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].

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 C2 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 C2 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 C6 atom is the greater steric hindrance at C2 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 Et3N.
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) Et₃N 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, сm⁻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=С, С=N).

1H NMR spectrum (400 MHz, DMSO-d₆), δ, ppm: 1.16 t (9Н, 3 СН₃СН₂, 3J 6.9 Hz), 2.34 s (3Н, Py-CH₃), 3.06–3.12 m (6Н, 3 СН₃СН₂), 6.91 s (1Н, H-Py), 8.83* br s (~1H, NH, NH₂). *Signals in antiphase.

13C DEPTQ NMR spectrum (101 MHz, DMSO-d₆), δC, 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 (Iон, %): 282 (18) [M-Et₃NH]+; 264 (15) [M-Et₃NH-18]; 255 (7) [282-HCN]; 236 (14) [M-Et₃NH-46]; 191 (88) [255-C(CN)₃]+; 155 (15) [191-HCl]+; 102 (27) [Et₃NH]+. Found, %: C 59.62; H 5.86; N 25.51. C₁₉H₂₂ClN₇ (M 383.88). Calculated, %: C 59.45; H 5.78; N 25.54.

References


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