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EFFICIENT SYNTHESIS OF *N*-ALKYLFORMIMIDOYL CYANIDES

Alvise Perosa, Maurizio Selva, * Pietro Tundo

Dipartimento di Scienze Ambientali dell'Università Cà Foscari di Venezia

Calle Larga S. Marta 2137, 30123 – Venezia

Fax: +39 041 2578620

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Abstract: *N*-Alkylformimidoyl cyanides (RRCHN=CHCN, **1**) were obtained through a very efficient oxidation of *N*-alkylaminoacetonitriles ($RRCHNHCH_2CN$, **2**) by aq. NaOCl. The reaction was run under very mild and simple conditions and afforded products (as *E/Z* isomer mixtures; *E/Z* ratio of 70-99%) in short reaction times (30-180 min), and in good to excellent yields (67-97%).

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N-Alkylformimidoyl cyanides (RRCHN=CHCN, **1**) were introduced as a new family of compounds in 1970. [1a] Their synthesis was accomplished through a two-step sequence involving *N*-chlorination of secondary amines ($RR'CHNHCH_2CN$, **2**) with both *t*-butyl or calcium hypochlorite, followed by dehydrochlorination with a base (Scheme 1). [1]

$$\underset{\mathbf{2}}{RR'CHNHCH_2CN} \xrightarrow{\text{i}} RR'CHN(Cl)CH_2CN \xrightarrow{\text{ii}} \underset{\mathbf{1}}{RR'CHN{=}CHCN}$$

Scheme 1. i: *t*-BuOCl or $Ca(OCl)_2$, CH_2Cl_2; ii: $Ca(OH)_2$, CH_2Cl_2

As a part of our research project on the reactivity of cyano-functionalized ketimines, [2] we were interested in derivatives **1** as double bond isomers of *N*-(1-arylalkylidene)cyanomethyl amines [$RR'C{=}NCH_2CN$, **3**]. However, the synthetic procedure of Scheme 1 shows several drawbacks: i) a week was required for each N-alkyl formimidoyl cyanide to be isolated, ii) *N*-chloroderivatives of reactant amines **2** needed to be isolated, and iii) the reaction temperature had to be carefully controlled to optimize yields (in the range of 25-70%). Alternative methods *via* the dehydrogenation of **2** with diethyl azodicarboxylate did not overcome such problems: *N*-*t*-butyl formimidoyl cyanide was obtained in a 72% yield after 8 days at 28 °C; moreover, the reaction was not successful for other secondary amines. [1b]

We wish to report here that the overall oxidation of **2** to **1** can be carried out as a one-pot reaction under very mild and simple conditions, using a commercial aqueous solution of NaOCl (Table).

* e-mail: selva@unive.it

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Table. *N*-alkylformimidoyl Cyanides by Oxidation of *N*-alkylaminoacetonitriles with NaOCl. [a]

$$\underset{\mathbf{2}}{RR'CHNHCH_2CN} \longrightarrow \underset{\mathbf{1}}{RR'CHN{=}CHCN}$$

Entry	Substrate, **2**		Conv'n (%)	Reaction Time (min)	Products, % Composition of reaction mixture		Yield, %
	R	R'			**1** (*E*/*Z*, %)[b]	RR'C=NCH$_2$CN	
1	**2a**: CH_3	CH_3	98	30	**1a**: 98 (99)		67
2	**2b**: CH_3	Et	93	45	**1b**: 93 (92)		70
3	**2c**: *t*-Bu		96	60	**1c**: 96 (99)		90
4	**2d**: cHex		99	50	**1d**: 98 (80)		75
5	**2e**: Ph	H	100	50	**1e**: 90 (67)	**3e**: 10	97
6	**2f**: Ph	CH_3	90	180	**1f**: 88 (70)	**3f**: 2	76
7	**2g**: Ph	Ph	85	140	**1g**: 25 (nd [c])	**3g**: 60	nd [c]

[a] All reactions were performed using an aqueous solution of NaOCl (1.5 M; 1.5 molar equiv. with respect to substrate). [b] Ratio of N=C bond isomers (*E*,*Z*) determined by ^{1}H NMR. [c] Not determined

In a typical experiment, *N*-*t*-butylaminoacetonitrile **2c** [3-8] (1 g, 8.9 mmol; entry 4) was added dropwise to a vigorously stirred aqueous solution of NaOCl (1.5 M; 10-13% available chlorine; 1.5 molar equiv. with respect to **2c**), the reaction temperature being kept below 10 °C. The reaction was followed by both GC and GC/MS and after 1 h, it showed that 95% conversion was reached with the formation of *N*-*t*-butyl formimidoyl cyanide **1c** as the sole product. The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, and, after filtration, ether was carefully removed under vacuum. Product **1c** was isolated in a 90% yield as a pale yellow liquid. The structure of the product was confirmed by ^{1}HNMR, GC/MS, and IR spectral data.[9] The product rapidly darkened on standing even when stored at –18 °C. The reaction of **2c** (1 g) was also repeated using commercial household bleach (5% available chlorine, 1.5 molar equiv. with respect to **2c**): after 50 min, work up of the mixture gave **1c** in a 81 % yield. In the case of the solid amine $Ph_2CHNHCH_2CN$ (**2f**; entry 7), the reaction was run dissolving **2f** (0.5 g) in dioxane (4 mL). When used neat, no reaction took place at all.

As indicated in the Table, all compounds **2** except **2f**, were oxidized cleanly to the corresponding derivatives **1** with good to excellent yields (67-97%) and short reaction times (30-180 min). In fact, the reaction of secondary amines such as piperidine or morpholine, with aq. NaOCl is reported to yield the corresponding

N-chloroamine derivatives; [10] and, only further treatment with a strong base (KOH) allowed dehydrochlorination to take place.[10a] This different reactivity was ascribed to the higher acidity of the α-methylene protons of **2** (with respect to simple secondary amines) which permitted the elimination to occur in a relatively weak basic solution (NaOCl 1.5 M, pH ≈ 9). In addition, for compounds **2**, the *N*-chlorination and dehydrochlorination sequence were probably concerted, since even at low conversion, no trace of *N*-chloro derivatives of **2** were observed.

As far as the structures of products **1** were concerned, ^{1}H NMR and NOE analyses revealed the presence of both *E* and *Z* isomers (as expected, *E* was predominant), though for **1a** and **1c** (entry 1 and 3), the formation of *E* isomers was nearly quantitative (99%). [9] In the Table, the *E/Z* ratio (%) is shown in parentheses. Moreover, the orientation of the double bond was affected by the presence of aryl groups. In the case of amines **2e-f**, the reaction showed the formation of minor amounts of the corresponding *N*-(1-arylalkylidene)-cyanomethyl amines (**3e** and **3f**: 10 and 2%, respectively; entry 5-6); while, the effect was much more evident for the diphenylmethyl derivative **2g** that gave **3g** as the major product (60%; entry 7). Both the aryl anchimeric assistance to elimination and/or the conjugation of the C=N bond with benzene rings could be taken into account for these results.

In conclusion, we have shown here that a very convenient methodology for the oxidation of *N*-alkyl aminoacetonitriles **2** to *N*-alkylformimidoyl cyanides **1** can be attained by using aq. NaOCl The reactions are very rapid, require no organic solvents, and products can be isolated in good to excellent yields. The experimental procedure are safe, simple and inexpensive as are the work-ups of the reaction mixtures.

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3 *N*-Alkylaminoacetonitriles **2a-g** were prepared according to established procedures. [1, 4] Characterization data were in agreement to those reported in the literature: R = R' = Me, **1a**; [1] R = Me, R' = Et, **1b**;[5] R~R' = *t*-Bu, **1c**; [1] R~R' = Cy, **1c**; [6] R = Ph, R' = H, **1d**; [7-8] R = Ph, R' = Me, **1e**. [5] R = R' = Ph, **1g**. white solid product, mp = 73-74.5 °C; ^{1}HNMR ($CDCl_3$) δ: 2.00 (brs, 1H, NH), 3.58 (s, 2H, CH_2CN), 5.10 (s, 1H, CH), 7.25-7.55 (m, 10H, 2Ph); GC/MS (70 ev) *m/z* (relative intensity): 222 (M^+, 19), 168 (12), 167 (70), 166 (13), 165 (39), 152 (21), 146 (11), 145 (100). 144 (19), 104 (39), 77 (17), 67 (24), 51 (11); IR (KBr): ν (cm^{-1}) 2243 (CN), 3342 (NH).

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9 **1a and 1c**: ^{1}H NMR were reported in ref. 1b; we observed only *E* isomers. **1a**: GC/MS (70 ev) *m/z* (relative intensity): 110 (M^+, 2), 95 (45), 78 (9), 68 (80), 57 (100), 53 (13), 41 (56), 39 (22). **1c**: GC/MS (70 ev) *m/z* (relative intensity): 98 (M^+, 2), 83 (91), 56 (100), 42 (18), 41 (15), 39 (11). Both products rapidly darkened on standing even when stored at –18 °C.

1b, (*E/Z* = 92%): bp = 66-69 °C, 20 mm; ^{1}H NMR ($CDCl_3$) ***E***, δ: 0.82 (t, 3H, CH_3, J = 7.4 Hz), 1.22 (d, 3H, CH_3, J = 6.5 Hz), 1.60 (quintet, 2H, CH_2, J = 7.4 Hz), 3.26 (sextet, 1H, CH, J = 6.5 Hz), 7.35 (s, 1H, N=CH); ***Z***, δ: 0.85 (t, 3H, CH_3, J = 7.6 Hz), 1.24 (d, 3H, CH_3, J = 6.5 Hz), 1.61 (quintet, 2H, CH_2, J = 7.6 Hz), 3.78 (d sextet, 1H, CH, J = 6.5 Hz; J' = 1.4 Hz), 7.32 (d, 1H, N=CH, J = 1.4 Hz); GC/MS (70 ev) *m/z* (relative intensity): 110 (M^+, 1), 95 (18), 82 (16), 81 (100), 68 (13), 57 (22), 54 (44). The product rapidly darkened on standing.

1d, (*E/Z* = 70%): deliquescent solid recrystallized from *n*-pentane; ^{1}H NMR ($CDCl_3$) ***E***, δ: 1.33-1.84 (m, 10H, chex), 3.27 (tt, 1H, CH, J_{eq} = 4.1 Hz, J_{ax} = 10.3), 7.39 (s, 1H, N=CH); ***Z***, δ: 1.33-1.84 (m, 10H, Cy), 3.73 (ttd, 1H, CH, J_{eq} = 4.1 Hz, J_{ax} = 10.1, J' = 1.5 Hz), 7.29 (d, 1H, N=CH, J' = 1.5 Hz); GC/MS (70 ev) *m/z* (relative intensity): 136 (M^+, 1), 121 (14), 108 (20), 107 (69), 96 (29), 94 (14), 93 (39), 83 (76), 82 (100), 81 (37), 80 (28), 79 (18), 68 (31), 67 (39), 66 (44), 55 (28), 54 (20), 53 (37), 52 (15), 41 (38), 40 (10), 39 (50). IR (NaCl tablets) *E*, *Z*: ν (cm^{-1}) 2236, 2215 (C≡N), 1676, 1616 (C=N). The yellow solid turned to brown in 24 h, even when stored at + 4° C.

1e, (*E/Z* = 67%): pale yellow oil; ^{1}H NMR ($CDCl_3$) ***E***, δ: 4.87 (d, 2H, CH_2, J = 2.0 Hz), 7.24-7.38 (m, 5H, Ph and 1H, N=C**H**); ***Z***, δ: 5.01 (d, 2H, CH_2, J = 2.5 Hz), 7.24-7.38 (m, 5H, Ph and 1H, N=C**H**); GC/MS (70 ev) *m/z* (relative intensity): 144 (M^+, 17), 92 (10), 91 (100), 89 (10), 65 (15). IR (NaCl tablets) *E*, *Z*: ν (cm^{-1}) 2222 (C≡N), 1688, 1650, 1624 (C=N). The initially pale yellow liquid rapidly darkened upon standing.

1f, (*E/Z* = 70%): colorless oil; ^{1}H NMR ($CDCl_3$) ***E***, δ: 1.59 (d, 3H, CH_3, J = 6.6 Hz), 4.59 (q, 1H, CH, J = 6.6 Hz), 7.29-7.39 (m, 5H, Ph and 1H, N=C**H**); ***Z***, δ: 1.59 (d, 3H, CH_3, J = 6.6 Hz), 5.04 (q, 1H, CH, J = 6.6 Hz, J' = 1.0 Hz), 7.29-7.39 (m, 5H, Ph and 1H, N=C**H**); GC/MS (70 ev) *m/z* (relative intensity): 158 (M^+, 6), 116 (20), 106 (10), 105 (100), 103 (12), 79 (12), 77 (21), 51 (9). IR (NaCl tablets) *E*, *Z*: ν (cm^{-1}) 2238, 2223 (C≡N), 1624, 1600 (C=N). The initially pale yellow liquid turned to brown in 24 h, even when stored at + 4° C. Characterization data of **3f** are in ref. 7

2g, not isolated: GC/MS (70 ev) *m/z* (relative intensity): 220 (M^+, 7), 168 (15), 167 (100), 166 (12), 165 (34), 152 (19), 116 (8), 89 (7), 77 (7), 51 (5).

3e: structure confirmed by independent synthesis of the product through the reaction of benzaldehyde and aminoacetonitrile hydrochloride. [8] Characterization data of **3f-g** were in ref. 2.

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