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The first isolation of α-hydroperoxy-*N*-arylimidoyl cyanides from 2-arylamino-2-alkenenitriles (α-cyanoenamines)

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Abstract

Treatment of *N*-1-(2-chloroalkylidene)arylamines **6** with KCN in CH_3CN at reflux afforded 2-arylamino-2-alkenenitriles **3** (42–58%), which underwent autoxidation, yielding the corresponding α-hydroperoxyimidoyl cyanides (95–100%). © 2000 Elsevier Science Ltd. All rights reserved.

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N-Alkyl α-cyanoenamines **1** and *N*-methyl-*N*-phenyl α-cyanoenamines **2** have received considerable attention as starting materials for the preparation of a variety of organic compounds.[1] Among them, trialkylketenimines,[2] prepared by treatment of **1** with methylmagnesium iodide in ether, followed by addition of water, reacted with singlet oxygen to give 3-alkylimino-1,2-dioxetanes, exhibiting weak chemiluminescence upon heating.[3] Nevertheless, α-hydroperoxy-*N*-alkylimidoyl cyanides, which may act as precursors to the above 1,2-dioxetanes have never been isolated. Furthermore, a survey of the literature shows that no 3-arylimino-1,2-dioxetanes were detected even under the same conditions as for the isolation of 3-alkylimino-1,2-dioxetanes.[3c]

In a continuation of our study on exploiting the synthetic utility of 2,5-diarylisoxazolidine-3-thiones **4**,[4] we have found that 2,5-diphenyl-4,4-dimethylisoxazolidine-3-thione **4a** (R^1=R^2=Me, Ar=Ar′=Ph)[5] reacted with diethylaluminum cyanide (Et_2AlCN) in toluene at reflux under a nitrogen atmosphere to give 3-methyl-2-phenylamino-2-butenenitrile **3a** (R^1=R^2=Me, Ar=Ph) in 41% yield[6] (Scheme 1). Interestingly, compound **3a** was slowly converted to α-hydroperoxy-*N*-phenylimidoyl cyanide **5a** (R^1=R^2=Me, Ar=Ph) either in crystalline or in a solution state in the air. The results prompted us to investigate the stability of other *N*-aryl α-cyanoenamines **3**, which could be readily prepared from *N*-aryl α-chloroaldimines **6**[7] and KCN in CH_3CN at reflux according to the literature method.[8] It has been found that all of the compounds **3** prepared undergo autoxidation, yielding hydroperoxides analogous to **5a**. Reaction times, yields, and mps of 2-arylamino-2-alkenenitriles **3** and α-hydroperoxy-*N*-arylimidoyl cyanides **5** are summarized in Table 1.

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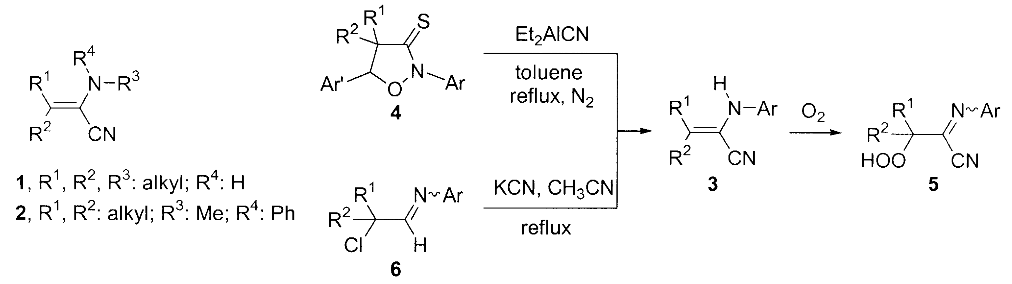


Scheme 1.

Table 1
Reaction times, yields, and mps of 2-arylamino-2-alkenenitriles **3** and α-hydroperoxy-*N*-arylimidoyl cyanides **5**

R^1	R^2	Ar	Compd.	Time (h)	Yield[a] (%)	Mp[b] (°C)	Compd.	Time (h)	Yield[a] (%)	Mp[b] (°C)
Me	Me	Ph	**3a**	8	55	61 - 63	**5a**	44	100	53 - 55
Me	Me	4-ClC_6H_4	**3b**	9	50	85 - 87	**5b**	58	97	c
Me	Me	4-BrC_6H_4	**3c**	13	42	91 - 93	**5c**	54	98	c
Me	Me	3-MeC_6H_4	**3d**	12	53	81 - 82	**5d**	59	97	c
Me	Me	4-MeC_6H_4	**3e**	9	58	74 - 76	**5e**	50	95	61 - 63
Me	Me	2-MeC_6H_4	**3f**	12	57	69 - 70	**5f**	54	98	54 - 57
Me	Me	4-$MeOC_6H_4$	**3g**	9	52	liquid	**5g**	44	98	c
Et	Et	Ph	**3h**	12	54	liquid	**5h**	360	95	c
Me	Et	4-MeC_6H_4	**3i**	12	56	liquid	**5i**	240	96	c
Et	Me	4-MeC_6H_4	**3j**		(**3i**:**3j** = 1:1)					
- $(CH_2)_5$ -		Ph	**3k**	12	57	82 - 84	**5j**	44	99	85 - 86

[a] Isolated yields. [b] Recrystallized from a mixture of *n*-hexane and CH_2Cl_2 except for **5j** (*n*-hexane). [c] Sticky solid.

The extent of the conversion of **3a** into **5a** was determined based on the chemical shifts ($CDCl_3$, 300 MHz) of the methyl protons of **3a** at δ 1.86 and 2.12 ppm and those of **5a** at δ 1.63 ppm as a single peak.

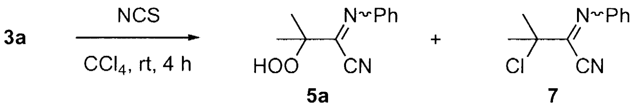
The conversion proceeded faster in non-polar solvents than in polar solvents as shown in Table 2. An analogous effect of the solvent effect was observed from rapid oxygen uptake of acyl cyanide in non-polar solvents.[3e] When R^1 and R^2 were methyl groups as in **3a**–**g**, it took 44 to 59 h for complete conversions to the corresponding **5a**–**g** in $CHCl_3$. In contrast, when one of the methyl groups was substituted for ethyl group as in a mixture of **3i** and **3j** or both R^1 and R^2 were ethyl groups as in **3h**, it took 240 h and 360 h, respectively, until the spots corresponding to **3** had completely disappeared. The results indicate that the presence of a bulkier group(s) than the methyl group at the β-position of *N*-aryl α-cyanoenamines **3** drastically retards the autoxidation. Nevertheless, it is interesting to note that the same reaction times took the same period (44 h) for the conversion of both **3k** (R^1-$(CH_2)_5$-R^2) and **3a** to the corresponding hydroperoxides **5j** and **5a**, respectively.

Unexpectedly, treatment of **3a** with *N*-chlorosuccinimide (NCS) in CCl_4 at room temperature gave **5a** as a major product (67%) along with α-chloro-*N*-phenylimidoyl cyanide **7** (22%), whereas compound **7** was obtained as a major product (61%) under nitrogen atmosphere (Scheme 2). The result may be due to no rigorous exclusion of oxygen in view of the formation of α-chloro-*N*-alkylimidoyl cyanides in almost quantitative yields under the same conditions.[10]

Compounds **5a**, **5e**, **5f**, and **5j** among the compounds **5** prepared were obtained in crystalline states

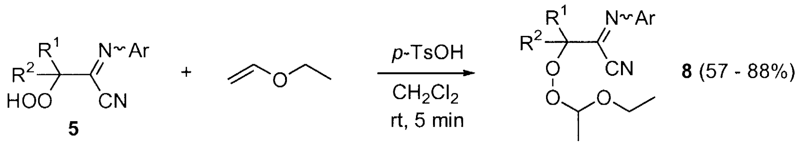
Table 2
Percentages for the conversion (**3a**→**5a**) for 44 h

Solvent	%
Benzene	100
CH_2Cl_2	100
$CHCl_3$	100
Et_2O	49
THF	56
CH_3COCH_3	74
EtOAc	26
CH_3CN	23
MeOH	8
Neat	9



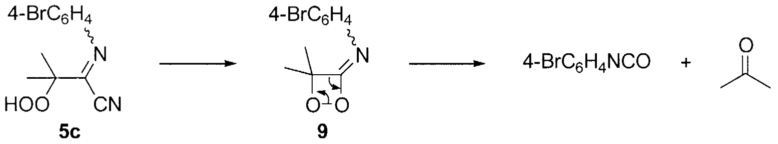
Scheme 2.

by recrystallization. However, compounds **5b**–**d** and **5g**–**i** were sticky solids, whose structures were identified by conversion to the corresponding peroxides **8b**–**d** and **8g**–**i**, respectively (Scheme 3), which gave satisfactory spectroscopic (NMR, IR) and analytical data.



Scheme 3.

Compounds **5** undergo slow decomposition in the air. For example, compound **5c** (R^1=R^2=Me, Ar=4-BrC_6H_4) showed several spots on TLC (R_f=0.35, *n*-hexane:EtOAc=5:1) in a few days (Scheme 4). The GC-MS data of the mixture exhibited a fragment with *m/z* 197, corresponding to the molecular weight of 4-bromophenylisocyanate, where the retention time was identical to that of the authentic sample. This result may be rationalized based on an intramolecular cyclization of **5c** to give 4,4-dimethyl-*N*-(4-bromophenyl)imino-1,2-dioxetane **9**, which subsequently undergoes decomposition to yield 4-bromophenylisocyanate and acetone. Analogous reactions have been reported for the formation of alkylisocyanates and carbonyl compounds from decomposition of 4-substituted 3-alkylimino-1,2-dioxetanes.[3a,b]



Scheme 4.

In summary, apart from 2-alkylamino-2-alkenenitriles, 2-arylamino-2-alkenenitriles undergo slow autoxidation to give their α-hydroperoxy-*N*-arylimidoyl cyanides. Some of them are isolable in crystalline states. Since the hydroperoxides undergo slow decomposition via *N*-arylimino-4,4-dimethyl-1,2-dioxetanes, they may be useful model compounds for further study of the working of natural bioluminescent systems.

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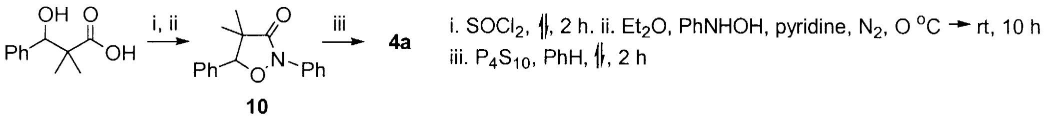

i. $SOCl_2$, ⥮, 2 h. ii. Et_2O, PhNHOH, pyridine, N_2, O °C → rt, 10 h
iii. P_4S_{10}, PhH, ⥮, 2 h

6. Typical procedure: To a solution of **4a** (386 mg, 1.36 mmol) in toluene (10 mL) was added Et_2AlCN (8.24 mmol, 1 M solution/toluene, 8.24 mL) under a nitrogen atmosphere. The mixture was heated for 9 h at reflux, followed by addition of water (1 mL) to the cooled reaction mixture. The white solids formed were filtered and washed with CH_2Cl_2 (50 mL×3). The filtrate was dried over $MgSO_4$. Evaporation of the solvent, followed by chromatography (silica gel, 70–230 mesh, 2×20 cm) of the residue with benzene gave 3-methyl-2-phenylamino-2-butenenitrile **3a** (96 mg, 41%): mp 61–63°C (*n*-hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86 (s, 3H, Me), 2.12 (s, 3H, Me), 4.87 (s, br, 1H, NH), 6.66 (d, 2H, J=8.4 Hz, ArH), 6.84 (t, 1H, J=8.0 Hz, ArH), 7.23 (t, 2H, J=8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.22, 22.03, 108.76, 114.23, 116.43, 119.98, 129.36, 143.81, 150.02; IR (KBr) 3360, 2208 (CN), 1633 cm^{-1}; MS (EI) *m/z* 172 (M^+, 100), 157 ($M^+{-}Me$, 89). Anal. calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.65; H, 7.12; N, 16.23.
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9. Crystalline compound **3a** (100 mg, 0.58 mmol) was dissolved in chloroform (10 mL). The conversion was monitored by TLC. The spot corresponding to **3a** (R_f=0.45, CH_2Cl_2) completely disappeared in 44 h. After removal of the solvent, ^1H and ^{13}C NMR spectra of the residue **5a** were taken. The ^1H and ^{13}C NMR spectra of **5a**–**j** were recorded at 300 and 75 MHz, respectively, in $CDCl_3$. Compound **5a**: mp 53–55°C (*n*-hexane–CH_2Cl_2); ^1H NMR δ 1.63 (s, 6H, 2Me), 7.09 (d, 2H, J=7.5 Hz, ArH), 7.32 (t, 1H, J=7.4 Hz, ArH), 7.44 (t, 2H, J=7.4 Hz, ArH), 8.86 (s, br, 1H, OOH); ^{13}C NMR δ 22.17, 84.96, 110.29, 120.05, 127.61, 129.26, 147.59, 147.70; IR (KBr) 3250, 2224 (CN), 1625 cm^{-1}. Anal. calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.86; H, 6.13; N, 13.92. Compound **5b**: sticky; ^1H NMR δ 1.61 (s, 6H, 2Me), 7.05 (dt, 2H, J=8.7, 2.0 Hz, ArH), 7.40 (dt, 2H, J=8.7, 2.0 Hz, ArH), 8.89 (s, br, 1H, OOH); ^{13}C NMR δ 22.11, 84.95, 110.15, 121.57, 129.43, 133.27, 146.15, 148.26; IR (neat) 3384, 2216 (CN), 1626 cm^{-1}. Compound **5c**: sticky; ^1H NMR δ 1.60 (s, 6H, 2Me), 6.97 (d, 2H, J=8.6 Hz, ArH), 7.55 (d, 2H, J=8.6 Hz, ArH), 8.93 (s, br, 1H, OOH); ^{13}C NMR δ 22.17, 84.97,

110.18, 121.19, 121.84, 132.44, 146.79, 148.42; IR (neat) 3384, 2216 (CN), 1632 cm^{-1}. Compound **5d**: sticky; ^{1}H NMR δ 1.61 (s, 6H, 2Me), 2.38 (s, 3H, Me), 6.81–6.91 (m, 2H, ArH), 7.11 (d, 1H, J=7.8 Hz, ArH), 7.31 (t, 1H, J=7.5 Hz, ArH), 9.04 (s, br, 1H, OOH); ^{13}C NMR δ 21.26, 22.15, 84.87, 110.30, 116.87, 120.63, 128.30, 129.06, 139.23, 147.38, 147.78; IR (neat) 3384, 2216 (CN), 1626 cm^{-1}. Compound **5e**: mp 61–63°C (*n*-hexane–CH_2Cl_2); ^{1}H NMR δ 1.59 (s, 6H, Me), 2.35 (s, 3H, Me), 7.03 (d, 2H, J=8.3 Hz, ArH), 7.20 (d, 2H, J=8.3 Hz, ArH), 9.24 (s, br, 1H, OOH); ^{13}C NMR δ 21.08, 22.18, 84.87, 110.58, 120.35, 129.80, 137.83, 145.19, 146.71; IR (KBr) 3408, 2208 (CN), 1626 cm^{-1}. Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.01; H, 6.41; N, 12.89. Compound **5f**: mp 54–57°C (*n*-hexane–CH_2Cl_2); ^{1}H NMR δ 1.62 (s, 6H, 2Me), 2.19 (s, 3H, ArMe), 6.86–6.92 (m, 1H, ArH), 7.15–7.29 (m, 3 H, ArH), 8.98 (s, br, 1H, OOH); ^{13}C NMR δ 17.62, 22.22, 84.93, 110.25, 117.72, 126.69, 127.36, 129.52, 130.72, 147.01, 147.83; IR (KBr) 3384, 2216 (CN), 1634 cm^{-1}. Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.98; H, 6.43; N, 12.81. **5g**: sticky; ^{1}H NMR δ 1.60 (s, 6H, 2Me), 3.82 (s, 3H, OMe), 6.94 (dt, 2H, J=9.0, 2.1 Hz, ArH), 7.22 (dt, 2H, J=9.0, 2.1 Hz, ArH), 9.20 (s, br, 1H, OOH); ^{13}C NMR δ 22.22, 55.44, 84.91, 111.04, 114.31, 122.74, 140.31, 144.48, 159.48; IR (neat) 3441, 2214 (CN), 1622 cm^{-1}. Compound **5h**: sticky; ^{1}H NMR δ 0.97 (t, 6H, J=7.5 Hz, 2Me), 1.88–2.12 (m, 4H, 2CH_2), 7.05 (t, 2H, J=7.8 Hz, ArH), 7.27 (t, 1H, J=7.5 Hz, ArH), 7.41 (t, 2H, J=7.6 Hz, ArH), 9.23 (s, br, 1H, OOH); ^{13}C NMR δ 7.00, 23.94, 89.43, 110.43, 119.83, 127.23, 129.14, 148.03, 148.12; IR (neat) 3360, 2208 (CN), 1622 cm^{-1}. Compound **5i**: sticky; ^{1}H NMR δ 1.00 (t, 6H, J=7.5 Hz, 2Me), 1.58 (s, 6H, 2Me), 1.80–2.05 (m, 4H, 2CH_2), 2.36 (s, 6H, 2Ar*Me*), 7.02 (d, 4H, J=8.3 Hz, 2ArH), 7.21 (d, 4H, J=8.3 Hz, 2ArH), 9.06 (s, br, 2H, 2OOH); ^{13}C NMR δ 7.42, 18.87, 21.02, 28.32, 87.33, 110.68, 120.25, 129.76, 137.74, 145.28, 146.81; IR (neat) 3360, 2208 (CN), 1616 cm^{-1}. Compound **5j**: mp 85–86°C (*n*-hexane); ^{1}H NMR δ 1.23–1.44 (m, 1H, C*H*H), 1.52–1.75 (m, 5H, methylene), 1.76–1.96 (m, 2H, CH_2), 2.02–2.20 (m, 2H, CH_2), 7.06 (d, 2H, J=8.1 Hz, ArH), 7.27 (t, 1H, J=7.5 Hz, ArH), 7.40 (t, 2H, J=7.7 Hz, ArH), 9.38 (s, br, 1H, OOH); ^{13}C NMR δ 20.99, 24.85, 30.30, 85.60, 110.30, 119.93, 127.36, 129.13, 147.95, 148.17; IR (KBr) 3352, 2216 (CN), 1626 cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60, N, 11.47. Found: C, 68.80; H, 6.62; N, 11.43.

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