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Preparation of 7,7-Bis(methoxycarbonyl)-2,5-Diaryl-3,4-Diazanorcaradienes

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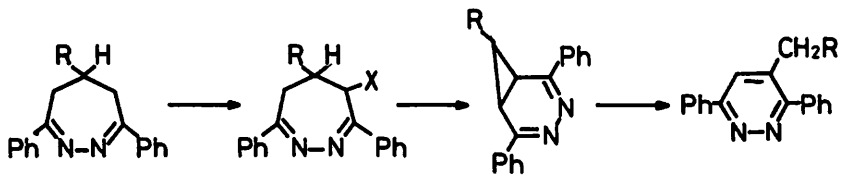
Abstract

5,5-Bis(methoxycarbonyl)-5,6-dihydro-3,7-diaryl-4*H*-1,2-diazepines (6) were prepared by the condensation of α-bromoacetophenone azines with dimethyl malonate in the presence of sodium methoxide. Halogenation of 6 afforded 7,7-bis(methoxycarbonyl)-2,5-diaryl-3,4-diazanorcaradienes (10) in excellent yields.

It has been reported that treatment of 3,7-diphenyl-5,6-dihydro-4*H*-1,2-diazepines (1) with halogenation-reagents results in ring contraction to pyridazines. The isolation of 3,4-diazanorcaradienes (2, R=H[1], Ph[2]) has been cited as evidence for their intermediacy in the contraction reaction which presumably proceeds by a halogenation-dehydrohalogenation process. However, halogenated intermediates have not been isolated (Scheme 1).

Scheme 1



1 (X=Cl, Br) 2 R= H, Me, Ph

Recently, We have reported that halogenation of 5,5-bis(ethoxycarbonyl)-dihydrodiazepines (3) bearing two electron-withdrawing groups affords 7,7-bis(ethoxycarbonyl)-3,4-diazanorcaradienes (4), in good yields, under controlled conditions (Scheme 2).

This paper is concerned with the preparation of 5,5-bis(methoxycarbonyl)-5,6-dihydro-3,7-diaryl-4*H*-diazepines, and with their halogenation which affords halogenated intermediates and diazanorcaradienes in good yields.

Results and Discussion

Preparation of 5,5-Bis(methoxycarbonyl)-5,6-dihydro-3,7-diaryl-4H-1,2-diazepines (6). The dihydrodiazepine 6 was prepared according to the reported method for synthesis of 3[3]. α-Bromoacetophenone azine (5)[4] was allowed to react with methyl malonate in the presence of sodium methoxide in methanol to give the expected 5,5-bis(methoxycar-bonyl)-5,6-dihydro-3,7-diphenyl-4*H*-1,2-diazepine (6a). Similarly, 3,7-di(tolyl), and 3,7-bis

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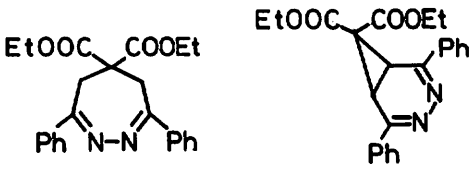
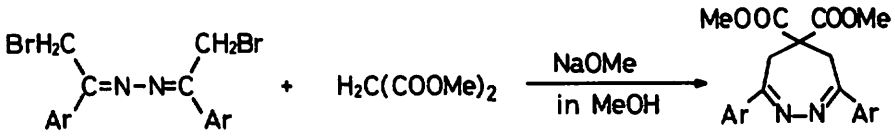
Scheme 2



3 4

(p-chlorophenyl) derivatives, 6b and 6c were prepared from the corresponding azines, 3b and 3c, respectively.

Scheme 3



5 6

a: Ar=Ph; b: Ar=p-MeC_6H_4; c: Ar=p-ClC_6H_4

Structural elucidation of 6 was accomplished on the basis of spectral data and the results of microanalyses, which are given with the yields and melting points in Table 1.

Halogenation. When 6a was treated with twice molar amount of bromine in methanol at room temperature, 5,5-bis(methoxycarbonyl)-4,6-dibromo-5,6-dihydro-3,7-diphenyl-4*H*-1,2-diazepine (7), mp 147-148℃, was obtained in 85% yield. On the other hand, the treatment of 6a with excess chlorine gas in methylene dichloride at -70℃ afforded 5,5-bis(methoxycarbonyl)-4,6-dichloro-5,6-dihydro-3,7-diphenyl-4*H*-1,2-diazepine (8) in 60% yield. When 6a was treated with excess gas at room temperature, 4,4,6,6-tetrachloro-dihydrodiazepine 9, mp 181-182℃, was obtained in 66% yield.

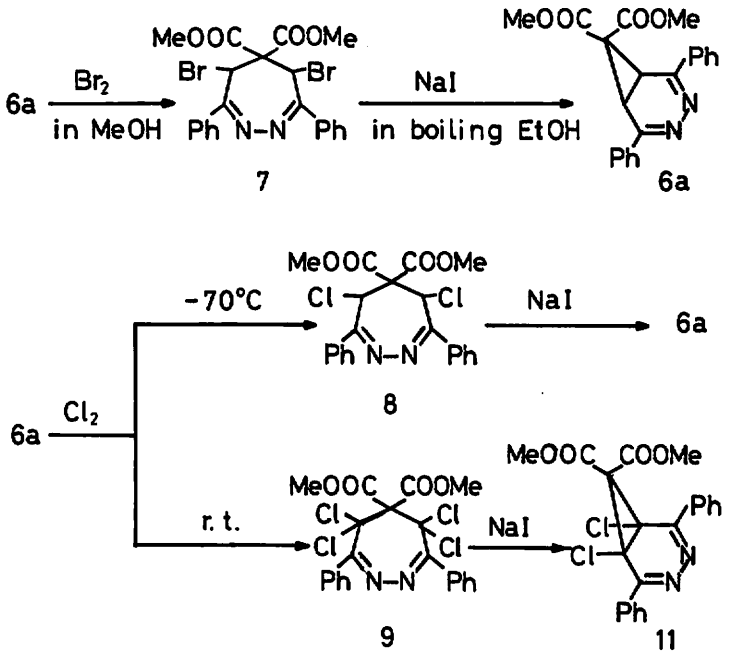
Dehalogenation of the Halogenated products. When dihalides, 7 and 8, were treated with sodium iodide in boiling ethanol, 7,7-bis(methoxycarbonyl)-2,5-diphenyl-3,4-diazanorca-

Table 1. 5,5-Bis (methoxycarbonyl)-5,6-dihydro-3,7-diaryl-4*H*-diazepines (6)

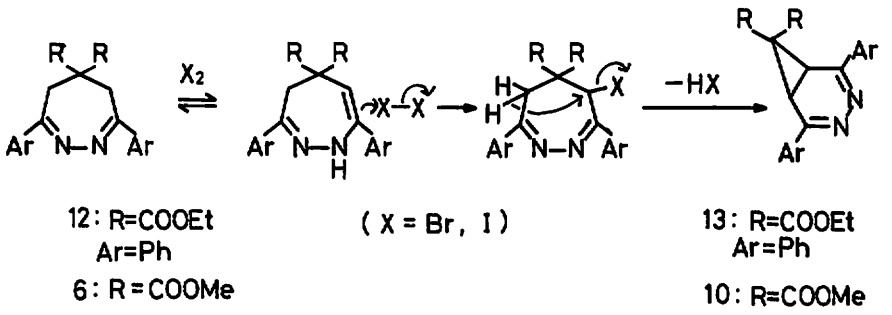
	Yiels %	Mp ℃	IR, νC=O cm^{-1}	^{1}HNMR($CDCl_3$) δ ppm	Found (Calcd) % C	H	N
6a	71	135-136	1750, 1730	3.32(4H, s, CH_2), 3.67(6H, s, CH_3) 7.3-7.9(10H, m, ArH)	69.04 (69.21)	5.55 (5.53)	7.64 (7.69)
6b	50	138-139	1743, 1725	2.40(6H, s, CH_3), 3.32(4H, s, CH_2) 3.70(6H, s, CH_3) 7.1-7.8(8H, m, ArH)	70.24 (70.39)	6.23 (6.16)	6.69 (7.14)
6c	58	188-189	1750, 1730	3.19(4H, s, CH_2), 3.62(6H, s, CH_3) 7.2-7.9(8H, m, ArH)	57.89 (58.21)	4.50 (4.19)	6.31 (6.47)

radiene (10a) was obtained in 41-60% yield. Similarly, treatment of the tetrachloride 9 with sodium iodide in boiling ethanol afforded the 1,6-dichloro-diazanorcaradiene (11) in 35% yield (Scheme 4).

Scheme 4



Scheme 5



a: Ar=Ph; b: Ar=p-MeC_6H_4; c: Ar=p-ClC_6H_4

Next, we have investigated the reaction of 6 with iodine in boiling ethanol. In contrast to the halogenation using bromine or chlorine, the dihydrodiazepines 6a-6c, did not give the halogenated dihydrodiazepine, but instead gave the respective norcaradienes 10 in excellent yield. When 5,5-bis(ethoxycarbonyl)-5,6-dihydro-3,7-diphenyl-4*H*-1,2-diazepine (12) was treated with an equimolar amount of bromine in methanol at room temperature, diazanorcaradiene 13 was obtained, Although the monobromide has not been isolated[31], it is clear that the diazanorcaradiene is formed *via* internal nucleophilic displacement of the monobromide as delineated in scheme 5. Similarly, the path way for the formation of

10 from 6 is interpreted as depicted in the scheme. The structures of 10a-10c, were confirmed on the basis of their spectral data and the results of microanalyses which are given with the melting points in Table 2.

Table 2. 7,7-Bis (methoxycarbonyl)-2,5-diaryl-3,4-diazanorcaradienes (10)

	Yiels %	Mp ℃	IR, νC=O cm^{-1}	^{1}HNMR($CDCl_3$) δ ppm	Found (Calcd) % C	H	N
10a	97	135-136	1745, 1730	3.38(2H, s, CH), 3.40(3H, s, CH_3) 3.92(3H, s, CH_3) 7.3-8.2(10H, m, ArH)	69.11 (69.60)	5.09 (5.01)	7.39 (7.73)
10b	89	166-167	1735	2.41(6H, s, CH_3), 3.37(2H, s, CH) 3.43(3H, s, CH_3), 3.93(3H, s, CH_3) 7.2-7.9(8H, m, ArH)	70.54 (70.75)	5.68 (5.68)	6.97 (7.18)
10c	91	188-189	1750, 1730	3.35(2H, s, CH), 3.44(3H, s, CH_3) 3.96(3H, s, CH_3) 7.4-8.1(8H, m, ArH)	58.10 (58.48)	4.00 (3.74)	6.71 (6.50)

Experiment

All the melting points are uncorrected. The NMR spectra were determined with a Hitachi R-1900 Model spectrometer, with TMS as the internal standard. The IR spectra were measured as KBr disks, and the MS were obtained on a Hitachi R-2500 mass spectrometer with a direct inlet and an ionization energy of 70 eV.

α-Bromoacetophenone azines (*5*). α-Bromoacetophenone azines 5a, 5b and 5c, were prepared by the bromination of corresponding acetophenone azines. 5a: mp 151-152℃ (lit,[4] mp 151-152℃); IR 1590cm^{-1} (C=N); 5b: mp 182-183℃ (lit,[3] mp 182-183℃; IR 1590cm^{-1} (C=N); 5c: mp 186-187℃ (lit,[3] 186-187℃); IR 1590cm^{-1} (C=N).

5,5-Bis (methoxycarbonyl)-5,6-dihydro-3,7-diaryl-4H-1,2-diazepines (*6*). A solution of the azine 5a (3.94g, 10mmol) in benzene (50ml) was added to a solution of dimethyl malonate (2.7g, 20mmol) in methanol (20ml), and then the reaction mixture was refluxed for 2 h. The mixture was poured into water (100ml) and the benzene layer was separated and evaporated in *vacuo* to leave crystals. Recrystallization from ethanol gave 2.6g (71%) of the dihydrodiazepine 6a. Similarly, 3,7-di(tolyl) and 3,7-bis (p-chlorophenyl) derivatives, 6b and 6c were prepared from the corresponding azines, 5b and 5c, respectively.

6a: ^{13}CNMR($CDCl_3$) δ 31.22 (t, 4- and 6-C), 53.29 (q, $COOCH_3$), 65.89 (s, 5-C), 126,56, 128.54, 130.31 (each d), 135.69 (s), 155.67 (s, 3- and 7-C), 169.86 (s, C=O); MS m/z (rel. intensity %) 364(M^+, 100), 333 (9.1), 305 (100), 276 (45.5), 244 (11.1), 217 (20.8), 201 (11.9), 169 (11.1), 141 (20.2), 116 (32.3), 76 (34.3), 50 (6.3).

6b: ^{13}CNMR($CDCl_3$) δ 21.31 (q, CH_3), 31.10 (t, 4- and 6-C), 53.23 (q, $COOCH_3$), 65.65 (s, 5-C), 126.44, 129.25 (each d), 133.00, 140.51 (each s), 155.55 (s, 3- and 7-C), 169.93 (s, C=O); MS m/z (rel. intensity %) 392(M^+, 100), 361 (9.4), 333 (87.2), 304 (82.0), 273 (17.2), 245 (30.6), 216 (10.2), 183 (8.6), 156 (18.8), 131 (31.8), 91 (29.3), 65 (9.3).

6c: ^{13}CNMR($CDCl_3$) δ 30.98 (t, 4- and 6-C), 53.41 (q, $COOCH_3$), 65.86 (s, 5-C),

127.87, 128.76(each d), 133.98, 136.63(each s), 154,64(s, 3- and 7-C), 169.62(s, C=O); MS m/z(rel. intensity %) 436(11.8), 434(61.4), 432(M^+, 90.1), 377(12.2), 375(66.8), 373(100), 348(7.5), 346(38.9), 344(56.2), 313(6.8), 287(11.5), 285(15.3), 236(7.3), 204(8.9), 176(21.3), 151(32.1), 111(20.3). The yield, other physical data, and results of microanalyses of 6 are given in Table 1.

Halogenation of the Dihydrodiazepine 6a. i) A solution of bromine(0.6g, 4mmol) in methanol (3mℓ) was added, drop by drop, over a period of 5 minute to a suspension of the dihydrodiazepine 6a (0.72g, 2 mmol) in methanol (10mℓ), and then the reaction mixture was stirred at room temperature for 10 minute. The mixture was added to water (50ml), and was extracted with benzene (40mℓ×2). The benzene extract was washed with water, dried over sodium sulfate, and then evaporated in *vacuo* to leave crystals, which on recrystallization from ethanol afforded 0.99g (95%) of 5,5-bis(methoxycarbonyl)-4,6-dibromo-4,5-dihydro-3,7-diphenyl-4*H*-1,2-diazepine (7), as yellow prisms. IR (KBr) 1745cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 3.67(6H, s, CH_3), 5.65 (2H, s, CH), 7.3-7.7 (6H, m), 7.9-8.3(4H, m); MS m/z 524, 522, 520(M^+). ii) Chlorination of 6a(0.72g, 2 mmol) with excess chlorine gas in methylene dichloride(40mℓ), at -70℃ for 1 h, afforded 5.5-bis(methoxycarbonyl)-4,6-dichloro-4,5-dihydro-3.7-diphenyl-4*H*-1,2-diazepine (8) in 60% (0.52g) yield. Mp 125-126℃, as yellow prisms; IR (KBr) 1745cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 3.80(6H, s, CH_3), 5.65(2H, s, CH), 7.3-8.1(10H, m, ArH); MS m/z 436, 434, 432(M^+).

Found: C, 57.72; H, 4.38; N, 6.10%. Calcd for $C_{21}H_{18}N_2O_4Cl_2$: C, 58.21; H, 4.20; N, 6.47%.

Similar reaction of 6a (0.72g, 2 mmol) with excess chlorine gas in methylene dichloride at room temperature for 2 h, afforded 5,5-bis (methoxycarbonyl)-4,6-dichloro-3,7-diphenyl-4*H*-1,2-diazepine (9) in 66%(0.66g) yield. Mp 181-182℃, as colorless prisms; IR(KBr) 1775, 1740cm^{-1}; ^{1}HNMR($CDCl_3$) δ 3.82(6H, s, CH_3), 7.4-7.9(10H, m, ArH); MS m/z 508, 506, 504, 502, 500(M^+).

Found: C, 49.92; H, 3.49; N, 5.40%. Calcd for $C_{21}H_{16}N_2O_4Cl_4$; C, 50.22; H, 3.21; N, 5.58%.

Dehalogenation of the Halogenated products with sodium iodide. A solution of the dibromide 7 (1.04g, 2 mmol) and sodium iodide (0.75g, 5 mmol) in ethanol (20mℓ) was refluxed for 2 h. The reaction mixture was poured into water (100mℓ) and extracted with benzene (40mℓ×2). The benzene extract was washed with aqueous sodium thiosulfate solution, water and dried over sodium sulfate, and then evaporated in *vacuo* to leave 0.44g (61%) of the diazanorcaradiene 10a. Similarly, treatment of the dichloride 8(0.86g, 2 mmol) and the tetrachloride 9 (1.00g, 2 mmol) with sodium iodide in boiling ethanol afforded 10a and 7,7-bis (methoxycarbonyl)-1,6-dichloro-2,5-diphenyl-3,4-diazanorcaradiene (11) in 60 and 35% yields respectively. 11: mp 159-160℃, yellow prisms; IR(KBr) 1750cm^{-1}; ^{1}HNMR($CDCl_3$) δ 3.54, 4.40(each 3H, s, CH_3), 7.2-8.2(10H, m, ArH); MS m/z 434, 432, 430 (M^+).

Found: C, 58.29; H, 3.92; N, 6.24%. Calcd for $C_{21}H_{16}N_2O_4Cl_2$; C, 58.48; H, 3.47; N, 6.50%.

Treatment of the dihydrodiazepines 6 with Iodine. A solution of the dihydrodiazepine 6a (0.72g, 2 mmol) and iodine (1.0g, 8 mmol) in ethanol (50mℓ) was refluxed for 4 h. The reaction mixture was poured into water (100mℓ) and extracted with benzene (40mℓ×2).

The benzene extract was washed with aqueous sodium thiosulfate solution, water, and dried over sodium sulfate, and then evaporated in *vacuo* to leave 0.70g (97 %) of the diazanorcaradiene 10a. Similarly, treatment of the dihydrodiazepines 6b and 6c with iodine in boiling ethanol afforded 7,7-bis(methoxycarbonyl)-2,5-di(tolyl)- (10b) and 7,7-bis(methoxycarbonyl)-2,5-bis(p-chlorophenyl)-3,4-diazanorcaradiene (10c) in 89 and 91% yields respectively.

10a: ^{13}CNMR ($CDCl_3$) δ 29.09 (d, 1- and 6-C), 31.99 (s, 7-C), 53.10(q, $COOCH_3$), 54.17(q, $COOCH_3$), 127.81. 128,57, 131.29(each d), 136.02(s), 155.22(s, C=N), 162.85 (s, C=O), 169.68(s, C=O); MS m/z(rel. intensity %) 362(M^+, 97.7), 331(6.8), 275 (11.1), 232(100), 215(18.1), 145(5.5), 105(23.3), 77(13.5).

10b: ^{13}CNMR($CDCl_3$) δ 21.58(q, $C_6H_4CH_3$), 29.00(d, 1- and 6-C), 32.08(s, 7-C), 53.04 ($COOCH_3$), 54.11 (q, $COOCH_3$), 127.72, 129.34 (each d), 133.43 (s), 41.70(eachs), 154.76(s, C=N), 162.94(s, C=O), 169.90(s, C=O), MS m/z(rel. intensity %) 390 (M^+, 100), 331(10.2), 303(14.5), 245(64.9), 231(67.9), 119(16.7), 91(8.4).

10c: ^{13}CNMR($CDCl_3$) δ 28.69(d, 1- and 6-C), 31.93(s, 7-C), 53.20(q, $COOCH_3$), 54.29(q, $COOCH_3$), 128.94, 129.03(each d), 134.34, 137.82(each s), 154.42(s, C=N), 162.63(s, C=O), 169.41(s, C=O); MS m/z (rel. intensity %) 434(9.5), 432 (50.1), 430(M^+, 73.7), 371(8.2), 367(9.3), 343(9.0), 265(100), 251(84.9), 249(14.6), 139(26.5), 111(7.8).

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