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Zinc-Promoted Reactions. 9.[1] The Fate of the Cyano Group in the Reduction of Simple Cyanoketones and N-Cyanoamines

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Abstract: The Zn/AcOH reduction of **1** leads only to the carbonyl reduction, while C-decyanation occurs in the case of **2**. The mechanism of the latter reaction is discussed. The N-decyanation of N-cyanoamines **3** and **4** involves an ionic mechanism, leading to N-acyl derivatives and isocyanic acid, the latter compound being ultimately reduced to formic acid.

Selective C-dehalogenation,[2] C-deacylation,[3,4] and C-desulfurization[5] were reported to occur when the correspondingly α-substituted ketones were treated with Zn powder in refluxing AcOH. These reactions, which practically do not affect the carbonyl function, can be interpreted in terms of a general mechanism involving a series of single electron transfers (SET).[6]

Zinc-promoted C-decyanation of α-cyanoketones was not described so far, albeit a few heterocyclic N-cyanoamines were reported to smoothly undergo reductive N-decyanation by treatment with Zn in aqueous AcOH.[7,8]

Aiming to verify the possibility that α-cyanoketones might undergo a Zn-promoted C-decyanation and also to investigate the mechanism of the above mentioned N-decyanation, we have studied the Zn/AcOH reduction of a few simple substrates like 3-oxo-3-phenylpropanenitrile, **1**, 2-oxo-2-phenylethanenitrile, **2**, 1-cyanopiperidine, **3**, and 1-cyanomorpholine, **4**.

RESULTS AND DISCUSSION

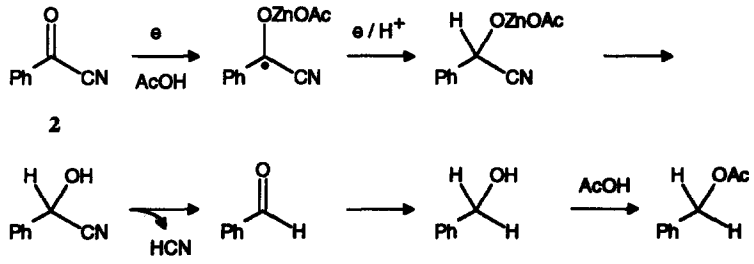
The reduction of cyanoketones **1** and **2** was studied under a variety of experimental conditions. The results reported in the Table show that the cyano group of **1** is completely resistant towards the action of zinc in anhydrous AcOH, while the carbonyl is mainly reduced to secondary alcohol or products derived therefrom. Noticeably, the presence of CF_3CO_2H gave a practically quantitative yield of $PhCH(OAc)CH_2CN$, while, as in the Zn/AcOH reduction of acetophenone, the presence of LiCl or dry HCl improved the full carbonyl reduction, reasonably through the intermediacy of chlorinated species.[9]

Table. Product Distribution in the Zn/AcOH Reduction of $PhCOCH_2CN$ (1) and PhCOCN (2) [a]

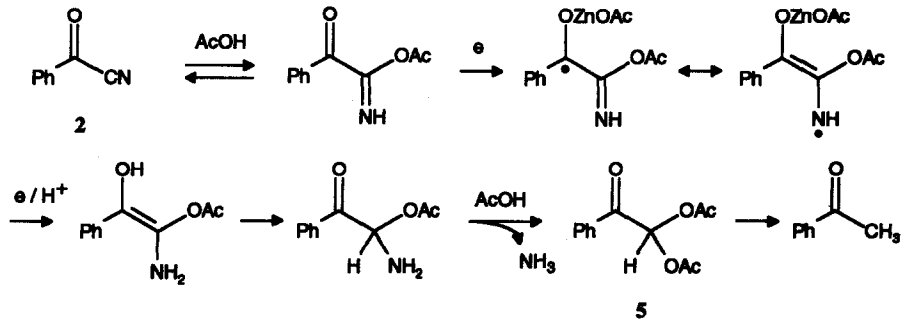
Substrate	Products	Coreagent			
		-	LiCl	TFA	HCl
1	$PhCH_2CH_2CN$	2	32	3	16
1	PhCH=CHCN	1	5	2	9
1	$PhCHOHCH_2CN$	41	23	-	-
1	$PhCH(OAc)CH_2CN$	56	40	95	75
2	$PhCH_2OH$	15	7	-	4
2	$PhCH_2OAc$	42	18	47	51
2	$PhCOCH_3$	20	3	16	2
2	$PHCH(OAc)CH_3$	13	19	23	21
2	$PhCH=CH_2$	-	17	11	15
2	$PhCH_2CH_3$	10	36	3	7

[a] Experimental conditions: 2 h at refluxing temperature. Conversion: 100%.

The reduction of **2** follows an entirely different course, involving two distinct pathways. The one leading to benzyl alcohol and its acetate simply requires the carbonyl reduction to 2-hydroxy-2-phenylethanenitrile, followed by cyanidrine breakdown, benzaldehyde reduction and acetylation.



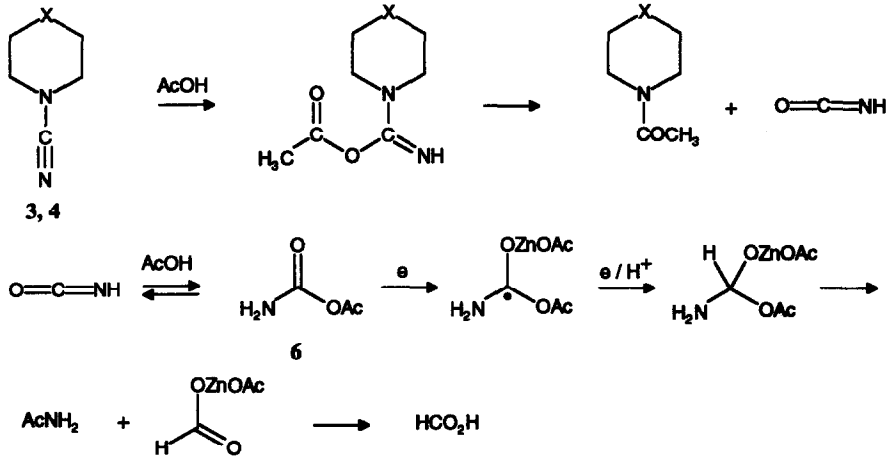
The other pathway, which leads to the full reduction of the cyano group, most probably involves the intermediate formation of acetophenone, the precursor of all the remaining products, as already reported in a previous paper.[9] However, the acetophenone formation most probably does not involve direct reduction of the cyano group, but rather a preliminary addition of the solvent, followed by reduction, according to the following mechanism.



In agreement with the above mechanism, which postulates that 2,2-diacetoxyacetophenone, **5**, is the acetophenone precursor, the Zn/AcOH reduction of an authentic sample of **5** gave $PhCOCH_3$, $PhCH(OAc)CH_3$, and $PhCH_2CH_3$. The deacetoxylation of α-acetoxyketones was already reported.[3,4]

As for the N-cyanoamines **3** and **4**, the Zn/AcOH reduction led to quantitative yield of 1-acetylpiperidine and 1-acetylmorpholine, respectively. During the reaction, performed in anhydrous medium, a crystalline Zn salt (highly soluble in aqueous AcOH) gradually separated from the hot solution. Analysis of this salt (m.p. 250°C with decomposition after repeated crystallisation from 98% AcOH) gave values for C, H, and Zn in fair agreement for a complex salt of formula $4Zn^{++} \cdot (HCOO^-)_4 \cdot (CH_3COO^-)_4 \cdot 4CH_3COOH$. The mass spectra of the salt, which is reported in the Experimental Section, support the above formulation.

The presence of formic acid as a constituent of the salt was confirmed by treating the crystals in boiling EtOH in the presence of traces of *p*-toluenesulfonic acid: the formation of ethyl formate was then ascertained by GLC analysis and GC/MS spectrometry in comparison with an authentic sample. It was then checked that piperidine and morpholine were not acetylated by refluxing in glacial AcOH even in the presence of $Zn(OAc)_2$, while **3** and **4** were quantitatively converted into the corresponding acetamides by simply refluxing in glacial AcOH. The latter result demonstrates that the N-decyanation of **3** and **4** does not occur through a reductive cleavage of the N-cyano bond, but rather through a purely ionic mechanism. The ionic pathway involves a preliminary AcOH addition to the cyano group, followed by an intramolecular transacetylation, isocyanic acid being the leaving group. The formation of formic acid may then be ascribed to Zn reduction of isocyanic acid (or its Zn salt).



Apparently, the above type of intramolecular transacetylation, reasonably involving a four membered transition state, is a rather general reaction. Thus, by refluxing phenyl and 1-naphthyl isocyanate in anhydrous AcOH, a quantitative yield of the corresponding acetamides was obtained. The intermediate formation of the mixed anhydride, analogous to **6**, was previously proposed, but it could not be isolated, due to its high reactivity.[10] Noticeably, in the above transacetylation, the leaving group was HCO_2H in the case of isocyanic acid, and CO_2 in the case of aryl isocyanate.

EXPERIMENTAL SECTION

Gas chromatographic analyses were carried out with a Carlo Erba HRGC 5300 Mega Series apparatus on 30 m × 0.25 mm i.d. × 0.33 μm SPB-35 column. GC/MS analyses were performed with a VG Quattro mass spectrometer on the same column. MS (70 eV) were performed with the same spectrometer. ^{1}H NMR spectra were recorded on a Bruker WP-80 spectrometer with $CDCl_3$ as the solvent.

Materials.

Anhydrous AcOH was prepared by refluxing (4 h) 99.8% AcOH (Merck) with Ac_2O (Merck). Stock solutions of approximately 0.3 M anhydrous HCl in AcOH were prepared by bubbling HCl gas in the solvent. 99% TFA (Aldrich) was used, without further purification, in 5% concentration. Compounds **1** - **4**, 1-naphthyl isocyanate, and phenyl isocyanate are commercial reagents (Aldrich).

General Procedure for the Reductions.

The reactions were performed in anhydrous AcOH in different systems at the refluxing temperature, using an approximately 1:3 molar ratio of substrate and zinc and occasionally in presence of 3 M anhydrous LiCl. A 0.2 M substrate was generally employed. The general work up was the following: the final mixture was diluted with three volumes CH_2Cl_2, filtered from unreacted zinc, repeatedly washed with H_2O and then with a saturated $NaHCO_3$ solution to remove AcOH; the residual CH_2Cl_2 solution, after drying over Na_2SO_4, was evaporated to dryness. GLC and GC/MS analyses of the residue were performed.

Product Distribution Analysis.

Identification of the products and their distribution in the crude reaction mixtures were accomplished by GLC, NMR, and GC/MS analyses and by comparison with commercial samples, when available. $PhCH(OH)CH_2CN$ was obtained by reduction of **1** with $NaBH_4$. $PhCH(OAc)CH_2CN$ was obtained by acetylation of $PhCHClCH_2CN$ with AcCl. $PhCHClCH_2CN$ was obtained by treating $PhCH(OH)CH_2CN$ with $SOCl_2$.

Synthesis of 2,2-Diacetoxyacetophenone.

4.60 G (3.86×10^{-2} moles) of $SOCl_2$ in 10 mL of benzene were slowly added to a suspension of 1.17 g (7.7×10^{-3} moles) of $PhCOCHO \cdot H_2O$ (Aldrich) in 10 mL of benzene under nitrogen atmosphere. When the substrate disappeared (GLC analysis) and the mixture became clear, the solution was evaporated and the residue dissolved in Ac_2O in the presence of AcONa. After 24 h at room temperature, the mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic layer, after solvent removal, was distilled with a Kugelrohr oven (oven temperature 150°C, 2 Torr). 0.97 G (4.1×10^{-3} moles) of $PhCOCH(OAc)_2$ were obtained. Yield 53%. ^{1}H NMR δ ($CDCl_3$): 8.30 - 6.97 (5H, m, C_6H_5); 3.35 (1H, br, CH); 2.20 (6H, s, $COCH_3$). MS of the product (EI, 70 eV) did not show the molecular ion.

Reduction of 3-Oxo-3-phenylpropanenitrile, **1**.

The reductions of **1** were performed according to the general procedure. Identification of the products

was made according to the following mass spectra. 3-Phenylpropanenitrile - M/z (%): 131 (42), 92 (11), 91 (100), 77 (16), 65 (29), 63 (12), 51 (15). 3-Phenylpropenenitrile - M/z (%): 129 (100), 103 (12), 102 (40), 78 (11), 76 (12), 51 (15), 50 (13). 3-Hydroxy-3-phenylpropanenitrile - M/z (%): 147 (3), 107 (100), 105 (15), 79 (92), 77 (68), 51 (25), 50 (10). 3-Acetoxy-3-phenylpropanenitrile - M/z (%): 189 (8), 162 (12), 149 (14), 147 (11), 146 (15), 130 (21), 129 (19), 120 (25), 107 (80), 105 (27), 103 (14), 102 (13), 79 (27), 77 (50), 51 (26), 43 (100).

Reduction of 2-Oxo-2-phenylethanenitrile, **2**.

The reductions of **2** were performed according to the general procedure. Identification of the products was made according to the following mass spectra. Acetophenone - M/z (%): 120 (44), 105 (100), 77 (88), 51 (41), 50 (18), 43 (19). Benzyl acetate - M/z (%): 150 (36), 108 (100), 91 (73), 90 (55), 89 (28), 79 (50), 77 (40), 65 (28), 63 (17), 51 (30), 50 (13), 43 (75). Benzyl alcohol - M/z (%): 108 (71), 107 (50), 91 (16), 79 (100), 77 (84), 51 (29). Phenylethane - M/z (%): 106 (38), 91 (100), 78 (10), 77 (13), 65 (13), 51 (13). Phenylethene - M/z (%): 104 (100), 103 (66), 78 (47), 77 (25), 63 (12), 52 (11), 51 (34), 50 (19). 1-Phenylethyl acetate - M/z (%): 164 (16), 122 (82), 107 (40), 105 (53), 104 (100), 79 (27), 78 (25), 77 (46), 51 (19), 43 (69).

Reduction of 1-Cyanopiperidine, **3**.

5 G (4.53×10^{-2} moles) of **3** were reduced with Zn (8 g) in anhydrous AcOH (200 mL) at refluxing temperature for 2 h. In order to detect any loss of unreacted volatile species, diphenylmethane was used as an internal standard. The hot crude mixture was filtered to remove zinc and cooled at room temperature. The white crystalline precipitate (4 g) was filtered. Evaporation of the solution yielded 100% of 1-acetyl-piperidine. - M/z (%): 128 (7), 127 (80), 112 (25), 99 (10), 98 (8), 84 (95), 70 (35), 57 (30), 56 (52), 55 (28), 54 (18), 53 (8), 44 (35), 43 (100), 42 (80), 41 (40).

The precipitate was repeatedly crystallised from 98% AcOH. M.p. 250°C with decomposition. Anal. Calcd for $C_{20}H_{32}O_{24}Zn_4$: C, 26.17; H, 3.51; Zn, 28.49. Found: C, 26.29; H, 3.28; Zn 27.9. M/z (%): 581 (5), 579 (10), 577 (50), 575 (78), 573 (100), 571 (95), 569 (60), 567 (25), 475 (5), 473 (7), 471 (10), 469 (10), 467 (5), 465 (3), 395 (5), 393 (10), 391 (28), 389 (37), 387 (28), 385 (15). The salt was also examined by positive ion FAB mass spectrometry in 2,2'-thiodiethanol matrix (Aldrich 99%). Samples were bombarded with 8 KV Cs beam from a standard VG FAB source. The spectrum shows several isotopic clusters due to the presence of four zinc atoms. We report only the highest peak of each cluster. M/z (%): $(M+Cs)^+$ 1049 (70), 1004 (40), 945 (72), 864 (78), 821 (45), 761 (40), 679 (100), 636 (43), 575 (60).

Reduction of 1-Cyanomorpholine, **4**.

5 G (4.46×10^{-2} moles) of **4** were reduced following the procedure described for **3**. 3 G of a crystalline product, identical with that obtained in the reduction of **3**, was obtained along with 94% of 1-acetylmorpholine and 6% 1-formylmorpholine. 1-Acetylmorpholine - M/z (%): 130 (8), 129 (20), 114 (17), 99 (5), 87 (12), 86 (30), 72 (15), 58 (10), 57 (80), 56 (50), 55 (10), 44 (15), 43 (100), 42 (50), 41 (20). 1-Formylmorpholine - M/z (%): 116 (5), 115 (80), 100 (75), 87 (12), 86 (35), 85 (10), 72 (20), 58 (20), 57 (80), 56 (90), 55 (10), 44 (40), 43 (43), 42 (100), 41 (20).

Reduction of 2,2-Diacetoxyacetophenone, 5.

The reductions of **5** were performed according to the general procedure. At refluxing temperature, $PhCH(OAc)CH_3$ was the only product; at room temperature, the product distribution was: 31% $PhCH_2CH_3$, 58% $PhCOCH_3$, 11% $PhCH(OAc)CH_3$.

Acetolysis of 1-Naphthyl Isocyanate.

The reaction was performed with 0.6 g of 1-naphthyl isocyanate in 5 mL of anhydrous AcOH in the presence of 0.36 g of $Zn(OAc)_2$ for 2 h at refluxing temperature. 100% of N-(1-naphthyl)acetamide was obtained. M/z (%): 186 (10), 185 (90), 143 (98), 140 (20), 126 (12), 116 (30), 115 (100), 113 (20), 89 (20), 62 (12), 51 (5), 43 (60).

Acetolysis of Phenyl Isocyanate.

The reaction was performed analogously to 1-naphthyl isocyanate. 100% of N-phenylacetamide was obtained. M/z (%): 135 (20), 94 (10), 93 (100), 77 (10) 67 (25), 65 (25), 63 (10).

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