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DIOXIMES AS SYNTHONS FOR MEDIUM RING HETEROCYCLIC COMPOUNDS

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Abstract - A simple and convenient synthetic approach to eight-, nine- and ten-membered nitrogen and oxygen containing heterocycles has been developed. 3,4-Diaryl-1,6,2,5-dioxadiazocines, (**3**) and (**4**), 3,4-diaryl-1,6,2,5-dioxadiazonines,(**5**) and 3,4-diaryl- 1,6,2,5-dioxadiazacyclodeca-2,4-dienes (**6**) are prepared in one-pot from vicinal dioximes (**1**) *via* dianion intermediate (**2**) and 1,2-dibromoethylene, l ,2-dichloroethane, 1 ,3-dibromopropane and 1 ,4-dichlorobutane, respectively. A plausible mechanism has bcen discussed.

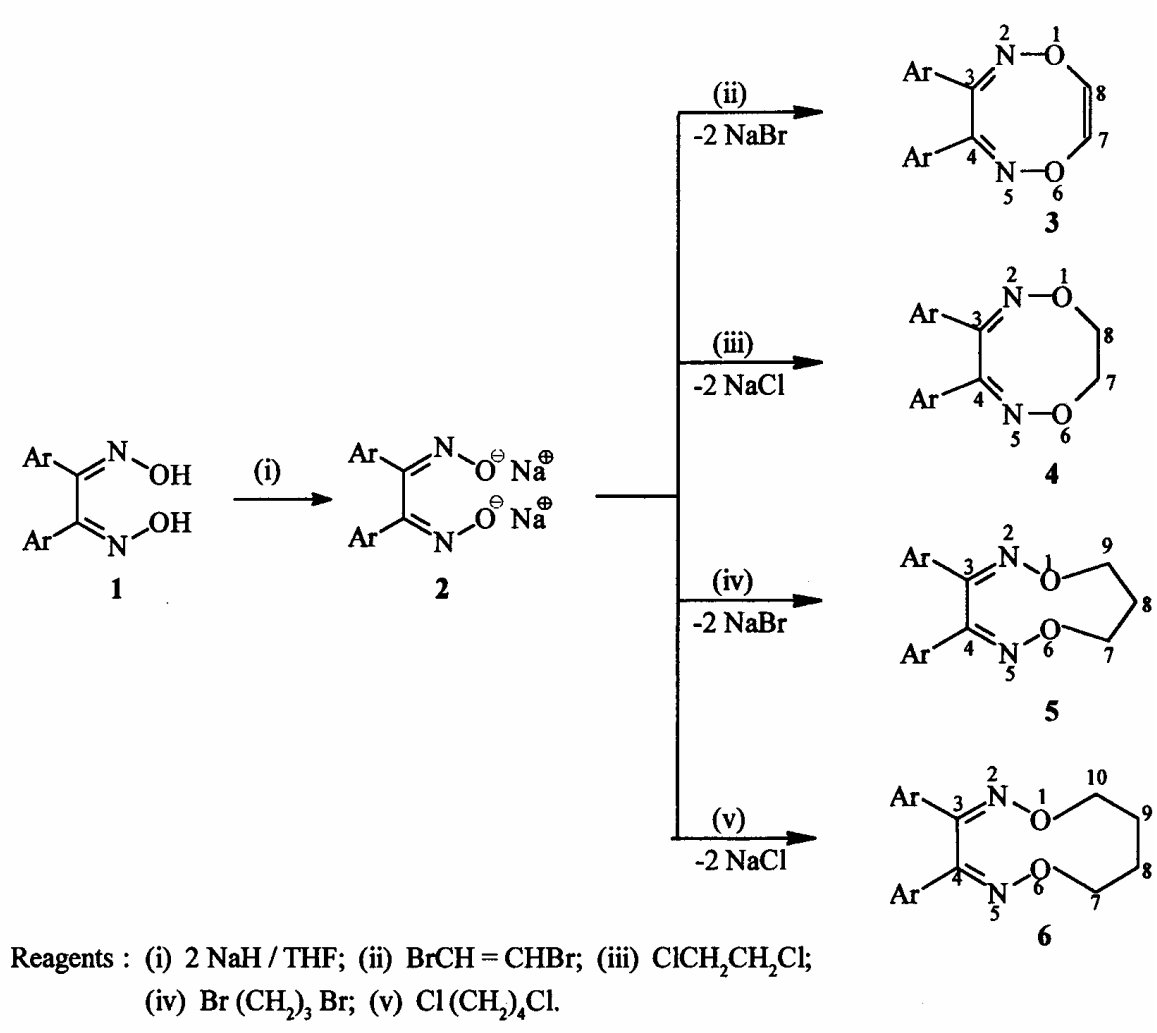
INTRODUCTION

Heterocyclic chemistry is the largest of the classical divisions of organic chemisty and is of the upmost importance from both the fundamental and applied points of view. Vicinal-dioximes have received considerable attention as model compounds which mimic biofunctions[1,2] and provide fertile grounds for various heterocyclic systems[2] . Dianions have bccome increasingly popular as strategic tools to the synthetic planner. Heteroatom-based vicinal dianions were explored by Koft and Williams.[3] Oxime-based dianions were explored by Kaiser. [4] Oxazepines and diazepines are the most popular ring systems among heterocycles because of their very strong pharmacological activities[5,6] and wide clinical use. 1,5,3,7-Dioxadiazocanes, [7] oxonine and a wide variety of azonine[8] have been prepared. In our continuing studies on the synthesis of new heterocyclic ring systems,[9~12] we herein describe the synthesis and characterization of eight-, nine- and ten-membered heterocycles containing two nitrogen and two oxygen atoms.

RESULTS AND DISCUSSION

Imino-oximes [13] are prepared by the condensation of appropriate carbonyl compounds and hydroxylamine . The oxime group is amphiprotic with a slightly basic nitrogen and a mildly acidic hydroxyl group. Only the Z-isomer of oxime forms a dianion. [13] Treatnent of vicinal- 1,2-ketoximes (**1**) with sodium hydride in dry THF in 1 :2 molar ratio generates 1,6-dianion (**2**), which attacks to 1,2-dibromoethene, 1,2-dichloroethane, 1,3-dibromopropane and 1 ,4-dichlorobutane leading to the formation of dioxadiazocines (**3**) and (**4**), dioxadiazonines (**5**) and dioxadiazodecines (**6**). This synthesis involves the initial formation of dianion (**2**) from sequential deprotonation of 1 ,2-dioximes (**1**) by sodium hydride.

Intermolecular nucleophilic attack of dianion to 1,2-dibromoethene and 1,2-, 1,3- and 1,4-dihaloalkanes leads to the formation of products (**3-6**). All these newcompounds are characterized on the basis of elemental analyses and spectral data (**Table 2**).



Reagents : (i) 2 NaH / THF; (ii) BrCH = CHBr; (iii) $ClCH_2CH_2Cl$;
(iv) $Br(CH_2)_3Br$; (v) $Cl(CH_2)_4Cl$.

Scheme 1

Ar	Compounds			
	3	**4**	**5**	**6**
C_6H_5-	a	a	a	a
p-ClC_6H_4-	b	b	b	b
p-$CH_3C_6H_4$-	c	c	c	c
p-$CH_3OC_6H_4$-	d	d	d	d

The spectral analysis showed IR bands for C=N and C-O groups in the expected regions. The NMR spectra of compunds 3 to 6 are consistent with the assigned structures. Only a few signals were observed in the ^{13}C NMR spectra of members of 3-6 because of the symmetry in many of the systems. The chlorine bearing carbons appear at δ 131.56-131.73 ppm, quite distinguishable from the other signals. As anticipated, the ^{13}C NMR analysis revealed signals at 126.4- 144.2 for aryloxy ring attached to carbon.

CONCLUSION

In the present paper, we have described a convenient one-pot synthesis of rare dioxadiazocines, dioxadiazonines, and dioxadiazacyclodecines from Z,Z-dioxime in overall good yields. These mild reaction conditions, low cost and reproducibly high yields contribute to the attractiveness of the present procedure. In addition this method is safer because it minimises the use of toxic or hazardous reagents. Further development of the chemistry encountered with dianions will be published shortly.

EXPERIMENTAL

Materials

The compounds 1,2-dibromoethylene, 1,2-dichloroethane, 1,3-dibromopropane and 1,4-dichlorobutane, hydroxylamine hydrochloride, benzil and substituted benzils were from Aldrich-chemie and used as supplied. Benzil dioxime, 4,4'-dichlorobenzil dioxime, 4,4'-dimethylbenzil dioxime and 4,4'-dimethoxybenzil dioxime were prepared by literature methods.[14,15] All operations were performed under nitrogen atmosphere and with thoroughly dried solvents and glassware. All solvents (AR or extra pure grade) used for spectroscopic and other physical studies were further purified by literature method. [16] The progress of the reactions was monitored by TLC on silica gel plates (Merck Kieselgel $60F_{254}$).

Physical measurements

Melting points were determined using a calibrated thermometer by Remi Digital Melting Point Apparatus and are uncorrected. Elemental analyses were performed with a Carlo-Erba 1100, Heraeous Varlo Erben 1108 apparatus from CDRI, Lucknow. IR spectra were recorded as KBr discs on a 983G Perkin-Elmer spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 instrument from National Chemical Laboratory, Pune, operating at 250 and 62.9 MHz, respectively in $CDCl_3$ solution. All chemical shifts are reported in ppm relative to TMS as an internal standard.

Preparations

Schiff bases. The compounds (**1a-d**) were prepared by literature methods. [12, 14] Benzil dioxime (**1a**) was obtained *via* a Schiff-base condensation reaction between benzil (10.5 g, 50 mmol) and hydroxylamine hydrochloride (9 g, 130 mmol) with the usual workup. Yield 9.5 g (79%). *Anal*. Caled for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.67. Found : C, 70.09; H, 4.52; N, 11.60.

3,4-Diphenyl-1,6,2,5-dioxadiazocine (3a). The benzil dioxime (1.15 g, 4.80 mmol) and dry THF (30 mL) were placed in a 100 mL, three-necked, round bottomed flask equipped with an efficient magnetic stirrer, an addition funnel, a nitrogen inlet and a condenser. The solution was stirred at rt and a suspension of sodium hydride (0.46 g, 9.60 mmol) in 20 mL of dry THF was added slowly over a period of 10 min. The mixture was stirred at reflux which became whitish yellow after 30 min. and finally pinkish light yellow after 2 h. The content was allowed to attain the rt. 1 ,2-Dibromoethene (0.40 mL, 4.80 mmol) was added dropwise with dropping funnel to the reaction vessel. After complete addition the solution turned white. The solution was stirred at rt (about 2-3h), during which no specific change was observed. The solution was then filtered to remove the sodiwn bromide formed during the course of the reaction. Removal of the solvent from the filtrate under reduced pressure *via* rotary evaporator gave the product, which was purified by column chromatography with n-hexane-ethyl acetate (8:1) to give the title compound, 0.33 g (64%), mp 210 °C.

All other dioxadiazocines (**3b-3d, 4a-4d**) were synthesized analogously as mentioned above. The physical and analytical data of the compounds are listed in **Table 1**. Ms m/z : **3a**, 264 (M^+); **3b**, 333 (M^+); **3c**, 292(M^+); **3d**, 324 (M^+); **4a**, 266 (M^+); **4b**, 335 (M^+); **4c**; 294 (M^+); **4d**, 326(M^+).

3,4-Diphenyl-1, 6,2,5-dioxadiazonine (5a). Compound **(5a)** was prepared by the reaction of 1.20 g (5.00 mmol) of benzildioxime (**1a**) with 0.5 1 mL (5.00 mmol) of 1,3-dibromopropane in analogy to the procedure for **3a**. The product (**5a**) was obtained as colorless platelets from CH_2Cl_2-n-hexane with mp 200 °C. Yield 0.84 g (60%).

All other dioxadiazonines (**5b-5d**) were synthesized analogously as mentioned above . The physical and analytical data of the compounds are listed in **Table** 1. Ms m/z : **5a**, 280 (M^+); **5b**, 349 (M^+); **5c**, 308 (M^+); **5d**, 340 (M^+).

3,4-Diphenyl-2, 5- diaza-1, 6-dioxacyclodeca-2,4-diene (6a). Compound (**6a**) was prepared from 1.10 g, (4.60 mmol) of (**1a**) and 0.50 mL (4.60 mmol) of 1,4-dichlorobutane in analogy to the procedure for **3a**. The product (**6a**) was obtained as colorless powder from CH_2Cl_2-n -hexane with mp 203 °C, Yield 0.73 g (62%).

All other dioxadiazodecines (**6b-6d**) were synthesized analogously as mentioned above. The physical and analytical data of the compounds are listed in **Table 1.** Ms m/z : **6a**, 294 (M^+); **6b**, 363 (M^+); **6c**, 322 (M^+); **6d**, 354 (M^+).

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Table - 1 *Physical and Analytical data of Compounds (3 - 6).*

Compd No.	Reactants in g			Product/ Physical state	Yield (%)	mp °C	Solvent of recrystal-isation	Analysis %, found/(Calcd.)			
	Oxime	NaH	R					C	H	N	Cl
3a	1.15	0.46	0.89	$C_{16}H_{12}N_2O_2$ White Solid	64	210	Metanol	72.51 (72.72)	4.03 (4.55)	10.22 (10.61)	-
3b	1.11	0.35	0.67	$C_{16}H_{10}N_2O_2Cl_2$ Cream Coloured Solid	59	205	Ethanol	57.42 (57.65)	2.66 (3.00)	8.03 (8.41)	20.56 (21.32)
3c	1.23	0.44	0.86	$C_{18}H_{16}N_2O_2$ Light Yellow Solid	54	203	Methanol	74.08 (73.97)	5.91 (5.48)	9.93 (9.59)	-
3d	1.14	0.37	0.71	$C_{18}H_{16}N_2O_4$ Yellowish Cream Solid	57	212	Methanol	66.03 (66.67)	4.51 (4.94)	8.17 (8.64)	-
4a	1.06	0.42	0.43	$C_{16}H_{14}N_2O_2$ White Solid	61	210 (d)	Ethanol	71.68 (72.18)	4.87 (5.26)	10.12 (10.53)	-
4b	1.19	0.37	0.38	$C_{16}H_{12}N_2O_2Cl_2$ Yellowish Cream Solid	54	180	Ethanol	57.07 (57.31)	3.11 (3.58)	8.00 (8.36)	20.97 (21.19)
4c	1.17	0.42	0.43	$C_{18}H_{18}N_2O_2$ Cream Coloured Powder	62	208	Methanol	73.96 (73.47)	6.57 (6.12)	9.89 (9.52)	-
4d	1.20	0.38	0.39	$C_{18}H_{18}N_2O_4$ Light Yellow Solid	56	195	Methanol	66.75 (66.26)	6.12 (5.52)	9.17 (8.59)	-

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Cómpd No.	Reactants in g			Product/ Physical state	Yield (%)	mp °C	Solvent of recrystal-isation	Analysis %, Found/(Calcd.)			
	Oxime	NaH	R					C	H	N	Cl
5a	1.20	0.48	1.01	$C_{17}H_{16}N_2O_2$ Cream Coloured Solid	60	200	Methanol	72.19 (72.86)	5.27 (5.71)	9.36 (10.00)	-
5b	1.25	0.39	0.82	$C_{17}H_{14}N_2O_2Cl_2$ Yellowish Cream Solid	57	210	Ethanol	58.07 (58.45)	3.88 (4.01)	7.61 (8.02)	19.58 (20.34)
5c	1.14	0.41	0.86	$C_{19}H_{20}N_2O_2$ White Powder	55	205	Ethanol	74.52 (74.03)	6.91 (6.49)	9.67 (9.09)	-
5d	1.26	0.40	0.85	$C_{19}H_{20}N_2O_4$ Cream Coloured Solid	59	196	Ethanol	67.38 (67.06)	6.12 (5.88)	8.73 (8.24)	-
6a	1.10	0.44	0.58	$C_{18}H_{18}N_2O_2$ Cream Coloured Solid	62	203	Methanol	73.01 (73.47)	5.84 (6.12)	9.11 (9.52)	-
6b	1.23	0.38	0.50	$C_{18}H_{16}N_2O_2Cl_2$ Cream Coloured Solid	58	215	Methanol	59.16 (59.57)	4.06 (4.41)	7.27 (7.71)	19.21 (19.55)
6c	1.29	0.46	0.61	$C_{20}H_{22}N_2O_2$ Light Yellow Solid	55	225	Methanol	74.91 (74.53)	7.32 (6.83)	9.17 (8.69)	-
6d	1.08	0.35	0.45	$C_{20}H_{22}N_2O_4$ White Powder	64	208	Ethanol	67.26 (67.79)	5.83 (6.22)	7.59 (7.91)	-

Molar Ratios are Oxime : NaH : R (1 : 2 : 1)

R = $C_2H_2Br_2$; $C_2H_4Cl_2$; $C_3H_6Br_2$; $C_4H_8Cl_2$.

Table 2 ***Spectral data for compounds (3 - 6).***

Compd	IR (cm^{-1})		NMR (δ ppm)	
	ν(C=N)	ν(C-O)	^{1}H	^{13}C
3a	1605	1170	6.84(d, J=12 Hz, 2H, CH=CH); 7.18-7.86 (m, 10H, Ar-H).	128.6-143.6(Ph); 168.65 (C-6 and C-7); 126.3,$^{2}J(^{13}C\text{-}^{1}H)$ =158 Hz(C-2 and C-3).
3b	1612	1185	6.94(d, J=12 Hz, 2H, CH=CH); 7.38-7.64 (m, 8H, Ar-H).	126.4-142.2(Ph); 170.20 (C-6 and C-7); 127.2,$^{2}J(^{13}C\text{-}^{1}H)$ =157 Hz(C-2 and C-3).
3c	1610	1176	6.78(d, J=12 Hz, 2H, CH=CH); 7.30-7.80 (m, 8H, Ar-H); 2.36(s, 6H, CH_3).	127.2-142.7(Ph); 169.26 (C-6 and C-7); 126.8,$^{2}J(^{13}C\text{-}^{1}H)$ =158 Hz(C-2 and C-3); 21.2(CH_3).
3d	1608	1180	6.81(d, J=12 Hz, 2H, CH=CH); 7.26-7.77 (m, 8H, Ar-H); 3.42(s, 6H, OCH_3).	128.7-143.2(Ph); 168.27 (C-6 and C-7); 27.1,$^{2}J(^{13}C\text{-}^{1}H)$ =157.5Hz(C-2 and C-3); 62.8(OCH_3).
4a	1615	1182	3.42(t, J=5.3 Hz, 4H, 2xOCH_2); 7.12-7.84 (m, 10H, Ar-H).	128.2-142.8(Ph); 167.82(C-6 and C-7); 68.2(C-2 and C-3).
4b	1612	1190	3.46(t, J=5.3 Hz, 4H, 2xOCH_2); 7.36-7.68 (m, 8H, Ar-H).	127.5-143.8(Ph); 168.2(C-6 and C-7); 67.6(C-2 and C-3).
4c	1607	1179	3.39(t, J=5.3 Hz, 4H, 2xOCH_2); 7.29-7.71 (m, 8H, Ar-H); 2.32(s, 6H, CH_3).	127.2-142.6(Ph); 167.32(C-6 and C-7); 69.1(C-2 and C-3); 21.6(CH_3).
4d	1613	1183	3.44(t, J=5.3 Hz, 4H, 2xOCH_2); 7.33-7.81 (m, 8H, Ar-H); 3.39(s, 6H, OCH_3).	128.5-143.2(Ph); 167.37(C-6 and C-7); 68.7(C-2 and C-3); 62.2(OCH_3).
5a	1615	1188	2.13(tt, J=7.3,6.3 Hz, 2H, CH_2); 4.12 (t, J = 9.3 Hz, 4H, 2xOCH_2); 7.15-7.88 (m, 10H, Ar-H).	127.4-143.7(Ph); 168.3(C-7 and C-8); 69.6(C-2 and C-4); 28.3 (C-3).
5b	1618	1184	2..02(tt, J=7.3,6.3 Hz, 2H, CH_2); 4.06 (t, J = 9.3 Hz, 4H, 2xOCH_2); 7.41-7.78 (m, 8H, Ar-H).	128.7-143.9(Ph); 168.42(C-7 and C-8); 71.4(C-2 and C-4); 28.1 (C-3).

Continued.....

Compd	IR (cm^{-1})		NMR (δ ppm)	
	ν(C=N)	ν(C-O)	^{1}H	^{13}C
5c	1610	1177	2.07(tt, J=7.3,6.3 Hz, 2H, CH_2); 4.21 (t, J = 9.3 Hz, 4H, 2xOCH_2); 7.17-7.91 (m, 8H, Ar-H); 2.27(s, 6H, CH_3).	127.3-142.9(Ph); 171.0(C-7 and C-8); 68.1(C-2 and C-4); 27.9 (C-3); 21.1(CH_3).
5d	1619	1181	2.11(tt, J=7.3, 6.3 Hz, 2H, CH_2); 4.08(t, J = 9.3 Hz, 4H, 2xOCH_2); 7.32-7.69 (m, 8H, Ar-H); 3.33(s, 6H, OCH_3).	126.9-143.6(Ph); 68.6(C-7 and C-8); 67.7(C-2 and C-4); 28.6 (C-3); 63.2(OCH_3).
6a	1608	1176	2.10(tt, J=7.3,6.3 Hz, 4H, CH_2); 4.16 (t, J = 5.3 Hz, 4H, 2xOCH_2); 7.22-7.90 (m, 10H, Ar-H).	126.7-144.2(Ph); 168.6(C-8 and C-9); 70.6(C-2 and C-5); 27.6 (C-3 and C-4).
6b	1614	1178	2.12(tt, J=7.3,6.3 Hz, 4H, 2xCH_2); 4.14 (t, J = 5.3 Hz, 4H, 2xOCH_2); 7.32-7.76 (m, 8H, Ar-H).	127.4-143.8(Ph); 168.2(C-8 and C-9); 71.3(C-2 and C-5); 27.2 (C-3 and C-4).
6c	1611	1183	2.09(tt, J=7.3,6.3 Hz, 4H, CH_2); 4.07 (t, J = 5.3 Hz, 4H, 2xOCH_2); 7.39-7.81 (m, 8H, Ar-H); 2.19(s, 6H, CH_3).	128.1-141.9(Ph); 167.9(C-8 and C-9); 70.7(C-2 and C-5); 26.9 (C-3 and C-4); 21.4(CH_3).
6d	1607	1189	2.14(tt, J=7.3,6.3 Hz, 4H, CH_2); 4.16(t, J = 5.3 Hz, 4H, 2xOCH_2); 7.30-7.91 (m, 8H, Ar-H); 3.36(s, 6H, OCH_3).	127.7-143.6(Ph); 166.8(C-8 and C-9); 72.1(C-2 and C-5); 27.3 (C-3 and C-4); 62.9(OCH_3).

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