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The Reaction of Malononitrile Dimer with 4-Methyl-2,6-Dichloronicotinonitrile †

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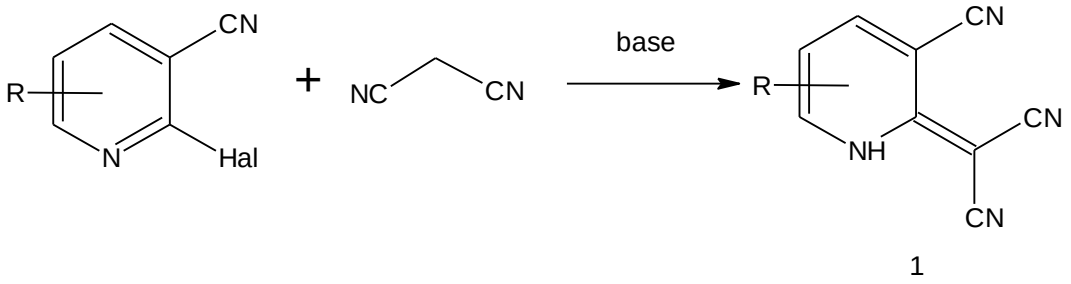
Abstract: The reaction of 4-methyl-2,6-dichloronicotinonitrile with malononitrile dimer (2-amino-1,1,3-tricyanopropene) in the presence of triethylamine leads to regioselective nucleophilic substitution of the chlorine atom at position 6 and the formation of triethylammonium 2-amino-3-(4-methyl-6-chloro-5-cyanopyridin-2-yl)-1,1,3-tricyanoprop-2-en-1-ide. The structure of the product was confirmed by X-ray studies.

Keywords: 2,6-dichloronicotinonitrile; malononitrile dimer; nucleophilic substitution; trimethylamine

1. Introduction

Halogenated pyridines attract the attention of researchers primarily as promising agrochemicals. Thus, insecticides, acaricides, herbicides with low phytotoxicity, fungicides, plant growth regulators, antidotes of the herbicide 2,4-D were found in a series of 2,6-dihalopyridines [1,2]. Also, due to the presence of reactive halogen atoms in the 2(6) positions, halopyridines and N-alkyl-2-halopyridinium salts are capable to react under nucleophilic substitution conditions, to provide a wide range of derivatives including condensed heterocyclic systems.

One of the important directions in the chemistry of halogenated pyridines is the reaction of 2-halopyridines with CH-acids. For example, the reaction with malononitrile lead to the formation of 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles 1 [3].



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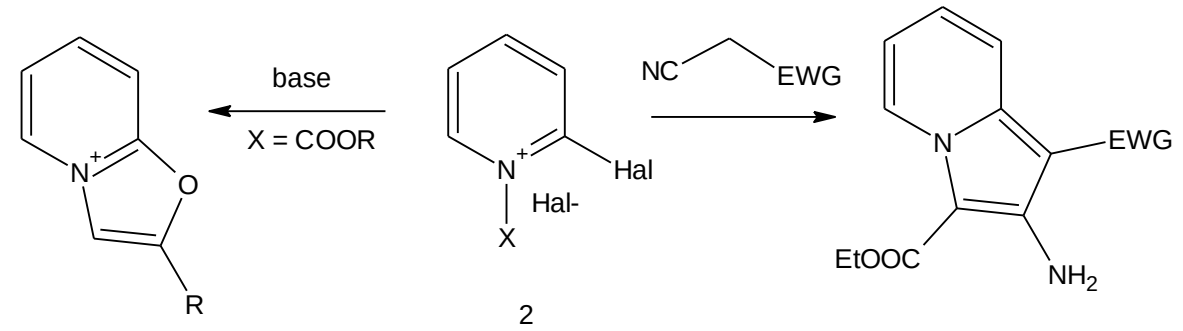
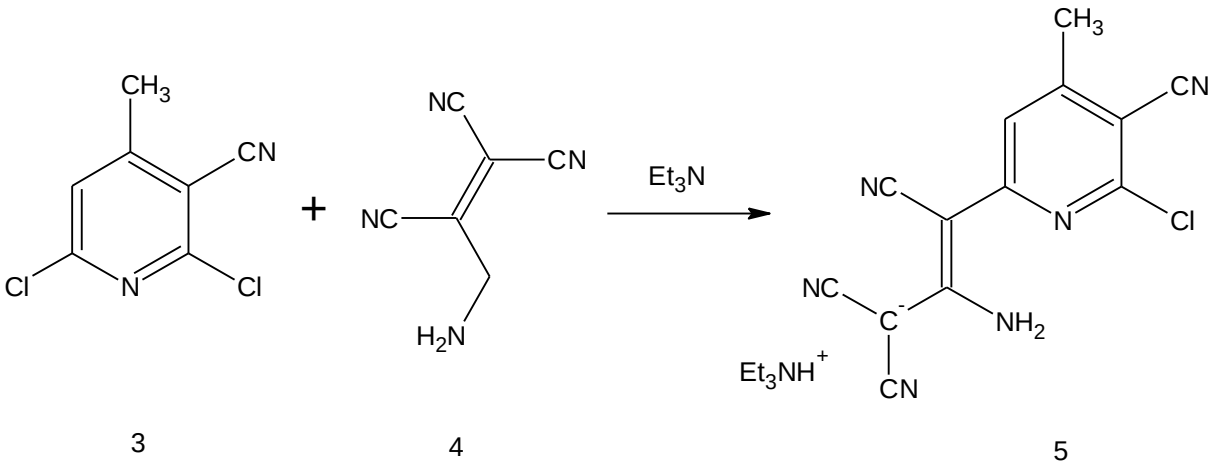
Scheme 1. The reaction of 2-chloronicotinonitrile with malononitrile in the persistence of base.

Noteworthy that the cyclization reactions with trinitriles 1 are useful for preparation of pharmaceuticals and agrochemicals. The use of malononitrile dimer as a CH-acid for the reaction with 2-chloropyridines is described only in a few papers. Thus, the reactions with 2-chloropyridinium salts 2 were reported [4,5].



Scheme 2. The reactions of 2-chloropyridinium salts.

It is known that the reactive chlorine atom at the C_2 atom can be easily replaced by the reactive nitrile anions with the formation of polynitriles. In continuation of our studies, we found that the reaction of 2,6-dichloropyridine **3** with malononitrile dimer 4 in the presence of base proceeds regioselectively and leads to the formation of compound 5 (Scheme 3), with the selective substitution of the chlorine atom at the position 6. The products of the reaction at C_2 atom were not detected. The Figure 1 presents the structure of product.



Scheme 3. Reaction of 4-methyl-2,6-dichloro-5-cyanopyridine with malononitrile dimer.

In our opinion, the probable reason for selective substitution at the C_6 atom is the greater steric hindrance at C_2 preventing the attack of bulky C-nucleophiles. We optimized the conditions for the preparation of compound 5, and the best results were obtained by heating the starting materials in a MeCN solution in the presence of Et_3N.

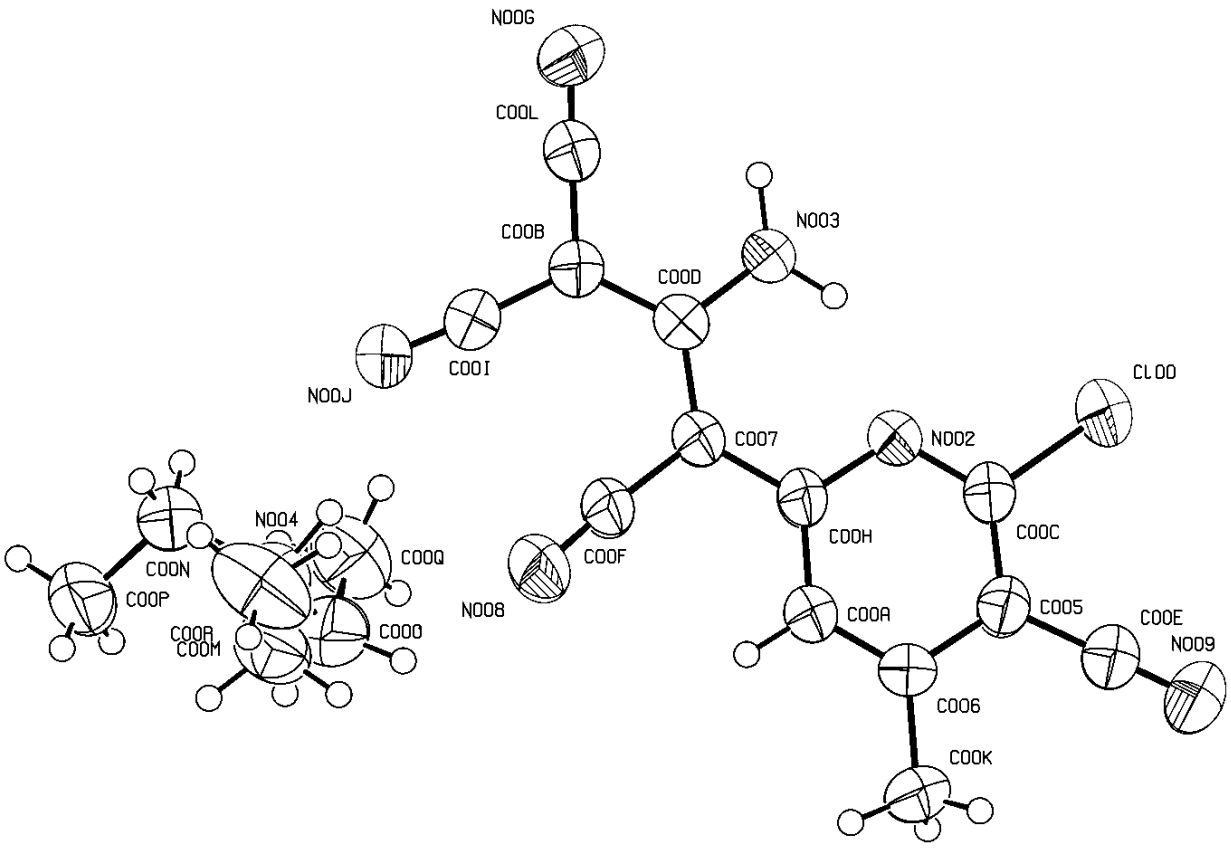


Figure 1. The structure of the product **5** (by X-ray studies).

2. Experimental

Triethylammonium 2-amino-3-(4-methyl-6-chloro-5-cyanopyridin-2-yl)-1,1,3-tricyanoprop-2-en-1-ide (5).

A solution of 1.4 g (10.6 mmol) of malononitrile dimer 4 and 1.61 g (15.9 mmol) Et_3N in 10 mL of acetonitrile was added to a solution of 1.11 g (5.3 mmol) of 4-methyl-2,6-dichloronicotinonitrile 3 [6] in 10 mL of dry acetonitrile. The resulting mixture was boiled for 10.5 h. Then the mixture was evaporated to ~1/2 of the volume and poured into 60 mL of ice water. The emulsion obtained was stirred until a suspension formed, the precipitate was filtered off and dried. After recrystallization from ethyl acetate, 1.41 g (70.5%) of product 5 with m.p. 153–154 °C was prepared. Salt 5 is a fine crystalline yellow-orange powder, soluble in EtOH, 1,4-dioxane, MeCN, slightly soluble in water. IR spectrum, ν, cm^{-1}: 3360 br s, 3159 br weak (N–H), 2222 weak, 2191 s, 2170 s, 2154 s (4 C≡N), 1620 weak, 1595 s (C=C, C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.16 t (9H, 3 $C\underline{H}_3CH_2$, ^3J 6.9 Hz), 2.34 s (3H, Py-CH_3), 3.06–3.12 m (6H, 3 $CH_3C\underline{H}_2$), 6.91 s (1H, H-Py), 8.83* br s (~1H, NH, NH_2). *Integral intensity is less than 1H, presumably due to partial deuterium exchange. ^{13}C DEPTQ NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 8.7*, 20.2*, 45.8, 97.8, 115.1*, 115.9, 119.7, 120.5, 149.6, 151.1, 161.0, 164.3. *Signals in antiphase. Mass spectrum (EI), *m*/*z* ($I_{отн}$, %): 282 (18) [M-Et_3NH]$^+$; 264 (15) [M-Et_3NH-18]; 255 (7) [282-HCN]$^+$; 236 (14) [M-Et_3NH-46]; 191 (88) [255-$C(CN)_2$]$^+$; 155 (15) [191-HCI]$^+$; 102 (27) [Et_3NH]$^+$. Found, %: C 59.62; H 5.86; N 25.51. $C_{19}H_{22}ClN_7$ (M 383.88). Calculated, %: C 59.45; H 5.78; N 25.54.

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