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3,3,4,4-Tetracyanoalkanones as expedient reagents for utilization of *N*,*N*-dimethylhydrazine

Oleg E. Nasakin,*[a] Elizaveta S. Ivanova,[a] Maxim A. Maryasov,[a] Vera V. Andreeva,[a] Sergey V. Karpov,[a] Olga A. Lodochnikova[b] and Denis Yu. Grishaev[c]

[a] *I. N. Ulyanov Chuvash State University, 428015 Cheboksary, Russian Federation. E-mail: ecopan21@inbox.ru*
[b] *A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. E-mail: lod_olga@mail.ru*
[c] *Pharmacy Research & Education Center, Kazan Federal University, 420021 Kazan, Russian Federation. E-mail: dionis.grishaev|@yandex.ru*

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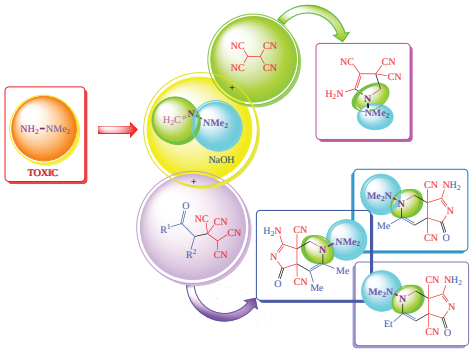
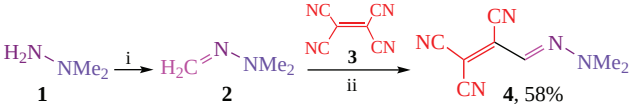
To utilize *N*,*N*-dimethylhydrazine, the corresponding formaldehyde hydrazone was reacted with 1,1,2,2-tetracyanoethane or 3,3,4,4-tetracyanoalkanones. The first process yielded 5-amino-1-dimethylamino-1,2-dihydro-3*H*-pyrrole-3,3,4-tricarbonitrile while the second afforded pyrrolo[3,4-*c*]quinolone multifunctional derivatives. These resultant products hold promise in molecular design and pharmaceutical chemistry.



Keywords: *N*,*N*-dimethylhydrazine, formaldehyde dimethylhydrazone, tetracyanoethylene, 3,3,4,4-tetracyanoalkanones, Thorpe–Ziegler type cyclization, 1,2-dihydro-3*H*-pyrrole-3,3,4-tricarbonitriles, 4,5-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-3a,7a-dicarbonitriles.

Despite its well-known energy benefits, 1,1-dimethylhydrazine **1** possesses certain disadvantages that hinder its application as a high-temperature fuel. It is characterized by exceptionally high toxicity, teratogenicity, and has the tendency to absorb water from the atmosphere thereby losing its usefulness.[1] The most efficient approach to utilize it involves an instantaneous exothermic reaction with formaldehyde[1,2] resulting in less toxic *N*,*N*-dimethyl-*N*′-methylenehydrazine **2**. Our study was aimed to highlight the unusual synthetic capabilities and practical application of compound **2**. We explored synthetic capabilities of compound **2** in reactions with CH-acids. Readily available 3,3,4,4-tetracyanoalkanones known for their sustainability, propensity for cascade transformations, and high synthetic potential possess good CH-acidity (pK_a 2.8–3.6). In principle, compound **2** under conditions of reactions with 3,3,4,4-tetracyanoalkanones may involve all of its structural fragments, namely, methylene and dimethylamino groups, leading to formation of the original compounds as well as further degradation products, dimethylamine and formaldoxime. Additionally, the intermediate compound formed upon C-addition is capable of generating a salt compound.

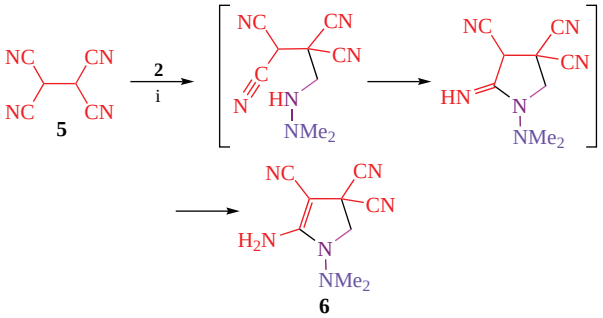


Scheme 1 *Reagents and conditions*: i, CH_2O (40% aq.), 40 °C, NaOH (see ref. 2); ii, NaOH, EtOAc, 40 °C (see ref. 3).

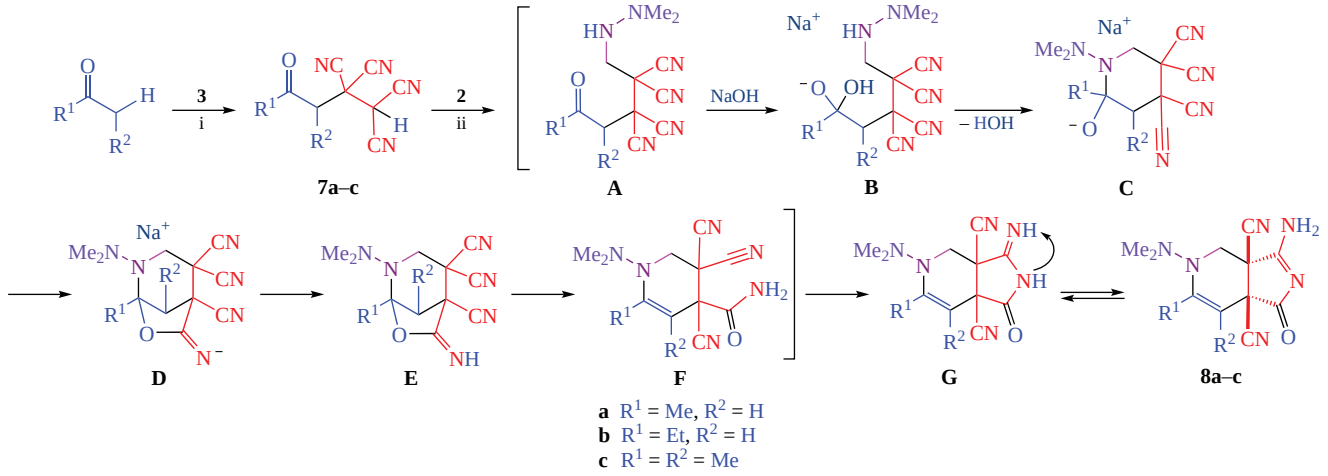
Previously,[3] we reported on the addition of hydrazone **2** to tetracyanoethylene **3** giving tricyano hydrazine derivative **4** in moderate yield (Scheme 1). Compound **4** looked potential antimicrobial dye and photosensitizer.

In this work, the reaction of hydrazone **2** at the CH-acid center of 1,1,2,2-tetracyanoethane **5** under basic conditions proceeded to form a five-membered ring affording 5-amino-1-dimethylamino-1,2-dihydro-3*H*-pyrrole-3,3,4-tricarbonitrile **6** (Scheme 2).

The reactions of more sophisticated 3,3,4,4-tetracyanoalkanones **7** with hydrazone **2** look more promising since under alkaline conditions compounds **7** are known to undergo intramolecular domino spiro-cyclization leading to 2,7-diazaspiro[4.4]non-3-ene derivatives.[4] Previously,[5] we tested such compounds of 2-(1,1,2,2-tetracyanoethyl)cycloalkanone type in



Scheme 2 *Reagents and conditions*: i, NaOH, EtOAc, room temperature.



Scheme 3 *Reagents and conditions*: i, ketone $R^1C(O)CH_2R^2$ (excess), dioxane, room temperature, 8–24 h, then cooling reaction mixture at 0–5 °C till the crystallization; H_2O (excess), mixing till the precipitation, maintaining at 0–5 °C, 10 min (see ref. 6); ii, NaOH, EtOAc, room temperature.

reactions with hydrazone **2** and obtained products containing a 3-amino-5-dimethylamino-1-oxo-4,5-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-3a,7a-dicarbonitrile fragment. In this paper, we did study relative linear available[6] 3,3,4,4-tetracyanoalkanones **7a–c** (Scheme 3). In fact, tetracyanoalkanones **7a–c** demonstrated similar reactivity towards hydrazone **2** (*cf.* ref. 5). Presumably, the first step of the transformation is the Michael addition of the CH-acid center of 3,3,4,4-tetracyanoalkanone **7a–c** to **2**. The Michael adduct **A** thus formed would undergo base-catalyzed intramolecular cyclization into **C**. Zwitterion **C** formed *via* the Thorpe–Ziegler type cyclization (imino lactone **D**), rearrangement (γ-lactam **E**), ring cleavage (amide **F**) and the second Thorpe–Ziegler type cyclization (tautomer **G**) is transformed into fused heterocycles **8a** (*m/z* 258.1200), **8b** (*m/z* 272.1400) or **8c** (*m/z* 272.1400) (see Scheme 3).

Structures **8a–c** feature the 5-aminopyrrolidin-2-one moiety which is present in numerous biologically active compounds. Such compounds include inhibitors of various enzyme classes, such as HIV-1 integrase[7] (an enzyme responsible for incorporating the HIV-1 DNA virus into the host cell chromosome), tyrosine kinase[8] (an enzyme involved in transferring the ATP phosphate moiety to the tyrosine acid moiety), and telomerase[9] (an enzyme that adds a specific sequence to the end of DNA chains while stabilizing chromosomes). The heterocyclic derivative is also a key structural element found in agonists, which are chemical compounds that elicit a biological response by interacting with specific receptors. For instance, it is present in agonists for serotonin,[10] chemokine[11] (a peptide that regulates leukocyte movement and their migration from blood to tissues), and endothelin[9] (which is comprised of 21 amino acids and functions as the most potent vasoconstrictor receptor). 5-Hydroxypyrrolidin-2-one serves as a constituent in medications utilized for the treatment of various disorders associated with nervous or cognitive functions, including memory issues, mental fatigue, and conditions affecting intellectual activity.[12]

In summary, accessible hydrazone **2** exhibits good reactivity toward various chemotypes of compounds. In particular, its reactions with available 3,3,4,4-tetracyanoalkanones afford promising adducts **8a–c** of multiply functionalized 4,5-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine chemotype. This renders it an essential starting material for the further syntheses of diverse organic structures.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.039.

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