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An Elimination Reaction of N-carbomethoxy-N,N-dimethylhydrazonium salts to Alkyl Nitriles

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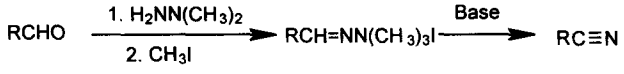
Abstract: A new kind of elimination of hydrazonium salts to alkyl nitriles has been developed. The reaction of hydrazones and chloroformates results in the formation of hydrazonium salts, which react *in situ* with water to afford alkyl nitriles. The elimination is adapted to a range of solvents and gives good yields of α-secondary and tertiary alkyl-substituted nitriles.

Introduction

The nitrile functional group is widely recognized as a useful intermediate in organic synthetic transformations.[1,2] A variety of synthetic methods for the introduction of the cyano group to organic compounds have been documented.[3] A general procedure for the preparation of nitriles involves the nucleophilic substitution of a leaving group with a metal cyanide. Organic halogen compounds, aryl sulphonates, alcohols, esters, ethers, nitro or amino compounds, and diazonium salts could be used as substrates suitable for this type of reaction. In most cases, the substitution reaction follows an S_N2 mechanism,[4] especially with primary halides. However, with secondary and tertiary alkyl halides, competition between substitution and elimination results in low yields of nitriles. A well known procedure more suitable for the synthesis of α-substituted nitriles involves the elimination reaction of N,N,N-trimethylhydrazonium salts and bases (Scheme 1).[5] First, the reaction of aldehydes and

Scheme 1



N,N-dimethylhydrazine with methyl iodide provides the desired hydrazonium salts, and then elimination of trimethylamine with bases (e.g. CH_3O^-/CH_3OH) yields the corresponding nitriles. Kinetic studies demonstrate that C-H bond cleavage is more advanced in the transition state than N-N bond breaking, but the eliminative process occurs through an E2 transition state.[6]

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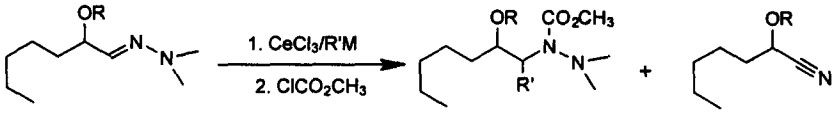
Results and Discussion

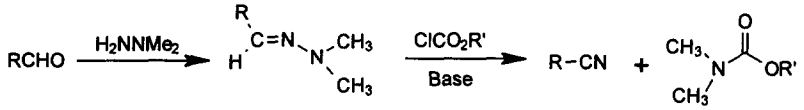
During our studies of the nucleophilic addition of organocerium reagents to α-alkoxyhydrazones, we found that some reactions resulted in the formation of nitriles (Scheme 2).[7] Our original assumption was that organocerium agents served as a base to facilitate elimination of N,N-dimethylcarbamate. However, further

Scheme 2



investigation showed that the elimination to nitriles occured in the absence of organocerium reagents or alkali base, thus prompting us to explore the scope and limitations of this facile elimination in terms of structure of hydrazones, the nature of bases, and solvents employed (Scheme 3). The results are outlined in Table 1.

Scheme 3



1a-l 2a-l 3a-l 4

1a. 2,6-Dimethyl-5-heptenal
1b. 2,2-Dimethyl-4-pentenal
1c. Trimethylacetaldehyde
1d. Octyl aldehyde
1e. 3-Phenylbutyraldehyde
1f. 2-Ethylhexanal
1g. 2-Triphenyloxyheptanal
1h. 4-Methoxybenzaldehyde
1i. Benzaldehyde
1j. 4-Nitrobenzaldehyde
1k. 2-Phenylpropionaldehyde
1l. 2-Benzyloxyheptanal

Elimination of α-secondary and tertiary substituted hydrazonium salts generally gives rise to very good yields of the corresponding nitriles. However, nitriles along with the corresponding aldehydes, products of hydrolysis, are obtained utilizing primary hydrazone moieties in the elimination reaction. For aromatic substituted hydrazones, complete hydrolysis of 4-methoxy benzaldehyde hydrazonium salt is observed, while no reaction occurs for the benzaldehyde hydrazone and 4-nitrobenzaldehyde hydrazone, even though N-carbomethoxy-N,N-dimethylhydrazonium salts **5** are originally formed. Failure to produce aryl nitriles is probably due to the stronger N-N bonding of aromatic hydrazones. Also, elimination reactions can be carried out in a variety of solvents tested.

This study shows that most hydrazones **2** readily react with chloroformates to form quaternary hydrazonium salts **5**. The ^{1}H nmr signal of the protons on the C = N in the salts moves significantly downfield ($\Delta \approx 2$ ppm), while the N - CH_3 protons show a broad peak at a slightly lower field. It is interesting to note that the signals for protons on the methoxy group appear at much higher field. Most of the hydrazonium salts are readily hydrolyzed in air, and are thermally unstable. An attempt at HRMS analysis of the salt derived from hydrazone **2e** resulted in the observation of the molecular ion peak of the corresponding hydrazone, a dissociated product. The proposed mechanism for the elimination reaction is depicted in Scheme 4. Treatment of the intermediate salts with water

Table 1: The Elimination Based on Different Conditions

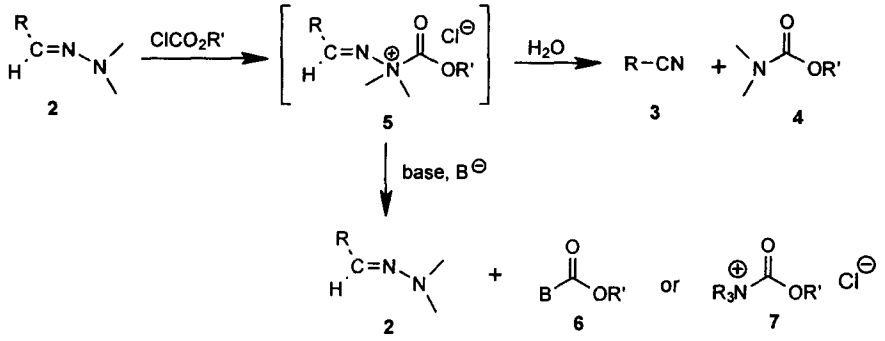
Entry	Hydrazone	Solvent	Base	Chloroformate	Nitrile	Y%[a]
1	**2a**	Et_2O	H_2O	$ClCO_2Me$	**3a**	78
2	**2b**	Et_2O	H_2O	$ClCO_2Me$	**3b**	64
3	**2c**	Et_2O	H_2O	$ClCO_2Me$	**3c**	90[b]
4	**2d**	Et_2O	H_2O	$ClCO_2Me$	**3d**	56
5	**2e**	Et_2O	H_2O	$ClCO_2Me$	**3e**	43
6	**2f**	Et_2O	H_2O	$ClCO_2Me$	**3f**	85
7	**2g**	Et_2O	H_2O	$ClCO_2Me$	**3g**	51
8	**2h**	Et_2O	H_2O	$ClCO_2Me$	**3h**	0
9	**2i**	Et_2O	H_2O	$ClCO_2Me$	**3i**	0
10	**2j**	Et_2O	H_2O	$ClCO_2Me$	**3j**	0
11	**2k**	Et_2O	H_2O	$ClCO_2Me$	**3k**	0
12	**2l**	Et_2O	H_2O	$ClCO_2Me$	**3l**	0
13	**2a**	Et_2O	H_2O	$ClCO_2Et$	**3a**	81
14	**2a**	Et_2O	H_2O	$ClCO_2Bn$	**3a**	75
15	**2a**	Et_2O	H_2O	$ClCO_2Ph$	**3a**	76
16	**2a**	Et_2O	H_2O	$MeCO_2Me$[c]	**3a**	0
17	**2e**	Et_2O	DBU	$ClCO_2Me$	**3e**	0
18	**2a**	Et_2O	DBU	$ClCO_2Me$	**3a**	0
19	**2e**	Et_2O	NaOMe	$ClCO_2Me$	**3e**	0
20	**2e**	Et_2O	Et_3N	$ClCO_2Me$	**3e**	0
21	**2h**	Et_2O	NaOMe	$ClCO_2Me$	**3h**	0
22	**2a**	CH_3Cl	H_2O	$ClCO_2Me$	**3a**	73
23	**2c**	CH_3Cl	H_2O	$ClCO_2Me$	**3c**	86[b]
24	**2a**	CH_2Cl_2	H_2O	$ClCO_2Me$	**3a**	76
25	**2b**	CH_2Cl_2	H_2O	$ClCO_2Me$	**3b**	61
26	**2a**	CH_2Cl_2	H_2O	$ClCO_2Et$	**3a**	71
27	**2a**	THF	H_2O	$ClCO_2Me$	**3a**	75

Note: *a*. Isolated yields of nitriles from the corresponding hydrazones; *b*. Determined by ^1H nmr, due to volatility of product; *c*. Dimethyl carbonate.

readily affords nitriles, while bases (NaOMe, DBU, Et_3N) attack the electrophilic carbonyl group to give rise to the reactant hydrazones **2**, and the corresponding carbonate **6** or quaternary ammonium salts **7**.

In conclusion, the above-described elimination reaction involves water as an effective base, and thus it is economic and convenient for workup. Also, the reaction provides an efficient route to the preparation of α-sterically hindered alkyl nitriles.

Scheme 4



Experimental Section

NMR spectra were recorded on a Varian 300 MHz spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C in $CDCl_3$ with either chloroform (7.26 ppm ^1H, 77.00 ppm ^{13}C) or TMS as a reference peak. Coupling constants, J, are reported in Hz. IR spectra were recorded on a Magna-IR™ spectrometer 550. High-resolution mass spectra were obtained on Kratos MS50TC Magnetic Sector Mass Spectrometer.

All commercially available chemicals were purchased from Aldrich Chemical Company, Milwaukee, WI. Butyllithium was titrated before use. THF and ether were distilled freshly from sodium/benzophenone. All reactions were carried out under an argon atmosphere in oven-dried (140 °C) glassware.

General procedure for the preparation of hydrazones 2. To a solution consisting aldehyde **1** (9.8 mmol, 1 equiv) in 50 mL of CH_2Cl_2 was added Na_2SO_4 (10 g) and N, N-dimethylhydrazine (1.11 mL, 14.6 mmol, 1.5 equiv). The reaction mixture was heated at reflux for 10 h. The mixture was allowed to cool to room temperature and filtered. The filtrate was concentrated to provide hydrazone **2** (99% pure by ^1H NMR).

(E)-2,6-Dimethyl-5-heptenal N, N-dimethylhydrazone (2a): IR (CCl_4): 3341, 2926, 1665, 1638; 1H NMR ($CDCl_3$, 300 MHz): δ 1.03 (d, 3H, J = 7.2, CH_3), 1.32-1.51 (m, 2H, CH_2), 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.98 (q, 2H, J = 7.5, CH_2), 2.28-2.40 (m, 1H, CH), 2.70 (s, 6H, NCH_3), 5.05-5.12 (m, 1H, =CH), 6.48 (d, 1H, J = 6.6, CH=N); ^{13}C NMR: δ 17.1, 18.5, 25.2, 35.1, 36.2, 42.8, 124.0, 130.7, 143.5. MS: 182.2, 170.2, 141.1, 127.1, 113.1, 100.1, 84.0, 70.1, 56.1,. HRMS. Calcd for $C_{11}H_{22}N_2$: 182.17830. Found: 182.17824.

(E)-2,2-Dimethyl-4-pentenal N, N-dimethylhydrazone (2b): IR (CCl_4): 3341, 2928, 1666, 1639; ^1H

NMR ($CDCl_3$, 300 MHz): δ 1.04 (s, 6H, CH_3), 2.14 (d, 2H, J =7.5, CH_2), 2.69 (s, 6H, NCH_3), 4.97-5.03 (m, 2H, $=CH_2$), 5.76-5.88 (m, 1H, =CH), 6.54(s, 1H, CH=N); ^{13}C NMR: δ 25.4, 36.7, 42.9, 45.5, 116.5, 134.8, 145.5. MS: 55.1, 70.1, 84.0, 113.1, 154.1. HRMS. Calcd for $C_9H_{18}N_2$: 154.14700. Found: 154.14681.

(E)-Trimethylacetaldehyde N, N-dimethylhydrazone (2c): ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, 9H, CH_3), 2.68 (s, 6H, NCH_3), 6.58 (s, 1H, CH=N); ^{13}C NMR: δ 27.8, 33.6, 42.6, 145.6.

(E)-Octyl aldehyde N, N-dimethylhydrazone (2d): ^1H NMR ($CDCl_3$,300 MHz): δ 0.87 (t, 3H, J = 6.9, CH_3), 1.22-1.32 (m, 10H), 2.22 (q, 2H, J = 6.9, CH_2), 2.72 (s, 6H, NCH_3), 6.68 (br, 1H, CH=N); ^{13}C NMR: δ 13.5, 22.1, 27.3, 28.6, 31.2, 32.5, 42.7, 138.4.

(E)-3-Phenylbutyraldehyde N, N-dimethylhydrazone (2e): IR (CCl_4): 3341, 2958, 1669, 1639; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (d, 3H, J = 6.9, CH_3), 2.47-2.52 (m, 2H, CH_2), 2.67 (s, 6H, NCH_3), 2.91 (q, 1H, J = 7.2, CH), 6.50 (t, 1H, J = 5.4, CH=N), 7.20-7.35 (m, 5H, Ph); ^{13}C NMR: δ 21.3, 38.6, 41.0, 42.93 125.7, 126.6, 128.0, 137.2, 146.2. MS:190.1, 105.1, 77.0, 85.1, 51.0. HRMS. Calcd for $C_{12}H_{18}N_2$: 190.14700. Found: 190.14704.

(E)-2-Ethylhexanal N, N-dimethylhydrazone (2f): IR (CCl_4): 3341, 2941, 1669, 1640; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 6H, J = 7.5, CH_3), 1.25-1.36 (m, 8H), 2.05-2.15 (m, 1H, CH), 2.71 (s, 6H, NCH_3), 6.46 (d, 1H, J = 7.2, CH=N); ^{13}C NMR: δ 11.0, 13.4, 22.3, 26.1, 28.8, 32.6, 42.8, 43.6, 144.0. MS: 170.2, 155.2, 141.1, 127.1, 99.1, 84.0, 70.1, 59.1. HRMS. Calcd for $C_{10}H_{22}N_2$: 170.17830. Found: 170.17815.

General procedure for elimination to nitriles 3: The chloroformate (1.5 mmol, 1.5 equiv) was added to a solution of hydrazone **2** (10 mmol, 1 equiv) in 10 mL of ether. The reaction mixture was stirred for 1.0 h at room temperature. Water (10 mL) was added, and the resultant mixture was stirred for 30 min. The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4), and concentrated. Chromatography on silica gel or distillation under reduced pressure gave the product **3**.

2,6-Dimethyl-5-heptenenitrile (3a): Oil; IR (CCl_4): 2979, 2936, 2879, 2240, 1745, 1456, 1388, 1267; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.30 (d, 3H, J = 7.5, CH_3), 1.50-1.80 (m, 2H, CH_2), 1.63 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.16 (q, 2H, J = 7.2, CH_2), 2.50-2.70 (m, 1H, CH), 5.00-5.10 (m, 1H, =CH); ^{13}C NMR: δ 17.75, 17.97, 24.82, 25.45, 25.71, 34.14, 122.15, 123.08, 133.60. MS: 137.1, 122.1, 109.1, 94.1, 83.1, 69.1, 55.1, 49.0, 41.0; HRMS. Calcd for $C_9H_{15}N$: 137.12045. Found: 137.12045.

2,2-Dimethyl-4-pentenanenitrile (3b): Oil; IR (CCl_4): 3081, 2979, 2929, 2877, 2236, 1703, 1472, 1369, 1261, 1201, 1093, 1642, 2236. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 6H, CH_3), 2.27 (d, 2H, J = 7.5, CH_2), 5.30-5.50 (m, 2H, $=CH_2$), 5.76-5.88 (m, 1H, =CH), ; ^{13}C NMR: δ 26.09, 44.92, 52.45, 119.77, 124.60, 132.08. MS: 109.1, 103.1, 94.1, 88.0, 83.1, 77.0, 68.1, 59.0, 55.1, 50.0; HRMS. Calcd for $C_7H_{11}N$: 109.08915. Found: 109.08926.

Octanenitrile (3d): ^1H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, J = 6.9, CH_3), 1.20-1.60 (m, 10H, CH_2), 2.32 (t, 2H, J = 6.9, CH_2); ^{13}C NMR: δ 13.5, 16.4, 21.5, 24.8, 27.9, 28.1, 31.1, 119.3.

3-Phenylbutanenitrile (3e): Oil; IR (CCl_4): 3030, 2968, 2932, 2247, 1496, 1454, 1422, 1382, 1016; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.45 (d, 3H, J = 6.9, CH_3), 2.58 (t, 2H, J = 7.5, CH_2), 3.16 (s, 1H, J = 7.2, CH), 7.20-7.35 (m, 5H, Ph); ^{13}C NMR: δ 20.3, 25.9, 36.1, 118.37, 126.3, 127.0, 128.5, 142.9. MS: 145.1, 130.1, 116.1, 105.1, 77.0, 63.0, 51.0. HRMS. Calcd for $C_{10}H_{11}N$: 145.08915. Found: 145.08924.

2-Ethylhexanaenitrile (3f): Oil; IR (CCl_4): 2962, 2935, 2863, 2237, 1462; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, 3H, J = 7.2, CH_3), 1.08 (t, 3H, J = 7.5, CH_3), 1.3-1.70 (m, 8H), 2.40-2.50 (m, 1H, CH); ^{13}C NMR: δ

10.88, 13.15, 21.63, 24.95, 28.71, 31.02, 32.65, 121.53. MS: 280.3, 214.2, 183.1, 167.2, 127.1, 102.1, 82.1, 57.1. HRMS. Calcd for $C_8H_{15}N$: 125.12045. Found: 125.11991.

(E)-3-Phenylbutyraldehyde N, N-dimethylhydrazonium methyl chloroformate (5e): Solid, Mp: dissociation; IR (KBr): 3020, 2958, 2000-2700 (broad), 1634, 1457, 1186; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (d, 3H, J = 6.9, CH_3), 2.50-2.95 (m, 11H), 3.10-3.20 (m, 1H, CH), 8.70 (t, 1H, J = 5.1, CH=N), 7.10-7.35 (m, 5H, Ph); ^{13}C NMR: δ 21.5, 36.4, 40.3, 45.4, 126.5, 126.6, 128.4, 143.9, 171.4.

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