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A new course of reduction of substituted 5,6-dihydro-4*H*-1,2-oxazines to furan derivatives

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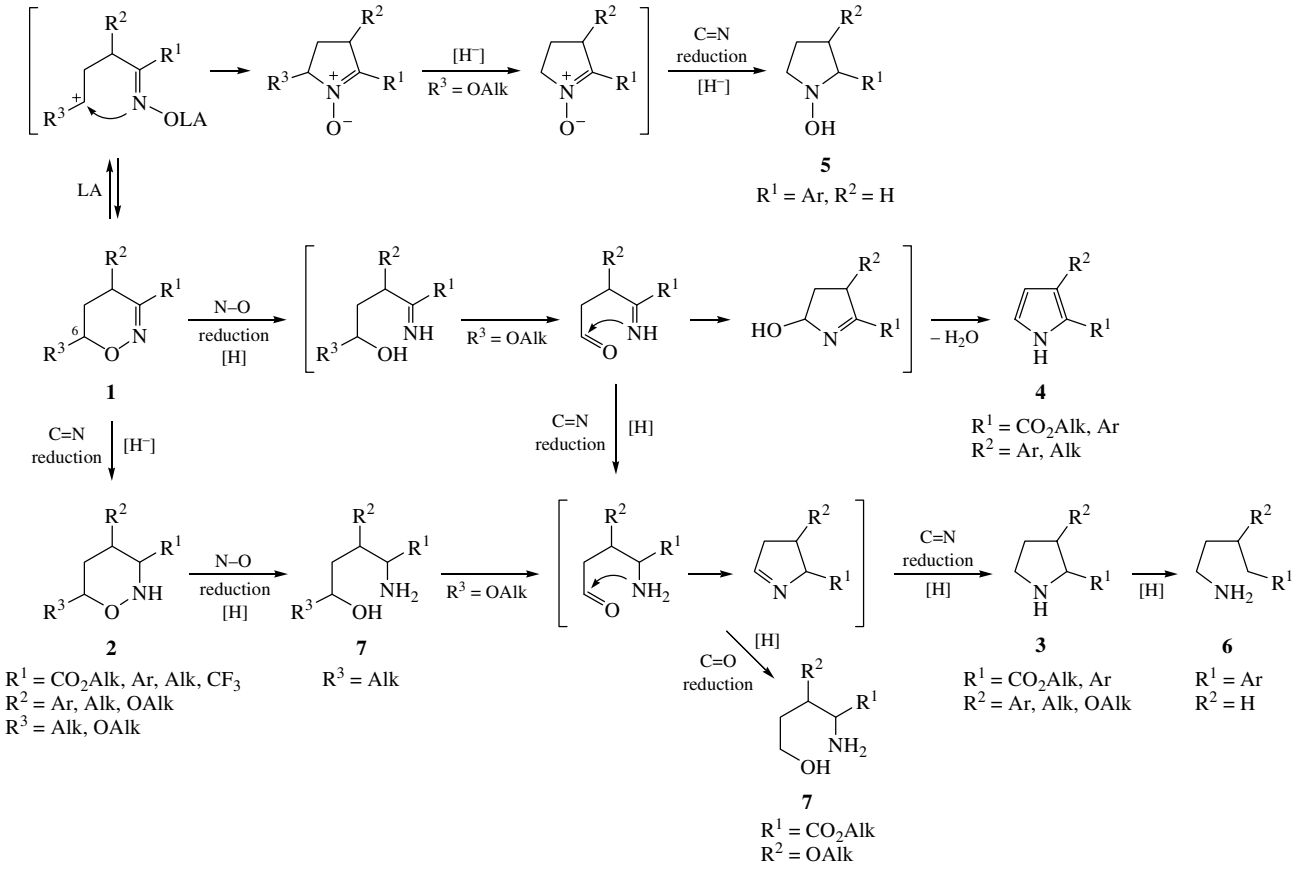
An unexpected result of the reduction of easily available 6-alkylsubstituted-5,6-dihydro-4*H*-1,2-oxazines to furan derivatives was observed.

The reduction of 5,6-dihydro-4*H*-1,2-oxazines **1** is one of their most fascinating reactions[1] because it allows one to convert these compounds into various heterocyclic systems: tetrahydrooxazines **2**,[2(a),(b)] pyrrolidines **3**,[3(a),(b)] pyrroles **4**,[4] *N*-hydroxypyrrolidines **5**,[5] acyclic amines **6**[6] and δ-amino alcohols **7**[7] (Scheme 1).

The process of oximino-fragment reduction in oxazines **1** represents a complicated sequence of hydrogenation and cyclization reactions, the actual result of which is governed by the nature of the starting substrate and reducing agent along with the reaction conditions. Thereby the sequence of N–O and C=N bond hydrogenolysis depends upon the reducing agent of choice, while the cyclization mode depends upon the substituent type in an oxazine ring. The reduction of accessible dihydrooxazines **1** carrying alkoxy substituting groups at the C-6 atom (R^3 = OAlk) was studied in greater detail. For such substrates, the formation of a pyrrolidine cycle is most typical (Scheme 1).

Recently, we developed a new approach towards functionalised 5,6-dihydro-4*H*-1,2-oxazines **8**,[3(b),8] which allows us to prepare these products from easily accessible precursors (Scheme 2).

Oxazines **8** which do not contain alkoxy substituents at the C-6 atom are investigated systematically in the reaction of reduction. This work is dedicated to the catalytic hydrogenation



Scheme 1

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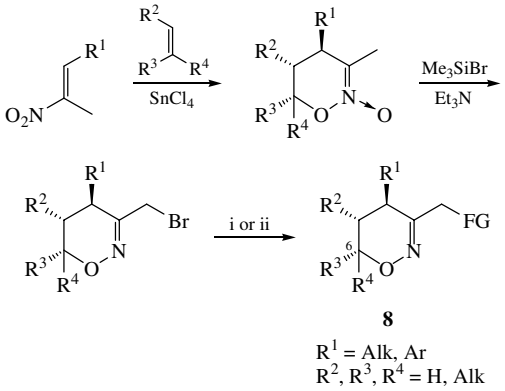


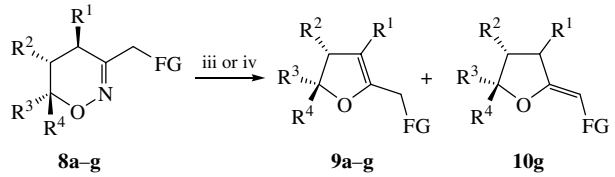
8

R^1 = Alk, Ar
R^2, R^3, R^4 = H, Alk

Scheme 2 *Reagents and conditions*: i, Bu^{t}OK, DMF, dimethylmalonate [FG = $CH(CO_2Me)_2$]; ii, CO, 1% $PdCl_2(PPh_3)_2$, MeOH (FG = CO_2Me).

of substrates **8**, which possess a CH_2FG residue [FG = CO_2Me, $CH(CO_2Me)_2$] as a substituent at the C-3 carbon atom.

We found that the reduction of oxazine **8** by hydrogen in the presence of Raney nickel in acetic acid leads to the formation of dihydrofuran derivatives **9**§ in medium or moderate yields (when oxazine **8g** is reduced, a mixture of dihydrofurans **9g** and **10g** is formed) (Scheme 3). Note that the furan ring formation in the course of oxazine hydrogenation was not observed as a rule.¶



8a–g **9a–g** **10g**

Scheme 3 *Reagents and conditions:* iii, 20 bar H_2, Ni_{Ra}, AcOH, 70–80 °C, 1 h; iv, Ni_{Ra}, AcOH, 100 °C, 1 h.

Table 1 summarises the yields and optimised preparation procedures for desired derivatives **9a–g** and **10g**. The above procedures were developed in a series of separate *ad hoc* experiments. Carrying out the reaction over 20 bar of hydrogen resulted in reduced yields of the desired dihydrofurans and formation of a complex mixture of non-identified products of exhaustive hydrogenation. When the reaction mixture was exposed to a hydrogen pressure under 10 bar in procedure (iii), the starting oxazine was not totally converted, and that adversely affected the desired product yield.

An increase in the temperature led, on the one hand, to a significant acceleration of the reaction, *e.g.*, at 100 °C, reduction proceeded with no overpressure of hydrogen [procedure (iv) in Table 1]. On the other hand, such toughening of conditions negatively affected the reaction yield of derivatives **9** and **10** in most cases.

Note that absolute acetic acid should be used in the reaction: even water traces in the reaction mixture lead to significantly reduced yields of the desired products.

Table 1 Reduction of **8**.

Compounds **8–10**	R^1	R^2	R^3	R^4	FG	Procedure	Yield of **9** (%)
a	Ph	H	Me	Me	$CH(CO_2Me)_2$	iii	81
b	4-$MeOC_6H_4$	H	Me	Me	$CH(CO_2Me)_2$	iii	60
c	4-ClC_6H_4	H	Me	Me	$CH(CO_2Me)_2$	iii	56
d	Ph	–$(CH_2)_3$–		H	$CH(CO_2Me)_2$	iii	38
e	Ph	–$(CH_2)_4$–		H	$CH(CO_2Me)_2$	iv	32
f	4-$MeOC_6H_4$	–$(CH_2)_4$–		H	$CH(CO_2Me)_2$	iv	30
g	Ph	H	Me	Me	CO_2Me	iii	66[a]

[a]For mixture of products **9g** and **10g** (ratio **9g**:**10g**, 1.6:1).

Analogous results were observed when the reaction was carried out with Pd/C in absolute methanol; however, the detected yields are inferior to the yields given in Table 1.

Column chromatography purification gave products **9a–g** and **10g** of NMR purity grade. Yet, getting satisfactory results of the elemental analysis for most species is impractical due to instability of these compounds.

The structure and configuration of products were confirmed by NMR spectroscopy (^1H, ^{13}C, INEPT, COSY, NOESY) and mass spectrometry. The presence of the CO_2R group and the C=C double bond was additionally confirmed by IR-spectroscopic data.

According to the proposed reaction scheme (Scheme 4), the relative configuration of stereocentres in starting oxazines **8** remains unchanged in resulting dihydrofurans **9**.††

§ *Preparation procedure for dihydrofurans* **9a–d**,**g** *and* **10g** (*procedure* iii). Methanol-washed (5×10 ml) Raney nickel (Acros, c.a. 100 mg) was added to a solution of oxazine **8** (1.0 mmol) in acetic acid (6.6 ml). The suspension was hydrogenated at 20 bar of H_2 and 80 °C with intense stirring for 1 h. Then, the resulting mixture was poured into a mixture of EtOAc (100 ml) and a saturated solution of Na_2CO_3 (100 ml). The aqueous phase was back-extracted with EtOAc (50 ml), the combined organic layer was washed with brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated in a vacuum, and the residue was subjected to column chromatography on silica gel.

Methyl 2-(5,5-dimethyl-3-phenyl-4,5-dihydro-2-furanyl)acetate **9g**: oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 6H, MeCO), 2.88 (s, 2H, H_2CCMe_2), 3.38 (s, 2H, H_2CCO_2Me), 3.75 (s, 3H, CO_2Me), 7.14–7.41 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 28.1 (2Me), 33.8 (*C*CO_2Me), 46.5 (*C*CMe_2), 52.2 (OMe), 83.2 (Me_2CO), 111.1 (*C*=CO), 125.9, 126.3 and 128.5 (Ph), 135.6 (*i*-Ph), 144.8 (C=*C*O), 170.2 (*C*O_2Me). IR (ν/cm^{-1}): 527, 666, 700, 737, 759, 794, 974, 1008, 1045, 1113, 1147, 1211, 1265, 1367, 1436, 1495, 1601, 1639, 1710, 1744, 2851, 2924. MS, *m*/*z* (%): 246 (M^+, 70).

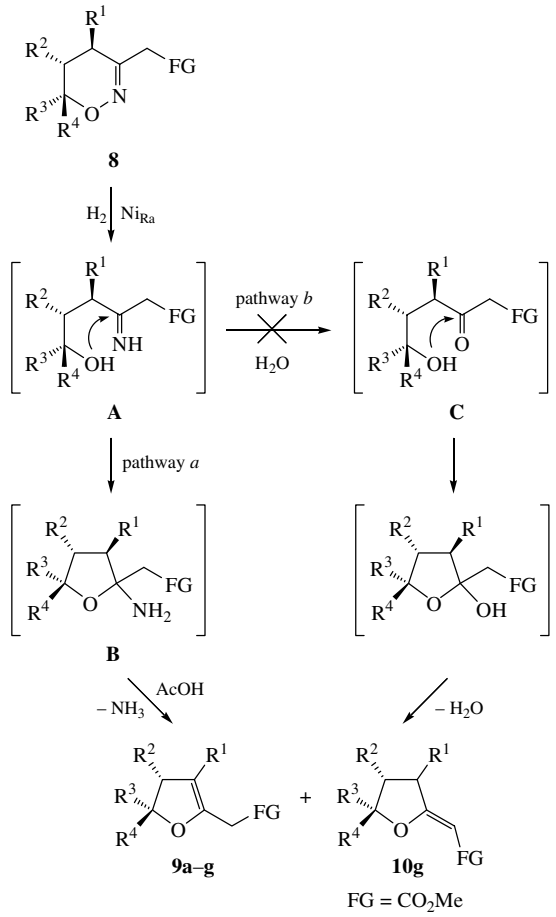
*Methyl 2-[5,5-dimethyl-3-phenyldihydro-2(3*H*)-furanyliden]acetate* **10g**: mp 108–110 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.47 and 1.64 (2s, 6H, MeCO), 2.03 (dd, 1H, H_2CCMe_2, *J* 12.5 and 11.8 Hz), 2.35 (dd, 1H, H_2CCMe_2, *J* 12.5 and 8.1 Hz), 3.62 (s, 3H, CO_2Me), 4.21 (ddd, 1H, *H*CPh, *J* 11.8, 8.1 and 1.5 Hz), 4.41 (d, 1H, *H*CCO_2Me, *J* 1.5 Hz), 7.22–7.41 (m, 5H, Ph). Characteristic 2D-NOESY correlations: *H*CCO_2Me/*H*CPh, *H*CCO_2Me/*o*-Ph. ^{13}C NMR ($CDCl_3$) δ: 26.6 and 28.5 (2Me), 45.6 (*C*CMe_2), 50.5 (*C*Ph), 51.0 (OMe), 88.5 (Me_2CO), 89.1 (*C*=CO), 127.5, 128.5 and 128.9 (Ph), 139.4 (*i*-Ph), 166.5 (C=*C*O), 174.8 (*C*O_2Me). MS, *m*/*z* (%): 246 (M^+, 36). IR (ν/cm^{-1}): 540, 645, 704, 761, 788, 808, 883, 901, 966, 1048, 1135, 1148, 1191, 1238, 1254, 1274, 1310, 1376, 1432, 1460, 1461, 1496, 1633, 1708, 2943, 2976. Found (%): C, 73.00; H, 7.72. Calc. for $C_{15}H_{18}O_3$ (%): C, 73.15; H, 7.37.

Preparation procedure for dihydrofurans **9e–f** (*procedure* iv). Methanol-washed (5×10 ml) Raney nickel (Acros, c.a. 100 mg) was added to a solution of oxazine **8e–f** (1.0 mmol) in acetic acid (6.6 ml). The resulting mixture was stirred at 100 °C for 1 h and then poured into a mixture of EtOAc (100 ml) and a saturated solution of Na_2CO_3 (100 ml). The aqueous phase was back-extracted with EtOAc (50 ml), the combined organic layer was washed with brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated in a vacuum and the residue was subjected to column chromatography on silica gel.

*Dimethyl 2-[(3a*S*,7a*S*)-3-phenyl-3a,4,5,6,7,7a-hexahydro-1-benzofuran-2-yl]methylmalonate* **9e**: oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.16, 1.26, 1.47, 1.64, 1.77 and 1.93 (6m, 8H, 4CH_2 of cyclohexane ring), 3.01 (d and m, 3H, H_2CCO and *H*CCPh, *J* 7.9 Hz), 3.66 and 3.72 (2s, 6H, CO_2Me), 3.79 (t, 1H, *H*CCO_2Me, *J* 7.9 Hz), 4.45 (ddd, 1H, HCO, *J* 7.2, 4.6 and 4.6 Hz), 7.13–7.36 (m, 5H, Ph). Characteristic 2D-NOESY correlations: *H*CO/*H*CCPh, *H*CCO_2Me/H_2CCO. ^{13}C NMR ($CDCl_3$) δ: 20.4, 21.9, 27.3 and 27.7 (4CH_2 of cyclohexane ring), 26.8 (*C*H_2CO), 44.0 (*C*HCPh), 49.4 (*C*CO_2Me), 52.6 (OMe), 79.9 (CHO), 118.7 (*C*=CO), 125.9, 127.5 and 128.5 (Ph), 134.9 (*i*-Ph), 149.1 (C=*C*O), 169.3 (*C*O_2Me). IR (ν/cm^{-1}): 700, 762, 954, 990, 1025, 1154, 1210, 1244, 1436, 1495, 1599, 1661, 1737, 2857, 2933. MS, *m*/*z* (%): 344 (M^+, 64).

¶ The only example of this kind is reported: when 4-vinyl-1,2-benzoxazines were hydrogenated in the presence of PtO_2, the formation of products with a condensed tetrahydrofuran unit was observed.[9]

†† This fact is additionally confirmed by the 2D NOESY spectral data.



Scheme 4

The reduction of oxazines **8** is described by the following formal scheme (Scheme 4, pathway *a*): first, in line with published data for 5,6-dihydro-4*H*-1,2-oxazines[1] and oximes,[10] N–O bond opening occurs with imine **A** formation followed by the recyclization of it into α-amino tetrahydrofuran **B**. The latter eliminates ammonia by the action of acetic acid, to give corresponding desired products **9a**–**g** and **10g**.

An alternative way of dihydrofuran **9** generation through γ-hydroxyketone **C** (pathway *b*) seems highly unlikely since the addition of water hinders the reaction from proceeding in the required course.[‡‡]

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[‡‡] At the same time, H.-U. Reissig and co-authors observed the formation of 1,4-diketones, when 3-vinyl-6-siloxy-5,6-dihydro-4*H*-1,2-oxazines where reduced with Raney nickel in aqueous methanol.[11]

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