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Synthesis of 2-halo-6-hydroxy-5,5-dimethyl(ethyl)-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles by the reaction of tetracyanoethylene with aldehydes

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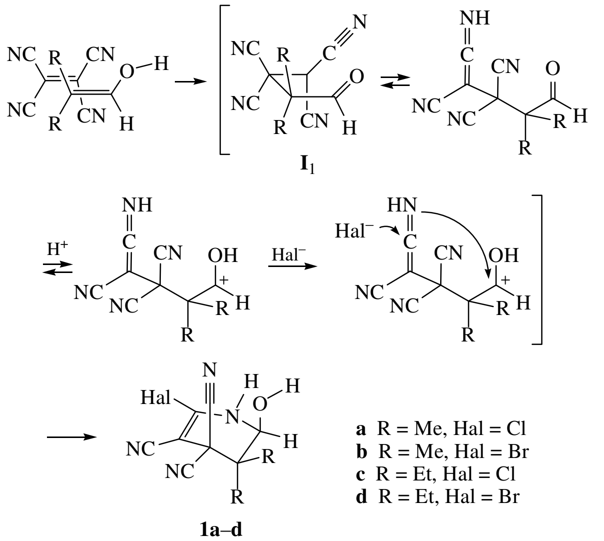
The reaction of tetracyanoethylene and isobutyraldehyde or 2-ethylbutanal in an excess of a hydrohalogen acid yields 2-halo-6-hydroxy-5,5-dimethyl(ethyl)-5,6-dihydro-3,4,4(1*H*)-pyridinetricarbonitriles, the crystal and molecular structures of which were characterised by IR, NMR, MS and X-ray analysis.

According to the chemistry of polynitriles,[1] tetracyanoethylene is a highly reactive pernitrile alkene. The synthesis and properties of its adducts with ketones are of considerable currently interest.[2] Some of them are promising anticancer drugs,[3] and others were used for the preparation of charge transfer complexes[4] and plane anion salts.[5] Despite a great number of publications on the tetracyanoethylation of carbonyl compounds,[1,2] information on the use of aldehydes in such transformations is absolutely missing.

It is well known that tetracyanoalkanones turn into dicyanopyridines in the presence of hydrohalogen acids.[6]



1a–d

We found that equimolar reactions of tetracyanoethylene with isobutyraldehyde or 2-ethylbutanal in THF or dioxane with an excess of a hydrohalogen acid yield 2-halo-6-hydroxy-5,5-dimethyl(ethyl)-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles **1a–d** in 58–64% yields.[†]

We assumed that the aldehyde interacts with tetracyanoethylene in the enol form leading to tetracyanoalkanal ($\mathbf{I}_1$).

According to published data,[7] nitriles react with aldehydes in the presence of acids. Therefore, we suggest that, in this case analogous processes take place. These are the protonation of the carbonyl group with the formation of a carbocation, which subsequently attacks the nitrile group as an electrophile simultaneously with halogen ion addition to the ketenimine moiety giving tetrahydropyridines **1a–d**.

We suppose this transformation is due to the nitrile–ketenimine tautomerization in intermediate $\mathbf{I}_1$, resulting in a high reactivity of terminal cyano groups towards electrophiles and also explaining the regioselective addition of halogen anion.

Compounds **1a–d** are stable and melt without decomposition.

The crystal and molecular structures of compounds **1a–d** were confirmed by IR and ^{1}H NMR spectroscopy, mass spectrometry[‡] and X-ray analysis (for **1a**).[§]

The test compounds contain spatially close nucleophilic and electrophilic centres, 1,3-diaxial hydroxy and cyano substituents of the tetrahydropyridine ring. Isolation of compounds with similar disposition of cyano and hydroxy groups is usually uncommon because of interaction of these moieties.[1(*d*)] According to X-ray analysis in our case, these groups are not only spatially close but also form far interactions between the unshared electron pair of oxygen and the electron-seeking π bond of the cyano group [O···C 2.722(2) Å]. This distance is noticeably smaller than the sums of van der Waals radii of appropriate oxygen and nitrogen atoms. The intramolecular angles C(6)–O···C(9) and O–C(6)···C(4) are equal to 90.9(1) and 90.6(1)°, respectively. In other words, the oxygen atom and the cyano group form spatial *n*,π interaction.

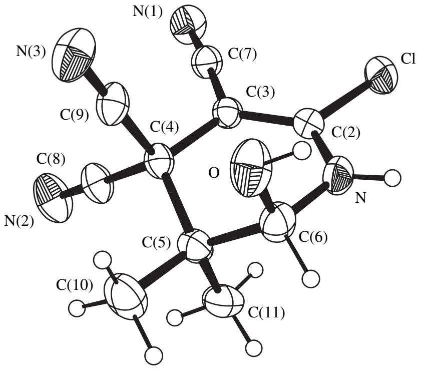


Figure 1 The view of **1a**, showing the atom-numbering scheme and 30% probability ellipsoids. Bond lengths (Å): Cl(1)–C(2) 1.7120(19), O–C(6) 1.395(3), N–C(2) 1.326(2), N–C(6) 1.448(3), N(1)–C(7) 1.144(2), N(2)–C(8) 1.131(3), N(3)–C(9) 1.134(3), C(2)–C(3) 1.358(2), C(3)–C(7) 1.406(2), C(3)–C(4) 1.521(2), C(4)–C(9) 1.483(3), C(4)–C(8) 1.486(2), C(4)–C(5) 1.572(3), C(5)–C(10) 1.529(3), C(5)–C(6) 1.531(3), C(5)–C(11) 1.532(3).

Table 1 Energy of formation of compounds **1a–d** and **1a–d** – H_2O.

Compound	Energy of formation/ kkal mol^{-1}	Energy of formation of dehydroxy derivatives/ kkal mol^{-1}
1a	67.9	134.4
1b	82.4	150.3
1c	67.3	128.8
1d	81.8	144.7

We suppose that such a combination of functional groups in the molecules of **1a–d** can be explained by reduced nucleophilic properties of the hydroxy group. It can be determined by quantum-mechanical calculations (PM3 method, HyperChem program) for the molecule of tetrahydropyridine **1a**. Low electron density of HOMO on the hydroxy group of **1a** indicates its reduced nucleophilic properties in an unexcited state. While appropriate the cyano group has reduced electrophilic properties because of a low electron density of its LUMO.

Hydroxy and amino groups at one carbon atom is the second low-stable combination. Such a vicinity without the removal of water is possible due to strong far interactions between the oxygen atom and the cyano group, as well as by torsional stress

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[†] *General procedure.* To a solution of tetracyanoethylene (0.005 mol) in 15 ml of dioxane were added 0.005 mol of isobutyraldehyde (or 2-ethylpropanal) and 1–2 ml of hydrochloric or hydrobromic acid. The solution was heated at 50–60 °C. The reaction was controlled by a hydroquinone test. After 1.5 h, the reaction mixture cooled to room temperature and was diluted with water (50 ml). The precipitate was filtered off and washed with water and diethyl ether.

[‡] *2-Chloro-6-hydroxy-5,5-dimethyl-5,6-dihydro-3,4,4(1*H*)-pyridinetricarbonitrile* **1a**: 65% yield, mp 220–223 °C. IR (ν_{max}/cm^{-1}): 3200–3400 ($\nu_{NH,OH}$), 2250 ($\nu_{C\equiv N}$), 2220 ($\nu_{C\equiv N}$). ^{1}H NMR (500 MHz, [$^2H_6$]DMSO) δ: 10.05 (s, 1H, NH), 7.2 (d, 1H, OH, *J* 4.3 Hz), 4.67 (d, 1H, CH, *J* 4.3 Hz), 1.37 (s, 3H, Me), 1.07 (s, 3H, Me). MS, *m/z*: 236 (M$^+$). Found (%): C, 50.63; H, 3.96; Cl, 14.85; N, 23.48. Calc. for $C_{10}H_9ClN_4O$ (%): C, 50.75; H, 3.83; Cl, 14.98; N, 23.67.

*2-Bromo-6-hydroxy-5,5-dimethyl-5,6-dihydro-3,4,4(1*H*)-pyridinetricarbonitrile* **1b**: 67% yield, mp 240–243 °C. IR, (ν_{max}/cm^{-1}): 3200–3400 ($\nu_{NH,OH}$), 2260 ($\nu_{C\equiv N}$), 2220 ($\nu_{C\equiv N}$). ^{1}H NMR (500 MHz, [$^2H_6$]DMSO) δ: 9.9 (s, 1H, NH), 7.14 (d, 1H, OH, *J* 3.7 Hz), 4.59 (d, 1H, CH, *J* 3.7 Hz), 1.37 (s, 3H, Me), 1.01 (s, 3H, Me). MS, *m/z*: 280 (M$^+$). Found (%): C, 42.68; H, 3.32; Br, 28.14; N, 19.75. Calc. for $C_{10}H_9BrN_4O$ (%): C, 42.73; H, 3.23; Br, 28.42; N, 19.93.

*2-Chloro-5,5-diethyl-6-hydroxy-5,6-dihydro-3,4,4(1*H*)-pyridinetricarbonitrile* **1c**: 57% yield, mp 178–180 °C. IR (ν_{max}/cm^{-1}): 3200–3400 ($\nu_{NH,OH}$), 2260 ($\nu_{C\equiv N}$), 2220 ($\nu_{C\equiv N}$). ^{1}H NMR (500 MHz, [$^2H_6$]DMSO) δ: 10.10 (d, 1H, NH), 7.18 (d, 1H, OH), 4.62 (t, 1H, CH), 2.05, 1.8, 1.75, 1.23 (m, 4H), 1.05 (t, 3H, Me), 0.93 (t, 3H, Me). MS, *m/z*: 264 (M$^+$). Found (%): C, 54.32; H, 5.04; Cl, 13.35; N, 21.08. Calc. for $C_{12}H_{13}ClN_4O$ (%): C, 54.45; H, 4.95; Cl, 13.39; N, 21.17.

*2-Bromo-5,5-diethyl-6-hydroxy-5,6-dihydro-3,4,4(1*H*)-pyridinetricarbonitrile* **1d**: 55% yield, mp 195–196 °C. IR (ν_{max}/cm^{-1}): 3200–3400 ($\nu_{NH,OH}$), 2260 ($\nu_{C\equiv N}$), 2220 ($\nu_{C\equiv N}$). ^{1}H NMR (500 MHz, [$^2H_6$]DMSO) δ: 10.00 (d, 1H, NH), 7.15 (s, 1H, OH), 4.58 (d, 1H, CH), 2.05, 1.8, 1.75, 1.23 (m, 4H), 1.08 (t, 3H, Me), 0.93 (t, 3H, Me). MS, *m/z*: 308 (M$^+$). Found (%): C, 46.49; H, 4.12; Br, 28.70; N, 18.06. Calc. for $C_{12}H_{13}BrN_4O$ (%): C, 46.62; H, 4.24; Br, 28.85; N, 18.12.

[§] *Crystallographic data for* **1a**: at 293(2) K, the crystals of $C_{10}H_9ClN_4O$ are monoclinic, space group $P2_1/c$, $a = 7.7222(7)$, $b = 14.0155(10)$, $c = 10.8273(10)$ Å, $\beta = 97.707(10)°$, $V = 1161.26(17)$ Å^3, $Z = 4$, $M = 236.66$, $d_{calc} = 1.354$ g cm^{-3}. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 267559. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2006.

caused by the repulsion of cyano and methyl groups in the case of water removal. This fact was supported by quantum-mechanical calculations (Table 1).

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