HETEROCYCLES FROM NITRILE OXIDES. PART V[1]. 4-AMINO-Δ^2-1,2,4-OXADIAZOLINES

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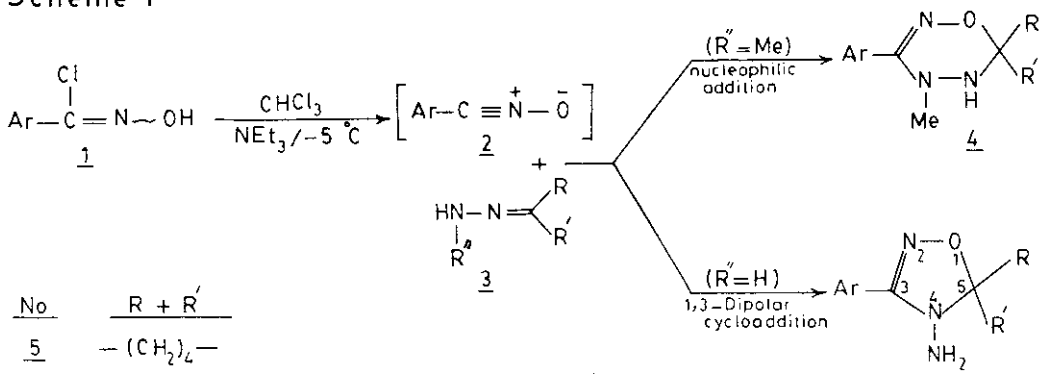
Abstract—Aryl nitrile oxides undergo 1,3-dipolar cycloaddition with alkanone hydrazones to give 4-amino-3-aryl-5,5-dialkyl-Δ^2-1,2,4-oxadiazolines. Lead tetraacetate oxidation of these 4-amino-Δ^2-1,2,4-oxadiazolines brings about smooth heteroring cracking into the corresponding nitrile, ketone, and nitrogen.

Nitrile oxides are known to undergo 1,3-dipolar cycloaddition with Schiff bases, as dipolarophiles, leading to Δ^2-1,2,4-oxadiazolines[2-5]. On the other hand, aza-nucleophiles, such as amines, react readily with nitrile oxides to give the corresponding nucleophilic addition products[6]. Dipolarophiles incorporating a nucleophilic center, such as hydrazones, are anticipated to react with nitrile oxides either by cycloaddition involving the azomethine bond or via nucleophilic addition involving the amino terminus. It is anticipated that competition between these two modes of reaction would arise when the dipolarophile incorporates an additional nucleophilic center. In this context, we recently[1] reported on the reaction of methylhydrazones with nitrile oxides, whereby initial nucleophilic addition, involving the methylamino group, took precedence over 1,3-dipolar cycloaddition (Scheme 1). We now extend our study to unsubstituted hydrazones **3** (R'' = H)[7].

As a consequence of the decreased nucleophilicity of the amino group in these substrates compared to methylhydrazones, preference for 1,3-dipolar cycloaddition over nucleophilic addition might take place in their reaction with nitrile oxides. Indeed, we found that aliphatic keto hydrazones **3** (R'' = H) do react readily with aryl nitrile oxides **2**, generated *in situ* from hydroxamoyl chlorides **1**, to give fair to good yields of the corresponding 1,3-dipolar cycloaddition products, namely 4-amino-Δ^2-1,2,4-oxadiazolines **5**-**12** (Scheme 1) as stable crystalline compounds. However, the reaction of **1** with alkanal hydrazones gave a complex mixture of intractable products. In a model case, it was possible to isolate the desired product **13i** in poor yield.

Scheme 1



No	R + R′
5	$-(CH_2)_4-$
6	$-(CH_2)_5-$
7	$-(CH_2)_6-$
8	$-(CH_2)_7-$
9	$-(CH_2)_2CH(Me)(CH_2)_2-$

No	R	R′
10	Me	Me
11	Et	Et
12	Et	Me
13	H	Et

The structural assignment of compounds 5–13 was based on analytical and spectral data (Table 1). The ir spectra of these compounds revealed two N-H absorption bands in the range 3200–3280 and 3320–3380 cm^{-1}, and a C=N bond stretching at about 1585–1600 cm^{-1}, normally observed for Δ^2-1,2,4-oxadiazolines[8]. In the ^{1}H-nmr spectra, the NH_2 protons appeared as an exchangeable singlet at about 3.50–3.60 ppm (2 H). The two methyls at C-5 in compounds 10 are equivalent and gave rise to one singlet at ca. 1.50 ppm (6H). The methylene protons of the cyclopentane ring in compounds 5 appeared as one broad signal at ca. 1.76–1.98 ppm (8H). A similar feature was observed for compounds 6 and 7, derived from cyclohexanone and cycloheptanone hydrazones, respectively.

The ^{13}C-nmr spectra of compounds 5–13 exhibited a characteristic signal in the region 100–110 ppm, indicative of an sp^3-carbon incorporated within a heteroring system and flanked by two electronegative atoms (oxygen and nitrogen)[9]. In the *off-resonance* spectra, this signal shows no splitting for 5–12, but appears as a doublet for compound 13i and is assigned to the quaternary C-5 carbon. The downfield signal located at about 157–158 ppm is assigned to the azomethine C-3 carbon. The mass spectra of these compounds displayed the correct molecular ions, albeit of low relative abundance. Under electron impact, two main ring fragmentation pathways (Scheme 2) were observed. Ring scission involving rupture of the weak N-O bond (path b) was predominant and gave rise to the resonance stabilized N-aminodiazirine radical cation [D] as base peak. Along with this ion, a low abundant fragment corr-

Table 1. Physical and Analytical Data for Compounds 5-13.

Compd	Ar	mp(°C)	Yield (%)	^{13}C-5 (ppm)	Mol. Formula	[M]$^+$	Calcd / Found (%) C	H	N
5a	C_6H_5	124-125	60	110.6	$C_{12}H_{15}N_3O$	217	66.34 66.73	6.96 6.95	19.34 19.20
5b	o-ClC_6H_4	135-136	44	109.8	$C_{12}H_{14}N_3OCl$	251/253	57.26 57.13	5.61 5.73	16.69 16.71
5c	m-ClC_6H_4	118-119	64	110.8	$C_{12}H_{14}N_3OCl$	251/253	57.26 57.08	5.61 5.77	16.69 16.71
5d	p-ClC_6H_4	104-105	67	110.2	$C_{12}H_{14}N_3OCl$	251/253	57.26 57.32	5.61 5.74	16.69 16.53
5e	m-BrC_6H_4	126-127	62	110.3	$C_{12}H_{14}N_3OBr$	295/297	48.67 48.48	4.76 4.83	14.19 14.20
5f	p-BrC_6H_4	99-100	57	110.4	$C_{12}H_{14}N_3OBr$	295/297	48.67 48.48	4.76 4.79	14.19 14.22
5g	m-$NO_2C_6H_4$	96-97	60	110.7	$C_{12}H_{14}N_4O_3$	262	54.96 54.63	5.38 5.34	21.36 21.30
5h	p-$NO_2C_6H_4$	112-113	58	110.8	$C_{12}H_{14}N_4O_3$	262	54.96 55.01	5.38 5.31	21.36 21.55
5i	p-MeC_6H_4	89-90	56	109.9	$C_{13}H_{17}N_3O$	231	67.51 67.37	7.41 7.49	18.17 18.31
6a	C_6H_5	145-146	56	100.5	$C_{13}H_{17}N_3O$	231	67.51 67.36	7.41 7.56	18.17 18.18
6c	m-ClC_6H_4	133-134	52	100.8	$C_{13}H_{16}N_3OCl$	265/267	58.76 58.60	6.07 6.29	15.81 15.88
6d	p-ClC_6H_4	143-144	55	100.1	$C_{13}H_{16}N_3OCl$	265/267	58.76 58.50	6.07 6.16	15.81 15.52
6e	m-BrC_6H_4	142-143	53	100.3	$C_{13}H_{16}N_3OBr$	309/311	50.34 50.07	5.20 5.29	13.55 13.27
6f	p-BrC_6H_4	146-147	58	100.2	$C_{13}H_{16}N_3OBr$	309/311	50.34 50.06	5.20 5.13	13.55 13.43
6g	m-$NO_2C_6H_4$	129-130	52	100.6	$C_{13}H_{16}N_4O_3$	276	56.51 56.29	5.85 5.97	20.28 20.39
6h	p-$NO_2C_6H_4$	159-160	54	100.8	$C_{13}H_{16}N_4O_3$	276	56.51 56.65	5.85 5.89	20.28 20.29
6i	p-MeC_6H_4	117-118	63	100.1	$C_{14}H_{19}N_3O$	245	68.54 68.40	7.81 7.78	17.13 17.32
7a	C_6H_5	149-150	60	103.3	$C_{14}H_{19}N_3O$	245	68.54 68.33	7.81 7.69	17.13 17.05
7c	m-ClC_6H_4	112-113	56	103.6	$C_{14}H_{18}N_3OCl$	279/281	60.10 60.08	6.48 6.35	15.02 15.21
7d	p-ClC_6H_4	98-99	62	103.5	$C_{14}H_{18}N_3OCl$	279/281	60.10 60.26	6.48 6.54	15.02 14.78
7e	m-BrC_6H_4	124-125	58	103.6	$C_{14}H_{18}N_3OBr$	323/325	51.86 51.71	5.60 5.64	12.96 12.88
7i	p-MeC_6H_4	107-108	60	103.2	$C_{15}H_{21}N_3O$	259	69.47 69.71	8.16 8.32	16.20 16.27
8c	m-ClC_6H_4	117-118	56	103.3	$C_{15}H_{20}N_3OCl$	293/295	61.32 61.16	6.86 6.73	14.30 14.27
8d	p-ClC_6H_4	126-127	58	103.1	$C_{15}H_{20}N_3OCl$	293/295	61.32 61.04	6.86 7.05	14.30 14.30
8f	p-BrC_6H_4	125-126	64	103.1	$C_{15}H_{20}N_3OBr$	337/339	53.26 53.17	5.96 6.08	12.42 12.36
9c	m-ClC_6H_4	115-116	62	100.7	$C_{14}H_{18}N_3OCl$	279/281	60.10 60.19	6.48 6.42	15.02 14.97
9d	p-ClC_6H_4	135-136	65	100.5	$C_{14}H_{18}N_3OCl$	279/281	60.10 59.88	6.48 6.32	15.02 15.06
9e	m-BrC_6H_4	114-115	63	100.7	$C_{14}H_{18}N_3OBr$	323/325	51.86 51.59	5.60 5.52	12.96 13.02
9h	p-$NO_2C_6H_4$	154-155	60	101.3	$C_{14}H_{18}N_4O_3$	290	57.92 57.96	6.25 6.19	19.30 19.23
10c	m-ClC_6H_4	90-91	60	100.0	$C_{10}H_{12}N_3OCl$	225/227	53.22 53.32	5.36 5.60	18.62 18.78
10d	p-ClC_6H_4	94-95	63	99.8	$C_{10}H_{12}N_3OCl$	225/227	53.22 53.33	5.36 5.58	18.62 18.77

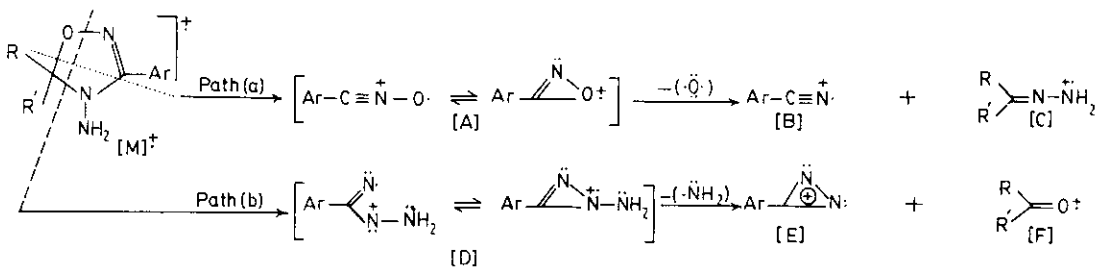
Table 1 (continued).

Compd	Ar	mp(°C)	Yield (%)	^{13}C-5 (ppm)	Mol. Formula	[M]$^+$	Calcd / Found (%) C	H	N
10e	m-BrC_6H_4	96-97	65	100.0	$C_{10}H_{12}N_3OBr$	269/271	44.46	4.48	15.56
							44.64	4.65	15.69
11c	m-ClC_6H_4	84-85	56	103.1	$C_{12}H_{16}N_3OCl$	253/255	56.81	6.36	16.56
							57.03	6.10	16.61
11d	p-ClC_6H_4	86-87	58	102.9	$C_{12}H_{16}N_3OCl$	253/255	56.81	6.36	16.56
							56.81	6.19	16.64
11e	m-BrC_6H_4	91-92	55	103.1	$C_{12}H_{16}N_3OBr$	297/299	48.34	5.41	14.09
							48.34	5.30	14.23
12c	m-ClC_6H_4	66-67	45	101.7	$C_{11}H_{14}N_3OCl$	239/241	55.12	5.89	17.53
							55.32	6.12	17.73
12d	p-ClC_6H_4	46-47	48	101.6	$C_{11}H_{14}N_3OCl$	239/241	55.12	5.89	17.53
							55.06	6.08	17.54
12e	m-BrC_6H_4	75-76	50	101.7	$C_{11}H_{14}N_3OBr$	283/285	46.50	4.97	14.79
							46.55	5.05	14.85
13i	p-MeC_6H_4	86-87	12	102.5	$C_{11}H_{15}N_3O$	205	64.37	7.37	20.47
							64.18	7.26	20.44

esponding to the ketone residue [F] was consistently observed. The alternative ring cleavage (path a) represents a *retro* 1,3-dipolar cycloaddition process, whereby the positive charge is retained either by the nitrile oxide [A] or by the hydrazone partner [C]. Ions [A] and [D] suffer further fragmentations to give [B] and [E] *via* expulsion of an oxygen atom or NH_2 radical, respectively. Similar fragmentation modes were reported for related Δ^2-1,2,4-oxadiazolines[10].

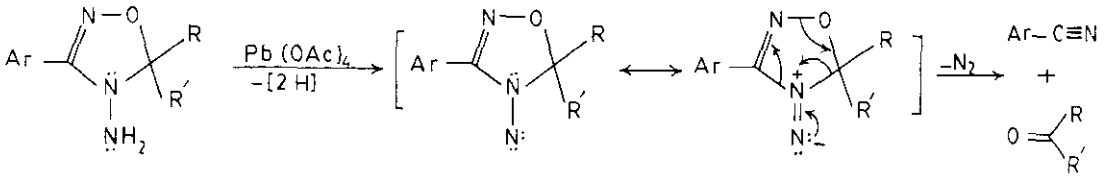
Compounds 5-12 gave upon treatment with lead tetraacetate almost quantitative yields of the corresponding aryl nitrile and ketone. This interesting heteroring-cracking takes place smoothly at 0° C with evolution of nitrogen. It is assumed

Scheme 2



that a transient azanitrene intermediate is initially formed which then extrudes nitrogen and collapses to the aforementioned products (Scheme 3) as the logical stable entities. Nitrene intermediates have been postulated to intervene in the lead tetraacetate oxidations of other related nitrogen heterocycles having an N-amino group[11]. This ring fragmentation of compounds 5-13 could be viewed as a unique chemical evidence in support of their structure.

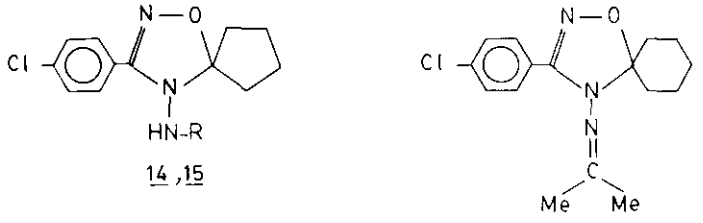
Scheme 3



In conclusion, the 1,3-dipolar cycloaddition, studied here, of nitrile oxides with aliphatic keto hydrazones constitutes a convenient synthetic route to the *hitherto* undescribed 4-amino-Δ^2-1,2,4-oxadiazoline. This reaction is reminiscent of the cycloaddition of **2** with oximes leading to 4-hydroxy-Δ^2-1,2,4-oxadiazolines[12].

It is worth mentioning that several Δ^2-1,2,4-oxadiazolines were reported to act as analgesics[13], coronary vasodilators[14], anaesthetics[15], anthelmintics[16], antispasmodics[17], antibacterial[18], and parasiticidal[19] agents. The amino-functionality at N-4 in compounds **5**-**13** provides a basic handle that enables access to a wide range of new derivatives, such as compounds **14**-**16** (*Scheme 4*).

Scheme 4



14, **15**

No	14	15
R	COMe	$COCH{=}CHCO_2H$

16

EXPERIMENTAL

Melting points (uncorrected) were determined on a Mel-Temp apparatus. Ir spectra (KBr pellets) were obtained on a Perkin Elmer 577 Spectrophotometer. Nmr spectra (in $CDCl_3$) were recorded on a Bruker WM-250, with tetramethylsilane as internal standard. Mass spectra were run on a Finnigan MAT 112 at 70 eV. Microanalyses were performed at Butterworth Laboratories, Middlesex, England. All chemicals and solvents were of commercial grade. Hydroxamoyl chlorides **1a**-**i** were prepared by chlorination of the respective aldoximes as previously described[20]. Hydrazones of cyclopentanone[21], cyclohexanone[22], cycloheptanone[23], cyclooctanone[24], 4-methyl-

cyclohexanone[25], the remaining dialkyl ketones[26], and propanal[27], employed in this work, were obtained by direct interaction of the particular carbonyl compound with hydrazine hydrate.

Preparation of Compounds **5-13**.

General Procedure: A solution of the appropriate hydroxamoyl chloride **1** (20 mmol) in chloroform (20 ml) was dropwise added to a cooled and stirred solution of the hydrazone **3** (50 mmol) and triethylamine (30 mmol) in chloroform (30 ml). Stirring was continued for 2 h and the reaction temperature was allowed to rise slowly to room temperature. The reaction mixture was washed with water (100 ml) and the organic layer was separated and dried over magnesium sulphate. The solvent was then removed in vacuo and the residue was recrystallized from the appropriate solvent. Except for compounds **9c-e,h**, which were recrystallized from petroleum ether (bp 40-60° C), all other compounds were recrystallized from chloroform / petroleum ether.

Preparation of Compound **14**.

Compound **5d** (10 mmol) was refluxed in acetic anhydride (10 ml) for 1 h. Excess acetic anhydride was then evaporated in vacuo and the residual solid product was recrystallized from chloroform / petroleum ether. Yield 80%. mp 149-150° C. Anal. Calcd C, 57.24; H, 5.49; N, 14.30. Found, C, 57.26; H, 5.44; N, 13.98.

Preparation of Compound **15**.

A mixture of **5d** (5 mmol) and maleic anhydride (5 mmol) was refluxed for 2 h in dry tetrahydrofuran (25 ml). The solvent was then removed under reduced pressure and the solid residue was recrystallized from chloroform / petroleum ether. Yield 60%. mp 175-176° C. Anal. Calcd C, 54.94; H, 4.61; N, 12.01. Found, C, 55.27; H, 4.53; N, 11.74.

Preparation of Compound **16**. Compound **6d** (10 mmol) was refluxed for 4 h in anhydrous acetone (25 ml), to which few drops of acetic acid have been added. Excess acetone was evaporated and the remaining solid was recrystallized from petroleum ether. Yield 92%. mp 87-88° C. Anal. Calcd C, 62.84; H, 6.59; N, 13.74. Found, C, 62.72; H, 6.53; N, 13.49.

Lead Tetraacetate Oxidation. In a typical experiment, lead tetraacetate (6 mmol) in dry methylene chloride (10 ml) was slowly added to a stirred ice-cold solution of compound **6d** (5 mmol) in methylene chloride (25 ml). After evolution of nitrogen has ceased (about 15 min), the reaction mixture was washed with water (20 ml), the organic layer was separated, dried ($Mg SO_4$), and the solvent was evaporated under reduced pressure. The remaining residue was crystallized from chloroform /

petroleum ether to give p-chlorobenzonitrile. Yield 90%. mp 92-93° C (unchanged upon admixture with a commercially available sample). Ir 2220 cm^{-1} (C≡N). The same result was obtained when the above reaction was conducted at ambient temperature or at -40° C.

In a separate run, the organic layer was concentrated to about 5 ml, diluted with ethanol (10 ml), and treated with excess of freshly prepared 2,4-dinitrophenylhydrazine reagent. The resulting orange precipitate was collected and crystallized from ethanol. Yield 82%. mp 161-162° C (unchanged upon admixture with an authentic sample of cyclohexanone 2,4-dinitrophenylhydrazone).

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