A New Facile Synthesis of 11-Oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines

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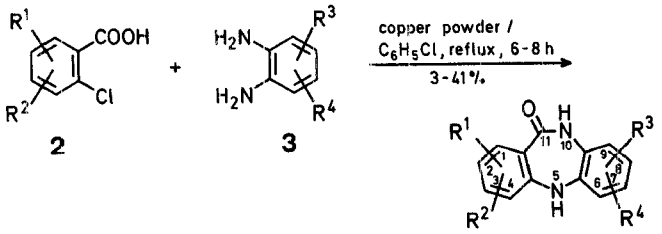
The dibenzodiazepinone system **1** is of interest in medicinal chemistry, being present in neuroleptic[1], antidepressant[2], and antiallergic[3,4] drugs. The synthesis of the basic precursor namely 11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**1a**), first reported in 1924[5] and later modified[6,7,8], is generally carried out in a three-step procedure involving condensation of anthranilic acid (or ester) with *o*-chloronitrobenzene to 2-(*o*-nitrophenylamino)-benzoic acid, followed by reduction to the corresponding 2-(*o*-aminophenylamino) derivative, and final cyclization of the latter.

We now report a one-step synthesis of **1a** in 40% yield, which consists of refluxing a mixture of equimolar amounts of 2-chlorobenzoic acid (**2a**), *o*-phenylendiamine (**3a**) and powdered copper in chlorobenzene for 6–8 h, the desired **1a** being isolated by concentration of the reaction solution. This method has been found to be of general usefulness for obtaining **1**, as indicated by the synthesis of derivatives **1b–j**, starting from the appropriate intermediates **2** and **3** (Scheme **A** and Table 1).



Scheme **A**

Table 1. Compounds **1a–j** prepared

Product 1	R^1	R^2	R^3	R^4	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a] or Lit. m.p. [°C]	I.R. (Nujol)[b] ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS)[c] δ [ppm]
a	H	H	H	H	40	256–257° (CH_3OH)	254–255°[7]	3330, 3180, 1645	6.83–7.79 (m, 8H); 7.86 (s, 1H)[d]; 9.89 (s, 1H)[d]
b	3-NO_2	H	H	H	3	>300°[e]	$C_{13}H_9N_3O_3$ (255.2)	3355, 3180, 1670	7.03 (s, 4H); 7.57–8.02 (m, 3H); 8.43 (s, 1H)[d]; 10.21 (s, 1H)[d]
c	2-NO_2	H	H	H	32	>300° (dioxan)	>300°[9]	3340, 3200, 1660	6.90–7.13 (m, 5H); 8.03–8.17 (m, 1H); 8.59 (s, 1H); 9.03 (s, 1H)[d]; 10.08 (s, 1H)[d]
d	2-NO_2	4-NO_2	H	H	35	303–305° (dioxan)	$C_{13}H_8N_4O_5$ (300.2)	3280, 3200, 1665	7.08 (apparent s, 4H); 8.70–8.86 (m, 2H); 9.66 (s, 1H)[d]; 10.63 (s, 1H)[d]
e	3-Cl	H	H	H	33	281–282° (CH_3OH)	271°[3]	3330, 3180, 1640	6.87–7.80 (m, 7H); 8.08 (s, 1H)[d]; 9.97 (s, 1H)[d]
f	H	H	7-CH_3	8-CH_3	41	267–268° (dioxan)	$C_{15}H_{14}N_2O$ (238.3)	3320, 3170, 1645	2.10 (s, 6H); 6.80–7.81 (m, 6H + 1H[d]); 9.77 (s, 1H)[d]
g	2-Cl	H	H	H	30	259–261°[f]	259–260°[3]	3330, 3180, 1640	7.00–7.70 (m, 7H); 8.03 (s, 1H)[d]; 10.02 (s, 1H)[d]
h	H	H	7-Cl	8-Cl	12	272–274° (CH_3OH)	$C_{13}H_8Cl_2N_2O$ (279.1)	3380, 3180, 1680	6.81–7.79 (m, 6H); 8.10 (s, 1H)[d]; 10.03 (s, 1H)[d]
i	2-NO_2	H	7-CH_3	8-CH_3	25	>300° (dioxan)	$C_{15}H_{13}N_3O_3$ (283.3)	3350, 3180, 1680	2.08 (s, 6H); 6.73–7.09 (m, 3H); 7.93–8.15 (m, 1H); 8.55 (s, 1H); 8.97 (br. s, 1H)[d]; 9.90 (s, 1H)[d]
j	3-Cl	H	7-CH_3	8-CH_3	27	>300°[g]	$C_{15}H_{13}ClN_2O$ (272.7)	3325, 3170, 1640	2.07 (s, 6H); 6.71–7.71 (m, 5H); 7.84 (s, 1H)[d]; 9.73 (s, 1H)[d]

[a] Satisfactory microanalyses obtained: C ±0.24, H ±0.12, N ±0.18, Cl ±0.11.
[b] Recorded on a Perkin-Elmer 297 Spectrometer.
[c] Recorded on a Varian EM 360 Spectrometer at 60 MHz.
[d] Exchangeable with D_2O.
[e] Triturated with isopropanol.
[f] Isolated in pure form from the reaction solvent.
[g] Triturated with methanol.

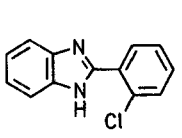
Table 2. Effect of the Amount of Copper on the Yield of **1a**

mol of Cu / mol of **2** and **3**	Yield [%] of **1a**
0.05	4
0.12	6
0.35	12
0.5	18
0.8	35
1	40
2	40
3	41

Product **1b** can only be prepared by this method and then only in low yield. Attempts to prepare **1a** from the methyl ester of **2a** were unsuccessful. During optimization experiments, it was observed that yields of **1a** were proportionally lowered by a decrease in the molar ratio of copper to reagents, but were essentially unaffected by increasing the amount of copper (Table 2).

When no catalyst was added, unchanged starting materials were recovered after refluxing for 40 h in chlorobenzene. After increasing the reaction temperature to 180–200 °C, 2-(*o*-chlorophenyl)-benzimidazole (**4**) was the only product isolated.

It should be noted that when the chlorine atom of **2** is further activated by nitro groups in the *ortho*/*para* positions, **1c** and **1d** are formed in the absence of copper, by condensation of *o*-phenylenediamine with the methyl ester of 2-chloro-5-nitro- or of 2-chloro-3,5-dinitro-benzoic acid. In our hands, the methods in the literature gave the expected compound only in the case of **1c**[9]. On the contrary, the compound claimed[10] to be **1d** was identified by I.R., N.M.R. spectral and microanalytical data to be the precursor **5**. However, **5** could be converted into **1d** by subsequent thermal cyclization.



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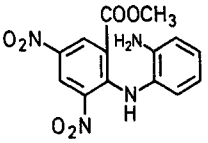

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11-Oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines (1a–j); General Procedure:

A well-stirred suspension of the appropriate 2-chlorobenzoic acid **2** (1 mol), the *o*-phenylenediamine **3** (1 mol) and finely powdered copper (63 g, 1 mol) in chlorobenzene (3000 ml) is heated for 8 h in a flask equipped with a Dean-Stark apparatus to continuously remove the water formed. The hot mixture is rapidly filtered and the filtrate is concentrated in vacuo to a volume of 1000 ml. Crude **1** is collected by filtration and purified by crystallization (Table 1).

2-(*o*-Chlorophenyl)-benzimidazole (4):

A mixture of *o*-phenylenediamine (**3**, $R^3 = R^4 = H$; 10.8 g, 0.1 mol) and *o*-chlorobenzoic acid (**2**, $R^1 = R^2 = H$; 15.7 g, 0.1 mol) is heated at 180–200 °C for 20 h. After cooling, the solid mass is extracted with dichloromethane (5 × 300 ml), the liquid phase filtered, and washed with dilute sodium hydrogen carbonate solution

(300 ml). The organic phase, clarified with charcoal, is evaporated and the residue crystallized from 2-propanol to give pure **4**; yield: 7.3 g (32%); m.p. 235°C.

$C_{13}H_9ClN_2$	calc.	C 68.28	H 3.97	Cl 15.50	N 12.25
(228.7)	found	68.01	4.03	15.41	12.18

^{1}H-N.M.R. (DMSO-d_6/TMS): δ = 7.2–8.0 (m, 8 H_{arom}); 12.75 ppm (s, 1 H, exchangeable with D_2O).

Methyl 2-(*o*-Aminophenylamino)-3,5-dinitrobenzoate (5):
A solution of methyl 2-chloro-3,5-dinitrobenzoate (7.8 g, 0.03 mol), *o*-phenylenediamine (3.25 g, 0.03 mol), and anhydrous sodium acetate (2.45 g, 0.03 mol) in dry ethanol (100 ml) is refluxed with stirring for 4 h. The solvent is evaporated and the residue purified by column chromatography on alumina, eluting with acetone, to give pure **5** in 60% yield; m.p. 166–167°C.

$C_{14}H_{12}N_4O_6$	calc.	C 50.60	H 3.64	N 16.86
(332.3)	found	50.74	3.63	16.75

I.R. (Nujol): ν = 3500, 3400, 3250, 1700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 3.33 (br.s, 2H, exchangeable with D_2O); 3.80 (s, 3H, CH_3); 6.61–7.22 (m, 4 H_{arom}); 8.80–8.91 (m, 2 H_{arom}); 10.11 ppm (s, 1 H, exchangeable with D_2O).

2,4-Dinitro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine (1d) by Thermal Cyclization of 5:
Compound **5** (5 g, 0.015 mol) is heated at 180°C for 1 h. After cooling, the mass is washed with chloroform (100 ml) and the residue crystallized from dioxan to give pure **1d**; yield: 3.6 g (80%).

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[1] Hunziker, F., Fischer, E., Schmutz, J. *Helv. Chim. Acta* **1967**, *50*, 1588.
[2] Schmutz, J. et al. *British Patent* 1066266 (1964), Wander AG; *C.A.* **1964**, *63*, 9971.
[3] Hunziker, F., Lauener, H., Schmutz, J. *Arzneim. Forsch.* **1963**, *13*, 324.
[4] Ackerman, H. et al. *J. Med. Exp.* **1962**, *6*, 205.
[5] Clemo, G.R., Perkin Jr., H.W., Robinson, R. *J. Chem. Soc.* **1924**, *125*, 1770.
[6] Burton, A., Gibson, C.S. *J. Chem. Soc.* **1924**, *125*, 2501.
[7] Hanze, A.R., Strube, R.E., Greig, M.E. *J. Med. Chem.* **1963**, *6*, 767.
[8] Monro, A.M., Quinton, R.M., Wrigley, T.I. *J. Med. Chem.* **1963**, *6*, 255.
[9] Nagarajan, K., Shah, R.K. *Indian J. Chem. Sect. B* **1976**, *14*, 1.
[10] Gupta, C.M., Bhaduri, A.P., Khanna, N.M. *Indian J. Chem.* **1968**, *6*, 758.