Autorecycling System for the Specific 1,4-Reduction of α,β-Unsaturated Carbonyl Compounds Catalysed by 1,5-Dihydro-5-deazaflavin

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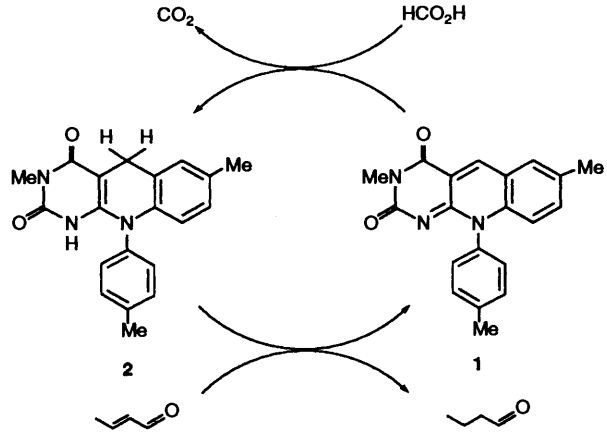
A useful autorecycling system for the specific 1,4-reduction of α,β-unsaturated carbonyl compounds to the corresponding saturated carbonyl compounds catalysed by a 10-aryl-5-deazaflavin in formic acid is reported. The specific reduction behaviour toward α,β-unsaturated carbonyl compounds is interpreted in terms of frontier molecular orbital theory (PM3 method).

As a general rule, α,β-unsaturated carbonyl compounds undergo attack by hydride ion in either a 1,2- or a 1,4-fashion. It is known that lithium aluminium hydride favours the 1,2-reduction of α,β- unsaturated carbonyl compounds to give the corresponding α,β-unsaturated alcohols and that sodium tetrahydroborate usually gives a mixture of 1,2- and 1,4-reduction products (saturated carbonyl compounds). Even modified complex hydride reagents lack the general specificity for 1,4-reduction towards saturated carbonyl compounds.[1] Furthermore, α,β-unsaturated carbonyl compounds are generally inert towards hydride ion from NADH models such as Hantzsch esters or 1-alkyl-1,4-dihydronicotinamides, except in a special case.[2] Thus, it is usually difficult to obtain selectively saturated carbonyl compounds by hydride reduction of α,β-unsaturated carbonyl compounds.

In earlier work, we demonstrated the first example of the reduction of inactivated simple carbonyl substrates to the corresponding alcohols by 1,5-dihydro-5-deazaflavin in the presence of strong proton sources such as hydrochloric acid or trifluoroacetic acid in stoichiometric yields.[3] Shinkai *et al.* showed 1-benzyl-3-carbamoyl-1,4-dihydroquinoline is also able to reduce benzaldehyde in 20–30% yield under acidic condition.[4] In addition, we reported the first example of an efficient autorecycling system for reduction of carbonyl compounds to alcohols using 5-deazaflavin and formic acid.[5]

In a preliminary communication,[6] we reported the first example of an autorecycling system for the specific reduction of the carbon–carbon double bond of α,β-unsaturated carbonyl compounds by a 1,5-dihydro-5-deazaflavin, which can be regarded as an NADH model. This paper describes a full account of the improved and convenient synthesis of 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **1** and the autorecycling system for the specific 1,4-reduction of α,β-unsaturated carbonyl compounds by 3,7-dimethyl-10-*p*-tolyl-1,5-dihydro-5-deazaflavin **2** which is produced by **1** and formic acid in the circulatory system (see Scheme 1). Moreover, the specific reduction behaviour toward α,β-unsaturated carbonyl compounds is interpreted in terms of frontier molecular orbital theory (PM3 method).



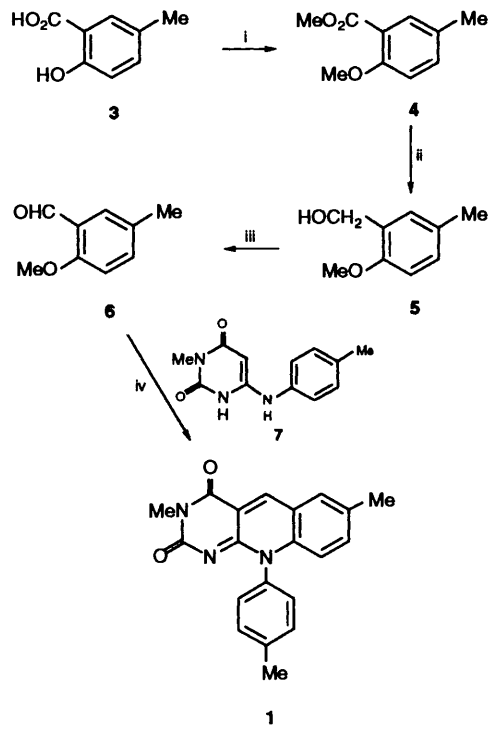
Scheme 1 Autorecycling system for 1,4-reduction of α,β-unsaturated compounds by formic acid, catalysed by 5-deazaflavin

Results and Discussion

Synthesis of 3,7-*Dimethyl*-10-p-*tolyl*-5-*deazaflavin* **1**.—We have previously reported the synthesis of 10-aryl-5-deazaflavins by the reaction of bis(6-anilino-3-methyluracil-5-yl)arylmethanes with diethyl azodicarboxylate in sulfolane (tetrahydrothiophene 1,1-dioxide).[5] However, we experienced difficulty in attempting to isolate the product from the reaction mixture, especially in the case of the preparation of compound **1**. Since the 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **1** was an excellent catalyst for formic acid reduction of benzaldehydes in the previous paper,[5] we tried to improve the synthesis of **1** and report here a convenient synthesis.

The sequential synthetic pathway is shown in Scheme 2. The heating of the 5-methylsalicylate **3** with iodomethane in dimethylformamide (DMF) in the presence of sodium hydride afforded methyl 2-methoxy-5-methylbenzoate **4**. Reduction then of compound **4** by lithium aluminium hydride gave 2-methoxy-5-methylbenzyl alcohol **5**, the subsequent oxidation of **5** which with pyridinium chlorochromate (PCC) yielded the desired 2-methoxy-5-methylbenzaldehyde **6**. Finally, the title compound **1** was synthesized by the condensation of the compound **6** thus obtained with 3-methyl-6-*p*-toluidinouracil **7**[7] in DMF at 150 °C. The structures of the products prepared here were verified by mass spectrometry and ^{1}H NMR spectroscopy, whilst some products were identified by comparison of IR and ^{1}H NMR spectra with those of authentic samples.

Autorecycling 1,4-*Reduction of* α,β-*Unsaturated Carbonyl Compounds to Saturated Carbonyl Compounds by* 1,5-*Dihydro*-5-*deazaflavins*.—In a previous report,[5] the 1,5-dihydro-5-deazaflavins, which were generated from 5-deazaflavins and formic acid, were generally found to be powerful reducing

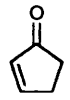
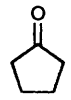
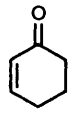
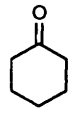
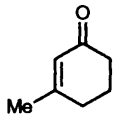
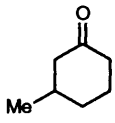
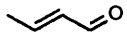
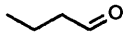
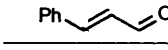
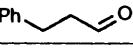


Scheme 2 Synthesis of 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **1**; *Reagents and conditions:* i, NaH, MeI, DMF, 70 °C; ii, $LiAlH_4$, Et_2O, O °C; iii, PCC, CH_2Cl_2, room temp.; iv, DMF, reflux

agents towards carbonyl compounds yielding the corresponding alcohols in a remarkable autorecycling reduction. Here we describe in detail the first example of an autorecycling system for the specific 1,4-reduction of carbon–carbon double bonds of α,β-unsaturated carbonyl compounds by a 1,5-dihydro-5-deazaflavin. The reaction occurs when the α,β-unsaturated carbonyl compound is heated under reflux in formic acid with a little 5-deazaflavin as catalyst. 3,7-Dimethyl-10-*p*-tolyl-5-deazaflavin **1** was selected as the catalyst, since it proved to be the most powerful reducing agent in the reduction of benzaldehyde to benzyl alcohol.[5] The reaction mixture was analysed by gas chromatography (GC) and the product was identified as the corresponding saturated carbonyl compound (see Table 1). No allylic alcohol or saturated alcohol was detected. In the reduction of cinnamaldehyde to 3-phenylpropionaldehyde the yield of the latter was determined from ^1H NMR spectrometry. It is notable that the catalyst **1** showed excellent activity for the formic acid reduction of cyclohex-2-enone and cinnamaldehyde giving high yields of cyclohexanone and 3-phenylpropionaldehyde, respectively. Under these conditions, 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **1** was initially hydrogenated by formic acid to form 3,7-dimethyl-10-*p*-tolyl-1,5-dihydro-5-deazaflavin **2**, which acts as the turnover catalyst for the specific 1,4-reduction (Scheme 1). Furthermore, it has been confirmed that this 1,4-reduction also occurs stoichiometrically using equimolar amounts of substrate and isolated **2** in formic acid under mild conditions.

Interpretation of the Interaction between α,β-Unsaturated Carbonyl Compound and Catalyst in Terms of Frontier Molecular Orbital Theory.—As described above, the 1,5-dihydro-5-deazaflavin **2** reduces specifically the carbon–carbon double bond of α,β-unsaturated carbonyl compounds. In order to obtain information about the conformational interaction between the frontier molecular orbitals (FMO) of both compounds, we carried out a modified neglect of diatomic overlap (MNDO) calculation on them. Since the size of

Table 1 Specific 1,4-reduction of α,β-unsaturated carbonyl compounds to saturated carbonyl compounds catalysed by 3,7-dimethyl-10-*p*-tolyl-1,5-dihydro-5-deazaflavin **2** in formic acid at 120 °C for 25 h

Substrate	Product	Catalytic Yield [a]	% Yield [b]
		1460	51
		2320	81
		260	9
		1890	66
		2860	100

[a] Yields based on the turnover of 3,7-dimethyl-10-*p*-tolyl-1,5-dihydro-5-deazaflavin. [b] Yields based on the starting α,β-unsaturated carbonyl compounds.

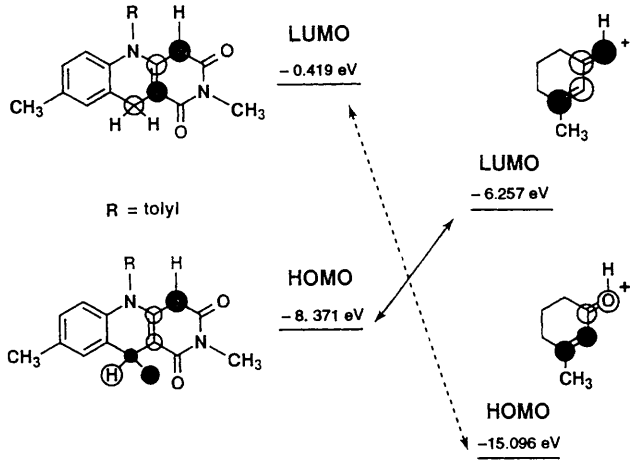


Fig. 1 Energy levels of frontier orbitals of **2** and α,β-unsaturated carbonyl compound

compound **2**, consisting of 44 atoms, is quite large, we decided to use the MNDO-PM3 method[8] for the present calculations. In the calculation, α,β-unsaturated carbonyl compounds were assumed to be protonated because the reaction proceeds under acidic conditions (in formic acid). The hydride ion transferred from the C-5 position of compound **2**, in contrast to one from a metal compound, might be expected to prefer a carbon–carbon double bond to a carbonyl group; this selectivity originates from a frontier molecular orbital theory explanation. The interaction between the highest occupied orbital HOMO of the nucleophilic reagent **2** and the lowest unoccupied molecular orbital LUMO of the substrate (an α,β-unsaturated carbonyl compound) is the dominant one in this reaction (Fig. 1). From the symmetry of the resultant orbitals, the interaction shown in Fig. 2 is expected to give the selectivity of the reduction. Because of this interaction, allylic and saturated alcohols are not detected. Shinkai *et al.* have reported[9] that hydrogen transfer from 1,5-

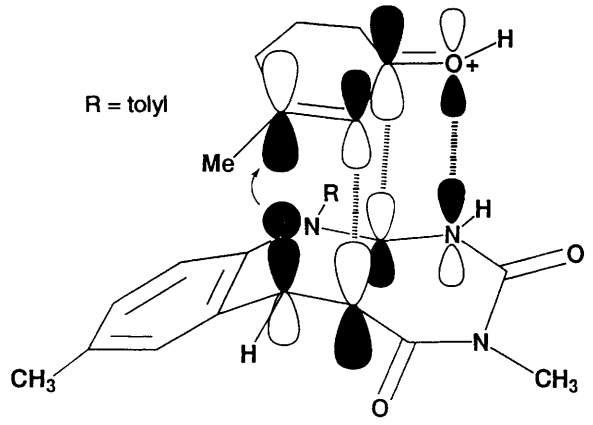


Fig. 2 HOMO–LUMO interaction between the catalyst **2** and α,β-unsaturated carbonyl substrate

dihydro-5-deazaflavin occurs exclusively from the axial C-5 position. This report supports our proposed mechanism.

In conclusion, the present reaction offers a useful auto-recycling system for the specific 1,4-reduction of α,β-unsaturated carbonyl compounds to the corresponding saturated carbonyl compounds.

Experimental

M.p.s were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were obtained in deuteriochloroform at 200 MHz on a JEOL FX 200 spectrometer with chemical shifts reported in ppm downfield from tetramethylsilane as internal standard; *J* values are given in Hz. Mass spectra (MS) were obtained on a JEOL JMS 01SG-2 instrument by direct insertion at 70 eV. All reactions were carried out under an inert atmosphere of argon, unless otherwise noted. Analysis by gas chromatography was performed under the following conditions; N_2: 2.3 kg cm^{-3}; air: 0.5 kg cm^{-3}; H_2: 0.6 kg cm^{-3}. The column consisted of silicone SE-30 2% Chromosorb WAW (60–80 mesh).

Methyl 2-Methoxy-5-methylbenzoate **4**.—A solution of 5-methylsalicylate **3** (3.0 g, 19.7 mmol) with sodium hydride (as 60% oil dispersion; 4.0 g, 100 mmol) and *N*,*N*-dimethylformamide in (DMF) (20 cm^3) was heated and stirred at 70 °C for 30 min after which methyl iodide (13.7 g, 96.5 mmol) was added to it. After being allowed to react for a further 1 h, the reaction mixture was cooled to room temperature, diluted with a little water and extracted with diethyl ether. The extract was dried ($MgSO_4$) and evaporated under reduced pressure to afford the oily product **4** in quantitative yield (Found: M$^+$, 180.078 46. $C_{10}H_{12}O_3$ requires *M*, 180.078 64); δ_H 2.30 (3 H, s, Me), 3.87 (3 H, s, OMe), 3.88 (3 H, s, CO_2Me), 6.87 (1 H, d, *J* 8.55, 3-H), 7.27 (1 H, dd, *J* 8.55, 2.45, 4-H) and 7.60 (1 H, d, *J* 2.45, 6-H). The colourless oily residue was used without further purification in the next reaction.

2-Methoxy-5-methylbenzyl Alcohol **5**.—Lithium aluminium hydride (1.3 g, 34.7 mmol) was added stepwise to a stirred solution of compound **4** (3.85, g, 21.4 mmol) in diethyl ether (80 cm^3) at 0 °C. After being stirred for 1 h, the reaction mixture was extracted with dichloromethane. The extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to afford the colourless oily product **5** (4.6 g, 87%) (Found: M$^+$, 152.083 17. $C_9H_{12}O_2$ requires *M*, 152.083 72); δ_H 2.28 (3 H, s, Me), 3.82 (3 H, s, OMe), 4.64 (2 H, s, CH_2), 6.77 (1 H, d, *J* 7.33, 3-H), 7.06 (1 H, *J* 7.33, 4-H) and 7.08 (1 H, s, 6-H).

2-Methoxy-5-methylbenzaldehyde **6**.—A solution of compound **5** (2.7 g, 17.8 mmol) in dichloromethane (20 cm^3) was added immediately to a stirred suspension of pyridinium chlorochromate (3.84 g, 17.8 mmol) in dichloromethane (20 cm^3) at room temperature. After 1 h, the black reaction mixture was diluted with a five-fold volume of anhydrous diethyl ether and the supernatant liquid was decanted. The insoluble residue was washed twice with diethyl ether. The combined supernatant liquid and extracts were filtered through silica gel to give a clear solution which upon concentration to dryness under reduced pressure afforded the colourless oily product **6** (2.1 g, 77%) (Found: M$^+$, 150.068 85. $C_9H_{10}O_2$ requires *M*, 150.068 07); δ_H 2.31 (3 H, s, Me), 3.90 (3 H, s, OMe), 6.89 (1 H, d, *J* 8.42, 3-H), 7.36 (1 H, d, *J* 8.42, 4-H), 7.63 (1 H, s, 6-H) and 10.44 (1 H, s, CHO).

3,7-Dimethyl-10-p-tolyl-5-deazaflavin **1**.—A mixture of compound **6** (2.0 g, 13.3 mmol) and 3-methyl-6-*p*-toluidinouracil **7**[7] (2.45 g, 10.6 mmol) in DMF (20 cm^3) was heated and stirred at 150 °C for 8 h. Upon cooling of the reaction mixture to room temperature, the product crystallized out. The crystals were filtered off, washed with a small amount of diethyl ether and recrystallized from ethanol to afford the pure product **1** (2.25 g, 64%), m.p. > 360 °C (lit.,[5] > 360 °C); δ_H 2.47 and 2.49 (2 × 3 H, 2 × s, 7-Me and 10-C_6H_4*Me*), 3.44 (3 H, s, 3-Me), 6.85 (1 H, d, *J* 9.04, 9-H), 7.14 (2 H, d, J_{AB} 7.58, 10-C_6*H*$_4$Me), 7.41 (2 H, d, J_{AB} 8.43, 10-C_6*H*$_4$Me), 7.45 (1 H, d, *J* 9.04, 8-H), 7.72 (1 H, s, 6-H) and 8.97 (1 H, s, 5-H).

General Procedure for Specific 1,4-*Reduction of α,β-Unsaturated Carbonyl Compounds to the Corresponding Saturated Carbonyl Compounds*.—A mixture of compound **1** (21.87 mg, 0.066 mmol) and an appropriate α,β-unsaturated carbonyl compound (1.888 mmol) in 98% formic acid (3 cm^3) was gently refluxed at 120 °C (oil-bath temperature) for 25 h. The reaction mixture was then analysed by gas chromatography; the yields of α,β-saturated carbonyl compounds are given in Table 1. In the reduction of cinnamaldehyde, the reaction mixture upon dilution with a little diethyl ether gave crystals of 3-phenylpropionaldehyde; the product yield was determined from the ^{1}H NMR spectroscopy.

MO Calculations upon the Catalyst **2** *and Substrate*.—In order to determine how the frontier orbital interactions influence the high selectivity in this reduction system, semi-empirical MO calculations on **2** and α,β-unsaturated carbonyl compounds were carried out with the MOPAC program by the MNDO-PM3 method. In the calculation, α,β-unsaturated carbonyl compounds were assumed to be protonated, since the reaction proceeds under acidic conditions. In the practical geometry optimization, the initial geometry of **2** was based on the isoalloxazine part of 9-bromo-3,7,8,10-tetramethylisoalloxazine,[10] because the electronic structure of 5-deazaflavin is expected to be essentially the same in the ground state. Standard bond distances and angles were applied for the tolyl part of **2** and α,β-unsaturated carbonyl compounds.

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