Organic Chemistry

New method for preparation of α-substituted acrylonitrile derivatives

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The method for the preparation of α-substituted acrylonitrile derivatives by the quaternization of the nitrogen atom of both Me_2N groups in the corresponding substituted 3-(dimethylamino)propanal dimethylhydrazones followed by the Hoffman decomposition of the resulting diiodides was developed.

Key words: transmetallation, quaternization, Hoffman decomposition, acrylonitriles, hydrazonium salts, dimethylhydrazones.

α-Functionalized acrylonitriles are an interesting class of highly reactive compounds used for the synthesis of systems with a quaternary carbon atom.[1—3] A number of methods for the synthesis of α-substituted acrylonitriles was proposed, but they were found to be suitable only for the preparation of simple α-alkyl and α-alkoxyacrylonitriles.[4,5]

Earlier,[6] we reported a general method of synthesis of α-substituted propenal dimethylhydrazones by metallation of β-dimethylaminopropanal dimethylhydrazone (**1**) with subsequent reaction of lithium derivative **2** with various electrophiles. Further selective quaternization of the β-dimethylamino group resulted in hydrazonium salts and Hoffman decomposition of the latter yielding the target α-substituted propenal dimethylhydrazones.

In the present work, we found that α-substituted hydrazones **3** react with an excess of methyl iodide to give diiodides **4**, whose decomposition under the action of bases results in α-substituted acrylonitriles **5** (Scheme 1).

It is noteworthy that such an approach allows one to obtain easily α,β-unsaturated nitriles **5c—e** containing an acetal group in the side chain, which opens ample opportunities for the synthesis of various heterocycles.

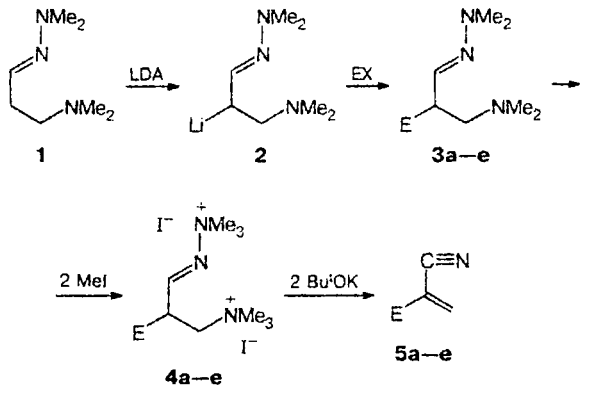
As noted earlier,[6] lithiated hydrazone **2** does not react with diethoxy(phenoxy)methane, which makes hydrazone **3e** difficult to obtain. An analysis of the literature data[7] shows that the Grignard reagents are more reactive with respect to orthoesters than the corresponding organolithium compounds, which is due to their higher Lewis acidity.

Indeed, an organomagnesium derivative obtained by addition of $MgBr_2$ to the lithiated hydrazone **2** easily reacts with diethoxy(phenoxy)methane to give acetal **3e**. Subsequent full quaternization of hydrazones **3a—e** and Hoffman decomposition of hydrazonium salts **4a—e** yield α-substituted acrylonitriles **5a—e**.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 9, pp. 1707—1709, September, 1999.

1066-5285/99/4809-1685 $22.00

Scheme 1



3—5	EX	E
a	Me_2CO [a]	$Me_2C(OSiMe_3)$
b	MeCHO [a]	$MeCH(OSiMe_3)$
c	$BrCH_2CH(OEt)_2$	$CH_2CH(OEt)_2$
d	$BrCH_2CH_2CH(OCH_2)_2$	$CH_2CH_2CH(OCH_2)_2$
e	$PhOCH(OEt)_2$ [b]	$CH(OEt)_2$

[a] After the reaction of a carbonyl compound with lithiated hydrazone was completed, the reaction mixture was worked up with chloro(trimethyl)silane.

[b] Lithiated hydrazone **2** was preliminarily transformed into an organomagnesium derivative.

Thus, our method allows one to obtain acrylonitriles containing various substituents in the α-position, whereas the previous methods of synthesis[4,5] of such compounds are not so versatile and have significant limitations.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) in $CDCl_3$.

α-Lithio-β-dimethylaminopropanal dimethylhydrazone (2). A 1.8 *N* solution of *n*-butyllithium (16.60 mL) in hexane (29.9 mmol) was added dropwise with stirring in a flow of argon to a solution of diisopropylamine (3.13 g, 31.0 mmol) in 90 mL of anhydrous THF at −5 °C. After 15 min, hydrazone **1** (4.25 g, 29.7 mmol) was added at the same temperature, and the reaction mixture was stirred at 0 °C for 1 h, whereupon the solution of lithiated hydrazone **2** was worked up with an electrophile.

Synthesis of α-substituted aminohydrazones 3a—e (general procedure). A solution of an electrophile (30 mmol) in 10 mL of THF was added with stirring in a flow of argon to a solution of lithiated hydrazone **2** at −70 °C for 20 min, and the reaction mixture was kept at 0 °C for 12 h (in the case of the reaction with diethoxy(phenoxy)methane, a solution of $MgBr_2$ (45 mmol) in 40 mL of THF was preliminarily added to the lithiated hydrazone **2**). Then, a 20% solution of NaCl (50 mL) was added with stirring. The organic layer was separated, and products from the aqueous layer were extracted with ether (30×40 mL). The combined organic extracts were dried over Na_2SO_4, and the residue was concentrated and distilled *in vacuo*.

Silylated derivatives **3a,b** were obtained as follows. After the reaction with an aldehyde or ketone was completed, the reaction mixture was cooled to −40 °C, and chloro(trimethyl)silane (40 mmol) was added for 10 min. The resulting solution was stirred at 0 °C for 1 h and worked up as described above.

2-Dimethylaminomethyl-3-methyl-3-(trimethylsilyloxy)-butanal dimethylhydrazone (3a). Yield 67%, b.p. 91 °C (1 Torr). Found (%): C, 57.13; H, 11.47; N, 15.39. $C_{13}H_{31}N_3OSi$. Calculated (%): C, 57.09; H, 11.42; N, 15.36. ^1H NMR ($CDCl_3$), δ: 0.1 (s, 9 H, Me_3Si); 1.3, 1.4 (both s, each 3 H, Me_2C); 2.2 (s, 6 H, $\underline{Me}_2NCH_2$); 2.3—2.7 (m, 3 H, $Me_2NC\underline{H}_2C\underline{H}$); 2.8 (s, 6 H, Me_2NN); 6.7 (d, 1 H, CH=N, J = 7 Hz).

2-Dimethylaminomethyl-3-(trimethylsilyloxy)butanal dimethylhydrazone (3b). Yield 56%, b.p. 80—81 °C (1 Torr). Found (%): C, 55.61; H, 11.24; N, 16.25. $C_{12}H_{29}N_3OSi$. Calculated (%): C, 55.55; H, 11.27; N, 16.19. ^1H NMR ($CDCl_3$), δ: 0.1 (s, 9 H, Me_3Si); 1.1 (d, 3 H, $\underline{Me}CH$, J = 6 Hz); 2.1 (s, 6 H, $\underline{Me}_2NCH_2$); 2.4—2.6 (m, 3 H, $Me_2NC\underline{H}_2C\underline{H}$); 2.7 (s, 6 H, $\underline{Me}_2NN$); 4.0 (m, 1 H, CHO); 6.4 (d, 1 H, CH=N, J = 7 Hz).

2-Dimethylaminomethyl-4,4-diethoxybutanal dimethylhydrazone (3c). Yield 54%, b.p. 90—91 °C (1 Torr). Found (%): C, 60.18; H, 11.32; N, 16.25. $C_{13}H_{29}N_3O_2$. Calculated (%): C, 60.20; H, 11.27; N, 16.20. ^1H NMR ($CDCl_3$), δ: 1.1 (t, 6 H, 2 $\underline{Me}CH_2$); 1.6—1.8 (m, 2 H, $C\underline{H}_2CH(OEt)_2$); 2.2 (s, 6 H, $\underline{Me}_2NCH_2$); 2.4—2.6 (m, 3 H, $Me_2NC\underline{H}_2C\underline{H}$); 2.8 (s, 6 H, Me_2NN); 3.3—3.7 (m, 4 H, 2 $MeC\underline{H}_2$); 4.6 (d, 1 H, $C\underline{H}(OEt)_2$, J = 5 Hz); 6.4 (d, 1 H, CH=N, J = 7 Hz).

2-Dimethylaminomethyl-4-(1,3-dioxolan-2-yl)butanal dimethylhydrazone (3d). Yield 77%, b.p. 110 °C (1 Torr). Found (%): C, 59.29; H, 10.29; N, 17.24. $C_{12}H_{25}N_3O_2$. Calculated (%): C, 59.25; H, 10.35; N, 17.27. ^1H NMR ($CDCl_3$), δ: 1.3 (m, 2 H, $C\underline{H}_2CH_2O_2C_2H_4$); 1.8 (m, 2 H, $CH_2C\underline{H}_2O_2C_2H_4$); 2.1 (s, 6 H, $\underline{Me}_2NCH_2$); 2.3—2.6 (m, 3 H, $Me_2NC\underline{H}_2C\underline{H}$); 2.7 (s, 6 H, $\underline{Me}_2NN$); 3.9—4.1 (m, 4 H, OCH_2CH_2O); 4.7 (t, 1 H, $C\underline{H}OC_2H_4$, J = 5 Hz); 6.5 (d, 1 H, CH=N, J = 7 Hz).

2-Dimethylaminomethyl-3,3-diethoxypropanal dimethylhydrazone (3e). Yield 56%, b.p. 95 °C (1 Torr). Found (%): C, 58.79; H, 11.01; N, 17.07. $C_{12}H_{27}N_3O_2$. Calculated (%): C, 58.74; H, 11.09; N, 17.13. ^1H NMR ($CDCl_3$), δ: 1.1 (t, 6 H, 2 $\underline{Me}CH_2$, J = 7 Hz); 2.15 (s, 6 H, $\underline{Me}_2NCH_2$); 2.5—2.7 (m, 3 H, $Me_2NC\underline{H}_2C\underline{H}$); 2.8 (s, 6 H, $\underline{Me}_2NN$); 3.4—3.7 (m, 4 H, 2 $MeC\underline{H}_2$); 4.5 (d, 1 H, $C\underline{H}(OEt)_2$, J = 4 Hz); 6.5 (d, 1 H, CH=N, J = 6 Hz).

Synthesis of α-substituted acrylonitriles 5a—e (general procedure). A solution of MeI (44 mmol) in 10 mL of acetone was added with stirring in an atmosphere of argon to a solution of α-substituted aminohydrazone **3a—e** (20 mmol) in 30 mL of anhydrous acetone at 0 °C for 10 min. The reaction mixture was stirred at 20 °C for 0.5 h and then refluxed for 2 h. After cooling, the solvent was removed *in vacuo* to the constant weight of the residue. Anhydrous THF (50 mL) was added, and the resulting suspension was cooled with stirring to −30 °C. Potassium *tert*-butoxide (40 mmol) was added in one operation in an atmosphere of argon, and the reaction mixture was stirred at 20 °C for 3 h and worked up with a 20% solution of NaCl (50 mL). After the organic layer was separated, the products in the aqueous layer were extracted with ether (4×40 mL). The combined organic extracts were dried over Na_2SO_4, and the residue was concentrated and distilled *in vacuo*.

2-(1-Methyl-1-trimethylsilyloxyethyl)acrylonitrile (5a). Yield 57%, b.p. 73 °C (1 Torr). Found (%): C, 58.82; H, 9.45; N, 7.84. $C_9H_{17}NOSi$. Calculated (%): C, 58.97; H, 9.35; N, 7.64. ^1H NMR ($CDCl_3$), δ: 0.1 (s, 9 H, Me_3Si); 1.3 (s, 6 H, Me_2C); 5.8, 6.0 (both s, each 1 H, CH_2=C).

2-(1-Trimethylsilyloxyethyl)acrylonitrile (5b). Yield 69%, b.p. 70 °C (1 Torr). Found (%): C, 56.24; H, 8.67; N, 8.15. $C_8H_{15}NOSi$. Calculated (%): C, 56.76; H, 8.93; N, 8.27. ^{1}H NMR ($CDCl_3$), δ: 0.1 (s, 9 H, Me_3Si); 1.3 (s, 3 H, MeCH); 4.3 (m, 1 H, CHO); 5.9, 6.0 (both s, each 1 H, CH_2=C).

2-(2,2-Diethoxyethyl)acrylonitrile (5c). Yield 62%, b.p. 65 °C (1 Torr). Found (%): C, 62.45; H, 9.06; N, 8.02. $C_9H_{15}NO_2$. Calculated (%): C, 63.88; H, 8.93; N, 8.28. ^{1}H NMR ($CDCl_3$), δ: 1.2 (t, 6 H, 2 $MeCH_2$, J = 7 Hz); 2.5 (d, 2 H, $CH_2CH(OEt)_2$, J = 6 Hz); 3.5—3.7 (m, 4 H, 2 $MeCH_2$); 4.6 (d, 1 H, $CH(OEt)_2$, J = 6 Hz); 5.8, 5.9 (both s, each 1 H, CH_2=C).

2-[2-(1,3-Dioxolan-2-yl)ethyl]acrylonitrile (5d). Yield 60%, b.p. 80 °C (1 Torr). Found (%): C, 62.46; H, 7.06; N, 9.30. $C_8H_{11}NO_2$. Calculated (%): C, 62.73; H, 7.24; N, 9.14. ^{1}H NMR ($CDCl_3$), δ: 1.8 (m, 2 H, CH_2CH); 2.3 (m, 2 H, CH_2CH_2CH); 3.3—4.0 (m, 4 H, OCH_2CH_2O); 4.8 (m, 1 H, $CH(OEt)_2$); 5.7, 5.8 (both s, each 1 H, CH_2=C).

2-Diethoxymethylacrylonitrile (5e). Yield 71%, b.p. 63 °C (1 Torr). Found (%): C, 61.93; H, 8.54; N, 9.12. $C_8H_{13}NO_2$. Calculated (%): C, 61.91; H, 8.44; N, 9.03. ^{1}H NMR ($CDCl_3$), δ: 1.2 (t, 6 H, 2 $MeCH_2$, J = 7 Hz); 3.5—3.7 (m, 4 H, 2 $MeCH_2$); 5.0 (s, 1 H, $CH(OEt)_2$); 6.1, 6.2 (both s, each 1 H, CH_2=C).

This work was financially supported by the Scientific Training Centers of Organometallic and Biomedical Chemistry within the framework of the Federal Target Program "Integration" (Grants 234 and K0599).

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Received March 10, 1999;
in revised form June 1, 1999