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Intermolecular Reductive Heterocyclization of Potassium 2-Acyl-1,1,3,3-tetracyanopropenides

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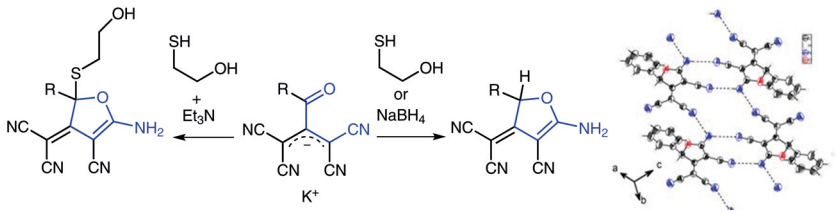

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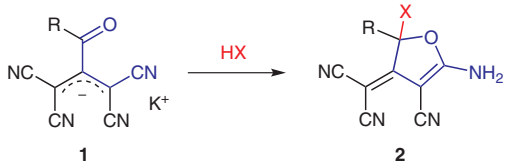
Abstract 2-Acyl-1,1,3,3-tetracyanopropenides undergo intermolecular reductive heterocyclization under the action of mercaptoethanol or sodium borohydride, resulting in the formation of 2-[5-amino-4-cyano-2-alkyl(aryl)furan-3(2*H*]-ylidene)malononitriles in high yields and excellent purities, These are of interest as potential precursors to organic nonlinear optical (NLO) materials and prospective antibiofilm antimicrobial agents.

Key words furans, heterocycles, nucleophilic addition, reduction, ring closure

2-Acyl-1,1,3,3-tetracyanopropenides **1**[1] are prospective starting compounds for the synthesis of various heterocycles. The presence of two types of electrophilic centers, a carbonyl group and the cyano groups in the anions of salts **1**, give rise to a heterocyclization pathway under the action of nucleophilic reagents resulting in the formation of five-membered heterocycles. We previously described the transformation of salts **1** into dihydrofuran derivatives (Scheme 1) via reactions with alcohols and oximes (X = OR'),[2] thiols (X = SR'),[3] and hydrogen halides (X = Cl, Br).[4]



Scheme 1 Synthesis of dihydrofuran derivatives via the reactions of 2-acyl-1,1,3,3-tetracyanopropenides with nucleophilic reagents

The presence of several reaction centers in compounds **2** gives rise to many possible heteroannulation pathways leading to the formation of 2-amino-3-cyanodihydrofurans for instance. The presence of an *ortho*-enaminonitrile fragment in such structures allows annulation of other heterocycles onto the furan. Annulation reactions of pyridines,[5] pyrimidines,[6] thiazines,[7] thiazaphosphines,[8] and dimerization[9] reactions are well known and examples of recyclization of 2-amino-3-cyanodihydrofurans into cyclopropanecarboxamide[10] and pyran[11] derivatives are also known.

In addition, dihydrofurans **2** are highly electron-deficient due to the dicyanomethylene fragment conjugated with the cyano group through the dihydrofuran cycle and can be used as an electron acceptor for the preparation of organic nonlinear optical (NLO) chromophores.[12] One of the most applicable electron acceptors widely used for this purpose is 4,5,5-trimethyl-3-cyano-2-(5*H*)-furanylidenepropane-dinitrile (TCF, Figure 1). TCF has gained interest as a strong acceptor end group suitable for incorporation into stable, high β-chromophores.[13,14] Dihydrofurans **2** are structural analogues of TCF, in this case the π-linker can bridge by means of the amino group through azomethine- or azo-group formation. The ability to vary the R and X substitution is important for the design of novel NLO chromophores.

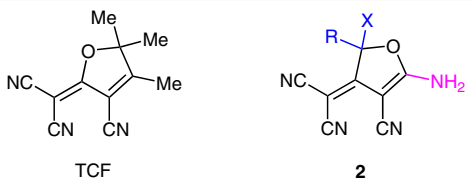
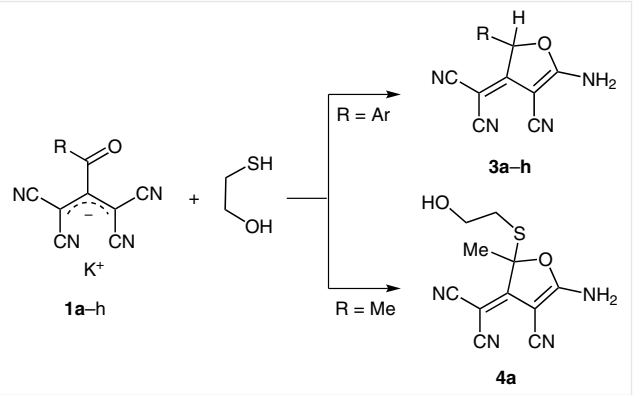


Figure 1

Furthermore, certain furan derivatives are considered as signaling molecules in certain Gram positive and Gram negative bacteria.[15] It is known that furan derivatives are able to suppress biofilm formation of Gram positive[16] and Gram negative[17] bacterial pathogens, including anaerobes.[18] Such compounds were as active against biofilm bacteria as planktonic bacteria in the same concentration, while biofilm bacteria were resistant to classical antibiotics at doses those needed to kill planktonic bacteria. Dihydrofurans **2** are therefore also of interest as potential antagonists of bacterial signaling molecules and therefore candidates for a new class of antibacterial agent with a completely novel mechanism of action. Our studies into the reductive intermolecular heterocyclization of 2-acyl-1,1,3,3-tetracyanopropenides **1** leading to dihydrofurans **2** with X = H formation are described in this Letter.

We have previously described the transformation of propenides **1** into 2-[5-amino-4-cyano-2-arylfuran-3(2*H*)-ylidene]malononitriles **3** in low yields under the action of concentrated hydroiodic acid.[19] However, this reductant has a range of disadvantages such as low reaction selectivity and possibility of side reactions. In this Letter, we describe the interaction of salts **1** with other reductants. For this purpose, sodium borohydride and mercaptoethanol were used.

The reaction of propenides **1** with mercaptoethanol in contrast to other thiols[3] does not need an acid catalyst and proceeds in aqueous solution at room temperature. This can be explained by the participation of the nonbonding electron pairs of the mercaptoethanol sulfur and oxygen atoms. The reaction is complete within a few minutes and leads to dihydrofurans **3** in 54–83% yields, depending on the structure of substituent R. The yields of **3** are reduced if R is an aromatic ring with electron-donating substituents (Table 1). In the case of propenides **1**, having a dimethoxybenzoyl group, compounds **3** are not formed. We have also found that propenide **1**, possessing an acetyl group in position 2, does not lead to formation of the corresponding 2-[5-amino-4-cyano-2-methylfuran-3(2*H*)-ylidene]malononitrile, but results in 2-[5-amino-4-cyano-2-(2-hydroxyethylthio)-2-methylfuran-3(2*H*)-ylidene]malononitrile (**4a**, Scheme 2).

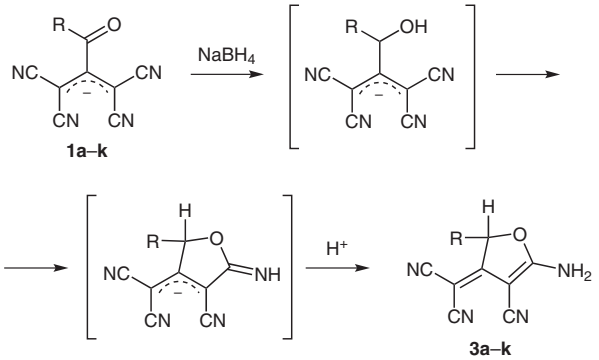


Scheme 2 Reaction of 2-acetyl(aroyl)-1,1,3,3-tetracyanopropenides **1** with mercaptoethanol

Table 1 Substituents and Yields of Dihydrofurans **3** and **4a** via the Reaction of Propenides **1** with Mercaptoethanol

Entry	Compd **3**	R	Yield (%)
1	**3a**	Ph	82
2	**3b**	4-ClC_6H_4	64
3	**3c**	4-MeC_6H_4	83
4	**3d**	4-$MeOC_6H_4$	54
5	**3e**	3-ClC_6H_4	73
6	**3f**	2,4-$Cl_2C_6H_3$	59
7	**3g**	4-PhC_6H_4	64
8	**3h**	2-thienyl	81
9	**4a**	Me	72

Sodium borohydride, in contrast to mercaptoethanol, is a more universal reductant. Propenides **1a–k** undergo reductive intermolecular heterocyclization under the action of aqueous sodium borohydride, followed by neutralization with the 5% sulfuric acid, resulting in the formation of the corresponding dihydrofurans **3** (Scheme 3) in 73–86% yields (Table 2).



Scheme 3 Reaction of 2-acyl-1,1,3,3-tetracyanopropenides **1** with sodium borohydride

The structure of dihydrofuran **3a** was established by single-crystal X-ray diffraction analysis (Figure 2 and Figure 3).[20]

In the crystal, neighboring molecules are linked to each other by means of hydrogen bonds N4–H1···N1 (symmetry code: x, 1+ y, z; distance N4–N1 is 2.934 Å) to form chains, which in turn, are linked in pairs with each other by means of center-symmetrical bonds N2–H5···N1 (symmetry code: 1–x, –y, 1–z; distance N2–N1 is 2.946 Å) to form 'tapes' running along the b axis.

Table 2 Substituents and Yields of Dihydrofurans **3a–k** via the Reaction of Propenides **1** with Sodium Borohydride

Entry	Compd **3**	R	Yield (%)
1	**3a**	Ph	86
2	**3b**	4-ClC_6H_4	79
3	**3c**	4-MeC_6H_4	81
4	**3d**	4-$MeOC_6H_4$	80
5	**3e**	3-ClC_6H_4	82
6	**3f**	2,4-$Cl_2C_6H_3$	81
7	**3g**	4-PhC_6H_4	79
8	**3h**	2-thienyl	84
9	**3i**	3,4-$(MeO)_2C_6H_3$	77
10	**3j**	2,5-$(MeO)_2C_6H_3$	73
11	**3k**	Me	62
12	**3a**	Ph	86

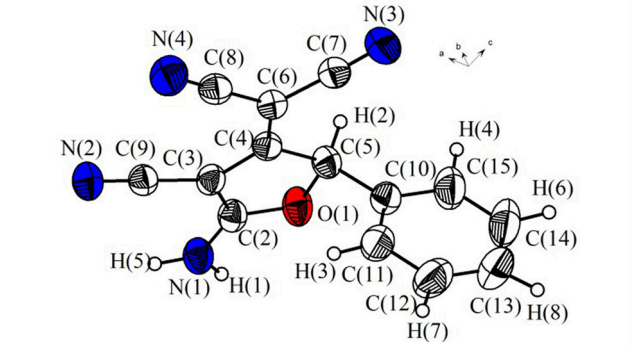


Figure 2 ORTEP view of 2-[5-amino-4-cyano-2-phenylfuran-3(2*H*)-ylidene]malononitrile **3a**

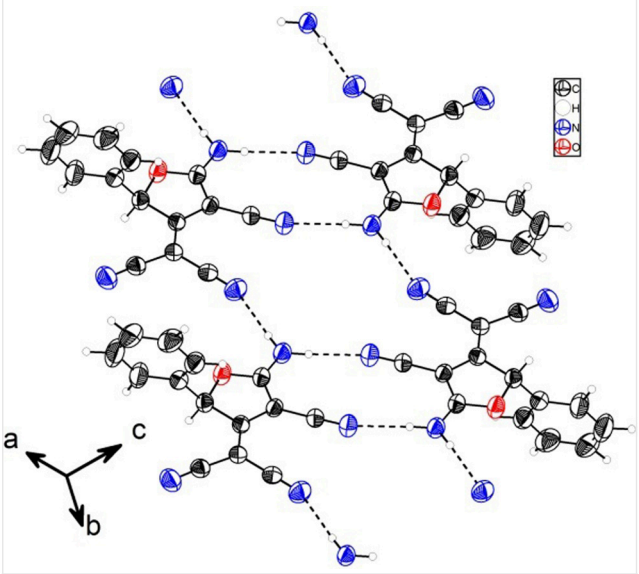
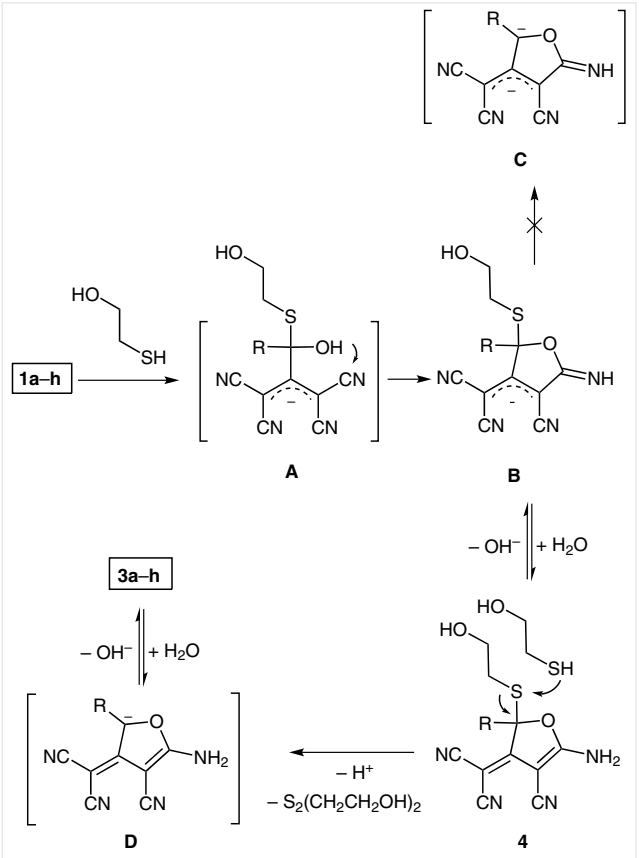


Figure 3 Fragment of crystal lattice of 2-[5-amino-4-cyano-2-phenylfuran-3(2*H*)-ylidene]malononitrile **3a**

Earlier we proposed that the process of reduction of propenides **1** via the reaction with hydrogen iodide is preceded by heterocyclization. The results of the reaction of propenides **1** with mercaptoethanol indicate indeed that the furan ring formation precedes the process of reduction. The possibility of isolating intermediate dihydrofurans **4** and their subsequent transformation into compounds **3** under the action of excess mercaptoethanol confirms this. The most probable mechanism for the reaction of tetracyanopropenides **1** with mercaptoethanol is via a nucleophilic addition of mercaptoethanol to the propenide carbonyl group to form the intermediate **A**. Next heterocyclization involving the hydroxyl group close to the cyano group leads to intermediate **B** (Scheme 4).

Intermediate **B** is an anion of a considerably weaker acid than the initial propenide **1**, and in water it is reversibly protonated with formation of the corresponding compounds **4**.



Scheme 4 A possible mechanism for the formation of the 2-[5-amino-4-cyano-2-methyl(aryl)furan-3(2*H*)-ylidene]malononitriles **3** via the reaction of propenides **1** with mercaptoethanol

The most probable mechanism for the reduction of intermediate **B** is via nucleophilic substitution on the sulfur atom to form intermediate **D**, protonation of which leads to the corresponding dihydrofuran **3**. Anion **D** is stabilized due

to delocalization of the negative charge around the dicyanomethylene fragment. Electron-donating R substituents destabilize the carbanion **D** which leads to a decrease in yield of **3** or completely inhibits the pathway. Nucleophilic substitution on the sulfur atom in intermediate **B** is very unlikely, because the dianion **C** formed in this case is not resonance-stabilized. The presence of base prevents the protonation of intermediate **B**, and the reduction does not occur. This leads to the formation of [2-(5-amino-4-cyano-2-(2-hydroxyethylthio)-2-arylfuran-3(2*H*)-ylidene]malononitriles **4** when using triethylamine as base (Table 3).

Table 3 Substituents and Yields of Dihydrofurans **4b–f** via the Reaction of Propenides **1** with Mercaptoethanol in the Presence of Triethylamine

Entry	Compd **4**	R	Yield (%)
1	**4b**	Ph	86
2	**4c**	4-MeC_6H_4	82
3	**4d**	2,5-$(MeO)_2C_6H_3$	73
4	**4e**	1-naphthyl	71
5	**4f**	4-PhC_6H_4	81

In conclusion, sodium borohydride is a universal reagent for reducing heterocyclization of propenides **1** to dihydrofurans **3**.[21] Mercaptoethanol is a more convenient reagent in order to synthesize dihydrofurans **3**[22] with non-electron-rich aryl substituents at position 2. Reacting propenides **1** with mercaptoethanol in the presence of triethylamine results in reaction stopping at the stage of sulfinyl-substituted furans **4**.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378832.

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(20) Figure 2 shows the atom numbering in **3a**. Displacement ellipsoids are drawn at the 50% probability levels. Cell parameters (**3a**): a = 13.9259(5), b = 8.8709(4), c = 10.5576(6) Å, β = 90°, β = 98.44(0)°, γ = 90°; V = 1290.12(10) Å^3, Z = 4, D_{calc} = 1.278 g cm^{-3}. The crystal is monoclinic and the space group is $P1\,21/c1$.
CCDC 912663 for **3a** contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(21) **Typical Procedure for the Preparation of 2-[5-Amino-2-aryl-4-cyanofuran-3(2*H*)-ylidene]malononitriles 3a–j via the Reaction of Propenides 1 with Sodium Borohydride**
$NaBH_4$ (0.56 g, 15 mmol) was added to a solution of potassium 2-acyl-1,1,3,3-tetracyanopropenide **1** (10 mmol) in H_2O (20 mL), and the mixture was stirred at r.t. until the reaction became colorless. The resulting solution was filtered and then neutralized by addition of aq 5% H_2SO_4. The white precipitate was filtered, recrystallized from AcOH, and dried in vacuo.
Compound **3a**: yield 82% (2.03 g; via reaction with mercaptoethanol) or 86% (2.13 g; via reaction with $NaBH_4$), white solid, mp 262–263 °C (dec.). ^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 6.81 (1 H, s, CH), 7.41–7.52 (5 H, m, Ph), 10.07 (2 H, s, NH_2). IR (mineral oil): 3318, 3115 (NH_2), 2223, 2212 (CN), 1663 (C=C) cm^{-1}. MS (EI, 70 eV): m/z (%) = 248 [M]$^+$ (53), 221 [M – HCN]$^+$ (7), 205 [M – HNCO]$^+$ (33), 178 [M – HNCO – HCN]$^+$ (100).
2-[5-Amino-4-cyano-2-methylfuran-3(2*H*)-ylidene]malononitrile (3k)
$NaBH_4$ (0.56 g, 15 mmol) was added to a solution of potassium 2-acetyl-1,1,3,3-tetracyanopropenide **1** (10 mmol) in H_2O (20 mL), and the mixture was stirred at r.t. until the reaction became colorless. The resulting solution was filtered, then neutralized by addition of aq 5% H_2SO_4 and subsequently extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($CaCl_2$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (SiO_2, EtOAc),

and the relevant fractions were concentrated in vacuo until a precipitate formed. The white solid was filtered, washed with hexane (3 × 5 mL) and dried in air; yield 62% (1.15 g), mp 208–210 °C (dec.). ^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 1.56 (3 H, d, ^3J = 6.6 Hz, CH_3), 5.84 (1 H, q, ^3J = 6.7 Hz, CH), 9.98 (2 H, br s, NH_2). IR (mineral oil): 3366, 3254 (NH_2), 2229, 2214 (CN), 1684 (C=C) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 186 [M]$^+$ (22), 159 [M – HCN]$^+$ (100), 116 [M – HNCO – HCN]$^+$ (47).

Typical Procedure for the Preparation of 2-[5-Amino-2-aryl-4-cyanofuran-3(2*H*)-ylidene]malononitriles 3a–h via the Reaction of Propenides 1 with Mercaptoethanol

Mercaptoethanol (1.95 g, 25 mmol) was added dropwise to a solution of potassium 2-acyl-1,1,3,3-tetracyanopropenide **1** (10 mmol) in H_2O (20 mL), and the mixture was stirred at r.t. for 10–15 min. The white precipitate was filtered, recrystallized from AcOH, and dried in vacuo.

2-[5-Amino-4-cyano-2-(2′-hydroxyethylthio)-2-methylfuran-3(2*H*)-ylidene]malononitrile (4a)

Mercaptoethanol (1.17 g, 15 mmol) was added dropwise to a solution of potassium 2-acetyl-1,1,3,3-tetracyanopropenide **1** (10 mmol) in H_2O (20 mL), and the mixture was stirred at r.t. for 10 min. The yellow precipitate was filtered, recrystallized from *i*-PrOH (10 mL), and dried in air; yield 72% (1.89 g), mp 205–207 °C (dec.). ^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 1.94 (3 H, s, CH_3), 3.79 (3 H, s, CH_3O), 2.52–2.58 (1 H, m, SCH_2), 2.60–2.67 (1 H, m, SCH_2), 3.51 (2 H, br s, OCH_2), 4.98 (1 H, br s, OH), 10.12 (2 H, br s, NH_2). IR (mineral oil): 3620 (OH), 3368, 3254 (NH_2), 2224, 2209 (CN), 1696 (C=C) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 262 [M]$^+$ (7), 185 (31), 184 (10), 78 (23), 60 [C_2H_4S]$^+$ (44), 59 (30), 47 (67), 43 (77). Anal. Calcd for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.68; H, 3.82; N, 21.71.

(22) **Typical Procedure for the Preparation of 2-[5-Amino-2-aryl-4-cyano-2-(2′-hydroxyethylthio]furan-3(2*H*)-ylidene)malononitriles 4b–f**

Mercaptoethanol (1.17 g, 15 mmol) was added dropwise to a solution of potassium 2-acyl-1,1,3,3-tetracyanopropenide **1** (10 mmol) in a mixture of EtOH (20 mL) and Et_3N (1.0 g, 10 mmol). The resulting mixture was stirred at r.t. until reaction was complete (TLC, 20–25 min), filtered, and the filtrate poured into distilled H_2O (40 mL) and subsequently neutralized by addition of aq 5% H_2SO_4. The white precipitate was filtered, recrystallized from *i*-PrOH (10 mL), and dried in air.

Compound **4b**: yield 86% (2.79 g), mp 137–139 °C (dec.). ^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 2.65–2.70 (1 H, m, SCH_2), 2.73–2.79 (1 H, m, SCH_2), 3.61 (2 H, t, ^3J = 6.4 Hz, OCH_2), 4.98 (1 H, br s, OH), 7.50–7.53 (3 H, m, Ar), 7.56–7.58 (2 H, m, Ar), 10.27 (2 H, br s, NH_2). IR (mineral oil): 3634 (OH), 3391, 3218 (NH_2), 2230, 2210 (CN), 1673 (C=C) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 324 [M]$^+$ (1), 248 (12), 178 (17), 92 (23), 77 (41), 60 [C_2H_4S]$^+$ (100), 59 (27).