Synthesis and cycloaddition reactions of α-substituted acrolein dimethylhydrazones containing an acetal group

V. E. Vahmistrov, N. P. Tsvetkov, A. B. Koldobsky, E. V. Vorontsov, and V. N. Kalinin★

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (095) 135 6549. E-mail: vkalin@ineos.ac.ru

A series of new α-substituted acrolein dimethylhydrazones containing an acetal group were synthesized. These hydrazones react with acrylonitrile or methyl acrylate according to the Diels—Alder reaction pattern to give substituted tetrahydropyridines. An unusual [2+4]- and [2+3]-cycloaddition cascade reaction involving α-diethoxymethylacrolein dimethylhydrazone was discovered.

Key words: dimethylhydrazones, azadienes, cascade reactions, cycloaddition, dienophiles.

The use of heterodienes in the Diels—Alder reaction is an efficient method for the formation of six-membered heterocycles.[1] In particular, dimethylhydrazones of α,β-unsaturated aldehydes are actively used in the synthesis of pyridine[2] and piperidine[3] derivatives. Previously,[4] we have developed a general method for the preparation of α-substituted acrolein dimethylhydrazones, including hydrazones containing a trimethylsilyloxy group in the substituent. Subsequently, in a study of the activity of the prepared compounds as dienes, we found[5] unusual sequences of cascade cycloaddition reactions.

This study is devoted to the synthesis and the reactivity of previously unknown azadienes **1a—c** containing an acetal function in the α-substituent.

Results and Discussion

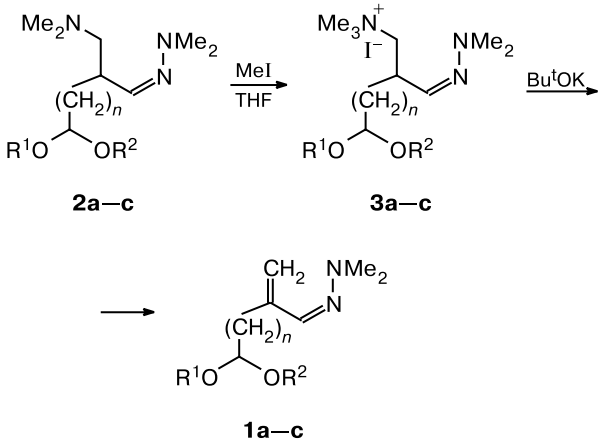
α-Substituted β-dimethylaminopropionaldehyde dimethylhydrazones **2a—c** were used as the starting compounds.[6] The selective quaternization of more basic β-dimethylamino group in hydrazones **2a—c** followed by the Hofmann degradation of iodomethylates **3a—c** *in situ* gave rise to the target acrolein dimethylhydrazones **1a—c** (Scheme 1).

It was found that unsaturated hydrazones **1b,c** react with acrylonitrile and methyl acrylate to give [2+4]-cycloadducts **4a—d** (Scheme 2); the optimal yields are attained by refluxing the starting azadienes **1b,c** in an excess of the corresponding dienophile.

Of special note is the high regioselectivity of the reaction; in all cases, only one pair of enantiomers was isolated after vacuum distillation.

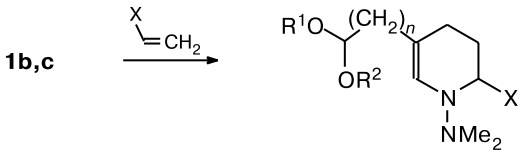
Our study of the reactivity of azadiene **1a** showed that its reaction with acrylonitrile does not stop after the formation of cycloadduct **5** (Scheme 3) but affords bicyclic product **8**.

Scheme 1



a: $R^1 = R^2 = Et$, $n = 0$;
b: $R^1 = R^2 = Et$, $n = 1$;
c: $R^1 + R^2 = CH_2—CH_2$, $n = 2$

Scheme 2

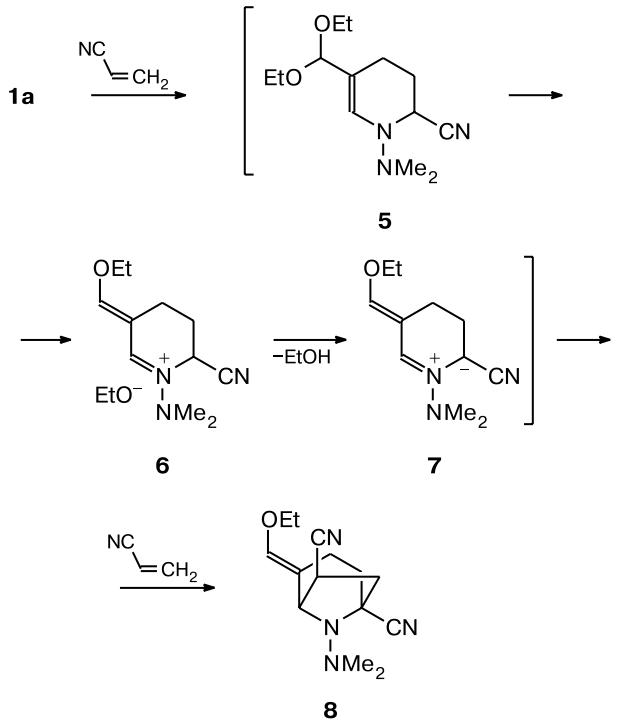


4: $R^1 = R^2 = Et$ (**a**, **b**), $R^1 + R^2 = CH_2—CH_2$ (**c**, **d**); $n = 1$ (**a**, **b**), 2 (**c**, **d**); X = CN (**a**, **c**), CO_2Me (**b**, **d**)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 223—225, January, 2004.

1066-5285/04/5301-0233

Scheme 3



This can be explained by an enhanced mobility of the ethoxy groups in compound **5** caused by the mesomeric effect of the ring N atom and resulting in the thermal dissociation of cycloadduct **5** into the iminium cation **6** and the ethoxide anion. The subsequent proton transfer between these two species yields 1,3-dipole **7**, which enters into [2+3]-cycloaddition with a second acrylonitrile molecule to give bicyclic compound **8**.

Cycloadduct **5** cannot be isolated from the reaction mixture, which attests to a lower rate of the primary cycloaddition compared to the subsequent transformations. This sequence of reactions proceeds with high regio- and stereoselectivities to give the final product **8**, after crystallization from a benzene—hexane mixture, in a high yield (~80%) and as a single pair of enantiomers.

The reaction of hydrazone **1a** with methyl acrylate affords a complex mixture of polymeric compounds, which is probably related to the difficulty of formation of the corresponding dipole caused by the fact that the ester group exerts a weaker acidifying effect than the nitrile group.

Thus, we prepared a series of acrolein dimethylhydrazones containing a protected aldehyde function in the substituent and showed that these compounds can be used in the diene synthesis to prepare substituted tetrahydropyridines. One more example of the [2+4]- and [2+3]-cycloaddition cascade sequence involving azadienes was found.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX 400 (400.13 (^{1}H) and 100.61 MHz (^{13}C)) and Avance 300 (300.13 (^{1}H) and 75.5 MHz (^{13}C)) spectrometers in $CDCl_3$. The ^{1}H and ^{13}C NMR signals were assigned using a series of 1D and 2D homo- and heteronuclear NMR experiments (^{1}H—^{1}H COSY45, ^{1}H—^{13}C HSQC, ^{1}H—^{13}C HMBC). Elemental analyses were performed at the Laboratory for Microanalysis of the A. N. Nesmeyanov Institute of Organoelement Compounds.

Synthesis of α-suibstituted acrolein dimethylhydrazones 1a—c (general procedure). A solution of MeI (3.24 mL, 7.38 g, 52 mmol) in 10 mL of THF was added dropwise with stirring under argon and cooling to 0 °C over a period of 10 min to a solution of α-substituted β-dimethylaminopropionaldehyde dimethylhydrazone **2a—c** [6] (50 mmol) in 100 mL of THF. The reaction mixture was left for 12 h and then cooled to −30 °C, and Bu^{t}OK (5.95 g, 53 mmol) was added. The mixture was stirred for 2 h at 20 °C and treated with 40 mL of a 20% aqueous solution of NaCl. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* and the residue was distilled.

2-Diethoxymethylprop-2-enal dimethylhydrazone (1a) was prepared from 2-dimethylaminomethyl-3,3-diethoxypropanal dimethylhydrazone (**2a**). Yield 8.1 g (81%), b.p. 65 °C (1 Torr). Found (%): C, 60.13; H, 9.99; N, 14.02. $C_{10}H_{20}N_2O_2$. Calculated (%): C, 59.97; H, 10.07; N, 13.99. ^{1}H NMR, δ: 1.17 (t, 6 H, 2 MeCH$_2$, J = 6.9 Hz); 2.72 (s, 6 H, Me$_2$N); 3.45—3.54, 3.56—3.65 (both m, 2 H each, 2 CH$_2$O); 5.25, 5.42 (both s, 1 H each, CH$_2$=C); 5.28 (s, 1 H, CH(OEt)$_2$); 6.88 (s, 1 H, CH=N). ^{13}C NMR, δ: 15.2 (2 MeCH$_2$); 42.4 (Me$_2$N); 62.3 (2 CH$_2$O); 99.3 (OCHO); 114.2 (CH$_2$=); 132.3 (CH=N); 142.6 (C=).

4,4-Diethoxy-2-methylenebutanal dimethylhydrazone (1b) was prepared from 2-dimethylaminomethyl-4,4-diethoxybutanal dimethylhydrazone (**2b**). Yield 8.2 g (77%), b.p. 82 °C (1 Torr). Found (%): C, 61.77; H, 10.28; N, 13.11. $C_{11}H_{22}N_2O_2$. Calculated (%): C, 61.65; H, 10.35; N, 13.07. ^{1}H NMR, δ: 1.19 (t, 6 H, 2 MeCH$_2$, J = 6.9 Hz); 2.66 (d, 2 H, CH$_2$C=, J = 5.4 Hz); 2.72 (s, 6 H, Me$_2$N); 3.45—3.54, 3.62—3.71 (both m, 2 H each, 2 CH$_2$O); 4.82 (t, 1 H, CH(OEt)$_2$, J = 5.4 Hz); 5.13, 5.22 (both s, 1 H each, CH$_2$=C); 6.98 (s, 1 H, CH=N). ^{13}C NMR, δ: 15.2 (2 MeCH$_2$); 36.2 (CH$_2$C=); 42.6 (Me$_2$N); 61.1 (2 CH$_2$O); 101.2 (OCHO); 117.1 (CH$_2$=); 135.8 (CH=N); 141.5 (C=).

α-Methylene(1,3-dioxolan-2-yl)butanal (1c) was prepared from 2-dimethylaminomethyl-4-(1,3-dioxolan-2-yl)butanal dimethylhydrazone (**2c**). Yield 8.2 g (83%), b.p. 106 °C (1 Torr). Found (%): C, 60.69; H, 9.12; N, 14.11. $C_{10}H_{18}N_2O_2$. Calculated (%): C, 60.58; H, 9.15; N, 14.13. ^{1}H NMR, δ: 1.81—1.90 (m, 2 H, CH$_2$CH); 2.41 (t, 2 H, CH$_2$C=, J = 7.9 Hz); 2.79 (s, 6 H, Me$_2$N); 3.77—3.86, 3.88—3.97 (both m, 2 H each, OCH$_2$CH$_2$O); 4.82 (t, 1 H, OCHO, J = 4.8 Hz); 5.01, 5.08 (both s, 1 H each, CH$_2$=C); 6.94 (s, 1 H, CH=N). ^{13}C NMR, δ: 21.9 (CH$_2$CH); 28.5 (CH$_2$C=); 38.7 (Me$_2$N); 60.8 (OCH$_2$CH$_2$O); 100.5 (OCHO); 110.5 (CH$_2$=); 131.6 (CH=N); 141.9 (C=).

Diels—Alder reactions of hydrazones 1b,c with acrylonitrile and methyl acrylate. Synthesis of tetrahydropyridines (general

procedure). Unsaturated hydrazone **1b,c** (15 mmol) was mixed with methyl acrylate (12.1 mL, 135 mmol) or acrylonitrile (8.8 mL, 135 mmol). The reaction mixture was refluxed for 13—23 h. The solvent was concentrated *in vacuo* and the residue was distilled.

5-(2,2-Diethoxyethyl)-1-dimethylamino-1,2,3,4-tetrahydropyridine-2-carbonitrile (4a). A mixture of hydrazone **1b** and acrylonitrile was refluxed for 13 h. The yield of **4a** was 3.12 g (78%), b.p. 123 °C (1 Torr). Found (%): C, 62.57; H, 9.36; N, 15.88. $C_{14}H_{25}N_3O_2$. Calculated (%): C, 62.89; H, 9.42; N, 15.72. ^{1}H NMR, δ: 1.11 (t, 6 H, 2 MeCH$_2$, J = 7.0 Hz); 1.92—2.18 (m, 6 H, 3 CH$_2$); 2.43 (s, 6 H, Me$_2$N); 3.35—3.45, 3.53—3.63 (both m, 2 H each, 2 CH$_2$O); 4.00 (t, 1 H, CHCN, J = 4.5 Hz); 4.42 (t, 1 H, OCHO, J = 5.6 Hz); 5.88 (s, 1 H, =CH). ^{13}C NMR, δ: 11.2 (2 MeCH$_2$); 19.3, 22.6, 35.4 (3 CH$_2$); 38.9 (Me$_2$N); 43.8 (CHCN); 57.4, 57.6 (2 O—CH$_2$); 98.4 (OCHO); 105.2 (=C); 115.7 (CN); 121.5 (=CH).

Methyl 5-(2,2-diethoxyethyl)-1-dimethylamino-1,2,3,4-tetrahydropyridine-2-carboxylate (4b). A mixture of hydrazone **1b** and methyl acrylate was refluxed for 21 h. The yield of **4b** was 3.64 g (81%), b.p. 123 °C (1 Torr). Found (%): C, 59.82; H, 9.35; N, 9.40. $C_{15}H_{28}N_2O_4$. Calculated (%): C, 59.98; H, 9.39; N, 9.33. ^{1}H NMR, δ: 1.11—1.19 (m, 6 H, 2 MeCH$_2$); 1.85—2.23 (m, 6 H, 3 CH$_2$); 2.40 (s, 6 H, Me$_2$N); 3.37—3.47, 3.54—3.67 (both m, 2 H + 3 H, 2 CH$_2$O and CHN); 3.70 (s, 3 H, OMe); 4.44—4.49 (m, 1 H, OCHO); 5.95 (s, 1 H, =CH). ^{13}C NMR, δ: 15.3 (2 MeCH$_2$); 24.5, 26.0, 39.4 (3 CH$_2$); 41.8 (Me$_2$N); 59.6 (OMe); 61.1 (2 CH$_2$O); 102.5 (OCHO); 109.5 (=C); 126.0 (=CH); 173.7 (CO$_2$Me).

1-Dimethylamino-5-[2-(1,3-dioxolan-2-yl)ethyl]-1,2,3,4-tetrahydropyridine-2-carbonitrile (4c). A mixture of hydrazone **1c** and acrylonitrile was refluxed for 19 h. The yield of **4c** was 2.9 g (77%), b.p. 140 °C (1 Torr). Found (%): C, 61.89; H, 8.37; N, 16.77. $C_{13}H_{21}N_3O_2$. Calculated (%): C, 62.13; H, 8.42; N, 16.72. ^{1}H NMR, δ: 1.65—1.76, 1.87—2.18 (both m, 2 H + 6 H, 4 CH$_2$); 2.46 (s, 6 H, Me$_2$N); 3.79—3.82, 3.90—3.94 (both m, 2 H each, OCH$_2$CH$_2$O); 4.01—4.03 (m, 1 H, CHCN); 4.79—4.83 (m, 1 H, OCHO); 5.86 (s, 1 H, =CH). ^{13}C NMR, δ: 22.3, 26.3, 29.0, 32.0 (4 CH$_2$); 42.6 (Me$_2$N); 47.8 (CHN); 64.6 (OCH$_2$CH$_2$O); 103.7 (OCHO); 112.8 (=C); 119.6 (CN); 123.1 (=CHN).

Methyl 1-dimethylamino-5-[2-(1,3-dioxolan-2-yl)ethyl]-1,2,3,4-tetrahydropyridine-2-carboxylate (4d). A mixture of hydrazone **1c** and methyl acrylate was refluxed for 23 h. The yield of **4d** was 3.70 g (87%), b.p. 152—156 °C (1 Torr). Found (%): C, 59.02; H, 8.44; N, 9.92. $C_{14}H_{24}N_2O_4$. Calculated (%): C, 59.14; H, 8.51; N, 9.85. ^{1}H NMR, δ: 1.63—1.74, 1.76—1.87, 1.88—2.09 (all m, 2 H + 1 H + 5 H, 4 CH$_2$); 2.37 (s, 6 H, Me$_2$N); 3.59—3.72 (m, 4 H, OMe and CHCN); 3.78—3.86, 3.89—3.94 (both m, 2 H each, OCH$_2$CH$_2$O); 4.77—4.84 (m, 1 H, OCHO); 5.88 (s, 1 H, H(6)). ^{13}C NMR, δ: 23.5, 25.8, 29.1, 32.0 (4 CH$_2$); 41.4 (Me$_2$N); 51.5 (OMe); 59.6 (CHN); 64.5 (OCH$_2$CH$_2$O); 103.8 (OCHO); 113.0 (=C); 123.5 (=CH); 173.4 (CO$_2$Me).

8-Dimethylamino-4-ethoxymethylene-8-azabicyclo[3.2.1]octane-1,6-dicarbonitrile (8) (a 4 : 1 crystal solvate with benzene). A mixture of hydrazone **1a** (2 g, 10 mmol) and acrylonitrile (8 mL, 6.4 g, 120 mmol) was refluxed for 12 h. Excess acrylonitrile was evaporated *in vacuo*. The residue was dissolved in 5 mL of benzene, and 15 mL of hexane was added. The separated oil was left for crystallization for ~12 h. The crystals were filtered off, washed with a slight amount of hexane, and dried in air. Yield 2.2 g (79%), m.p. 97.5—98.5 °C. Found (%): C, 66.44; H, 7.92; N, 19.85. $C_{62}H_{86}N_{16}O_4$. Calculated (%): C, 66.52; H, 7.74; N, 20.02. ^{1}H NMR, δ: 1.30 (t, 3 H, MeCH$_2$, J = 7.0 Hz); 1.75—1.85, 2.38—2.48 (both m, 1 H each, CH$_2$C); 2.24—2.34, 2.77—2.87, 2.88—2.95 (all m, 2 H + 1 H + + 1 H, =CCH$_2$ and CH$_2$CHN); 2.64 (s, 6 H, NMe$_2$); 3.31—3.41 (m, 1 H, CHCN); 3.88 (q, 2 H, CH$_2$O, J = 7.0 Hz); 4.10 (d, 1 H, CHN, J = 5.9 Hz); 6.06 (d, 1 H, CH=C, J = 2.4 Hz); 7.42 (s, 1.5 H, 0.25 PhH). ^{13}C NMR, δ: 15.3 (MeCH$_2$); 16.7 (CH$_2$C=); 29.2 (CH$_2$CH$_2$CCN); 31.1 (CHCN); 36.4 (NCCHCH$_2$CCN); 46.8 (NMe$_2$); 58.3 (CHN); 60.1 (CCN); 68.1 (OCH$_2$); 107.9 (=C); 118.5 (CHCN); 120.3 (CCN); 128.3 (PhH); 143.4 (OCH=).

This work was financially supported by the Program of the Presidium of the Russian Academy of Sciences "Targeted Synthesis of Compounds with Specified Properties and Development of Functional Materials Based on Them" (State Contract No. 10002-251/P-09/118-125/100603-587 2KN01-03).

References

1. D. L. Boger, *Chem. Rev.*, 1986, **86**, 781; D. L. Boger and S. W. Weinreb, *Hetero Diels—Alder Methodology in Organic Synthesis*, Academic Press, New York, 1987.
2. E. Pascual-Alfonso, C. Avendano, and J. C. Menendez, *Synlett*, 2000, 205.
3. J. Barluenga and M. Tomas, *Adv. Heterocycl. Chem.*, 1993, **57**, 1.
4. A. B. Koldobsky, V. E. Vakhmistrov, and V. N. Kalinin, *Dokl. Akad. Nauk*, 1996, **346**, 771 [*Dokl. Chem.*, 1996 (Engl. Transl.)].
5. N. P. Tsvetkov, V. E. Vakhmistrov, A. B. Koldobsky, A. A. Korlyukov, and V. N. Kalinin, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 308 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 326].
6. N. P. Tsvetkov, V. E. Vakhmistrov, A. B. Koldobsky, and V. N. Kalinin, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1707 [*Russ. Chem. Bull.*, 1999, **48**, 1685 (Engl. Transl.)].

Received September 10, 2003;
in revised form October 29, 2003