A Facile Synthesis of 2,4,8,10-Tetrahalo-6,12-diaryldibenzo[*b*,*f*][1,5]diazocines [1]

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3,5-Dihalo-2-aminobenzophenones **2** on prolonged reflux in dry pyridine gave 2,4,8,10-tetrahalo-6,12-diaryldibenzo[*b*,*f*][1,5]diazocines **3** in high yields. Attempted condensation of **2** with glycine ester hydrochloride under identical reaction conditions failed to afford 1,4-benzodiazepines.

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Dibenzo[*b*,*f*][1,5]diazocines are a class of eight membered heterocycles of biological importance [2] because of their antigonodotropic, hypotensive, blood cholesteral lowering and estrogenic activities. We have reported earlier one direct synthesis of dibenzo[*b*,*f*][1,5]diazocines from 3-aryl-2,1-benzisoxazoles employing Lawesson reagent [3]. Various literature reports are also available for the acid catalysed synthesis of this class of compounds from *o*-aminobenzophenones [4]. Interestingly, there is hitherto no report available for nitrogen base mediated bimolecular self condensation of *o*-aminobenzophenones; though the condensation of glycine ester hydrochloride and *o*-aminobenzophenones is reported to be facilitated by nitrogen bases [5]. Our continued studies on 2,1-benzisoxazoles [6] have led us to report here another improved and facile synthesis of dibenzo[*b*,*f*][1,5]diazocines from dihaloamino-

Table 1

Reaction Conditions and Physical Properties of Compounds **2**

2	X	Y	R	Reaction temperature	Time (hours)	Recrystallization Solvent	Mp (°C)	Yield (%)
a	Cl	H	H	Room	12	Methanol	94	80
b	Br	H	H	Room	12	Methanol	87	72
c	Cl	CH_3	H	Room	14	Ethanol	104	73
d	Cl	H	OCH_3	Room	10	Methanol	98	75
e	Cl	H	$OCOCH_3$	Room	10	Ethanol	108	70
f	NO_2	H	H	80°	6	Ethanol	161	56

Table 2

Analytical and Spectroscopical Data of Compound **2**

Compound No	Molecular formula	Analysis (%) Calcd./Found C	H	N	NMR ppm (Deuteriochloroform)	IR (Potassium Bromide) cm^{-1}	MS M^+ m/z
2a	$C_{13}H_9NOCl_2$	58.67 58.82	3.40 3.30	5.26 5.10	6.86-7.86 (m, 7H) 6.53 (bs, 2H)	3450, 3350 1635, 1620	266
2b	$C_{13}H_9NOClBr$	50.27 50.13	2.52 3.12	4.51 4.60	6.80-7.80 (m, 7H) 6.50 (bs, 2H)	3380, 3280 1645, 1600	310
2c	$C_{14}H_{11}NOCl_2$	60.02 60.41	3.96 3.83	4.99 4.87	2.53 (s, 3H) 6.60 (bs, 2H) 7.23-7.53 (m, 6H)	3410, 3300 1635, 1600	280
2d	$C_{14}H_{11}NO_2Cl_2$	56.78 56.52	3.74 3.93	4.73 4.62	3.75 (s, 3H) 6.65 (bs, 2H) 6.95-7.95 (m, 6H)	3460, 3350 1625, 1600	296
2e	$C_{15}H_{11}NO_3Cl_2$	55.56 55.21	3.44 3.18	4.32 4.62	2.15 (s, 3H) 6.30 (bs, 2H) 7.00-7.65 (m, 7H)	3450, 3345 1765, 1630 1610	324
2f	$C_{13}H_9N_2O_3Cl$	56.43 56.13	3.28 3.64	10.13 9.98	6.90-8.90 (m, 9H) 6.40 (bs, 2H)	3465, 3415 1640, 1600 1550, 1370	276

benzophenones under the influence of nitrogen bases.

3,5-Dichloro-2-aminobenzophenones **2a-f** were prepared from 3-aryl-2,1-benzisoxazoles **1a-f** and thionyl chloride employing our own procedure [7]. Reaction of thionyl chloride in excess with **1a-f** under anhydrous condition afforded **2a-f** in good yields. The physical properties and spectroscopical data are given in Table 1 and 2.

Upon refluxing of 3,5-dichloro-2-aminobenzophenone (**2a**) in dry pyridine with a catalytic amount of piperidine under a nitrogen atomosphere for 20 hours and workup afforded 2,4,8,10-tetrachloro-6,12-diphenyldibenzo[*b*,*f*][1,5]-diazocine (**3a**) as greenish-yellow crystals, mp 206-207° in high yields (90%). The structure was confirmed based on spectral, elemental analysis and also comparison with a standard sample [8]. Thus the ir spectra of **3a** showed a strong band in the region 1630 cm^{-1} characteristic of >C=N- stretching frequency. The nmr spectrum of **3a** showed a multiplet of aromatic protons in the region δ 6.75-7.75. The mass spectra showed the molecular ion peak (M^+) at m/z 496 with the characteristic pattern of four chlorine atoms. Similarly dihalo compounds **2b-e** and also halonitro compound **2f** under similar reaction conditions gave **3b-f** in high yields (75-92%). The physical properties and analytical data have been incorporated in Table 3 and 4 (Scheme 1).

Employing the procedure of Sternbach *et al.* [5] the condensation of **2a** with glycine ethyl ester hydrochloride failed to give the expected product 7,9-dichloro-5-phenyl-1,4-benzodiazepine-2-one (**4a**), rather afforded tetrahalodibenzo[*b*,*f*][1,5]diazocine **3a** as the sole product [9]. The ir spectra did show characteristic absorption for >C=N- stretching frequency at 1630 cm^{-1}, but bands for >NH or >C=O were absent. Also the ^1H nmr spectrum showed a aromatic multiplet in the region δ 6.65-7.75 without any signal in the aliphatic region. The mass spectra showed molecular ion peak (M^+) at m/z 496 and mixture mp with **3a** was undepressed which confirmed the structure of the product as **3a** and discarded the structure **4a**.

This contrast behaviour of **2** for enhancement of bimolecular self condensation may be revealed due to the presence of an *ortho*-chloro group in **2**. The support for this observation was further achieved by the fact that 2-amino-5-chlorobenzophenone (**5a**) [10] devoid of an *ortho*-chloro group as in **2**, on prolong reflux in pyridine underwent self

Table 3

Reaction Time and Physical Properties of Compound **3**

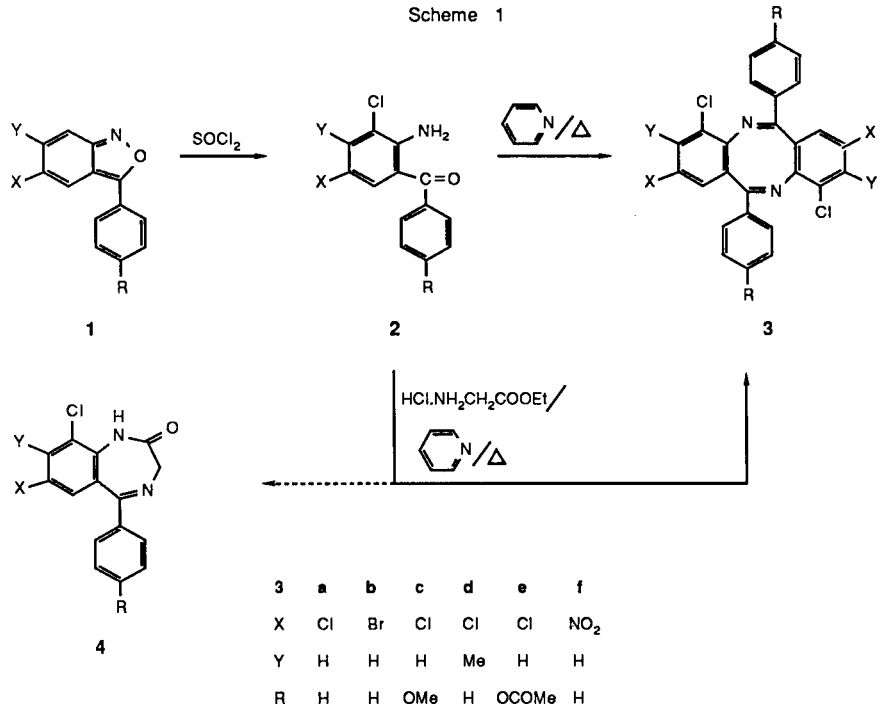
3	X	Y	R	Reaction time (hours)	Recrystallization Solvent	Mp (°C)	Yield (%)
a	Cl	H	H	20	Acetone	206-208	90
b	Br	H	H	20	Acetone	220-221	92
c	Cl	H	OMe	18	Acetonitrile	190-192	78
d	Cl	Me	H	18	Acetone	230-233	75
e	Cl	H	OCOMe	15	Acetonitrile	265-268	80
f	NO_2	H	H	14	Methanol	288-291	84

Table 4

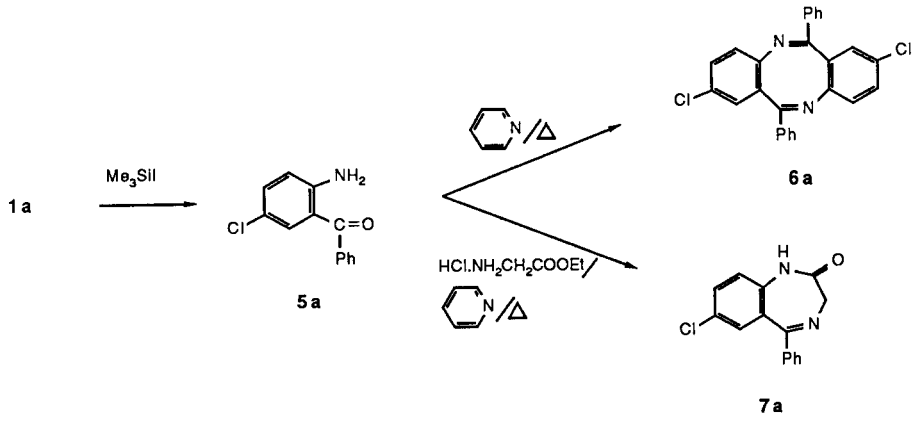
Analytical and Spectroscopical Data of Compound **3**

Compound No	Molecular formula	Analysis (%) Calcd./Found C	H	N	NMR ppm (Deuteriochloroform)	IR (Potassium Bromide) cm^{-1}	MS M^+ m/z
3a	$C_{26}H_{14}Cl_4N_2$	62.93 62.55	2.84 2.53	5.65 5.30	6.76-7.73 (m, 14H)	1630	496
3b	$C_{26}H_{14}Br_2Cl_4N_2$	53.37 53.25	2.41 2.32	4.79 4.65	6.70-7.85 (m, 14H)	1630	585
3c	$C_{28}H_{18}Cl_4N_2O_2$	60.46 60.35	3.26 3.11	5.04 5.10	3.75 (s, 6H) 6.70-7.60 (m, 12H)	1635	556
3d	$C_{28}H_{18}Cl_4N_2$	64.15 64.01	3.46 3.38	5.34 5.24	3.16 (s, 6H) 6.50-7.60 (m, 12H)	1635	524
3e	$C_{30}H_{18}Cl_4N_2O_4$	58.85 58.80	2.96 2.82	4.58 4.55	2.15 (s, 6H) 6.50-7.70 (m, 12H)	1630 1700	612
3f	$C_{26}H_{14}Cl_2N_4O_4$	60.37 60.33	2.73 2.68	10.83 10.79	6.50-7.55 (m, 14H)	1350 1535 1635	517

Scheme 1



Scheme 2



condensation giving 2,8-dichloro-6,12-diphenyldibenzo-[*b*,*f*][1,5]diazocine (**6**) only in very poor yield (Scheme 2).

EXPERIMENTAL

Melting points were determined in open capillaries in a Buchi oil-heated apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 237B spectrometer in potassium bromide discs. The ^{1}H nmr spectra were recorded on a Varian T-60 instrument using TMS as internal reference. Mass spectra were recorded on an AEIMS-30 instrument at 70 ev.

General Procedure for Preparation of 3,5-Dichloro-2-aminobenzophenone (**2**).

The substrate **2** was prepared from 3-aryl-2,1-benzisoxazole (**1**) as reported previously [7]. Namely, freshly distilled thionly chloride (50 ml) was added to 3-phenyl-5-chloro-2,1-benzisoxazole (1 g, 4.4 mmoles) under magnetic stirring and allowed to react for 12 hours at room temperature. The solvent was removed under reduced pressure to give a red sticky compound. Addition of methanol (10 ml) and trituration gave a yellow crystalline solid, which was filtered, and recrystallised from methanol to afford yellow crystalline needles **2a** (0.93 g, 80%), mp 94°.

General Procedure for the Preparation of 2,4,8,10-Tetrachloro-6,12-diphenyldibenzo[*b*,*f*][1,5]diazocine (**3**).

To a solution of **2a** (1 g, 3.7 mmoles) in dry pyridine (60 ml) was added piperidine (0.8 ml) and the solution was refluxed under nitrogen atmosphere for 4 hours. The reaction mixture was distilled to remove pyridine (10 ml) and then replaced with dry pyridine (10 ml) and continued reflux for another 16 hours. The solvent was removed by distillation under reduced pressure and the concentrated mixture was poured into water (100 ml) and extracted with chloroform, washed with water and dried. Removal of solvent and recrystallisation afforded greenish yellow crystals of **3a** (1.67 g, 90%), mp 204-206°.

Attempted Condensation of **2a** with Glycine Ethyl Ester Hydrochloride.

To a solution of **2a** (1.0 g, 3.7 mmoles) and glycine ethyl ester hydrochloride (1.39 g, 10 mmoles) in dry pyridine (60 ml) was added piperidine (0.8 ml) and the solution of refluxed for 4 hours. The solution was distilled to remove pyridine (10 ml) and replaced with fresh dry pyridine (10 ml) and refluxed for another 16 hours. Removal of the solvent gave a thick solution to which water (100 ml) was added. Extraction with chloroform, washing with water, drying and removal of solvent yielded a solid, which on crystallisation from acetone afforded **3a** (1.52 g, 82%) as greenish yellow crystals, mp 204-206°; ir (potassium bromide): 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.76-7.73 (14H, m); ms: m/z 496 (M^+).

Attempted Self Condensation of *o*-Amino-5-chlorobenzophenone (**5a**).

To a solution of **5a** (1 g, 4.3 mmoles) in dry pyridine (60 ml) was added piperidine (0.8 ml) and refluxed for 20 hours. Usual workup as above and separation of unreacted aminoketone by recrystallization afforded **6a** (0.09 g, 5%), mp 215-217° as light yellow crystals, ir (potassium bromide): 1620 cm^{-1}, ^1H nmr (deuteriochloroform): δ 6.60-7.70 (16H, m); ms: m/z 426 (M^+).

7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one (**7a**).

Following the procedure of Sternbach *et al.* [4], **5a** (1.00 g, 4.3 mmoles) and glycine ethyl ester hydrochloride (1.39 g, 10 mmoles) were refluxed in dry pyridine (80 ml) to obtain 7-chloro-5-phenyl-1,4-benzodiazepine-2(1*H*)-one (**7a**) as colorless plates (0.60 g, 52%), mp 216-217°.

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REFERENCES AND NOTES

[1] Dedicated to Prof. W. Pfleiderer on the occasion of his 60th birthday.

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[8] Compound **3a** was obtained as a standard sample from the acid catalysed bimolecular self-condensation of 3,5-dichloro-2-aminobenzophenone (**2a**).

[9] There was no formation of 1,4-benzodiazepine derivatives but a small quantity of the unreacted aminobenzophenone could be recovered.

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