

## An Improved Method for the Preparation of 3-Substituted 10,11-Dihydro-5H-[b,f]azepine Derivatives

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The tricyclic ring system 10,11-dihydro-5H-dibenz[*b,f*]azepine, i.e. iminodibenzyl [1] and its substituted derivatives are important pharmaceutical intermediates of a number of antidepressant and antipsychotic drugs [2–5].

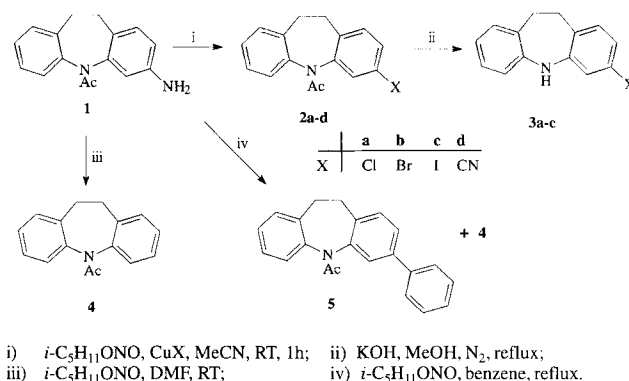
Presence of the certain electron-withdrawing substituent on the aromatic ring at the 3 position (*e.g.* chloroimipramine, clocapramine, clocipramine) generally increases the pharmacological activity [6, 7]. For the synthesis of the key intermediate 3-chloro-10,11-dihydro-5H-dibenz[*b,f*]azepine (**3a**) several methods were developed [8–14], however these are not based on the substitution of the 5H-dibenz[*b,f*]azepine skeleton directly.

There is only one patent [15] for the direct conversion of the 3-amino derivative, which applies the conventional Sandmeyer reaction resulting in moderate yields and low purity because of the several competing side reactions.

In this paper we describe a simple and efficient modification of the above procedure. On the course of our investigation we studied the one step conversion of aryl amines to aryl halides by alkyl nitrite and anhydrous copper(II) halides ( $\text{CuCl}_2$ ,  $\text{CuBr}_2$ ) or halogenated methane derivatives ( $\text{CCl}_4$ ,  $\text{CHCl}_3$ ,  $\text{CHBr}_3$ , etc.), which were presented earlier by Cadogan *et al.* and Doyle *et al.* [16–18]. These methods are limited to benzene and naphthalene derivatives resulting in the halogenated product in high yield under simple reaction conditions.

Applying the conditions described, however, a combined reaction mixture was obtained without the expected 3-chloro- or 3-bromo-derivatives. The reaction of 3-amino-5-acetyl-10,11-dihydro-5H-dibenz[*b,f*]azepine (**1**) with anhydrous copper(II) halides and isopentyl nitrite in dry acetonitrile at room temperature (15–25 °C) was found optimal instead of the temperature given (65–100 °C) with regard to yields and purity of the products. In this way **2a–c** were obtained after 2–7 hours in moderate to high yield (44–85%). With  $\text{CuCN}$  we obtained the corresponding 3-cyano derivative (**2d**) under similar conditions in moderate (30%) yield.

At lower temperature (0–5 °C) no reaction was observed. The treatment of 5-acetyl derivatives (**2a–c**) with KOH in



Scheme 1

refluxing methanol gave the 3-chloro- or 3-bromo- and 3-iodo-iminodibenzyl (**3a–c**) in excellent yield (90–95%). It is worth to note that although iminodibenzyl derivatives are known for 30 years the 3-iodo- and 3-phenyl- iminodibenzyl derivatives (**2c**, **3c** and **5**) are new compounds.

The reductive deamination of compound **1** took place with isopentyl nitrite in *N,N*-dimethyl-formamide [19] as hydrogen donor in good yield (64%) at room temperature within 2–3 hours. Finally, we realized the arylation of the compound **1** by reaction with isopentyl nitrite in an excess of benzene at 60–80 °C according to Cadogan [20]. After evaporation and chromatography of the reaction mixture we obtained two main products (**5** and **4**) in poor yield (26 % and 10 % respectively).

## Experimental

Melting points were determined using an electrothermal block and are uncorrected. IR spectra were measured in KBr with a Perkin-Elmer 177 instrument.  $^1\text{H-NMR}$  spectra were

**Table 1** Physical and spectroscopic data of compounds prepared **2a–d**, **3a–c**, **4** and **5**

Product/ yield (%)	<i>m. p.</i> (°C)	Analysis (%)			<sup>1</sup> H-NMR $\delta$ , ppm	IR $\nu$ (cm <sup>-1</sup> )	MS (70 eV) <i>m/z</i> (%)
		Calcd./ C	Found H	Found N			
<b>2a</b> /85	124–125 <sup>a)</sup>	70.72	5.19	5.15	2.00 (s, 3H, COCH <sub>3</sub> ),	1665,1487,	271 (M <sup>+</sup> , 20),
		70.95	5.42	5.21	2.70–2.90 (m, 2H), 3.20–3.48 (m, 2H), 7.00–7.40 (m, 7H)	1323, 761	229(100), 214(18), 194(48)
<b>2b</b> /72	140–142 <sup>b)</sup>	60.77	4.46	4.43	2.00 (s, 3H, COCH <sub>3</sub> ),	1657,1369,	316(M <sup>+</sup> , 21),
		60.96	4.60	4.50	2.70–2.90 (m, 2H), 3.20–3.40 (m, 2H), 6.95–7.55 (m, 7H)	1321,760	315(23), 274(96), 273(100)
<b>2c</b> /44	129–130	52.91	3.88	3.85	2.00 (s, 3H, COCH <sub>3</sub> ),	2912,1656,	363(M <sup>+</sup> , 29),
		53.23	4.02	3.97	2.70–2.90 (m, 2H), 3.20–3.45 7.10–7.30 (m, 4H), 7.42–7.70 (m, 3H)	1363,1319, 759	321(100), 306(8), 193(41)
<b>2d</b> /30	135–137	77.84	5.38	10.67	2.00 (s, 3H, COCH <sub>3</sub> ),	2917,2850,	262(M <sup>+</sup> , 5),
		78.05	5.50	10.78	2.75–3.05 (m, 2H), 3.30–3.50 (m, 2H), 7.20–7.40 (m, 7H)	1737,1672, 720	237(26), 220(20), 195(100), 180(30)
<b>3a</b> /95	87–89 <sup>c)</sup>	73.20	5.26	6.10	3.05 (s, 4H, H-10,11), 5.95	3374,2946,	29(M <sup>+</sup> , 100), 214(32),
		73.41	5.48	6.15	(s, 1H, NH), 6.70–7.20 (m, 7H)	1582,1488	194(50), 178(9)
<b>3b</b> /92	99–100	61.33	4.41	5.11	3.04 (t, 4H), 5.95 (s, 1H, NH),	3370,2845,	275(M <sup>+</sup> +1,90),
		61.60	4.58	5.20	6.68–7.12 (m, 7H)	1582,1484, 749	74(M <sup>+</sup> , 42), 273(100), 258(20), 194(85)
<b>3c</b> /90	99–101	52.36	3.76	4.36	3.02 (t, 4H), 5.92 (s, 1H, NH),	3373,2843,	21(M <sup>+</sup> , 100), 306(11),
		52.55	3.87	4.51	6.68–6.83 (m, 3H), 7.00–7.10 (m, 4H)	1580,1481	229(5), 194(72)
<b>4</b> /64	93–95 <sup>d)</sup>	80.98	6.40	5.90	2.00 (s, 3H, COCH <sub>3</sub> ), 2.70–2.92	1672,1489	237(M <sup>+</sup> , 8), 195(24),
		81.12	6.59	5.98	(m, 2H), 3.25–3.50 (m, 2H),	1372,1325,	180(8), 108(5), 43(100)
<b>5</b> /26	125–127	84.31	6.11	4.47	2.05 (d, 3H, <i>J</i> =8.5Hz, COCH <sub>3</sub> ),	3028,2935,	313(M <sup>+</sup> , 34), 271(100),
		84.59	6.25	4.53	2.76–2.98 (m, 2H), 3.28–3.55 (m, 2H), 7.15–7.62 (m, 12H)	1674,1486, 699	56(12), 229(6), 194(12)

<sup>a)</sup> Lit. *m.p.* 126 °C [15], <sup>b)</sup> Lit. *m.p.* 141–143 °C [15], <sup>c)</sup> Lit. *m.p.* 87–89 °C [15] Lit. *m.p.* 84.5–86 °C [10], <sup>d)</sup> Lit. *m.p.* 95–96 °C [11]

recorded on a Varian Gemini-200 spectrometer at 200 MHz in CDCl<sub>3</sub> (internal standard Me<sub>4</sub>Si,  $\delta$  = 0.00 ppm) at room temperature. Ascending thin layer chromatography was performed on precoated plates of silica gel 60F 254 (Merck) and the following developing systems were used: benzene-EtOH/*n*-hexane (4:1:3; v/v) and benzene/*n*-hexane (1:1; v/v) and spots were visualised by using UV lamp or iodine vapor. Mass spectra were scanned on a VG TRIO-2 spectrometer in EI mode at 70 eV.

### 3-Substituted 5-Acetyl-10,11-dihydro-5H-dibenz[*b,f*]azepine (**2a–d**). General Procedure

Anhydrous copper(II) halide (CuCl<sub>2</sub>, CuBr<sub>2</sub>) or CuI or CuCN respectively, (0.06 mol) isoamyl nitrite (0.075 mol) and dry acetonitrile (150 ml) were added to a three-necked round-bottom flask and the mixture was stirred. 12.30 g (0.05 mol) of **1** was slowly added over a period of 10 min to the reaction solution while the temperature was kept at room temperature (15–25 °C). During this addition the reaction mixture turned dark brown as nitrogen was evolved. The stirring was continued for 2–7 hours (monitoring by TLC), then mixture was poured into 100 ml of 20% aqueous hydrochloric acid and extracted with chloroform (3×100 ml) and the organic layer was washed twice with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The product was purified by crystallization from a mixture of benzene/*n*-hexane (**2a,b**) or by column chromatography (**2c,d**) on silica gel using chloroform as eluent. Recrystallization was performed from EtOH.

### 3-Substituted 10,11-Dihydro-5H-dibenz[*b,f*]azepine (**3a–c**). General Procedure

2.00 g (0.035 mol) of KOH were dissolved in 15 ml of methanol, 0.01 mol of 3-halogenated-5-acetyl-iminodibenzyl (**2a–c**) were added and the whole was refluxed for 5–6 hours in a nitrogen atmosphere. The solution was then concentrated almost to dryness and then water was added. The crude product was taken up in diethylether and evaporated and crystallized from *n*-hexane.

### Reductive Deamination of the Compound **1**

#### 5-Acetyl-10,11-dihydro-5H-dibenz[*b,f*]azepine (**4**)

1.23 g (0.005 mol) of amine **1** were added to the mixture of 15 ml dry *N,N*-dimethylformamide (DMF) and 1 ml of isoamyl nitrite at room temperature, then the dark solution was stirred for 2–3 hours and it was poured into 50 ml of 1:1 hydrochloric acid, extracted with chloroform and after washing with water the organic layer was evaporated. The residue was purified by column chromatography (silica gel packing, chloroform as eluent) and crystallized from EtOAc.

#### 3-Phenyl-5-acetyl-10,11-dihydro-5H-dibenz[*b,f*]azepine (**5**)

4.94 g (0.02 mol) of **1** was dissolved in 50 ml benzene and 3.27 g (0.028 mol) of isoamyl nitrite was added to this solution. The mixture was stirred at room temperature for 20 min, then refluxed for 2 hours. The mixture was evaporated Column chromatography of the residue with chloroform as eluent on

silica gel packing resulted first **5** ( $R_f$ : 0.55 in benzene/EtOH/*n*-hexane 4:1:3 system) then **4** ( $R_f$ : 0.49).

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