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Contraction of Substituted 3,7-Diphenyl-5,6-dihydro-4*H*-1,2-diazepines to 3,6-Diphenylpyridazine

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Abstract

ω-Bromoacetophenone azine (**1**) in the reaction with carbanions from malononitrile and ethyl cyanoacetate under mild conditions afforded, instead of the expected double substituted derivatives of acetophenone, azine cyclic 5,5-disubstituted 3,7-diphenyl-5,6-dihydro-4*H*-1,2-diazepines (**2a,b**). 1,2-Diazepines (**2a,b**) prepared in this way showed their thermal unstability and underwent a ring transformation at the temperature of boiling xylene. The product of this very easy transformation was 3,6-diphenylpyridazine (**3**).

Key words: Thermal contraction, 5,5-disubstituted 3,7-diphenyl-5,6-dihydro-4*H*-1,2-diazepine, 3,6-diphenylpyridazine, ω-bromacetophenone azine

Introduction

During investigation of an application scope of "criss-cross" cycloaddition reactions [1] and during preparation of newly substituted substrates [2] for these reactions we observed unusual behaviour of the prepared substrates.

The formation of seven-membered ring from ω-bromoacetophenone azine and malononitrile or ethyl cyanoacetate in ethanol in the presence of sodium ethoxide has been already mentioned in the literature [3].

The ring contraction in the series of variously substituted diazepines and their 5-thia or 5-selena heteroanalogs seems to be an intrinsic property of seven-membered rings. Thus, 2,7-dihydro-3,6-diphenyl- 1,4,5-thiadiazepine [4] as well as 2,7-dihydro-3,6-diphenyl-1,4,5-selenadiazepine [5] undergo ring contraction with the evolution of hydrogen sulfide or selenide in boiling diethylene glycol. Although the standard procedure for preparation of the pyridazine ring involves the action of hydrazine on 1,4-dicarbonyl compound or its equivalent [6] the transformation mentioned above was extended into practical application for conducting materials by Japanese authors [7]. Another type of a ring contraction leading to 3,6-diphenylpyridazines via 3,4-diazanorcaradienes was described [8] for molecules of 5-alkyl or aryl substituted 5,6-dihydro-3,7-diphenyl-4*H*-1,2-diazepines during their halogenation. Similarly halogenation of 5,5-disubstituted 5,6-

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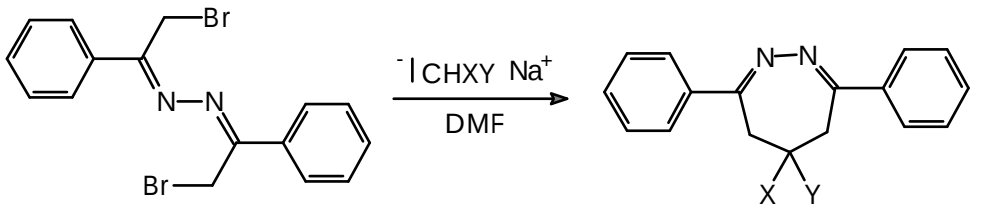


1 **2** a X = COOEt, Y = CN b X, Y = CN

Scheme 1.

dihydro-3,7-diphenyl-4*H*-1,2-diazepine with two electron-withdrawing groups in position 5 afforded besides 3,4-diazanorcaradiene, its chlorinated derivative and 4,4-disubstituted methylene-3,6-diphenyl-1*H*-pyridazine, 3,6-diphenylpyridazine in various yields [9]. A low yield of 3,6-diphenylpyridazine was formed in the reaction of 3,6-diphenyl-1,2,4,5-tetrazine with diethylamine under reflux for a week [10]. A thermal contraction of compounds similar to **2a,b** has not been observed so far.

Results and Discussion

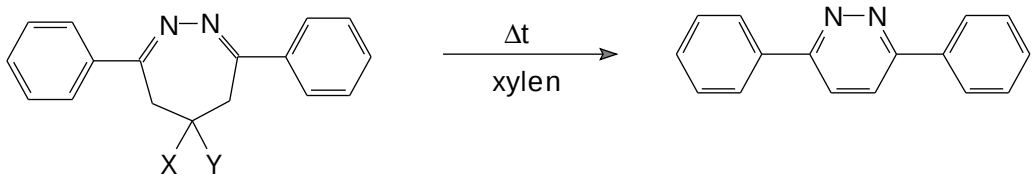
When ω-bromoacetophenone azine (**1**) was treated with carbanions from malononitrile or ethyl cyanoacetate under mild conditions specified in experimental part we observed that instead of expected double substituted derivatives of acetophenone azine cyclic 5,5-disubstituted 3,7-diphenyl-5,6-dihydro-4*H*-1,2-diazepines (**2**) were formed (Scheme 1).

During attempts to crystallize 5,5-disubstituted 3,7-diphenyl-5,6-dihydro-4*H*-1,2-diazepines (**2a,b**) from xylene, we observed their instability and therefore we searched for the final product of their transformation. We found they both underwent a very easy unusual contraction of the seven-membered ring to conjugated 3,6-diphenylpyridazine (**3**) so confirming instability of the seven-membered ring and pointing out another way to ring contraction (Scheme 2). Such a reaction under thermal stress has not been observed yet.

The structure of **3** has been identified by spectral methods and confirmed by X-ray analysis. The structure of **3** is of particular interest. Although one would expect all three rings orientated in one plane only to enable conjugation they are not. The dihedral angle of the central circle plane and the side phenyl group is 29.1(1) degree (the second phenyl is symmetry-related) (Scheme 3). The bond distances and angles of **3** are given in Table 5.

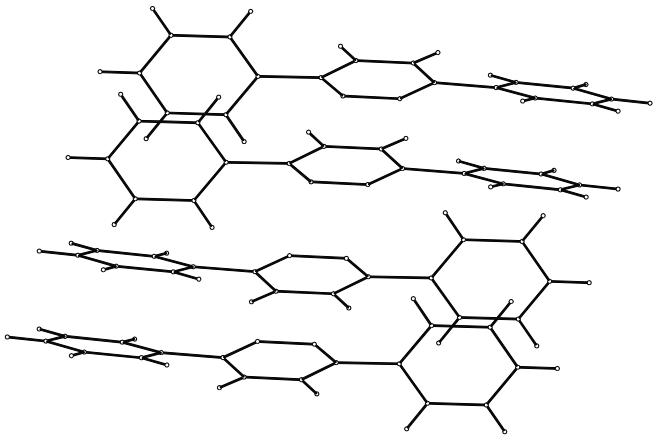
Experimental Section

^{1}H and ^{13}C NMR spectra were recorded using Tesla BS 587 and Tesla 567 spectrometers in deuteriochloroform unless otherwise stated and chemical shifts are reported in ppm on the δ scale relative to internal TMS. Mass spectra were recorded using Finningan-Mat-TSQ 70 instrument. IR spectra were measured in KBr pallets using a Bruker CS 43 instrument. Melting points were uncorrected. The course of the reactions was investigated by TLC on silica gel plates Silufol UV 254 Kavalier, Votice. The X-ray crystallography measurements were carried out on a Enraf Nonius CAD4 diffractometer using graphite-monochromated MoK_a radiation (l = 0.71073 Å). A plate-like crystal of **1** was grown from ethyl acetate. A prismatic crystal of **3** was selected from the preparative batch. The crystals were mounted on glass fibres with epoxy cement. Absorption was neglected. The crystallographic details are summarized in Table 1. The structure of **1** was solved by



2a,b **3**

Scheme 2.



Scheme 3. *Crystal packing of compound **3**.*

the direct method and that of **3** by the heavy atom method (SHELXL86) [11]; both structures were refined by a full matrix least squares procedure based on F^2 (SHELXL93) [12]. Hydrogen atoms were placed in calculated positions [C-H = 0.96 Å, $U_{iso}(H) = 1.2\ U_{iso}(C)$] except the hydrogens of the pyridazine ring which, because of their importance in assigning the chemical picture, were located in the difference map and refined isotropically. The final difference Fourier map had no peaks of chemical significance. Scattering factors were those implemented in the SHELX programs. Positional parameters and bond distances and angles are given in Tables 2–5. Supplementary material is available from J.P. on request – namely, tables of observed and calculated structure factors and anisotropic thermal parameters of non-H atoms, Cambridge Structural Database search and data for related structures, standard CIF files generated by SHELXL93.

Acetophenone azine was prepared according to the literature [13].

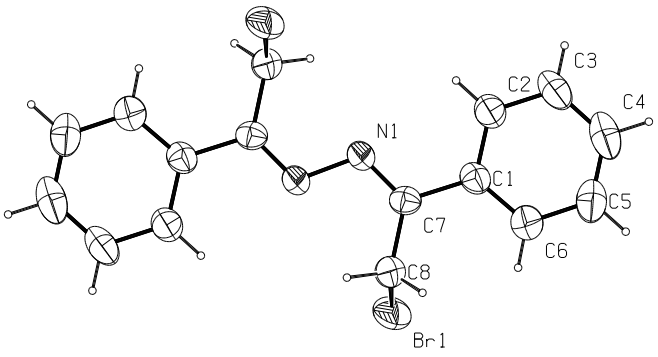


Fig. 1. *ORTEP diagram of compound **1***

Table 1. *Crystallographic Data for compounds **1** and **3**.*

	1	**3**
(a) Crystal Parameters		
Formula	$C_{16}H_{14}Br_2N_2$	$C_{16}H_{12}N_2$
Mw	394.12	232.28
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$ (No.14)	$C2/c$ (No.15)
a, Å	4.3913(9)	27.649(2)
b, Å	10.409(2)	5.7458(9)
c, Å	16.621(3)	7.5905(5)
β, °	96.17(2)	103.590(6)
V, Å^3	755.3(3)	1172.2(2)
Z	2	4
d(calcd), g/cm^3	1.733	1.316
d(measd), g/cm^3 [a]	1.75	1.32
μ(Mo K_a), mm^{-1}	5.357	0.079
Temperature, K	293(2)	293(2)
Crystal size, mm	0.1×0.2×0.3	0.07×0.1×0.46
Colour	orange	colourless
(b) Data Collection		
Scan limits (θ), °	0≤25	0≤25
Data collected: h	±5	±32
k	0.12	0.6
l	±19	±8
Reflections collected	2571	1942
Reflections unique (R_{int})	1329(0.0568)	1029 (0.0296)
Reflections observed ($F_o>4\sigma(F_o)$)	841	876
Standard reflections	3 after every 1 h	
Variation in standards,%	3	4
(c) Refinement		
R(F),%[b]	4.82	3.42
R(wF),%[c]	9.02	11.09
GOF[d]	1.030	0.795
Δ/σ(max)	-0.002	0.005
Δ(ρ), e/Å^3	-0.99; 0.73	-0.17; 0.10

[a] flotation in aq. $ZnBr_2$;
[b] $R(F) = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$;
[c] $R(wF) = \Sigma(w^{0.5}(||F_o| - |F_c||)/w^{0.5}|F_o|)$;
$w = [\delta^2(F_o^2) + w_1P^2 + w_2P]^{-1}$; $P = [max(F_o^2) + 2\ F_c^2]/3$;
$w_1(w_2) = 0.0755(0.81)$ for 1, 0.0797(0.0) for 3;
$GOF = (\Sigma(w||F_o| - |F_c||/N_o - N_v)^{0.5}$.

Table 2. *Atomic coordinates [× 10^4] and equivalent isotropic displacement parameters [× 10^3·Å^2] for* ***1****. U(eq) is defined as one third of the trace of the orthogonalized* $\mathbf{U_{ij}}$ *tensor.*

	x	y	z	U(eq)
Br(1)	328(2)	1629(1)	4711(1)	61(1)
N(1)	-663(12)	5043(5)	4596(2)	48(1)
C(1)	-1181(13)	4170(5)	3279(3)	41(1)
C(2)	-3192(14)	5147(6)	2999(3)	50(2)
C(3)	-4488(16)	5163(7)	2204(4)	62(2)
C(4)	-3820(17)	4199(7)	1686(4)	66(2)
C(5)	-1895(16)	3234(6)	1952(4)	61(2)
C(6)	-563(15)	3216(6)	2742(3)	52(2)
C(7)	231(11)	4168(5)	4132(3)	38(1)
C(8)	2475(14)	3152(5)	4413(3)	46(1)
H(2)	-3666	5794	3351	60
H(3)	-5808	5824	2019	74
H(4)	-4693	4208	1151	80
H(5)	-1470	2581	1599	74
H(6)	767	2553	2916	63
H(8A)	3810	3460	4875	55
H(8B)	3730	2946	3985	55

Table 3. *Bond lengths (Å) and angles (°) for* ***1****. Symmetry code: i; -x,1-y,1-z*

Br(1)-C(8)	1.936(6)	C(7)-N(1)-N(1)(i)	113.9(6)
N(1)-C(7)	1.282(6)	C(6)-C(1)-C(2)	118.1(5)
N(1)-N(1)(i)	1.409(9)	C(6)-C(1)-C(7)	121.6(5)
C(1)-C(6)	1.381(8)	C(2)-C(1)-C(7)	120.2(5)
C(1)-C(2)	1.394(8)	C(3)-C(2)-C(1)	120.5(6)
C(1)-C(7)	1.486(7)	C(4)-C(3)-C(2)	119.8(6)
C(2)-C(3)	1.382(8)	C(5)-C(4)-C(3)	120.3(6)
C(3)-C(4)	1.374(9)	C(4)-C(5)-C(6)	120.4(6)
C(4)-C(5)	1.356(10)	C(1)-C(6)-C(5)	120.8(6)
C(5)-C(6)	1.380(8)	N(1)-C(7)-C(1)	116.7(5)
C(7)-C(8)	1.486(7)	N(1)-C(7)-C(8)	123.6(5)
		C(1)-C(7)-C(8)	119.7(5)
		C(7)-C(8)-Br(1)	109.8(4)

Table 4. *Atomic coordinates [× 10^4] and equivalent isotropic displacement parameters [× 10^3·Å^2] for* ***3****. U(eq) is defined as one third of the trace of the orthogonalized* $\mathbf{U_{ij}}$ *tensor*

	x	y	z	U(eq)
N(1)	240(1)	3981(2)	2963(2)	42(1)
C(1)	1003(1)	2192(3)	4445(2)	35(1)
C(2)	1160(1)	4123(3)	5542(2)	41(1)
C(3)	1650(1)	4349(3)	6458(3)	47(1)
C(4)	1994(1)	2665(4)	6296(3)	50(1)
C(5)	1842(1)	748(4)	5225(3)	48(1)
C(6)	1351(1)	502(3)	4308(2)	42(1)
C(7)	477(1)	1974(3)	3430(2)	35(1)
C(8)	241(1)	-156(3)	2970(3)	41(1)
H(2)	932	5268	5656	49
H(3)	1751	5642	7190	57
H(4)	2326	2827	6908	59
H(5)	2073	-392	5117	57
H(6)	1252	-807	3593	50
H(8)	413(6)	-1607(34)	3270(24)	49(5)

Table 5. *Bond lengths (Å) and angles (°) for* ***3****. Symmetry code: i; -x,y,*-z*

N(1)-C(7)	1.334(2)	C(7)-N(1)-N(1)(i)	120.12(9)
N(1)-N(1)(i)	1.346(3)	C(6)-C(1)-C(2)	118.6(2)
C(1)-C(6)	1.387(2)	C(6)-C(1)-C(7)	120.9(2)
C(1)-C(2)	1.394(2)	C(2)-C(1)-C(7)	120.5(2)
C(1)-C(7)	1.483(2)	C(3)-C(2)-C(1)	120.5(2)
C(2)-C(3)	1.377(3)	C(5)-C(4)-C(3)	119.6(2)
C(3)-C(4)	1.382(3)	C(4)-C(5)-C(6)	120.5(2)
C(4)-C(5)	1.375(3)	C(5)-C(6)-C(1)	120.5(2)
C(5)-C(6)	1.381(3)	N(1)-C(7)-C(8)	121.4(2)
C(7)-C(8)	1.392(2)	N(1)-C(7)-C(1)	115.3(2)
C(8)-H(8)	0.96(2)	C(8)-C(7)-C(1)	123.3(2)
		C(8)(i)-C(8)-C(7)	118.46(10)
		C(8)(i)-C(8)-H(8)	119.7(11)
		C(7)-C(8)-H(8)	121.8(11)

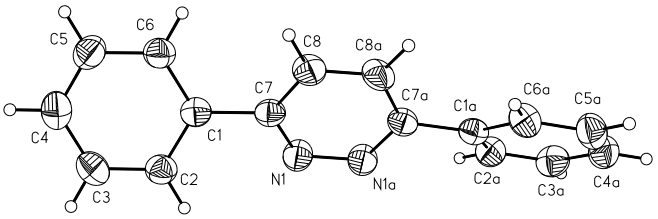


Fig. 2. *ORTEP diagram of compound **3**.*

*ω-Bromacetophenone azine (**1**)*

To a solution of 5 g (21.2 mmol) of acetophenone azine in 200 ml of acetic acid (100%) with magnetic stirring, bromine (7.7 g; 43.3 mmol) was added dropwise. After a few minutes the reaction mixture lost the colour of bromine and it was then poured onto crushed ice. The orange slurry was filtered and washed with water. After crystallization from acetone, orange crystals were obtained (3.75 g, 45%); mp 154 –156 °C. CI MS *m/z* 395 (MH^+, 100%). ^{1}H NMR δ 4.52 (4H, *s*, CH_2Br), 7.73 (10H, *m*, Ar-H). IR (bromoform) 640, 690, 780, 1020, 1205, 1290, 1450, 1565, 1600.

*5,5-Disubstituted 3,7-diphenyl-5,6-dihydro-4H-1,2-diazepines (**2**)*

To a suspension of 0.5 g (20.8 mmol) of sodium hydride in dry DMF under external cooling with ice, ethyl cyanoacetate (2.37 g; 20.8 mmol in 10 ml of DMF) in the case of **2a** and malonitrile (1.37 g; 20.8 mmol in 10 ml of DMF) in the case of **2b** was added dropwise. After the reaction ceased (about 10 min) ω-bromoacetophenone azine (4.1 g; 10.4 mmol) was added. The reaction was followed by TLC. When the initial product disappeared, DMF was removed by a rotary vacuum evaporator to dryness. Then water with NaCl was added and the product was extracted to ether. For further work up, see the separate procedures.

*Ethyl 3,7-diphenyl-5-cyano-5,6-dihydro-4H-1,2-diazepine-5-carboxylate (**2a**)*

When the ether was evaporated, over two days the red oil became crystalline. After washing the crystals with ethanol and petroleum ether, slightly pink crystals were recovered (1.25 g, 35%). mp 102–104 °C. CI MS *m/z* 346 (MH^+, 100%). ^{1}H NMR δ 1.22 (3H, *t*, CH_3), 3.17 (2H, *d*, CH_2), 3.47 (2H, *d*, CH_2), 4.12 (2H, *q*, CH_2) 7,73 (10H, *bm*, Ar-H). ^{13}C NMR δ 13.52.(CH_3), 32.25 (O-CH_2), 53.66, 63.90 (CH_2), 118.18 (CN), 126.74, 128.60, 130.63, 135.02, 153.79 (C = N), 165.99 (C = O). IR cm^{-1} 691, 766, 1092, 1212, 1259, 1322, 1345, 1446, 1552, 1732 (C = O), 2250 (CN), 3059.

*3,7-Diphenyl-5,6-dihydro-4H-1,2-diazepine-5,5-dicarbonitrile (**2b**)*

The crystalline product which was formed after the evaporation of the ether was washed with water and crystallized from toluene (1.2 g, 39%). mp 174–176 °C. CI MS *m/z* 299 (MH^+, 100%). ^{1}H NMR δ 3.43 (4H, *d*, CH_2), 7.77 (10H, *bm*, Ar-H). ^{13}C NMR δ 33.90 (CH_2), 40.32, 114.47 (CN), 127.07, 129.17, 131.49, 134.31, 152.15. IR cm^{-1} 692, 766, 895, 1026, 1048, 1092, 1213, 1344, 1446, 1493, 1551, 2251 (CN), 3060.

*3,6-Diphenylpyridazine (**3**)*

The starting procedure was the same as for the preparation of compound **2a** and **2b**. The residue after evaporation of the solvent was dissolved in xylene and kept boiling under reflux for 5 h. After cooling, yellow crystals appeared (0.96 g, 40%). mp 226–228 °C. CI MS *m/z* 233 (MH^+, 100%), 221 (5), 123 (3), 102 (3), 61 (3), 59 (8). ^{1}H NMR (DMSO) δ 7.93 (12H, *m*, Ar-H). IR cm^{-1} 694, 744, 758, 868, 1020, 1127, 1155, 1311, 1408, 1449, 1488, 1548, 3055.

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