in **7** (Scheme 4). In



Scheme 3. *Reagents*: **a** EtOH, $NaBH_4$.



Scheme 4. *Reagents*: **a** CH_3CN, LiBr, $NaBH_4$.

both cases, the reaction with borohydride salts resulted in the cleavage of the exocyclic carbonyl group.

Our results (Table 1) indicate that the ratio of **2a** to **3a** is both solvent and metal ion dependent. The effect of temperature was minimized by performing all reactions under equivalent conditions. Reduction of **1** by borohydride in the alcoholic solution would be expected to yield initially the respective metal alkoxide or borate ester of **2**.[25,26] As there should be little difference between the pK_a values for the solvent and the product then an equilibrium reaction with protonation of the alkoxide of **2**, or transesterification of the borate ester, by the solvent will result in the formation of **2**. Compound **3** can be considered to be the result of ring opening of product **2**, or fragmentation of the metal alkoxide of **2**, and subsequent reduction of the exposed aldehyde group. Both of these processes would be expected to be dependent upon the stability of the interaction with a Lewis acidic species in a given solvent.[27–29]

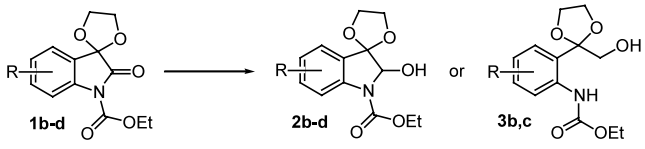
Other factors, in addition to the electron withdrawing inductive effect of the dioxolane ring, which would increase the reactivity of the endocyclic amide carbonyl group, that may play important roles in deciding the reaction outcome, include complexation of Lewis acidic species with the carbamate group. Such complexation would be expected to facilitate solvolysis in protic media or fragmentation of the respective alkoxides in non-protic media, although in the latter case a more polar non-protic solvent (CH_3CN versus THF) could help to stabilize the alkoxide metal ion pair. Ring opening could be favoured by the formation of more stable aggregates in less polar solvents due to relief of ring strain and/or due to a more stable anion as a consequence of resonance through the carbamate structure.

Table 2. Preparation of **2b–d** and **3b,c**

Entry	Substrate	Product **2** (%)[a]	Product **3** (%)[b]
1	**1b**	90	94
2	**1c**	80	89
3	**1d**	83	–

[a] $NaBH_4$, MeOH procedure. Compounds were purified by filtration through a short column of silica eluting with CH_2Cl_2:EtOAc.

[b] $NaBH_4$, THF procedure. Compounds were purified by filtration through a short column of silica eluting with CH_2Cl_2:EtOAc.



Scheme 5. (**1–3**) **b** R = 5-CH_3; **c** R = 5-I; **d** R = 4,6-diBr.

Based upon our findings, compounds **2b–d** and **3b–c** were prepared from compounds **1b–d**. The results are summarized in Table 2 (Scheme 5).[30] Under all conditions tested, compound **1d** gave only compound **2d** upon reduction. The bromine atom bonded to the aromatic C-4 position may exert a steric interaction with the dioxolane ring, thus favouring the α-hydroxylactam structure of compound **2d**.

In conclusion we have developed a method for the regioselective synthesis of *spiro*-3,3-(ethylenedioxy)-2-hydroxyindole carbamates (**2**) and [2-(2-hydroxymethyl-[1,3]dioxolan-2-yl)-phenyl]-carbamates (**3**) from readily available isatin derivatives.[31] The regioselective reduction of the endocyclic carbonyl group is attributed to assistance from the neighbouring dioxolane ring which participates in the co-ordination of the Lewis acid thus activating the carbonyl group and directing the reduction reaction. Compounds **2** are C-3 protected indoxyls, analogous to compounds prepared from the oxidation of indoles.[32,33]

Acknowledgements

The authors wish to thank FAPERJ and CNPq for financial assistance in the development of this work. S.J.G. also acknowledges the Fundação Oswaldo Cruz, Farmanguinhos, Rio de Janeiro, for financial support from the PAPES II program.

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30. Spectroscopic data: **Compound 2a, 2-Hydroxy-3,3-[ethylenedioxy]-2,3-dihydro-indole-1-carboxylic acid ethyl ester**: Recrystallized from hexane:CH_2Cl_2 (2:1); Colourless needle crystals, **mp** 99–100°C; **IR** (cm^{-1}): 3433, 2978, 2906, 1709, 1611, 1488, 1406, 1312, 1257, 992, 776; **Mass** *m*/*z* (%): 265 ($M^{+\bullet}$, 12), 209 (18), 149 (100), 119 (55); **HRMS**: calculated for $C_{13}H_{15}NO_5$ 265.0950, observed 265.0947; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.72 [1H, d, *J* 8.1], 7.35 [2H, m], 7.05 [1H, t, *J* 8.1], 5.54 [1H, s], 4.05–4.40 [6H, m], 1.45 [3H, t, *J* 7.1]; **^{13}C NMR** Pendant (50.32 MHz): δ 14.7 [CH_3], 62.4 [CH_2], 65.2 [CH_2O], 66.7 [CH_2O], 86.3 [CH], 110.2 [C], 115.5 [CH], 123.6 [CH], 124.7 [CH], 126.2 [C], 132.1 [CH], 142.0 [C], 153.4 [C]. **Compound 2b, 2-Hydroxy-3,3-(ethylenedioxy)-5-methyl-2,3-dihydro-indole-1-carboxylic acid ethyl ester**: Yellow oil. **IR** (cm^{-1}): 3406, 2983, 2906, 1694, 1499, 1140, 1055, 829, 771; **Mass** *m*/*z* (%): 279 ($M^{+\bullet}$, 22), 223 (24), 163 (100), 133 (34); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.65 [1H, bs], 7.20 [2H, m], 5.41 [1H, d, *J* 6.1], 4.10–4.40 [6H, m], 3.75 [1H, bs], 2.32 [3H, s], 1.38 [3H, t, *J* 7.1]; **^{13}C NMR** Pendant (50.32 MHz): δ 14.7 [CH_3], 21.0 [CH_3], 62.3 [CH_2O], 65.2 [CH_2O], 66.7 [CH_2O], 86.5 [CH], 115.3 [CH], 124.9 [CH], 132.8 [CH], 133.4 [C]. **Compound 2c, 2-Hydroxy-3,3-(ethylenedioxy)-5-iodo-2,3-dihydro-indole-1-carboxylic acid ethyl ester**: Recrystallized from hexano:CH_2Cl_2; white cubes, **mp** 128°C; **IR** (cm^{-1}): 3399, 3376, 2975, 1734, 1693, 1600, 1472, 1259, 829, 779; **Mass** *m*/*z* (%): 391 ($M^{+\bullet}$, 22), 335 (36), 275 (100), 245 (34). **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.50–7.70 [3H, m], 5.39 [1H, d, *J* 6.1], 4.10–4.50 [6H, m], 3.68 [1H, bd], 1.39 [3H, t, *J* 7.1]; **^{13}C NMR** Pendant (50.32 MHz): δ 14.7 [CH_3], 62.6 [CH_2O], 65.4 [CH_2O], 66.9 [CH_2O], 85.9 [C], 86.4 [CH], 109.5 [C], 117.6 [CH], 128.8 [C], 133.7 [CH], 140.8 [CH], 141.9 [C], 153.0 [C]. **Compound 2d, 2-Hydroxy-3,3-(ethylenedioxy) - 4,6 - dibromo - 2,3 - dihydro - indole - 1 - carboxylic acid ethyl ester**: Recrystallized from hexano:CH_2Cl_2; pale yellow cubes, **mp** 128–129°C; **IR** (cm^{-1}): 3435, 3130, 3083, 2974, 2898, 1716, 1592, 1571; **Mass** *m*/*z* (%): 423 (M, 12), 367 (12), 307 (100), 277 (20); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.01 [1H, bs], 7.39 [1H, d, *J* 1.7], 5.35 [1H, s], 4.10–4.50 [6H, m], 1.40 [3H, t, *J* 7.1]; **^{13}C NMR** Pendant (50.32 MHz): δ 14.6 [CH_3], 62.9 [CH_2O], 66.1 [CH_2O], 67.3 [CH_2O], 86.9 [CH] 110.3 [C], 117.9 [CH], 120.0 [C], 123.3 [C], 126.5 [C], 130.2 [CH], 145.0 [C], 152.7 [C]. **Compound 3a, [2-(2-Hydroxymethyl-[1,3]dioxolan - 2 - yl) - phenyl] - carbamic acid ethyl ester**: Recrystallized from hexane:CH_2Cl_2; colourless needle crystals, **mp** 115°C; **IR** (cm^{-1}): 3467, 3365, 2990, 2961, 2909, 1713, 1593, 1541, 1241, 1032, 767; **Mass** *m*/*z* (%): 267 ($M^{+\bullet}$, 5), 236 (100), 190 (15), 146 (70); **HRMS**: calculated for $C_{13}H_{17}NO_5$: 267.1107, observed: 267.1104; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.54 [1H, bs, NH], 8.07 [1H, d, *J* 8.1], 7.47 [1H, d, *J* 8.1], 7.33 [1H, t, *J* 8.1], 7.04 [1H, t, *J* 8.1], 4.22 [4H, m], 3.98 [2H, m], 3.76 [2H, d, *J* 6.1], 2.17 [1H, bt, OH], 1.32 [3H, t, *J* 7.0]; **^{13}C NMR** Pendant (50.32 MHz): δ 14.7 [CH_3], 61.3 [CH_2O], 65.39 [CH_2O], 65.51 [CH_2O], 110.1 [C], 121.0 [CH], 123.1 [CH], 126.5 [C], 127.3 [CH], 130.0 [CH], 136.8 [C], 154.0 [C=O]. **Compound 3b, [2-(2-Hydroxymethyl-[1,3]dioxolan-2-yl)-4-methylphenyl]-carbamic acid ethyl ester**: Recrystallized from hexane:CH_2Cl_2; pale yellow needles, **mp** 68–69°C; **IR** (cm^{-1}): 3375, 2981, 2957, 2921, 2900, 1732, 1596, 1525, 1234, 1062; **Mass** *m*/*z* (%): 281 ($M^{+\bullet}$, 5), 250 (100), 222 (10), 204 (30), 160 (60); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.42 [1H, bs, NH], 7.94 [1H, d, *J* 8.6], 7.28 [1H, s, *J* 8.6], 7.16 [1H, d, *J* 8.6], 4.15 [4H, m], 4.10 [2H, m], 3.75 [2H, s], 2.30 [3H, s], 2.14 [1H, bs, OH], 1.32 [3H, t, *J* 7.2]; **^{13}C NMR** Pendant (50.32 MHz): δ 14.7 [CH_3], 20.9 [CH_3], 61.2 [CH_2], 65.3 [CH_2], 65.5 [CH_2], 110.1 [C], 121.2 [CH], 126.5 [C], 127.6 [CH], 130.5 [CH], 132.6 [C], 134.1 [C], 154.0 [C]. **Compound 3c, [2-(2-Hydroxymethyl-[1,3]dioxolan-2-yl)-4-iodophenyl]-carbamic acid ethyl ester**: Recrystallized from hexane:CH_2Cl_2; pale yellow needles, **mp** 142°C; **IR** (cm^{-1}): 3453, 3326, 3069, 2995, 2957, 2902, 1715, 1583, 1530, 1244, 1080, 1039; **Mass** *m*/*z* (%): 393 ($M^{+\bullet}$, 4), 362 (100), 316 (16), 272 (48); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.49 [1H, bs, NH], 7.77 [1H, d, *J* 8.7], 7.69 [1H, d, *J* 2.1], 7.50 [1H, dd, *J* 8.7, 2.1], 4.10 [4H, m], 3.93 [2H, m], 3.61 [2H, s],

3.03 [1H, bs, OH], 1.22 [3H, t, *J* 7.1]; **^{13}C NMR** Pendant (50.32 MHz): δ 14.5 [CH_3], 61.1 [CH_2], 65.3 [CH_2], 86.0 [C], 109.2 [C], 122.4 [CH], 129.3 [C], 135.8 [CH], 136.5 [C], 138.2 [CH], 153.5 [C-12].

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