Autorecycling System for Reduction of Carbonyl Compounds to Alcohols by 1,5-Dihydro-5-deazaflavins

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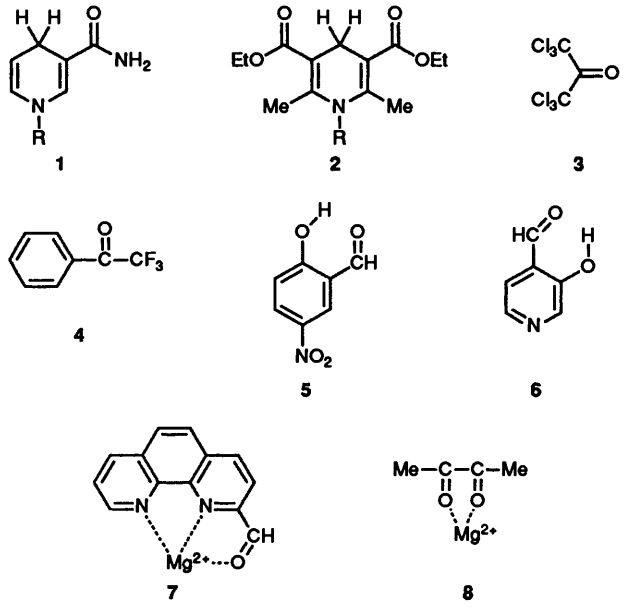
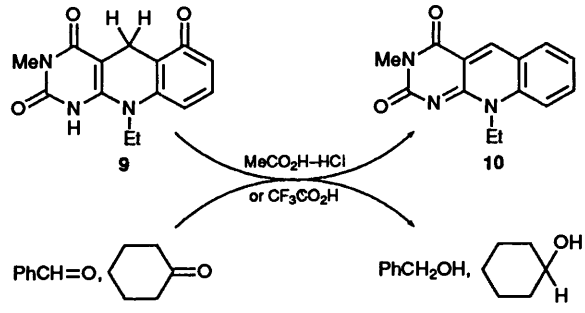
An effective recycling system for the reduction of carbonyl compounds to alcohols by 1,5-dihydro-5-deazaflavins, which were produced from 5-deazaflavins and formic acid in a circulatory system, was constructed for the first time, in such a way that the compound catalyses the reduction, by formic acid, of benzaldehyde. In particular, the reduction using 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin at 120 °C for 50 h proceeded until the benzaldehyde substrate was exhausted to give 100% yield of benzyl alcohol. The yield based on the catalyst was 3120%, which means 31 recyclings of the catalyst.

The biomimetic reduction of carbonyl compounds by NADH models such as *N*-alkylnicotinamides **1** or Hantzsch esters **2** has been extensively studied. However, these NADH models can reduce only carbonyl compounds which are highly activated by



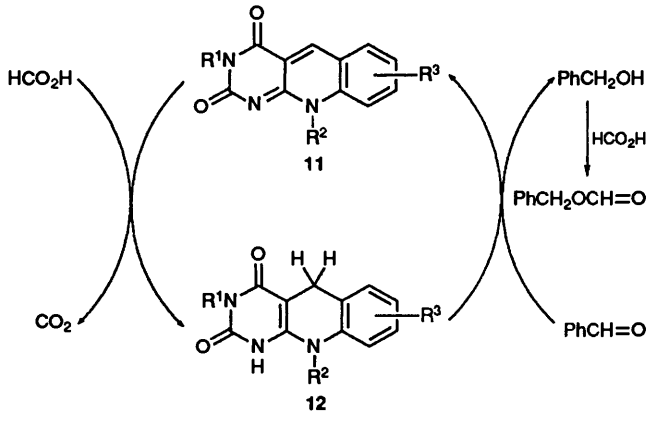
the presence of electron-deficient groups **3**, **4** and *ortho*-phenolic hydroxy groups **5**, **6**, or by the presence of metal ions **7**, **8**.[1] It has been demonstrated that such model NADH reductions of carbonyl compounds are facilitated by the presence of general acid catalysts such as acetic acid and hydrochlorides of tertiary amines.[2] For instance, Ohnishi and Kitami[3] succeeded in reducing benzaldehyde by 1,4-dihydronicotinamides (10-fold excess) with the aid of Mg^{2+} ions in 2–9% yield. Also, 1,5-dihydro-5-deazaflavin, which is a model of NADH, has been shown to reduce *ortho*-hydroxy-substituted aromatic aldehydes to the corresponding alcohols.[4]

In earlier work we have demonstrated the first example of the reduction of simple inactivated carbonyl substrates to the corresponding alcohols by 1,5-dihydro-5-deazaflavin (or 5-deazaisoalloxazine; 'NADH in flavin clothing'[5]) in the presence of strong proton sources such as hydrochloric acid or trifluoroacetic acid in stoichiometric yields.[6] Thus, benzaldehyde and cyclohexanone were reduced by heating 10-ethyl-3-methyl-1,5-dihydro-5-deazaflavin **9** in refluxing acetic acid in the presence of concentrated hydrochloric acid to give high yields of the acetates of benzyl alcohol and cyclohexanol, while compound **9** was oxidized to 10-ethyl-3-methyl-5-deazaflavin **10** quantitatively (Scheme 1). Shinkai *et al.* showed that 3-carbamoyl-*N*-benzyl-1,4-dihydroquinoline is also able to reduce benzaldehyde in 20–30% yield under acidic conditions.[7]

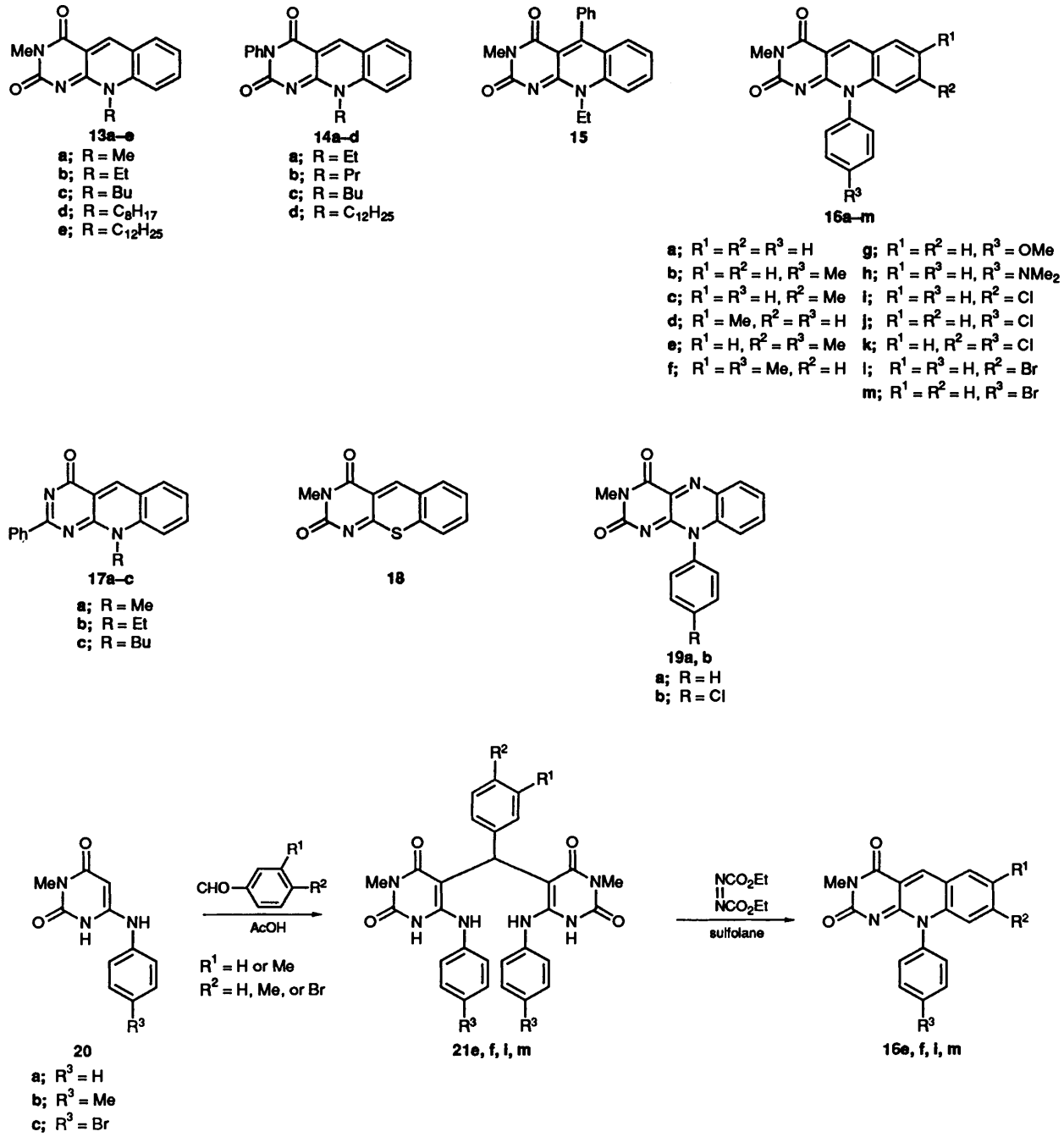


Scheme 1

Subsequently, in 1981, we reported in a preliminary communication[8] that in the reduction of carbonyl compounds by 1,5-dihydro-5-deazaflavin **12**, the latter was automatically recycled in formic acid (Scheme 2). That was the first example of an efficient autorecycling system for reduction of carbonyl compounds to alcohols using 5-deazaflavin **11** and formic acid. In this paper, we give a full account of the preparation of some new 5-deazaflavins and the autorecycling reduction of carbonyl compounds to alcohols by 1,5-dihydro-5-deazaflavins which are



Scheme 2



Scheme 3

produced by 5-deazaflavin and formic acid in a circulatory system. The influence of the introduced substituents upon the autorecycling reduction activities of the 5-deazaflavins is also discussed.

Results and Discussion

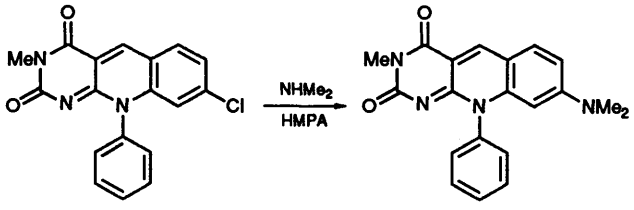
Synthesis of 10-*Alkyl-5-deazaflavins* **13–16**, *Analogues* **17**, **18** *and* 10-*Arylflavins* **19**.—The 10-alkyl or 10-aryl-5-deazaflavins **13–16**,[9–13] analogues **17**,[11] **18**[14] and 10-arylflavins **19**[15] were prepared according to our previous reports. In particular, some new compounds **16e**, **f**, **h**, **l**, **m** of 10-aryl-5-deazaflavin derivatives{10-arylpyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones} were synthesized in the following manner. The requisite starting materials, aryl-bis(6-anilino-3-methyluracil-5-yl)methanes **21e**, **f**, **l**, **m**, were readily obtained by heating 6-anilino-3-methyluracils **20a–c**[13,16] with appropriate arylaldehydes in acetic acid for 30 min. The bis-uracil-methane type structure for compounds such as **21** has been established in a previous study.[13] Subsequent fusion of compounds **21e**, **f**, **l**, **m** with an excess of diethyl azodicarboxylate (DEAD) in the presence of sulfolane at 180–185 °C for 30 min afforded the corresponding 10-aryl-3-methyl-5-deazaflavins **16e**, **f**, **l**, **m** (Scheme 3). On the other hand, 3-methyl-8-dimethylamino-10-phenyl-5-deazaflavin **16h** was synthesized by treatment of 8-chloro-3-methyl-10-phenyl-5-deazaflavin **16i**[13] with an excess of 40% aqueous dimethylamine in hexamethylphosphoramide (HMPA) with stirring at 100 °C for 5 h (Scheme 4). Confirmation of the structures of compounds **16** were based on the satisfactory analytical and spectral data.

Autorecycling Reduction of Carbonyl Compounds to Alcohols by 1,5-*Dihydro-5-deazaflavins*.—As expected, the 1,5-dihydro-5-deazaflavins **12**, which were produced from 5-deazaflavins **11** and formic acid, showed generally strong reducing power

Table 1 Reduction of benzaldehyde to benzyl alcohol (identified as benzyl formate) by 5-deazaflavins or analogues and formic acid at 120 °C for 10 h

Catalyst	Recycling number of the catalyst	Yield (%)[a] of benzyl formate
13a	1.07	3.7
13b	1.60	5.6
13c	1.77	6.2
13d	0.39	1.4
13e	0.20	0.7
14a	<0.20	<0.7
14b	1.19	4.2
14c	1.66	5.8
14d	<0.20	<0.7
15	<0.10	<0.3
16a	5.98	20.9
16c	6.76	23.6
17a	1.30	4.5
17b	0.80	2.8
17c	<0.10	<0.3
18	<0.10	<0.3
19a	<0.20	<0.7
19b	<0.20	<0.7

[a] Yields based on benzaldehyde are given.



16l **16h**

Scheme 4

towards carbonyl compounds to yield the corresponding alcohols with remarkable autorecycling in the reduction. Thus, benzaldehyde was reduced by heating the 5-deazaflavin **11** and excess of benzaldehyde (about 30 equiv.) in refluxing 98% formic acid to give benzyl alcohol, which was isolated as benzyl formate (Scheme 2). On treatment of the reaction mixture with sodium hydroxide, the benzyl formate was readily converted into benzyl alcohol in quantitative yield (GLC). With formic acid alone, no reduction of benzaldehyde proceeded under the reaction conditions. Hence, 5-deazaflavin **11** is initially hydrogenated by formic acid to the corresponding 1,5-dihydro-5-deazaflavin **12**, which acts as a turnover catalyst. In fact, heating 10-ethyl-3-methyl-5-deazaflavin **11** (R^1 = Me, R^2 = Et, R^3 = H) in refluxing formic acid for several hours gave the corresponding 10-ethyl-3-methyl-1,5-dihydro-5-deazaflavin **12** (R^1 = Me, R^2 = Et, R^3 = H; m.p.[17] 285 °C) in about 60% yield. Table 1 shows the results for the reduction of benzaldehyde by several 5-deazaflavins **13–16**, analogues **17**, **18**, or flavins **19** with formic acid at 120 °C for 10 h. In the case of 5-deazaflavins **13–16** as catalyst, a significant substituent effect was observed; in particular 10-aryl-5-deazaflavins **16a**, **c** exhibited a strong reducing ability toward benzaldehyde. In contrast to catalysts **16a**, **c**, the analogue **18** and the corresponding flavins **19a**, **b** did not show any appreciable reducing abilities.

Since the 10-aryl-5-deazaflavins **16** manifested excellent reducing capacity as described above, the autorecycling reduction of benzaldehyde to benzyl alcohol by other 10-aryl-3-methyl-1,5-dihydro-5-deazaflavins, which were produced in the reaction of 10-aryl-3-methyl-5-deazaflavins **13a–m** and formic acid at 120 °C for several hours, was examined carefully as shown in Table 2. The reaction mixture was analysed by gas chromatography and the yield of benzyl alcohol was determined

Table 2 Reduction of benzaldehyde to benzyl alcohol by 10-aryl-3-methyl-5-deazaflavins and formic acid at 120 °C

Catalyst	Yield %[a] (%)[b]			
	5 h	10 h	25 h	50 h
16a	290 (10)	598 (21)	930 (33)	1250 (44)
16b	350 (12)	700 (24)	1620 (54)	2380 (80)
16c	270 (9)	676 (24)	1330 (45)	2730 (91)
16d	470 (16)	790 (26)	1460 (49)	2360 (79)
16e	340 (11)	550 (18)	1180 (38)	2530 (81)
16f	300 (10)	660 (21)	1790 (57)	3120 (100)
16g	180 (6)	400 (13)	510 (16)	700 (22)
16h	50 (2)	110 (3)	220 (7)	460 (14)
16i	60 (2)	180 (6)	360 (11)	560 (18)
16j	90 (3)	140 (4)	290 (9)	470 (15)
16k	Trace	Trace	90 (3)	300 (9)
16l	110 (3)	260 (7)	360 (10)	700 (19)
16m	Trace	Trace	100 (3)	340 (10)

[a] Yields based on the 1,5-dihydro-5-deazaflavins are given. [b] Yields based on the starting benzaldehyde are given in parentheses.

from benzyl formate as a product of time elapsed in the reaction. The 10-aryl-3-methyl-5-deazaflavins **16b–f** with a methyl group as the substituent on the ring exhibited more potency in the autorecycling reduction, than did those with halogens or a dimethylamino group. It is noted that 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **16f** exhibited excellent catalytic activity for formic acid reduction of benzaldehyde, and the reaction proceeded until the benzaldehyde substrate was exhausted to give 100% yield of benzyl alcohol. The yield based on the 5-deazaflavin catalyst was 3120%, which means 31 recyclings of the catalyst.

Moreover, the 5-deazaflavin-dependent reduction was applied to the reduction of other aryl aldehydes and ketones. Table 3 shows the results for the reduction of benzaldehyde derivatives to benzyl alcohol derivatives by 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **16f** and formic acid at 120 °C for 25 h. As the result, the substrates having an electron withdrawing group such as 4-chloro-, 2,4-dichloro-, and 4-bromo-benzaldehyde were more easily reduced to the corresponding benzyl alcohol derivatives than the substrates having an electron releasing group such as *p*-tolualdehyde and *p*-anisaldehyde. In addition, Table 4 shows the results for the reduction of cyclohexanone and cyclopentanone to cyclohexanol and cyclopentanol, respectively, under the same reduction conditions as mentioned above. As shown in the Table, cyclohexanone was reduced easily in the recycling system, but cyclopentanone was difficult to reduce.

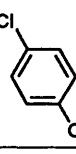
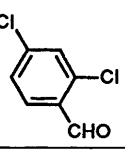
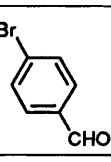
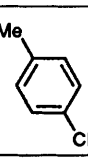
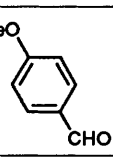
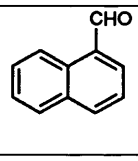
In conclusion, the present study offers a useful and practical autorecycling system for the reduction of carbonyl compounds to alcohols in a simple method, and we believe that stereospecific autorecycling reduction could be achieved by modifying the structure of the 5-deazaflavin. Therefore, the present method would be significant from the viewpoints of practical value as well as synthetic organic chemistry.

Experimental

All melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were measured at 60 MHz with a JEOL JNM 3H-60 spectrometer (tetramethylsilane as an internal standard) in trifluoroacetic acid; *J* values are given in Hz. The identity of compounds was confirmed by comparison of infrared spectra (Nujol mulls) using a JASCO IR-A1 spectrophotometer.

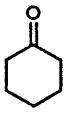
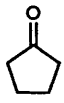
General Procedure for the Preparation of 10-*Aryl*-3-*methylpyrimido*[4,5-b]*quinoline*-2,4(3H,10H)-*diones* (10-*Aryl*-3-*meth-*

Table 3 Reduction of benzaldehyde derivatives to benzyl alcohol derivatives by 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **16f** and formic acid at 120 °C for 25 h

Substrate						
Yield (%)[a]	1140	1670	920	670	Trace	370
Yield (%)[b]	(40.4)	(61.4)	(35.7)	(22.6)		(11.9)

[a] Yields based on the 1,5-dihydro-5-deazaflavins are given. [b] Yields based on benzaldehyde derivatives are given in parentheses.

Table 4 Reduction of ketones to alcohols by 3,7-dimethyl-10-*p*-tolyl-5-deazaflavin **16f** and formic acid at 120 °C

	Yield %[a] (%)[b]	
Substrate	10 h	25 h
	160 (5)	320 (10)
	Trace	Trace

[a] Yields based on the 1,5-dihydro-5-deazaflavins are given. [b] Yields based on ketones are given in parentheses.

yl-5-deazaflavins) **16e, f, l, m** via *Aryl-bis*(6-*anilino*-3-*methyluracil*-5-*yl*)*methanes* **21e, f, l, m**.—A mixture of 6-anilino-3-methyluracil **20**[13,16] (4 mmol) and the appropriate aryl aldehyde (3 mmol) in acetic acid (40 cm^3) was heated at reflux for 30 min. The mixture was evaporated under reduced pressure to afford a solid residue which contained the corresponding *intermediate* **21e, f, l, m**. Then, a mixture of the residue with DEAD (diethyl azodicarboxylate) (12 mmol) and sulfolane (12 mmol) was heated at 180–185 °C (oil-bath temperature) for 30 min. After cooling, the mixture was diluted with ethanol (*ca.* 15 cm^3) and allowed to stand at room temperature overnight to precipitate yellow crystals. Recrystallization from ethanol gave the corresponding 10-*aryl*-3-*methyl*-5-*deazaflavins* **16e, f, l, m** as yellow needles.

The reaction of 3-methyl-6-(*p*-toluidino)uracil **20b** and *p*-tolualdehyde gave 3,8-*dimethyl*-10-p-*tolyl*-5-*deazaflavins* **16e** (50%), m.p. 346 °C (Found: C, 72.7; H, 5.2; N, 12.7. $C_{20}H_{17}N_3O_2$ requires C, 72.5; H, 5.2; N, 12.7%); δ_H 2.65 (6 H, s, 8-Me and 10-C_6H_4*Me*), 3.66 (3 H, s, 3-Me), 7.15–8.53 (7 H, m, ArH) and 9.85 (1 H, s, 5-H).

The reaction of 3-methyl-6-(*p*-toluidino)uracil **20b** and *m*-tolualdehyde gave 3,7-*dimethyl*-10-p-*tolyl*-5-*deazaflavins* **16f** (43%), m.p. > 360 °C (Found: C, 72.6; H, 5.3; N, 12.7. $C_{20}H_{17}N_3O_2$ requires C, 72.5; H, 5.2; N, 12.7%); δ_H 2.68 (6 H, s, 7-Me and 10-C_6H_4*Me*), 3.65 (3 H, s, 3-Me), 7.15–8.47 (7 H, m, ArH) and 9.84 (1 H, s, 5-H).

The reaction of 6-anilino-3-methyluracil **20a** and 4-bromobenzaldehyde gave 8-*bromo*-3-*methyl*-10-*phenyl*-5-*deazaflavins* **16l** (33%), m.p. > 360 °C (Found: C, 56.6; H, 3.1; N, 10.8. $C_{18}H_{12}BrN_3O_2$ requires C, 56.6; H, 3.2; N, 11.0%); δ_H 3.63 (3 H, s, 3-Me), 7.43–8.60 (8 H, m, ArH) and 9.96 (1 H, s, 5-H).

The reaction of 6-(4-bromoanilino)-3-methyluracil **20c** and benzaldehyde gave 10-(4-*bromophenyl*)-3-*methyl*-5-*deazaflavins* **16m** (39%), m.p. > 360 °C (Found: C, 56.6; H, 3.1; N, 10.9. $C_{18}H_{12}BrN_3O_2$ requires C, 56.6; H, 3.2; N, 11.0%); δ_H 3.66 (3 H, s, 3-Me), 7.26–8.69 (8 H, m, ArH) and 10.01 (1 H, s, 5-H).

8-*Dimethylamino*-3-*methyl*-10-*phenyl*-5-*deazaflavin* **16h**.—A stirred solution of 8-chloro-3-methyl-10-phenyl-5-deazaflavin **16i**[13] (0.5 g, 1.48 mmol) and 40% aqueous dimethylamine (0.50 cm^3, 4.44 mmol) in HMPA (3 cm^3) was heated at 100 °C for 5 h. After cooling, the solution was diluted with water to afford a yellow precipitate. Recrystallization of the precipitate from ethanol gave yellow needles (0.46 g, 89%), m.p. > 360 °C (Found: C, 69.3; H, 5.2; N, 16.1. $C_{20}H_{18}N_4O_2$ requires C, 69.35; H, 5.2; N, 16.2%); δ_H 3.13 (6 H, s, NMe_2), 3.57 (3 H, s, 3-Me), 7.12–8.11 (8 H, m, ArH) and 9.07 (1 H, s, 5-H).

General Procedure for Autorecycling Reduction of Carbonyl Compounds to Alcohols by 1,5-*Dihydro*-5-*deazaflavins*.—A mixture of 5-deazaflavins **13–16**, analogues **17**, **18**, or flavins **19** (0.066 mmol) and the appropriate carbonyl compounds (1.888 mmol) in 98% formic acid (3 cm^3) was heated gently at reflux at 120 °C (oil-bath temperature) for 5, 10, 25 or 50 h with stirring. Then the reaction mixture was analysed by gas chromatography [metal column (3 mm × 1 m): silicone SE-30 2% Chromosorb WAW (60–80 mesh)] and the products were identified as the formates of the corresponding alcohols.

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