Reactions of *N*-(ω-Chloroalkanoyl)-carbonimidic Dichlorides: A New Synthesis of 2-Oxo-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazoles, 2-Oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazoles, and 2-Oxo-2,3,5,10-tetrahydro-1*H*-imidazo[1,2-*b*][2,4]benzodiazepines

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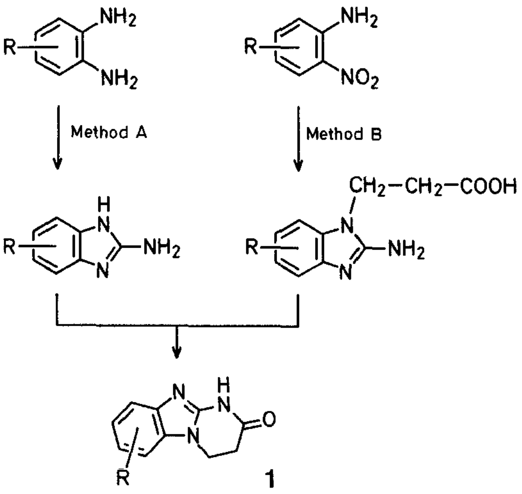
We recently needed a convenient synthesis of partially hydrogenated 2-oxopyrimido[1,2-*a*]benzimidazoles. Known methods[1,2] for the preparation of 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazoles (**1**; Scheme A) presented several drawbacks.

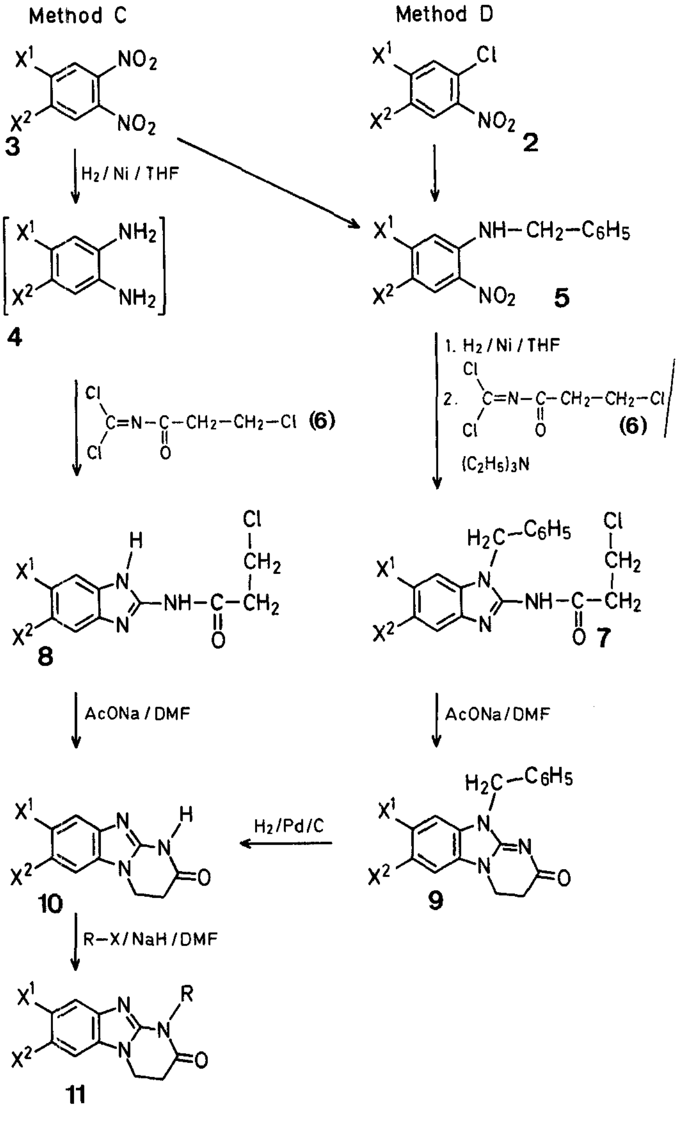


Scheme A

Method A involved the cyclocondensation of *o*-phenylenediamine with cyanogen bromide to give a 2-aminobenzimidazole which was submitted to cyclocondensation with an alkyl acrylate or acryloyl chloride; in the case of substituted benzimidazoles, this method inconveniently yielded a mixture of two isomeric products.

Method B involved the preparation of 2-aminobenzimidazole-1-propanoic acid from 2-nitroaniline in a three-step sequence, followed by cyclization to **1**; not only was this process time consuming, but it required severe conditions which limited the variety of substituents in products **1**.

We have now found that 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazoles (**10**) can be conveniently prepared by



2-5, 7-10	X^1	X^2
a	H	H
b	H_3CO-	H_3CO-
c	$H_3CO-CH_2-CH_2-O-$	$H_3CO-CH_2-CH_2-O-$
d	H	CF_3
e	H_3CO-	$H_3CO-C(=O)-$
f	$i\text{-}C_3H_7-O-$	$i\text{-}C_3H_7-O-$

Scheme B

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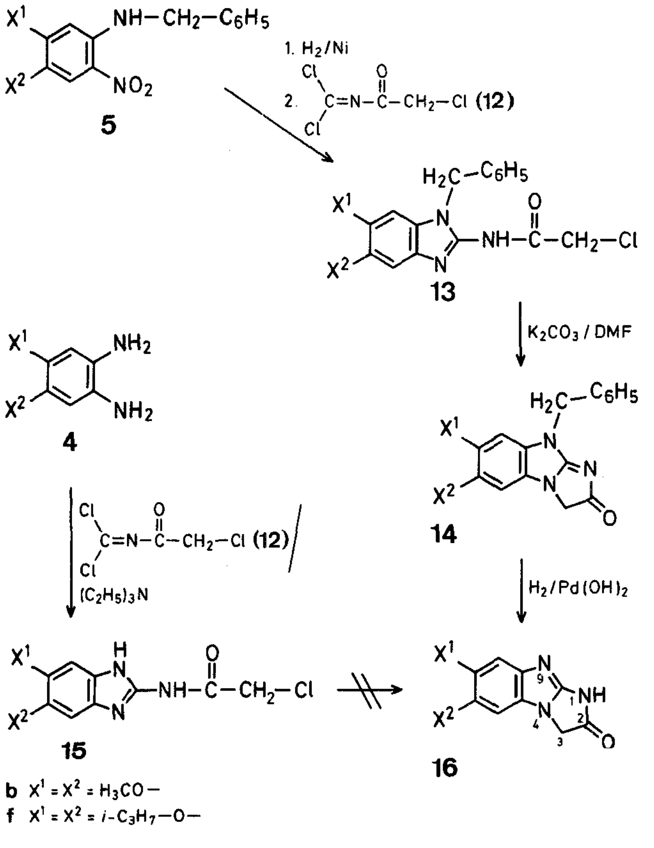
cyclocondensation of *o*-phenylenediamines (**4**) with *N*-(3-chloropropanoyl)-carbonimidic dichlorides[3] (**6**) followed by intramolecular cyclization of the benzimidazole derivative **8** (Scheme **B**, Method C). If the benzimidazole intermediate **8** has an unsymmetrically substituted benzene ring the formation of isomeric products **10** should be expected. In this case, selective cyclization can be achieved by using the respective *N*-benzyl-2-nitroaniline (**5**) as starting material. The benzyl group thus introduced into intermediate **7** can be easily removed from the cyclization product **9** by catalytic hydrogenation (Scheme **B**, Method D).

Methods C and D are generally carried out by hydrogenation of a solution of the *o*-dinitrobenzene **3** or 2-nitroaniline **5** in dry tetrahydrofuran, followed by the successive addition of triethylamine and *N*-(3-chloropropanoyl)-carbonimidic dichloride (**6**) to the filtered mixture at room temperature, and cyclization of the isolated but not purified products **7** or **8** by heating with sodium acetate in dimethylformamide. Condensation of the *o*-phenylenediamines **4** with carbonimidic dichloride **6** may also be performed in boiling tetrahydrofuran without the addition of triethylamine; in this case, the hydrochloride of benzimidazole derivative **8** is obtained.

Compounds **10** can be alkylated with alkyl halides to give the 1-substituted derivatives **11**.

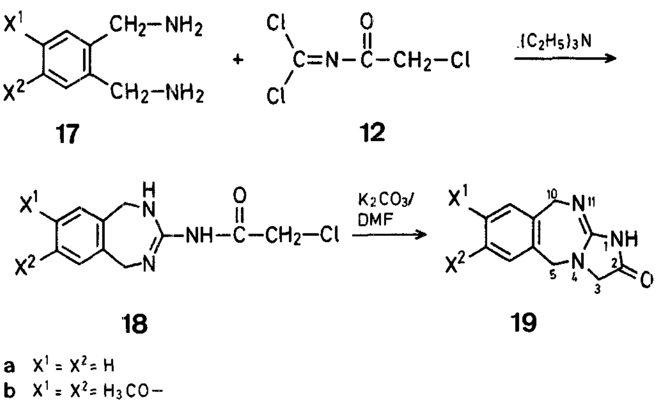
Compounds **5** are readily available from the corresponding *o*-halonitrobenzenes (**2**) or *o*-dinitrobenzenes[4] (**3**) by conventional procedures.

We extended the present method to the synthesis of 2-oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazoles (**16**, Scheme **C**) and 2-oxo-2,3,5,10-tetrahydro-1*H*-imidazo[1,2-*b*][2,4]benzodiazepines (**19**, Scheme **D**) by condensing *N*-benzyl-*o*-phenylenediamines (from the reduction of **5**) or *o*-bis[aminomethyl]benzenes (**17**), respectively, with *N*-chloroacetylcarbonimidic dichloride (**12**). In both cases, the use of potassium carbonate in dimethylformamide in the second cyclization step afforded the best yields (products **14** and **19**). Debenzylation of compounds **14** failed with palladium on carbon and could only be achieved in poor yield using palladium hydroxide.



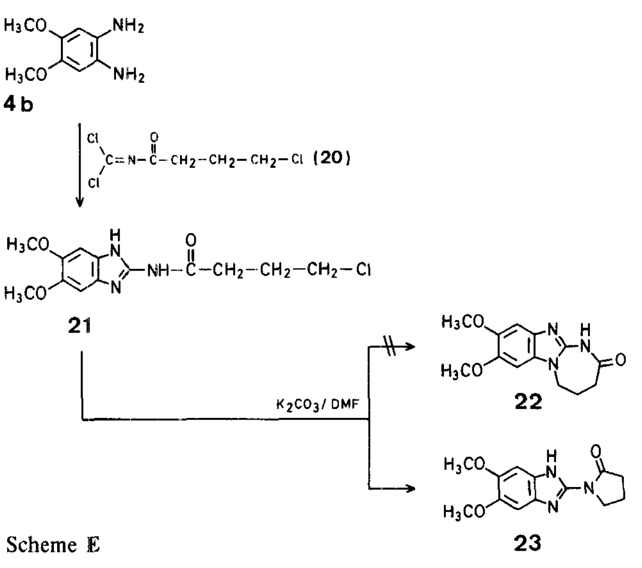
Scheme **C**

Attempts to cyclize 1-unsubstituted 2-chloroacetylaminobenzimidazoles (**15**) were unsuccessful.



Scheme **D**

It is worthy of note that the cyclocondensation of the *o*-phenylenediamine **4b** with *N*-(4-chlorobutanoyl)-carbonimidic dichloride (**20**) followed by cyclization of the resultant benzimidazole derivative **21** did not lead to the formation of a diazepinobenzimidazole derivative (**22**) but afforded the *N*-(2-benzimidazolyl)-lactam **23** (Scheme E).



Scheme **E**

10-Benzyl-2-oxo-7-trifluoromethyl-2,3,4,10-tetrahydropyrimido[1,2-*a*]benzimidazole (9d); Typical Procedure:

A solution of *N*-benzyl-2-nitro-4-trifluoromethylaniline (**5d**; 14.3 g, 48 mmol) in tetrahydrofuran (170 ml) is hydrogenated in the presence of Raney nickel (5 g) at 60°C. After removal of the catalyst by filtration, triethylamine (9.6 g, 95 mmol) and then *N*-(3-chloropropanoyl)-carbonimidic dichloride (**6**; 9 g, 48 mmol) are added at a temperature below 40°C. The mixture is stirred for 1 h. The solvent is then removed under reduced pressure and the residue washed with ether and water and dried (yield of crude **7d**: 13.5 g). This solid product and sodium acetate (8.7 g) are heated in boiling dimethylformamide for 1 h. The solvent is then removed under reduced pressure and the product washed with water and dried; yield of **9d**: 8.9 g (53%); m.p. 182–184°C (ethyl acetate).

$C_{18}H_{14}F_3N_3O$	calc.	C 62.60	H 4.08	N 12.16
(345.3)	found	62.75	3.91	12.46

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Table. Preparation of 2-Oxo-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazoles (**10**), 2-Oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazoles (**16**), and 2-Oxo-2,3,5,10-tetrahydro-1*H*-imidazo[1,2-*b*][2,4]benzodiazepines (**19**)

Starting Materials	Intermediate Product No.	Intermediate Product Yield[a] [%]	Final Product	Yield[b] [%]	m.p.[c] [°C] (solvent)	Molecular Formula[d] or m.p. [°C] reported	^{1}H-N.M.R. (solvent/TMS$_{int}$) δ [ppm]
4a, 6	**8a**	84	**10a**	**8a → 10a**: 55	257-259° (pyridine)	260-262° (DMF)[2]	—
3b, 6	**8b**	90	**10b**	**8b → 10b**: 36	252-254° (DMF)	$C_{12}H_{13}N_3O_3$ (247.2) (264-265°[1])	(DMSO-d_6): 2.9 (t, 2H); 3.8 (d, 6H); 4.25 (t, 2H); 4.4-4.5 (m, 1H); 7.1 (d, 2H)
3c, 6	**8c**	56	**10c**	**8c → 10c**: 37	163-165° (acetonitrile)	$C_{16}H_{21}N_3O_5$ (335.35)	($CDCl_3$): 2.9 (t, 2H); 3.5 (s, 6H); 3.7-4.4 (q+t, 10H); 6.65 (s, 1H); 7.35 (s, 1H); 11.7-11.9 (m, 1H)
5d, 6	**7d**	73	**10d**	**7d → 9d**: 54 **9d → 10d**: 75	326-328° (pyridine)	$C_{11}H_8F_3N_3O$ (255.2)	(DMSO-d_6): 2.95 (t, 2H); 4.35 (t, 2H); 7.3-8.0 (m, 3H); 11.55 (s, 1H)
5e, 6	**7e**	62	**10e**	**7e → 9e**: 48 **9e → 10e**: 66	301-303° (DMF)	$C_{13}H_{13}N_3O_4$ (275.25)	(F_3C-COOD): 2.9 (t, 2H); 3.3-3.7 (2s, 6H); 4.15 (t, 2H); 6.95 (s, 1H); 7.65 (s, 1H)
5b, 12	**13b**	67	**16b**	**13b → 14b**: 55 **14b → 16b**: 14	263-265° (DMF)	$C_{11}H_{11}N_3O_3$ (233.2)	(DMSO-d_6): 3.8 (s, 6H); 4.6 (s, 2H); 7.0 (s, 1H); 7.05 (s, 1H)
5f, 12	**13f**	51	**16f**	**13f → 14f**: 46 **14f → 16f**: 28	193-194° (ethanol)	$C_{15}H_{19}N_3O_3$ (289.3)	($CDCl_3$): 1.0-1.5 (d, 12H); 3.95 (s, 2H); 4.1-4.8 (m, 2H); 6.65 (s, 1H); 7.2 (s, 1H); 10.9 (s, 1H)
17a, 12	**18a**	33	**19a**	**18a → 19a**: 39	280° (dec)	>280° (dec)[5, e]	[*methanesulfonate*] (DMSO-d_6): 2.4 (s, 3H); 4.35 (s, 2H); 4.7 (s, 2H); 4.85 (s, 2H); 7.4 (s, 4H)
17b, 12	**18b**	35	**19b**	**18b → 19b**: 45	260° (dec) (DMF)	$C_{13}H_{15}N_3O_3$ (261.3)	(F_3C-COOD): 3.7 (s, 6H); 4.3 (s, 2H); 4.5 (s, 2H); 4.55 (s, 2H); 6.7 (s, 2H)

[a] Yield of crude product.

[b] Yield of isolated pure product.

[c] Not corrected.

[d] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.25; H, ±0.20; N, ±0.25.

[e] Satisfactory microanalyses obtained for the methanesulfonate of **19a**; $C_{12}H_{15}N_3O_4S$ (297.3); m.p. 209-211 °C (ethanol).

^{1}H-N.M.R. ($CDCl_3$/TMS$_{int}$): δ=2.9 (t, 2H); 4.25 (t, 2H); 5.35 (s, 2H); 7.0-7.65 ppm (m, 8H).

10-Benzyl-8-methoxy-7-methoxycarbonyl-2-oxo-2,3,4,10-tetrahydropyrimido[1,2-*a*]benzimidazole (9e):

This compound is prepared in the same manner as **9d**; yield of **9e**: 45%; m.p. 238-240 °C (methanol).

$C_{20}H_{19}N_3O_4$	calc.	C 65.74	H 5.24	N 11.50
(365.4)	found	65.48	5.36	11.66

^{1}H-N.M.R. ($CDCl_3$/TMS$_{int}$): δ=2.95 (t, 2H); 3.8-4.1 (2s, 6H); 4.3 (t, 2H); 5.35 (s, 2H); 6.75 (s, 1H); 7.4 (s, 5H); 7.65 ppm (s, 1H).

2-Oxo-7-trifluoromethyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazole (10d); Typical Debenzylation Procedure:

A solution of *N*-benzyl derivative **9d** (4.7 g, 13.6 mmol) in acetic acid (80 ml) is hydrogenated at 80 °C in the presence of 10% palladium on carbon [30% palladium hydroxide on carbon is used for compounds **14**]. The mixture is then filtered, the solvent evaporated, and the residue washed with water and recrystallized from pyridine; yield: 2.6 g (75%); m.p. 326-328 °C.

$C_{11}H_8F_3N_3O$	calc.	C 51.77	H 3.16	F 22.33	N 16.46
(255.2)	found	51.81	3.03	22.10	16.65

1-Benzyl-2-oxo-7-trifluoromethyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazole (11d):

Compound **10d** (5.3 g, 20 mmol) is added to a stirred suspension of sodium hydride (50% in oil; 1 g) in dimethylformamide (60 ml) and the mixture heated at 70-80 °C for 1 h. Benzyl bromide (3.4 g, 20 mmol) is then added and heating is continued for 3 h at 70 °C. The solvent is evaporated and the residue poured into water (80 ml), isolated by suction, and washed with ether; yield: 3.6 g (52%); m.p. 191-193 °C (ethyl acetate).

$C_{18}H_{14}F_3N_3O$	calc.	C 62.60	H 4.08	F 16.50	N 12.16
(345.3)	found	62.47	3.98	16.38	12.01

^{1}H-N.M.R. ($CDCl_3$/TMS$_{int}$): δ=3.05 (t, 2H); 4.21 (t, 2H); 5.33 (s, 2H); 7.16-7.83 ppm (m, 8H).

9-Benzyl-6,7-dimethoxy-2-oxo-2,3-dihydro-9*H*-imidazo[1,2-*a*]benzimidazole (14b); Typical Procedure:

A solution of *N*-benzyl-4,5-dimethoxy-2-nitroaniline (**5b**; 49 g, 0.17 mol) in tetrahydrofuran (300 ml) is hydrogenated in the presence of Raney nickel (12 g). The catalyst is then filtered off and triethylamine (34.4 g, 0.34 mol) and *N*-chloroacetylcarbonimidic dichloride (**12**; 30 g, 0.17 mol) are successively added to the stirred filtrate (containing 2-amino-1-benzylamino-4,5-dimethoxybenzene) at a temperature below 40 °C. Stirring is continued for 1 h and the solid product **13b** is isolated by suction, washed with water and with ether, and dried; yield of crude **13b**: 40.9 g. This solid and potassium carbonate (50 g) are heated in boiling dimethylformamide for 45 min. The mixture is then filtered, the filtrate evaporated, and the remaining product washed with water and acetone; yield of **14b**: 23.7 g (43%); m.p. 198-200 °C (ethanol).

$C_{18}H_{17}N_3O_3$	calc.	C 66.86	H 5.30	N 13.00
(323.3)	found	66.92	5.32	12.98

^{1}H-N.M.R. ($CDCl_3$/TMS$_{int}$): δ=3.9 (s, 3H); 4.0 (s, 3H); 4.5 (s, 2H); 5.4 (s, 2H); 6.8 (d, 2H); 7.5 ppm (s, 5H).

2-Chloroacetylamino-5,6-dimethoxybenzimidazole (15b):

A solution of 4,5-dimethoxy-2-nitroaniline (18.1 g, 91 mmol) in tetrahydrofuran (150 ml) is hydrogenated in the presence of Raney nickel (5 g) at 60-70 °C. After removal of the catalyst, triethylamine (18 g, 180 mmol) and tetrahydrofuran (150 ml) are added, followed by the slow addition of *N*-chloroacetylcarbonimidic dichloride (**12**; 15.7 g, 90 mmol) at a temperature below 40 °C. The mixture is then cooled to 0 °C and the resultant precipitate isolated by suction, washed with water, and dried; yield of **15b**: 13.5 g (55%); m.p. 230-232 °C (ethanol/dimethylformamide).

$C_{11}H_{12}ClN_3O_3$	calc.	C 48.98	H 4.48	N 15.58
(269.7)	found	48.92	4.51	15.70

^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$): δ=3.85 (s, 6H); 4.4 (s, 2H); 7.1 (s, 2H); 10-12 ppm (broad, 2H).

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4,5-Dimethoxy-2-(2-oxopyrrolidino)-benzimidazole (Lactam 23):
This compound is prepared from 4,5-dimethoxy-1,2-diaminobenzene (**4b**; 15.2 g, 90 mmol) and *N*-(4-chlorobutanoyl)-carbonimidic dichloride (**20**; 18.2 g, 90 mmol) in tetrahydrofuran (180 ml) in a manner analogous to that described for the preparation of **14b** from the intermediate *o*-phenylenediamine; yield of **23**: 11.7 g (50%); m.p. 210–212°C (isopropanol/ethanol).

$C_{13}H_{15}N_3O_3$	calc.	C 59.75	H 5.78	N 16.08
(261.3)	found	59.65	5.73	16.19

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 2$–2.9 (m, 4H); 3.95 (s, 6H); 4.15 (t, 2H); 7.25 (s, 1H); 10.95 ppm (s, 1H).

Received: May 24, 1983

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[4] See, for example: M. Tomita et al., *Yakugaku Zasshi* **71**, 850 (1951); *C. A.* **46**, 3054 (1952).

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