$TiCl_4$-INDUCED FUNCTIONALISATION OF DIBENZO[b,f][1,4] DIAZOCINE-6,11-(5H,12H)-DIONES

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Abstract - Dibenzo[b,f][1,4]diazocine-6,11-diones (1) were converted to the corresponding 6,11-disubstituted amino derivatives (3) when treated with secondary amines in the presence of titanium tetrachlorideanisole complex. Formation of the (benzimidazol-2-yl)benzamides (4) as the side products was observed in the case of substituted 1.

In our programme to find novel amoebicidal agents, we were interested in synthesising 6,11-disubstituted aminodibenzo[b,f][1,4]diazocines. Herein we report the use of titanium tetrachloride-anisole complex in converting dibenzo[b,f][1,4]diazocine-6,11(5H,12H)-diones to the desired compounds.

The dibenzodiazocinediones (1a-c) required as starting materials were prepared according to the reported procedure[1]. Condensation of O-phenylenediamine with diethyl phthalate in the presence of sodium hydride in tetrahydrofuran furnished dibenzo[b,f][1,4]diazocine 1a. 2-Nitro-and 2-methyldibenzo[b,f][1,4]diazocines (1b, 1c) were prepared in a similar way (Scheme I, Table I).

Scheme I

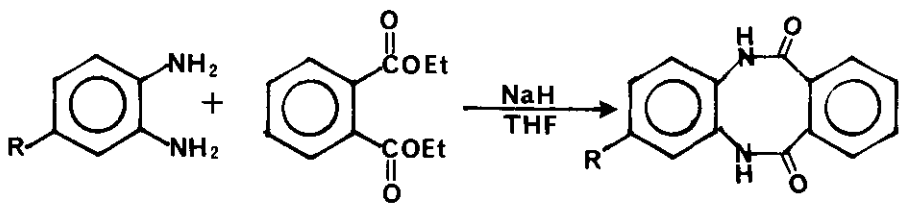
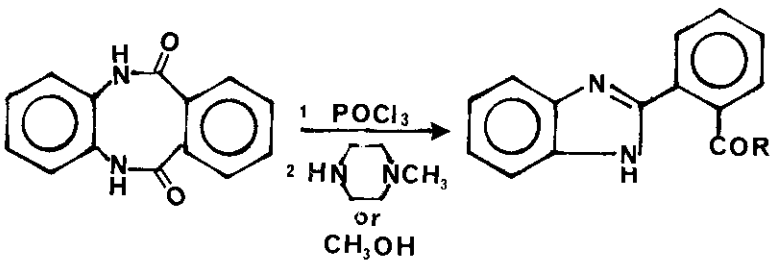


Table I

	R	Mp. °C	Yield (%)
1a	H	301-03	60
1b	CH_3	254-56	25
1c	NO_2	257-60	56

Initially, the conversion of the diones to the desired compounds was attempted through treatment of 1a with $POCl_3$ followed by reaction in situ with appropriate amines. Similar to previously reported results[1] of the treatment of 1a with $POCl_3$ and subsequent reaction with methanol which provided methyl 2-(benzimidazol-2-yl)benzoate 2b, in our case, too, only the rearranged amide viz, N-methylpiperazino-2-(benzimidazol-2-yl)benzamide 2a was obtained (Scheme II).

Scheme II



1a

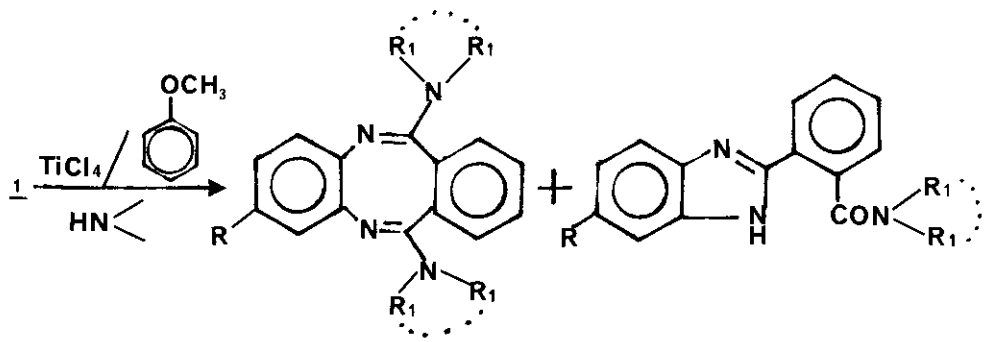
2

2a R = N NCH3

2b R = OCH_3

The diones were readily converted to the amines 3 using titanium tetrachlorideanisole[2] complex (Scheme III).

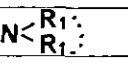
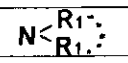
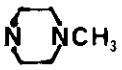
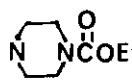
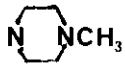
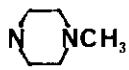
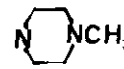
Scheme III



3 4

The reaction is found to be general, affording the amine 3 in fair to good yield as seen from the table II. The substitution in the aromatic ring affects the yield of the amine 3. Thus 2-methyldibenzodiazocine 1b on titanium tetrachloride induced reaction gave 59% of the amine 3d and 15% of the rearranged amide 4a . The nitro-substituted dibenzodiazocine 1c gave the corresponding amide 4b as an only isolable product .

Table II

1	3					4				
		R		Mp,°C	Yield %		R		Mp,°C	Yield %
1a	3a	H		186-88	73				-	
1a	3b	H		240-43	68				-	
1a	3c	H		255-57	37				-	
1b	3d	CH_3		253-55	59	4a	CH_3		178-80	15
1c				-		4b	NO_2		225-28	15

EXPERIMENTAL

Melting points are uncorrected. IR spectra were taken in KBr using a Perkin Elmer 157 Spectrophotometer. Chemical shifts (δ) are in parts per million relative to tetramethylsilane. Coupling constants (J values) are in Hertz (Hz). ^{1}HNMR spectra were run on a Varian T-60 Spectrometer.

Preparation of dibenzo[b,f][1,4]diazocine 1a

This compound was prepared according to the reported procedure[1].

Preparation of 2-methyldibenzo[b,f][1,4]diazocine 1b

To a stirred solution of 4.88 g (0.04 m) of 4-methyl-1,2-phenylenediamine and 8.88 g (0.04 m) of diethyl phthalate in 70 ml of dry tetrahydrofuran was added 1.92 g (0.08 m) of a 50% oil dispersion of sodium hydride in small portions while maintaining the temperature of the reaction mixture at 0°C. After the addition of sodium hydride, the reaction mixture was stirred at 0°C for 14 h, followed by stirring at room temperature. The resulting dark solution was diluted with 30 ml of water and acidified with aqueous HCl. The solid that precipitated was filtered and washed with water, benzene and ether to afford 2.4 g (25%) of compound 1b. An analytical sample was obtained by recrystallisation from methanol/$CHCl_3$ (1:1) mp 254-256°C; IR(KBr): 3200 cm^{-1} (NH), 1685 (C=O); ^{1}HNMR (d_6DMSO): δ 2.2 (s, 3H, $-CH_3$), 7.0 (br s, 3H, aromatic), 7.4 (br s, 4H, aromatic); Anal. calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.27; H, 5.13; N, 11.48%.

Preparation of 2-nitrodibenzo[b,f][1,4]diazocine 1c

Similar to the preparation of 1b, 1c was prepared in 56% yield. An analytical sample was made in the following way. The crude product was dissolved in aqueous NaOH and decolourised using activated charcoal. To the clear aqueous NaOH solution, aqueous HCl was added. The solid that precipitated was filtered and washed with benzene, ether and dried. It was then crystallised from dimethylformamide to give 1c (10 g; 56%) as a bright yellow solid, mp 257-260°C; IR(KBr): 3250 cm^{-1} (NH), 1700 cm^{-1} (C=O), 1350 cm^{-1} (NO_2); Anal.calcd for $C_{14}H_9N_3O_4$. C, 59.36; H, 3.20; N, 14.84. Found: C, 58.96; H, 3.56; N, 15.22%.

Preparation of 6,11-di-N-methylpiperazin-dibenzo[b,f][1,4]diazocine 3a

To a solution of dibenzo[b,f][1,4]diazocine-6,11-dione 1a (1.7 g, 0.0075 m) in N-methylpiperazine (10 ml) was added dropwise to a cooled solution of titanium tetrachloride (3.13 g, 2 ml; 0.0165 m) in anisole (10 ml). The reaction mixture was then heated at 125°C for 2.5 h. It was poured into ice and extracted with chloroform. The organic layer was dried over anhydrous sodium sulphate, concentrated in vacuum and the residue passed through a column of neutral alumina. Elution with chloroform/methanol (5%) afforded the desired amine 3a as a white solid (73%). An analytical sample was obtained by recrystallisation from a mixture of CH_2Cl_2-pentane as colourless needles, mp 186-188°C; ^{1}HNMR ($CDCl_3$): δ 2.2 - 2.6 (m, 2H), 7.5 (m, 8H); Anal. calcd for $C_{24}H_{30}N_6 0.5H_2O$; C, 70.04; H, 7.59; N, 20.42. Found: C, 70.42; H, 7.39; N, 20.23%.

Preparation of 6,11-dimorpholinodibenzo[b,f][1,4]diazocine 3b

Similar to the preparation of 3a, 3b was prepared in 68% yield. An analytical sample was obtained by recrystallisation from a mixture of CH_2Cl_2-pet. ether as a grey solid, mp 240-243°C; ^{1}HNMR ($CDCl_3$): δ 2.6 (brt, 8H, NCH_2), 3.7 (brt, 8H, OCH_2), 7.7 (m, 8H, aromatic); Anal. calcd for $C_{22}H_{24}O_2.0.5H_2O$: C, 68.55; H, 6.54; N, 14.54. Found: C, 68.35; H, 6.31; N, 14.68%.

Preparation of 6,11-di-N-carbethoxypiperazinodibenzo[b,f][1,4]diazocine 3c

Similar to the preparation of 3a, 3c was prepared in 37% yield. An analytical sample was obtained by recrystallisation from a mixture of $CHCl_3$-pet. ether as white crystals, mp 255-257°C; ^{1}HNMR ($CDCl_3$) : δ 1.1 (t, J=7Hz, 6H, $OCH_2\underline{CH_3}$), 2.35 (brt, 8H, $H_5C_2OCN\underline{CH_2}$), 3.4 (brt, 8H, $N\underline{CH_2}$), 4.0 (q, J=7Hz, 4H, $O\underline{CH_2}CH_3$), 7.5 (m, 8H, aromatic); Anal. calcd for $C_{28}H_{34}N_6O_4$: C, 64.84; H, 6.61; N, 16.21. Found: C, 64.71, H, 6.99, N, 15.98%.

Preparation of 6,11-di-N-methylpiperazino-2-methyldibenzo[b,f][1,4]diazocine 3d and benzamide 4a

The reaction was carried out similar to the experimental procedure for the preparation of 3a. The isolation of 3d and 4a was done in the following way. The crude reaction product was passed through a column of neutral alumina. Elution with a mixture of benzene/ethyl acetate (1:1) afforded benzamide 4a as a solid. Recrystallisation of the solid from CH_2Cl_2 - pet. ether furnished 4a as colourless crystals in 15% yield: mp 178-180°C; ^{1}HNMR ($CDCl_3$ + d_6DMSO): δ 2.4 (m, 7H), 3.1 (t, 2H), 3.7 (t, 2H), 7.1 (m, 7H), 7.8 (brs, 1H); IR(KBr): 3300 cm^{-1} (b, NH), 1620 cm^{-1} (CONH); MS m/e 333 (M-1).

Further elution of the column with ethyl acetate/methanol (95:5) furnished the desired amine 3d as a white solid in 59% yield. Analytical sample was obtained by recrystallisation from CH_2Cl_2-pet. ether as colourless crystals, mp. 253-255°C; ^{1}HNMR ($CDCl_3$) : δ 2.0 - 2.4 (m, 17H), 3.4 (br t, 8H), 7.5 (m, 7H); MS m/e 416 (M^+); Anal. calcd for $C_{25}H_{32}N_6$: C, 72.08; H, 7.74; N, 20.18. Found : C, 72.22; H, 7.32; N, 20.50%.

Preparation of N-methylpiperazino-2-(6-nitrobenzimidazo-2-yl)benzamide 4b

The reaction was carried out similar to the experimental procedure for the preparation of 3a using the diazocine 1c. The product 4b was isolated in the following way. The crude reaction mixture was passed through a column of neutral alumina. Elution with ethyl acetate/benzene (7:3) furnished the benzamide 4b as a yellow solid in 15% yield. An analytical sample was obtained by recrystallisation from CH_2Cl_2/pet. ether mp. 225-228°C; IR(KBr): 3100 cm^{-1} (b, NH), 1620 cm^{-1} (CONH), 1340 cm^{-1} (NO_2); ^{1}HNMR ($CDCl_3$) : δ 2.3 (m, 7H), 3.3 (t, 2H), 4 (t, 2H), 7.6 (m, 7H), 8.2 (brs, 1H); Anal. calcd for $C_{19}H_{19}N_5O_3$: C, 62.45; H, 5.24; N, 19.17. Found : C, 62.06; H, 5.01; N, 18.94%.

ACKNOWLEDGEMENTS

Our thanks are due to Dr. J. Reden for his encouragement and to Dr. P. K. Inamdar for the spectral and analytical data.

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Received, 24th December, 1984