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A new convenient synthesis of aroyl cyanides via the formation of cyanohydrin nitrate intermediates

Takuya Sueda *, Masashi Shoji, Kiyoharu Nishide

Faculty of Pharmaceutical of Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure City, Hiroshima 737-0112, Japan

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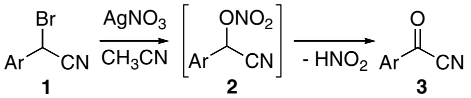
ABSTRACT

The treatment of α-bromoarylacetonitriles with $AgNO_3$ generates cyanohydrin nitrate intermediates, which easily eliminate nitrous acid with the formation of carbonyl bond to afford aroyl cyanides in good to high yields.

Organonitrates have been widely used in explosives, propellants, and medications for heart conditions; however, there has been little utilization of organonitrates in organic synthesis.[1] On the basis of similarities in the kinetics of alkyl nitrates and alkyl halides, it has been proposed that the nitrate group acts as pseudohalides.[2] On the other hand, a reaction of special interest is the elimination of α-hydrogen, which results in carbenes for alkyl halides but in carbonyl compounds for alkyl nitrates.[3] We report here that α-hydrogen elimination of cyanohydrin nitrates **2** generated from the reaction of the corresponding α-bromoarylacetonitriles **1** with $AgNO_3$ proceeds smoothly to give aroyl cyanides **3** in high yields (Scheme 1).

Acyl cyanides are versatile synthetic intermediates and have been utilized in a variety of transformations of CO and CN functions,[4] and Sharpless recently reported that cycloaddition of azide to aroyl cyanides gives aroyltetrazols in high yields.[5] Generally, acyl cyanides have been prepared from reactions of acid halides with a variety of metal cyanides. These reactions often produce acyl cyanide dimers as well as acyl cyanides in substantial quantities because of their strong carbonyl activities. Therefore, many modifications have been reported and have led to some improvements.[6] An alternative method is the oxidation of cyanohydrins with MnO_2, PDC, and $RuCl_2(PPh_3)_3$/*tert*-BuOOH.[7] Our present study provides a new and convenient synthetic route to aroyl cyanides **3** starting from α-bromoarylacetonitriles **1**, which are easily available from the reaction of arylacetonitriles with *N*-bromosuccinimide.[8]



Scheme 1. Aroyl cyanides from the reaction of α-bromoarylacetonitriles with $AgNO_3$.

Acetone cyanohydrin nitrate has been synthesized from the reaction of acetone cyanohydrin with fuming HNO_3/Ac_2O and used as a nitrating reagent of amines.[9] We tried to synthesize a hitherto unknown benzaldehyde cyanohydrin nitrate, α-nitrooxyphenylacetonitrile **2a**, from the nucleophilic substitution reaction of α-bromophenylacetonitrile **1a** with $AgNO_3$ in CH_3CN at room temperature. Surprisingly, benzoyl cyanide **3a** was obtained in 59% yield and a small amount of **2a** was observed in the ^1H NMR spectrum of the reaction crude product (Table 1, entry 1). Generally, elimination of α-hydrogen from organonitrates requires the use of bases or strong acid.[10] To the best of our knowledge, this is the first report of the direct synthesis of aroyl cyanides **3** from the corresponding α-bromoarylacetonitriles **1**.[11] Our efforts were directed toward finding the optimal conditions for the direct conversion of **1a** into **3a**. Increased equivalent of $AgNO_3$ and prolonged reaction times lead to no improvement in the yield of **3a** (Table 1, entries 2–3). Furthermore, when the reaction was performed under basic conditions, no desired product was obtained at all (Table 1, entries 4–6). Finally, this was settled by heating the reaction mixture, and when **1a** was treated with 1.3 equiv of $AgNO_3$ in CH_3CN at 50 °C for 5 h, **3a** was obtained in 80% yield (Table 1, entry 8).

The scope and limitations of the reaction with α-bromoarylacetonitriles **1** were also examined, and the results are shown in Table 2.[12] Various functional groups such as ether, alkyl, halogen,

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* Corresponding author. Tel./fax: +81 82 373 8933.
E-mail address: t-sueda@ps.hirokoku-u.ac.jp (T. Sueda).

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Table 1
Reactions of α-bromophenylacetonitrile (**1a**, Ar = Ph) with $AgNO_3$[a]

Entry	Equivalent		Conditions	Yields[b] (%)		
	$AgNO_3$	Additive		**2a**	**3a**	**1a**[c]
1	1.1	—	rt, 2 h	3	59	39
2	1.5	—	rt, 24 h	7	57	14
3	2.0	—	rt, 2 h	48	39	0
4	1.3	$(i\text{-Pr})_2NEt$ (1.3)	rt, 5 h	0[d]	0	0
5	1.3	K_2CO_3 (1.3)	rt, 5 h	0	0	55
6	1.3	Ag_2O (1.3)	rt, 5 h	0[d]	0	0
7	1.1	—	50 °C, 5 h	4	62	4
8	1.3	—	50 °C, 5 h	2	80	0
9	1.5	—	50 °C, 5 h	2	76	0

[a] Reactions were carried out using **1a** (0.1 mmol), $AgNO_3$, and additive in CH_3CN (1 ml) under N_2.
[b] Determined by analysis of the ^1H NMR spectra of the reaction crude.
[c] Recovered yield.
[d] Complex mixture.

Table 2
Aroyl cyanides (**3**) from the reaction of α-bromoarylacetonitriles (**1**) with $AgNO_3$ at 50 °C[a]

Entry			$AgNO_3$	Time (h)	Yield[b] (%)	
	Ar	**1**			**3**	**1**[c]
1	Ph	**1a**	1.3	5	**3a** (79)	0
2	p-$MeOC_6H_4$	**1b**	1.3	5	**3b** (81)	0
3	p-MeC_6H_4	**1c**	1.3	5	**3c** (83)	0
4	p-BrC_6H_4	**1d**	1.3	5	**3d** (84)	0
5	p-$MeOC(O)C_6H_4$	**1e**	1.3	5	**3e** (72[d])	**1e** (8[d])
6	p-$MeOC(O)C_6H_4$	**1e**	2.0	5	**3e** (82)	0
7	m-$MeOC_6H_4$	**1f**	1.3	5	**3f** (84)	0
8	m-MeC_6H_4	**1g**	1.3	5	**3g** (75)	0
9	m-BrC_6H_4	**1h**	1.3	5	**3h** (65[d])	**1h** (31[d])
10	m-BrC_6H_4	**1h**	1.3	10	**3h** (78[d])	**1h** (12[d])
11	m-BrC_6H_4	**1h**	2.0	10	**3h** (75)	0
12	m-$MeOC(O)C_6H_4$	**1i**	1.3	5	**3i** (71[d])	**1i** (17[d])
13	m-$MeOC(O)C_6H_4$	**1i**	2.0	5	**3i** (68)	0
14	o-$MeOC_6H_4$	**1j**	1.3	5	**3j** (85)	0
15	o-MeC_6H_4	**1k**	1.3	5	**3k** (86)	0

[a] See Ref. 12.
[b] Isolated yields.
[c] Recovered yields.
[d] Determined by analysis of the ^1H NMR spectra of the reaction crude.

Table 3
Selective formation of α-nitrooxyphenylacetonitrile[a]

Entry	**1**	Conditions	Yields[b] (%)		
			2	**3**	**1**[c]
1	**1a**	−20 °C, 24 h	**2a** (18)	**3a** (0)	**1a** (70)
2	**1a**	0 °C, 10 h	**2a** (81)	**3a** (0)	**1a** (0)
3	**1a**	0 °C, 5 h	**2a** (25[d])	**3a** (60)	**1a** (0)
4	**1b**	−20 °C, 2 h	**2b** (93[d])	**3b** (0)	**1b** (0)

[a] Reactions were carried out using **1** (0.1 mmol) and $AgNO_3$ (0.11 mmol) in CH_3CN (1 ml) under N_2, except for entry 3 (10-fold scale) and entry 4 (50-fold scale).
[b] Determined by analysis of the ^1H NMR spectra of the reaction crude.
[c] Recovered yield.
[d] Isolated yield.

Table 4
Conversion of cyanohydrin nitrate intermediates (**2**) into the corresponding aroyl cyanides (**3**)[a]

Entry	**2**	Additive (equiv)	Yields[b] (%)	
			3	**2**[c]
1	**2a**	—	**3a** (51)	**2a** (35)
2	**2b**	—	**3b** (17)	**2b** (64)
3	**2b**	AgBr (1.0)	**3b** (18)	**2b** (82)
4	**2b**	$AgNO_3$ (0.3)	**3b** (100)	**2b** (0)
5	**2b**	$Bu_4N^+NO_3^-$ (0.3)	**3b** (100)	**2b** (0)
6	**2b**	K_2CO_3 (1.0)	**3b** (84)	**2b** (4)
7	**2b**	$(i\text{-Pr})_2NEt$ (1.0)	**3b** (80)	**2b** (5)
8	**2b**	Alumina, N (50 mg)	**3b** (37)	**2b** (60)
9	**2b**	Alumina, B (50 mg)	**3b** (50)	**2b** (23)
10	**2b**	Aluminam B (100 mg)	**3b** (100)	**2b** (0)
11	**2b**	4 Å MS (50 mg)	**3b** (83)	**2b** (0)

[a] Reactions were carried out using **2** (0.1 mmol) in CH_3CN (1 ml) at 50 °C for 5 h under N_2.
[b] Determined by analysis of the ^1H NMR spectra of the reaction crude.
[c] Recovered yield.

and ester on the phenyl ring survived under the reaction conditions. The rate of reaction, however, was affected by the electronic nature of the substituents. Electron-donating substituents such as MeO and Me gave the corresponding aroyl cyanides in good yields, which were independent of any position on the phenyl ring. On the other hand, electron-withdrawing groups decreased the rate of the reaction. For example, when bromo(3-bromophenyl)acetonitrile **1h** was treated with 1.3 equiv of $AgNO_3$ at 50 °C for 5 h, 31% of **1h** was recovered (Table 2, entry 9). Since no nitrate intermediate **2h** was observed, the decreased rate of the reaction is probably caused by the lower reactivity of **1h** toward $AgNO_3$.

We then turned our attention to isolation of α-nitrooxyphenylacetonitrile. As shown in entry 1 of Table 3, the reaction at −20 °C afforded **2a** selectively, although a large amount of the starting **1a** was recovered. The selective formation of **2a** was also performed at elevated reaction temperature (Table 3, entry 2). However, it seems that **2a** is relatively unstable, which resulted in a low isolation yield (Table 3, entry 3).[12] The electron-donating substituents appear to accelerate the formation of cyanohydrin nitrates and stabilize them. Thus, **2b** was selectively synthesized at −20 °C in high yield and no aroyl cyanide was observed (Table 3, entry 4).

α-Nitrooxyphenylacetonitrile **2a** was directly converted into benzoyl cyanide **3a** by heating at 50 °C in CH_3CN for 5 h in 51% yield (Table 4, entry 1). **2b** was converted only in 17% yield under similar conditions (Table 4, entry 2). Thus, heating at 50 °C did not lead to complete conversion of cyanohydrin nitrates **2** to aroyl cyanides **3**. Table 4 shows the reaction of cyanohydrin nitrates **2** under various reaction conditions. No effect was observed for the addition of AgBr, which was produced in situ via nucleophilic substitution of α-bromoarylacetonitriles **1** with $AgNO_3$ (Table 4, entry 3). On the other hand, addition of a catalytic amount of $AgNO_3$ gave aroyl cyanide **3b** exclusively (Table 4, entry 4). A similar result was obtained with tetrabutylammonium nitrate (Table 4, entry 5). These results suggest that there is a mechanism involving intermediate formation of cyanohydrin nitrates **2** followed by elimination of nitrous acid to give aroyl cyanides **3**. **3b** was also obtained from the reactions with various species listed in Table 4.

When benzyl nitrate was heated at 50 °C in CH_3CN for 24 h in the presence of $AgNO_3$, benzaldehyde was not detected and the starting nitrate ester was recovered quantitatively.[10] Furthermore, α-nitrooxydecanenitrile was not converted into the corresponding acyl cyanide under similar conditions.[13] These differences in the reactivity of nitrate esters for the elimination reactions of nitrous acid should be due to the acidity of α-proton.[14] We computed the proton affinity for the organonitrates examined in this study.[15] The effects of the electron-withdrawing CN group and conjugating aromatic substituents actually resulted in much lower proton affinity (Table 5).

In conclusion, we have shown that various aroyl cyanides can be prepared directly from α-bromoarylacetonitriles. Our procedure involving the generation of organonitrates might be applicable to the synthesis of reactive carbonyl compounds involving adjacent electron-withdrawing and conjugating groups.

Selected spectroscopic data. For **2a**: mp = 68–70 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.45 (m, 5H), 6.36 (s, 1H); ^{13}C NMR

Table 5
Relative proton affinity ($RR'C^-ONO_2 \rightarrow RR'C(H)ONO_2$)[a]

R	R′	B3LYP/6-311+G(2d,p)	MP2/6-311+G(2d,p)
Ph	H	+34.59	+31.82
Me	CN	+20.19	+19.38
Ph	CN	0	0
p-$MeOC_6H_4$	CN	+4.17	+3.45

[a] All values (in kcal/mol) are calculated for 298 K and 1 atm. Enthalpies were calculated by using HF/6-31+G(d) optimized geometry.

(150 MHz, $CDCl_3$) δ 131.6, 129.6, 128.7, 127.7, 114.2, 71.0; IR ($CHCl_3$) 1668, 1281, 1263, 827 cm^{-1}; HRMS Calcd for $C_8H_6N_2O_3$: 178.0378. Found: 178.0381; Anal. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 53.55; H, 3.51; N, 15.48. For **2b**: mp = 45–46 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.29 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.1, 130.6, 119.4, 114.9, 114.4, 70.9, 55.5; IR ($CHCl_3$) 1665, 1283, 1256, 833 cm^{-1}; HRMS Calcd for $C_9H_8N_2O_4$: 208.0484. Found: 208.0482; Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.08; H, 3.96; N, 13.36.

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