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Alkylation of Methylene-Active Compounds with Halo Acetals and Hydrolysis of the Alkylation Products

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Abstract—A preparative procedure has been proposed for the alkylation of CH acids with halo acetals and hydrolysis of the alkylation products to furan derivatives and lactones.

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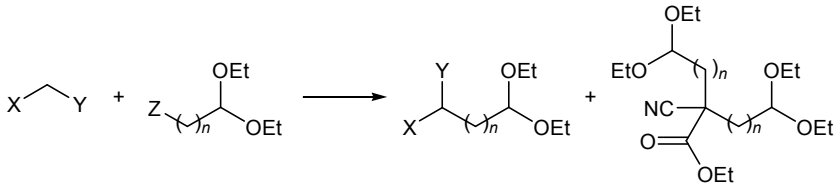
Alkylation of compounds containing an activated methylene group with halo- and polyhaloalkanes and alkenes was the subject of a number of studies [1–4]. However, there are no published data on introduction of an aldehyde fragment via C-alkylation of methylene-active compounds. Alkylation of the latter with halo aldehydes is inappropriate since the initial reactants and products are capable of undergoing various base-catalyzed transformations, which leads to considerable reduction of the yield. The use of acetal protection seems to be convenient for the above purpose.

Herein, we report a convenient preparative procedure for the alkylation of methylene-active compounds with halo acetals in DMSO in the presence of potassium carbonate. The alkylation of acetylacetone (**1a**), ethyl acetoacetate (**1b**), and ethyl cyanoacetate (**1c**) in DMSO in the presence of excess K_2CO_3 with bromoacetaldehyde diethyl acetal (**2a**) and 3-chloropropionaldehyde diethyl acetal (**2b**) afforded the corresponding *C*-monoalkyl derivatives **3**–**7** (Scheme 1). In the reactions of **2a** and **2b** with **1c** *C*,*C*-dialkyl derivatives **8** and **9** were also formed. No *O*-alkylation products were detected. The ratio of the mono- and dialkylation products of **1c** depended on the reaction conditions and was 70:30 at 20–30°C. Elevated temperature favored formation of dialkyl derivatives.

The alkylation of 5,5-dimethylcyclohexane-1,3-dione (**10**, dimedone) with acetal **2a** in DMSO in-

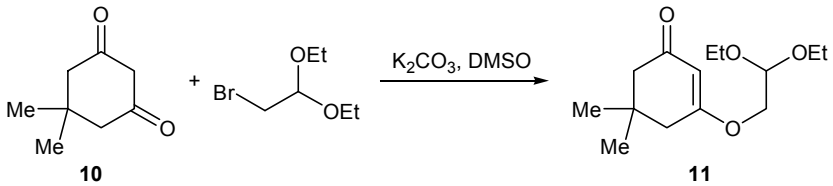
Scheme 1.



1a–1c **2a**, **2b** **3–7** **8**, **9**

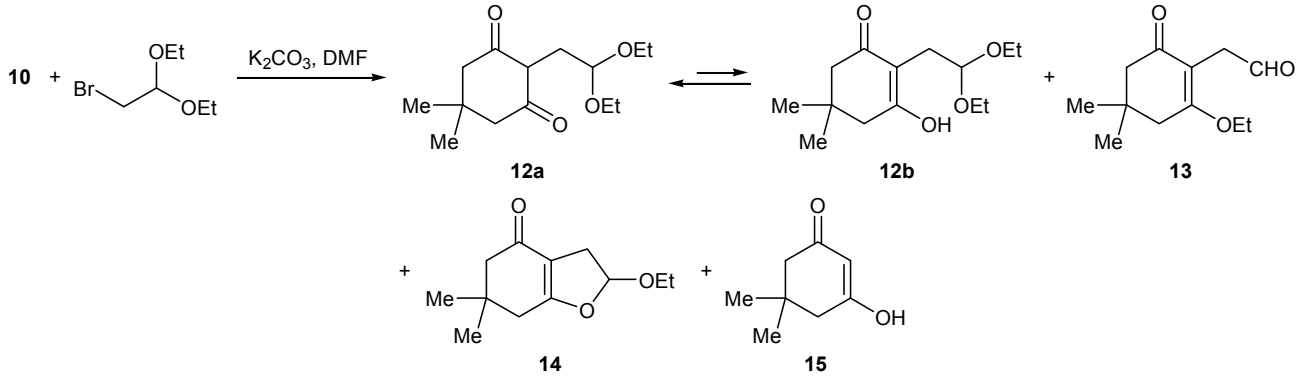
1, X = Y = Ac (**a**); Y = COOEt: X = Ac (**b**), CN (**c**); **2**, Z = Br, *n* = 1 (**a**); Z = Cl, *n* = 2 (**b**); **3**, X = Y = Ac; Y = COOEt, **4**, **5**, X = Ac; **6**, **7**, X = CN; **3**, **4**, **6**, **8**, *n* = 1; **5**, **7**, **9**, *n* = 2.

Scheme 2.

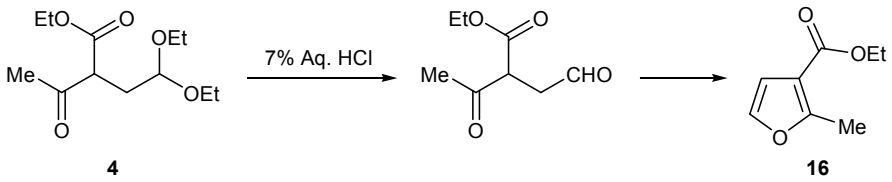


10 **11**

Scheme 3.



Scheme 4.



volved exclusively the oxygen atom to give enol ether **11** (Scheme 2). When the reaction was carried out in DMF, the product mixture contained mainly *C*-alkyl derivative **12** and products of its subsequent transformations, enol ether **13**, hexahydrobenzofuran derivative **14**, and dimedone enol **15** (Scheme 3).

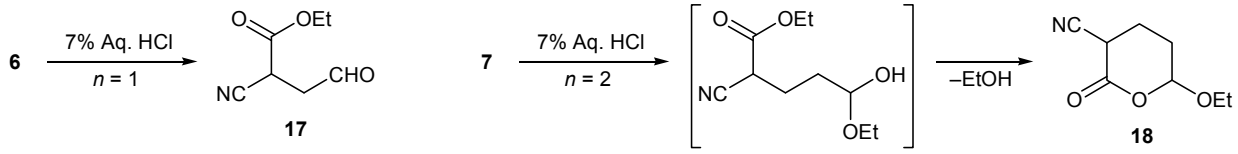
The resulting acetals were readily hydrolyzed with 7% aqueous HCl to the corresponding aldehydes. The aldehydes obtained from acetylacetone and ethyl acetoacetate derivatives turned out to be unstable and underwent intramolecular cyclization to furan **16** (Scheme 4). The hydrolysis of acetals **6** and **7** and diacetal **8** involved exclusively the acetal moiety, while the cyano group remained intact. This was confirmed by IR and NMR spectra. Acetal **6** was hydrolyzed to aldehyde **17**, whereas acetal **7** was converted into lactone **18** instead of the expected aldehyde (Scheme 5). Presumably, lactone **18** was formed as a result of cyclization of intermediate hemiacetal with participation of the ester group.

Likewise, the hydrolysis of bis(diethyl acetal) **8** afforded lactone **19** rather than expected dialdehyde via cyclization of intermediate hemiacetal with elimination of ethanol (Scheme 6).

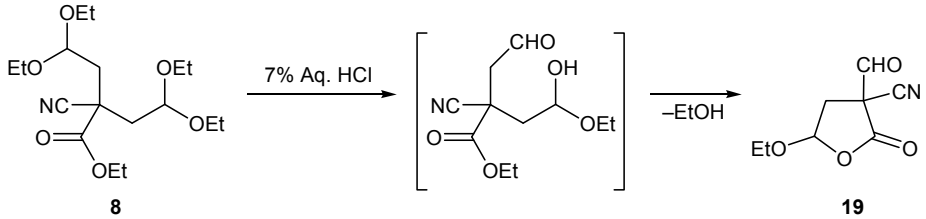
EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AV-300 spectrometer at 300 and 75 MHz, respectively, using TMS as internal reference. The IR spectra were measured on a Varian-300(FT-X) instrument from samples prepared as thin films.

Scheme 5.



Scheme 6.



General procedure for the alkylation of methylene-active compounds. Halo acetal **2a** or **2b**, 0.25 mol, was added with stirring to a mixture of 0.25 mol of the corresponding CH acid and 28 g (0.2 mol) of calcined potassium carbonate in 100 mL of DMSO. The mixture was stirred for 15 h at 70–80°C (in the reactions with **2a**), or at 100–120°C (**2b**), cooled, and treated with water and diethyl ether (2×100 mL). The combined extracts were dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure.

3-(2,2-Diethoxyethyl)pentane-2,4-dione (3) was synthesized from 25 g (0.25 mol) of **1a** and 49 g (0.25 mol) of **2a**. Yield 32 g (48%), bp 108–111°C (10 mm), n_D^{20} = 1.4483. IR spectrum, ν, cm^{-1}: 3464 (OH, enol), 1727, 1704, 1682 (C=O), 1600 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.00–1.25 m (8H, CHC**H**$_2$CH, CH$_3$), 2.20 q (2H, CH$_2$, ^3J = 7.5), 2.25 s (6H, CH$_3$CO), 3.30 t (1H, CHCO, ^3J = 7.5), 4.10 q (4H, CH$_2$O, ^3J = 6.4), 4.68 t [1H, C**H**(OEt)$_2$, ^3J = 9]. ^{13}C NMR spectrum, δ$_C$, ppm: 18 (CH$_2$**C**H$_3$), 29 (**C**H$_3$C), 42 (CH), 62 (OCH$_2$), 70 (CH), 102 (CH), 202 (CO). Found, %: C 60.83; H 9.14. C$_{11}$H$_{20}$O$_4$. Calculated, %: C 61.11; H 9.25.

Ethyl 2-acetyl-4,4-diethoxybutanoate (4) was synthesized from 30 g (0.25 mol) of **1b** and 49 g (0.25 mol) of **2a**. Yield 25 g (44%), bp 114–116°C, n_D^{20} = 1.4370. IR spectrum, ν, cm^{-1}: 1753 (C=O, ester), 1727 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.2 m (6H, CH$_3$), 1.25 t (3H, CH$_3$, ^3J = 6.4), 2.20 q (2H, CH$_2$, ^3J = 7.5), 2.25 s (3H, CH$_3$CO), 3.40–3.70 m (5H, OCH$_2$, CH), 4.18 q (2H, CH$_2$O, ^3J = 6.4), 4.50 t [1H, C**H**(OEt)$_2$, ^3J = 9.5]. ^{13}C NMR spectrum, δ$_C$, ppm: 19 (CH$_2$**C**H$_3$), 30 (**C**H$_3$CO), 42 (CH**C**H$_2$), 62 (OCH$_2$), 72 (CH), 99 (CHO), 165 (C=O), 203 (C=O). Found, %: C 57.83; H 8.61. C$_{12}$H$_{22}$O$_5$. Calculated, %: C 58.06; H 8.87.

Ethyl 2-acetyl-5,5-diethoxypentanoate (5) was synthesized from 30 g (0.25 mol) of **1b** and 42 g (0.25 mol) of **2b**. Yield 28.5 g (42%), bp 121–123°C (2 mm), n_D^{20} = 1.4247. IR spectrum, ν, cm^{-1}: 1753 (C=O, ester), 1727 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 m (8H, CH$_3$, CHC**H**$_2$), 1.25 t (3H, CH$_3$, ^3J = 6.4), 2.20 m (1H, CH$_2$C**H**), 2.25 s (3H, CH$_3$C=O), 3.40–3.70 m (5H, OCH$_2$, CH), 4.18 q (2H, CH$_2$O, ^3J = 6.4), 4.50 t [1H, C**H**(OEt)$_2$, ^3J = 9]. ^{13}C NMR spectrum, δ$_C$, ppm: 18 (CH$_2$**C**H$_3$), 20.50 (CH$_2$CH$_2$), 29 (**C**H$_3$CO), 42 (CH**C**H$_2$), 62 (OCH$_2$), 72 (CH), 99 (CHO), 165 (C=O), 203 (CH$_3$**C**O). Found, %: C 59.64; H 9.11. C$_{13}$H$_{24}$O$_5$. Calculated, %: C 60.00; H 9.23.

Ethyl 2-cyano-4,4-diethoxybutanoate (6) was synthesized from 30 g (0.25 mol) of **1c** and 30 g (0.25 mol) of **2a**. Yield 26 g (38%), bp 105–106°C (2 mm), n_D^{20} = 1.4287. IR spectrum, ν, cm^{-1}: 2264 (CN), 1753 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10–1.28 m (6H, CH$_3$), 1.30 t (3H, CH$_3$), 2.25 q (2H, CCH$_2$C, ^3J = 9), 3.50 t (1H, CH, ^3J = 8.5), 3.60–3.80 m (4H, OCH$_2$), 4.20 q (2H, CH$_2$O, ^3J = 6.4), 4.70 t [1H, C**H**(OEt)$_2$, ^3J = 9]. ^{13}C NMR spectrum, δ$_C$, ppm: 18 (CH$_2$**C**H$_3$), 41.70 (CH**C**H$_2$), 62 (OCH$_2$), 72 (CH), 99 (CHO), 118 (CN), 165 (C=O). Found, %: C 57.38; H 8.01; N 5.79. C$_{11}$H$_{19}$NO$_4$. Calculated, %: C 57.64; H 8.29; N 6.11.

Ethyl 2-cyano-5,5-diethoxypentanoate (7) was synthesized from 30 g (0.25 mol) of **1c** and 42 g (0.25 mol) of **2b**. Yield 19 g (33%), bp 128–130°C (2 mm), n_D^{20} = 1.4363. IR spectrum, ν, cm^{-1}: 2263 (CN), 1756 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90–1.40 m (11H, CH$_3$, CC**H**$_2$CH$_2$), 2.30 m (2H, CH$_2$CH$_2$), 3.60–3.80 m (5H, CH$_2$O, CHC=O), 4.20 q (2H, CH$_2$O, ^3J = 6.4), 4.60 t [1H, C**H**(EtO)$_2$, ^3J = 9]. ^{13}C NMR spectrum, δ$_C$, ppm: 17.6 (CH$_2$**C**H$_3$), 20.6 (**C**H$_2$CH), 41.7 (**C**HCH$_2$), 62 (OCH$_2$), 72 (CH), 99 (CHO), 118 (CN), 165 (C=O). Found, %: C 58.93; H 8.41; N 4.51. C$_{12}$H$_{21}$NO$_4$. Calculated, %: C 59.27; H 8.61; N 5.76.

Ethyl 2-cyano-2-(2,2-diethoxyethyl)-4,4-diethoxybutanoate (8). Yield 13.5 g (30%), bp 135–137°C (2 mm), n_D^{20} = 1.4375. IR spectrum, ν, cm^{-1}: 2236 (CN), 1753 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10–1.28 m (12H, CH$_3$), 1.30 t (3H, CH$_3$, ^3J = 6.4), 2.10 d. (4H, CCH$_2$C, ^3J = 9), 3.45–3.60 q (8H, CH$_2$O, ^3J = 6.4), 4.20 q (2H, CH$_2$O, ^3J = 6.4), 4.78 t [2H, C**H**(OEt)$_2$, ^3J = 8.5]. ^{13}C NMR spectrum, δ$_C$, ppm: 19 (CH$_2$**C**H$_3$), 41 (CH$_2$), 33.3 (NC**C**), 62 (OCH$_2$), 101 (CHO), 118 (CN), 165 (C=O). Found, %: C 59.01; H 8.73; N 4.21. C$_{17}$H$_{32}$NO$_6$. Calculated, %: C 58.13; H 9.28; N 4.05.

Ethyl 2-cyano-2-(3,3-diethoxypropyl)-5,5-diethoxypentanoate (9). Yield 11 g (13%), bp 153–155°C (2 mm), n_D^{20} = 1.4432. IR spectrum, ν, cm^{-1}: 2236 (CN), 1753 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10–1.28 m (16H, CH$_3$, CH$_2$CH$_2$), 1.30 t (3H, CH$_3$, ^3J = 6.4), 2.10 m (4H, CH$_2$CH$_2$), 3.40–3.60 q (8H, CH$_2$O, ^3J = 6.4), 4.20 q (2H, CH$_2$O, ^3J = 6.4), 4.78 t [2H, C**H**(OEt)$_2$, ^3J = 9]. ^{13}C NMR spectrum, δ$_C$, ppm: 19 (CH$_2$**C**H$_3$), 20.5 (**C**H$_2$CH), 41 (CH$_2$), 32 (NC**C**), 62 (OCH$_2$), 99 (CHO), 118 (CN), 165 (C=O). Found, %: C 60.68; H 9.03; N 3.47. C$_{19}$H$_{35}$NO$_6$. Calculated, %: C 61.12; H 9.38; N 3.75.

3-(2,2-Diethoxyethoxy)-5,5-dimethylcyclohex-2-en-1-one (11) was synthesized from 35 g (0.25 mol) of **10** and 52 g (0.25 mol) of **2a**. Yield 13.7 g (6 1%), bp 145–150°C (10 mm). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 s (6H, CH_3), 1.20 t (6H, CH_3, ^3J = 6.4), 2.20 s (2H, CH_2C=), 2.35 s (2H, CH_2C=O), 3.60 m and 3.70 m (4H, OC**H**$_2$CH$_3$), 3.85 d (2H, OCH_2, ^3J = 9), 4.80 t (1H, CH, ^3J = 9), 5.30 s (1H, CH=). Found, %: C 63.27; H 8.89. $C_{14}H_{22}O_4$. Calculated, %: C 65.62; H 9.37.

Compounds 12–15. Following the above general procedure, 52 g (0.25 mol) of acetal **2a** was added to a solution of 35 g (0.25 mol) of **10** and 30 g (0.22 mol) of K_2CO_3 in 100 mL of DMF. The diethyl ether extract divided into three layers after a time.

The upper ether layer was separated and evaporated to give 2-(2,2-diethoxyethyl)-5,5-dimethylcyclohexane-1,3-dione (**12**). Yield 5.1 g (23%), white crystals, mp 142°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): **12a**: 1.00 s (6H, CH_3), 1.10 t (6H, CH_3, ^3J = 6.4), 1.3 m (2H, CH_2), 2.20 s (4H, CH_2), 3.40 m and 3.60 m (4H, OC**H**$_2$CH$_3$), 3.50 t (1H, CHC=O, ^3J = 8), 4.20 t (1H, CH, ^3J = 9); **12b**: 2.25 d (2H, CH_2C=, ^3J = 9.5), 9.14 br.s (1H, OH). Found, %: C 64.21; H 8.87. $C_{14}H_{23}O_4$. Calculated, %: C 65.88; H 9.01.

The second layer was treated with butyl acetate, the extract was dried, and the solvent was distilled off to leave white crystals of a mixture of isomeric 2-(2-ethoxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-acetaldehyde (**13**) and 2-ethoxy-6,6-dimethyl-2,3,6,7-tetrahydro-1-benzofuran-4(5*H*)-one (**14**). Yield 4.7 g (28%). ^{1}H NMR spectrum (mixture **13**/**14**), δ, ppm: 0.90 s (6H, CH_3), 1.10 t (3H, CH_3, ^3J = 6.4 Hz), 2.20 m (8H, CH_2), 3.50 m (2H, OCH_2), 4.20 m (OCH_2), 4.60 m (1H, CH_2C**H**O, ^3J = 9 Hz), 9.80 br.s (1H, CHO). Found, %: C 66.22; H 8.07. $C_{12}H_{18}O_3$. Calculated, %: C 68.57; H 8.57.

The third layer was filtered and treated with acetone–diethyl ether. The extract was evaporated to obtain 3-hydroxy-5,5-dimethylcyclohex-2-en-1-one (**15**). Yield 3.2 g (20%), yellow crystals, mp 138–140°C. ^{1}H NMR spectrum, δ, ppm: 0.90 s (6H, CH_3), 2.10 s (4H, CH_2), 5.20 s (1H, CH=), 10.90 br.s (1H, OH). Found, %: C 54.63; H 5.87. $C_8H_{12}O_4$. Calculated, %: C 55.81; H 6.97.

General procedure for the hydrolysis of acetals 4 and 6–8. A mixture of 0.1 mol of acetal **4** or **6–8** and 0.12 mol of 7% aqueous HCl was stirred for 3 h at 70–80°C. The product was isolated by distillation.

Ethyl 2-methylfuran-3-carboxylate (16) was obtained from 4.8 g of **4**. Yield 2.2 g (66%), bp 86–89°C (2 mm), n_D^{20} = 1.4554. IR spectrum, ν, cm^{-1}: 3100 (CH), 1756 (C=O), 1110 (COC). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 t (3H, CH_3, ^3J = 6.4), 2.20 s (3H, CH_3), 3.60 q (2H, OCH_2, ^3J = 6.4), 5.80 d (1H, 4′-H, ^3J = 2), 7.20 d (1H, 5′-H, ^3J = 2). ^{13}C NMR spectrum, δ_C, ppm: 18 (CH_2**C**H$_3$), 22 (CH_3), 63 (OCH_2), 109.9 and 143.3 (C^4, C^5), 203 (CO). Found, %: C 62.09; H 6.31. $C_8H_{10}O_3$. Calculated, %: C 62.33; H 6.42.

Ethyl 4-oxo-2-cyanobutanoate (17) was obtained from **6**. Yield 3.3 g (82%), bp 118–119°C (8 mm), n_D^{20} = 1.4390. IR spectrum, ν, cm^{-1}: 3489 (OH, enol), 2263 (CN), 1753 (C=O, ester), 1716 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 t (3H, CH_3, ^3J = 6.4), 2.30 m (2H, CH_2C=O), 3.20 t (1H, CHCN, ^3J = 8.50), 4.00 q (2H, OCH_2, ^3J = 6.4), 9.30 t (1H, CHO, ^3J = 2). Found, %: C 53.76; H 5.61; N 9.00. $C_7H_9NO_3$. Calculated, %: C 54.19, H 5.80; N 9.03.

6-Ethoxy-2-oxotetrahydro-2*H*-pyran-3-carbonitrile (18) was obtained from 8.5 g of **7**. Yield 5.2 g (88%), bp 130–132°C (10 mm), n_D^{20} = 1.4460. IR spectrum, ν, cm^{-1}: 2263 (CN), 1716 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 t (3H, CH_3), 1.20–1.40 m (4H, CH_2CH_2), 3.20 t (1H, CHCN, ^3J = 8), 4.20 q (2H, OCH_2, ^3J = 6.4), 4.80 t (1H, C**H**OEt, ^3J = 9). ^{13}C NMR spectrum, δ_C, ppm: 18 (CH_2**C**H$_3$), 20 and 23 (CH_2CH_2), 33.3 (**C**HCN), 63 (OCH_2), 97 (CHO), 118 (CN). Found, %: C 56.63; H 6.21; N 8.04. $C_8H_{10}NO_3$. Calculated, %: C 56.82; H 6.50; N 8.28.

5-Ethoxy-2-oxo-3-(2-oxoethyl)oxolane-3-carbonitrile (19) was obtained from 12 g of **8**. Yield 5.6 g (80%), bp 143–146°C (2 mm), n_D^{20} = 1.4465. IR spectrum, ν, cm^{-1}: 2263 (CN), 1760 (C=O), 1716 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 t (3H, CH_3, ^3J = 6.4), 1.40 d (2H, 4-H, ^3J = 2), 2.85 d (2H, 3-CH_2, ^3J = 2), 3.6 m (2H, OCH_2), 4.70 t (1H, 5-H, ^3J = 8.5), 9.30 t (1H, CHO, ^3J = 2). ^{13}C NMR spectrum, δ_C, ppm: 18 (CH_2**C**H$_3$), 22 (C^4), 30 (C^3), 43.6 (3-CH_2), 63 (OCH_2), 66.7 (C^5), 118 (CN), 178 (C^2), 203 (CHO). Found, %: C 54.44; H 5.29; N 6.83. $C_9H_{11}NO_4$. Calculated, %: C 54.82; H 5.58; N 7.10.

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