Pergamon

Tetrahedron 54 (1998) 5775–5780

TETRAHEDRON

ω-Substituted-2-(polyenamino)- or Annelated Nitropyridines from 1-(3-Cyano-5-nitropyridyl-2)- pyridinium Salts

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Received 12 February 1998; revised 16 March 1998; accepted 19 March 1998

Abstract. The interaction of 1-(3-cyano-5-nitropyridyl-2)pyridinium salts with different nucleophilic reagents yields 2-substituted 3-cyano-5-nitropyridine, including 2-polyenamino derivatives. 3-Nitro-5(H)-5-iminodipyrido[1,2-a:3,2-e]pyrimidine hydrochloride is synthesized by the reaction of 2-chloro-3-cyano-5-nitropyridine with 2-aminopyridine.

In the course of our study of the synthesis of polyheterocycles containing functionalized condensed pyridine ring, we have investigated the utility of 2-chloro-3-cyano-5-nitropyridine **(1)** for obtaining a series of 2-substituted 3-cyano-5-nitropyridines **(3a-c)** and **(4)**, the last being the product of **(3d)** intramolecular-condensation[1,2]. The aim of this work is to investigate the synthetic potential of 1-(3-cyano-5-nitropyridyl-2)pyridinium chloride **(2)**, easily available from **(1)**.

It was expected that this strongly electron deficient compound might demonstrate three types of reactivity towards nucleophiles: A) nucleophilic substitution of pyridinium ring typical of 1-(4-pyridyl)pyridinium salts[3-8] and much less characteristic to 1-(2-pyridyl)pyridinium salts. The latters react with phosphorous acid giving pyridyl-2-phosphonic acids[5], with thioles giving the corresponding dipyridylsulphides[6] and with alkali followed by the reaction with anilines giving 2-aminopyridines[9]. The yields are very low, that is believed to be a result of higher stability to nucleophilic attack of 1-(2-pyridyl)pyridiniums compared to their 4-pyridyl analogues[8,10]. B) nucleophilic addition to $C=N^+$ bond followed by the elimination of glutaconic aldehyde derivatives (the Zincke-Koenigs reaction) with the formation of 2-amino-3-cyano-5-nitropyridine **(7)**. C) nucleophilic addition to $C=N^+$ bond with the α-cleavage of pyridine ring leading to ω-substituted 2-aminopolyenepyridines.

We hoped that the relative stability of 1-(2-pyridyl)pyridinium salts to nucleophilic substitution could make the most synthetically appealing but unexplored route C predominant, at least in some cases.

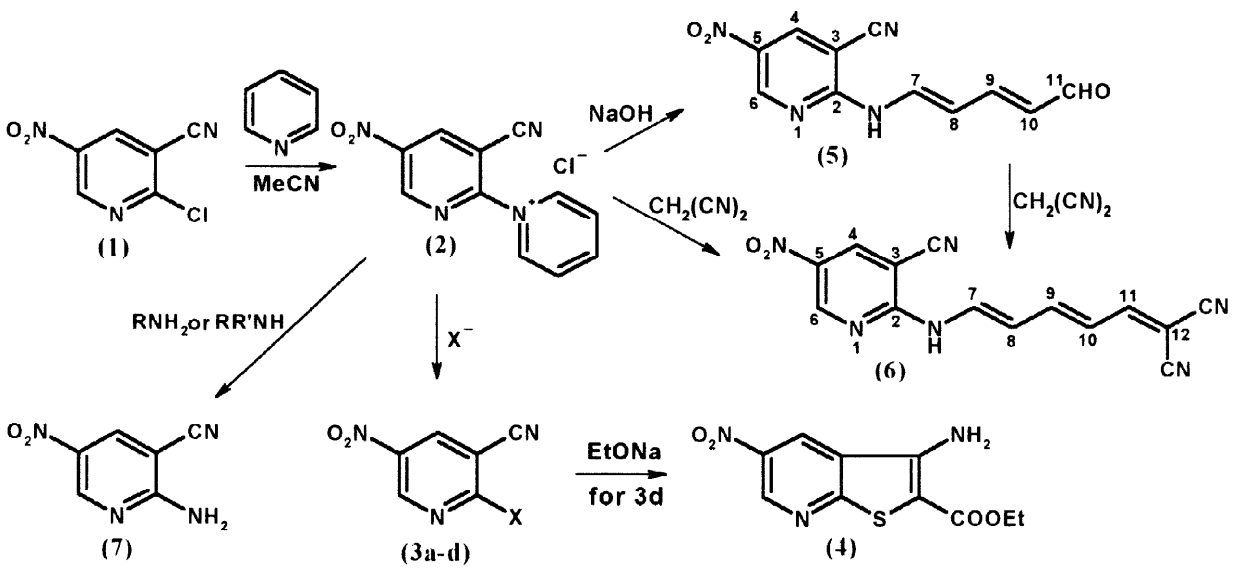
In fact, the reaction of **(2)** with the simplest nucleophile OH^- smoothly gives 4-formyl-1,3-butadienylamino derivative **(5)** in almost quantitative yield. In order to test the possibility of one-pot polyene chain elongation, we tried malonodinitrile anion, which led to the desired **(6)** in high yield. Also, **(6)** was obtained from **(5)** by direct reaction with malonodinitrile. Thus, the nucleophile softness-hardness is not the driving force of pyridinium ring cleavage *via* the route C.

0040-4020/98/$19.00
PII: S0040-4020(98)00265-8

The reactivity of **(2)** towards the previously used set of nucleophiles is similar to that of **(1)**, *i.e.* in this case pyridinium ring behaves as a leaving group. The yields of **(3a-c)** practically coincide with the yields of direct substitution of Cl in **(1)**. The only exception is the obtaining of **(3d)**, which was later converted into 2-ethoxycarbonyl-3-amino-5-nitrothieno[2,3-b]pyridine **(4)** under Thorpe-Ziegler conditions.

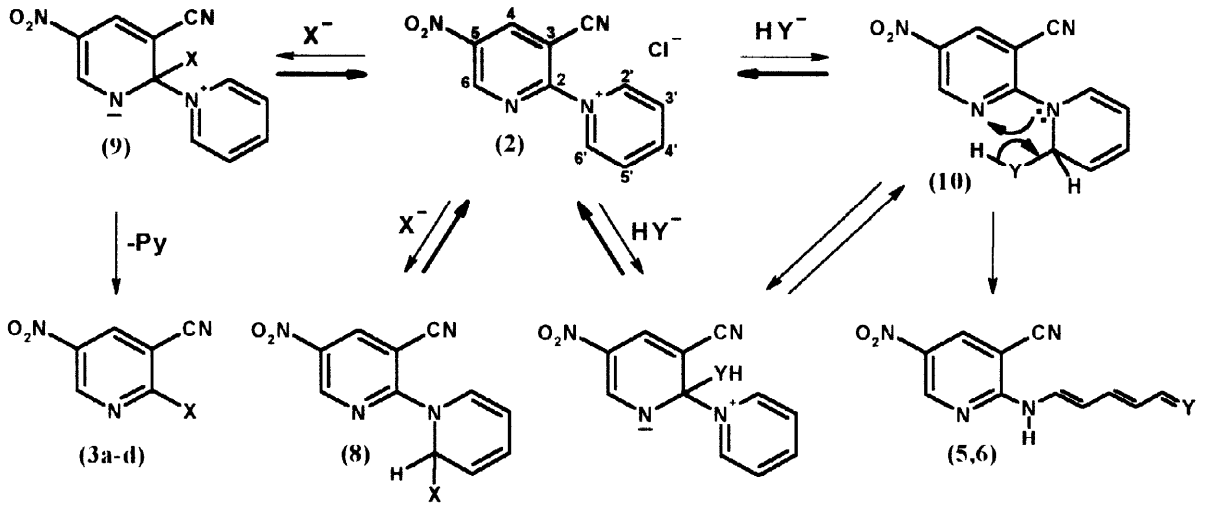
The interaction of the salt **(2)** with aniline, benzylamine and piperidine proceeds *via* Zincke way and leads, independently of the amine chosen, to 2-amino-3-cyano-5-nitropyridine **(7)**. The latter gives somehow better yield of **(7)** - 77%, compared to 64% for the two primary amines. 4-Nitroaniline and 2-aminopyridine do not cleave **(2)** in these conditions.

The yields of the compounds obtained vary from moderate to high, their structures have been confirmed by ^{1}H NMR, mass-spectra and elemental analysis.

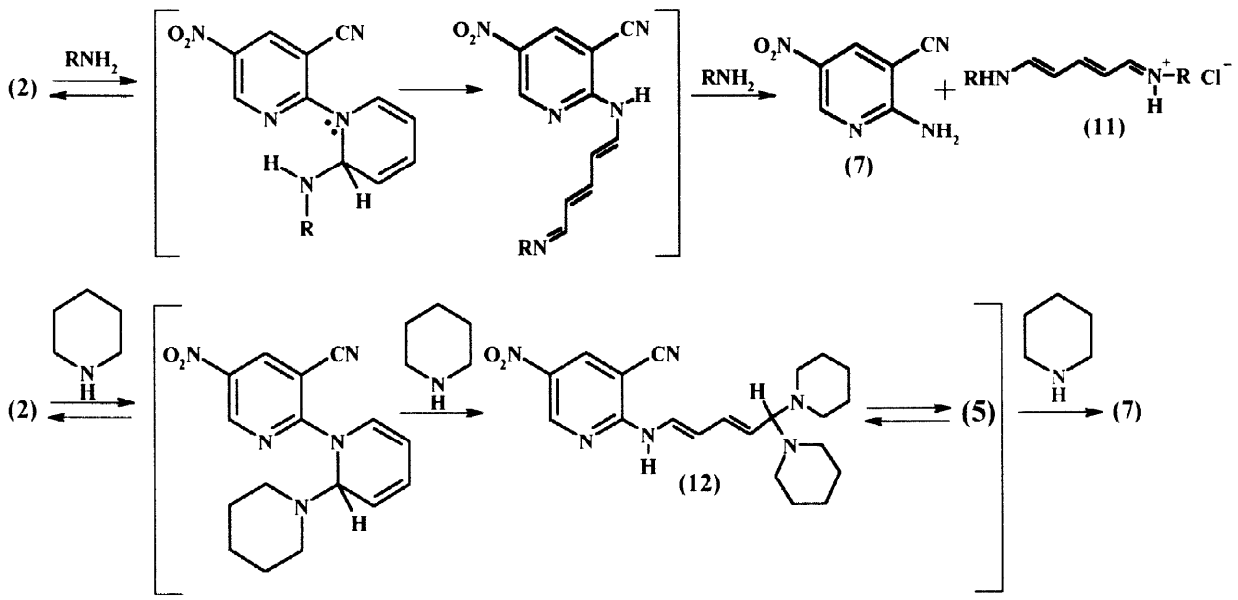


a) X=OMe; b) X=OPh; c) X=SPh; d) X=SCH_2COOEt

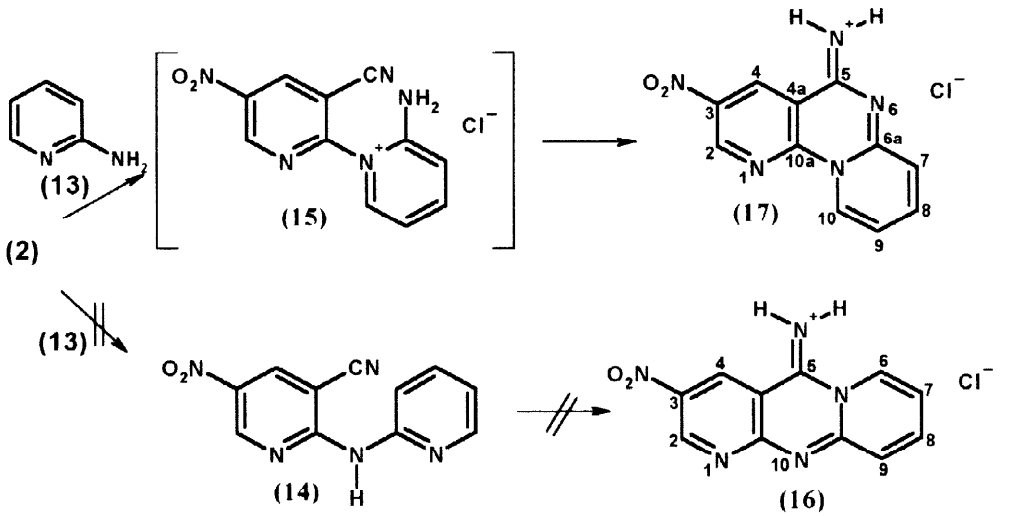
The obtained results may be interpreted as follows. The direction of the interaction of 1-(2-pyridyl)pyridinium salt **(2)** with nucleophilic agents depends on the type of used nucleophile, which can be classified as X^- (RO^-,RS^-) and HY^- (HO^-, $HC^-(CN)_2$) or RR'NH ($PhNH_2$, $PhCH_2NH_2$, piperidine). Both anions X^- and HY^- are able to attack competitively and reversibly the positions 2 or 2' of the pyridyl-pyridinium system. The addition of X^- at the position 2' leads to the neutral molecule **(8)**, while the addition at position 2 leads to the zwitter-ion **(9)**. The equilibrium in both cases is shifted towards **(2)**, but for zwitter-ion **(9)** the pyridine elimination with the formation of 2-substituted 3-cyano-5-nitropyridines **(3a-d)** is unreversible. For HY^- - anions the directions of reactions leading to compound **(10)** are possible. In the latter the proton shift from Y to nitrogen atom of dihydropyridine fragment triggers the cleavage of the cycle with unreversible formation of polyenes **(5,6)**.



In the case of amines the attacking particles are not the anions, but the neutral molecules of nucleophile. In the reaction with primary amines the products of the ring opening are amine **(7)** and diaminotrienes **(11)**. Dianile **(11a)** (R=Ph) has been isolated after the reaction of salt **(2)** with aniline. The easy interaction of aldehyde **(5)** with aniline leading to aminopyridine **(7)** is an argument in favor of transamination as one of the stages of these reactions. In the case of piperidine the possible intermediates are aminal **(12)** or the product of its hydrolysis - aminoaldehyde **(5)**.



The obtained data are the basic for the study of reaction of chloro-derivative **(1)** with 2-aminopyridine **(13)**. In this case the process can proceed in the two directions - the N-arylation of exocyclic amino-group with formation of **(14)** or initial quaternization of pyridine ring with formation of **(15)**. According to IR-spectra the reaction product has no cyano-group, i.e. the reaction is not stopped on the arylation stage and is accompanied by cyclization with participation of cyano-group, leading to the linear **(16)** or angular **(17)** tricyclic structure.



IR, ^{1}H NMR and mass-spectra do not allow to distinguish correspondence of the structures **(16)** and **(17)**. In the ^{1}H NMR spectra of this compound in CD_3COOD signals of pyridine cycles protons are present at δ 7,63 (br.tr.), 7,77 (d., $^3J_{III}$=8Hz), 8,39 (br.tr.), 9,89 (br.s., J=2,3Hz), 9,91 (br.d., $^3J_{HH}$=7Hz), 9,97 (strongly br. s.) (intensivity of each signal is 1H) p.p.m. The observed singlets are unambiguously related to C_2-H and C_4-H, while the broadening of the singlet at 9,97 p.p.m. makes it impossible to observe spin-spin meta-interaction. The broadening of other signals is probably caused by an exchange connected with the presence of another protonated form of **(16)** or **(17)**. The addition of NaOD to the solution eliminates it's broadening.

The choice between the structures **(16)** and **(17)** was made with ^{13}C NMR spectrum. It is evident that for structure **(16)** C_5 signal must be a multiplet (heteronuclear spin-spin interaction with $C_{4\text{-}H}$ and $C_{6\text{-}H}$), but for structure **(17)** it must be a doublet (spin-spin interaction with $C_{4\text{-}H}$ only). In addition for structure **(17)** it is possible to expect the presence of distant heteronuclear spin-spin interaction between C_{10a} and $C_{9\text{-}H}$ (zigzag arrangement of bonds). Heteronuclear selective decoupling shows that C_5 is doublet with $^3J_{C5,C4\text{-}H}$=3,8Hz (δ $C_{4\text{-}H}$ =9,91 p.p.m.) and is observed the long-range interaction with $C_{9\text{-}H}$ (δ $C_{9\text{-}H}$=7,63 p.p.m.) with $^4J_{C10a,C9\text{-}H}$=3,Hz for C_{10a}.

So, the first stage of reaction of salt **(1)** with 2-aminopyridine **(13)** is the quaternization with the formation of salt **(15)**. Then the second stage is the cyclization into heterocyclic compound **(17)** with the participation of cyano and primary amino-group.

Thus, depending on the nature of pyridinum ring and nucleophile, 1-(3-cyano-5-nitropyridyl-2)pyridinium salts can serve as handy building blocks for new classes of condensed or functionalized pyridines.

Experimental

NMR-spectra were recorded using «Unity plus 400 MHz» (Varian) with TMS as internal standard in D_6-DMSO. Mass-spectra were performed using SSQ-710 «Finnigan-MAT» mass-spectrometer with direct

introduction of the samples. Mass-spectra FAB were performed using ionization by Xe atoms, glycerol was used as matrix on a copper target. TLC control: «Silufol UV-254», UV-detection.

1-(3-Cyano-5-nitropyridyl-2)pyridinium chloride (2). Pyridine (1,9 ml, 23,51 mmol) was added to the solution of **1** (1 g, 5,54 mmol) in 20 ml of acetonitrile, and the mixture was stirred for 3,5 h at 15°C. The precipitate was filtered off, washed with cold acetonitrile and **2** (1,34 g, 94%) was obtained, m.p. 295°C (methanol), FAB: Cat⁺ 227. ^{1}H NMR: 8,45 (t, 2H, 3',5'-H), 9,00 (t, 1H, 4'-H), 9,50 (d, 2H, 2',6'-H), 9,57 (d, 4-H), 9,76 (d, 6-H). Found: C 50,2; H 2,5; N 21,5. $C_{11}H_7ClN_4O_2$ requires: C 50,2; H 2,7; N 21,4.

2-Methoxy-3-cyano-5-nitropyridine (3a). Triethylamine (0,192 g, 1,9 mmol) was added to the solution of **2** (0,5 g, 1,9 mmol) in 10 ml of methanol, and the mixture was stirred for 1 h at 15°C. After diluting with cold water, the precipitate was filtered off and **3a** (0,3 g, 88%) was obtained, m.p. 121-122°C (ethanol), M⁺ 179. ^{1}H NMR: 4,14 (s, OCH_3), 9,16 (d, 4-H), 9,31 (d, 6-H). Found: C 47,1; H 2,9; N 23,6. $C_7H_5N_3O_3$ requires: C 46,9; H 2,8; N 23,5.

2-Phenyloxy-3-cyano-5-nitropyridine (3b). Phenol (0,094 g, 1 mmol) and sodium acetate (0,082 g, 1 mmol) were added to the solution of **2** (0,2 g, 0,76 mmol) in 10 ml of methanol. The reaction mixture was stirred for 1 h at 15°C. The precipitate was filtered off, washed with water, **3b** (0,18 g, 40%) was obtained, m.p. 155-156°C (ethanol), M⁺ 241. Found: C 59,3; H 2,8; N 17,3. $C_{12}H_7N_3O_3$ requires: C 59,7; H 2,9; N 17,5.

2-Phenylthio-3-cyano-5-nitropyridine (3c). Thiophenol (0,11 g, 1 mmol) and sodium acetate (0,082 g, 1 mmol) were added to the solution of **2** (0,2 g, 0,76 mmol) in 10 ml of methanol. The reaction mixture was stirred for 1 h at 15°C. The precipitate was filtered off, washed with water and **3c** (0,15 g, 76%) was obtained, m.p. 128-130°C (ethanol), M⁺ 257. Found: C 56,0; H 2,7; N 16,4. $C_{12}H_7N_3O_2S$ requires: C 56,3; H 2,9; N 16,6.

2-Ethoxycarbonylemethylthio-3-cyano-5-nitropyridine (3d). Ethyl thioglycolate (0,12 g, 1 mmol) and sodium acetate (0,082 g, 1 mmol) were added to the solution of **2** (0,2 g, 0,76 mmol) in 10 ml of methanol. The reaction mixture was stirred for 1 h at 15°C. The precipitate was filtered off, washed with methanol and water, **3d** (0,13 g, 63%) was obtained, m.p. 97-98°C (ethanol), (Lit.[11] m.p. 100-101°C), M⁺ 267.

1-Formyl-4(3-cyano-5-nitropyridyl-2)aminobutadiene (5). Sodium hydroxide was added to the solution of **2** (1 g, 3,8 mmol) in 15 ml of water. The reaction mixture was stirred for 1 h at 15°C. The precipitate was filtered off, washed with water and **5** (0,87 g, 94%) was obtained, m.p. 216°C (ethanol), M⁺ 244. ^{1}H NMR: 6,10 (q, 10-H), 6,63 (q, 8-H), 7,53 (q, 9-H), 8,08 (d, 7-H), 8,98 (d, 4-H), 9,23 (d, 6-H), 9,48 (d, CHO), 11,05 (br. sign., N-H). Found: C 54,2; H 3,3; N 23,3. $C_{11}H_8N_4O_3$ requires: C 54,1; H 3,3; N 23,0.

1,1-dicyano-6(3-cyano-5-nitropyridyl-2)aminohexatriene (6). Malonodinitrile (0,26 g, 4 mmol) and triethylamine (0,404 g, 4 mmol) were added to the solution of **2** (1 g, 3,8 mmol) in 10 ml of methanol. The reaction mixture was stirred for 1 h at 15°C. The precipitate was filtered off, washed with methanol and **6** (0,7 g, 63%) was obtained, m.p. 271-272°C (ethanol), M⁺ 292. ^{1}H NMR: 6,58 (q, 8-H), 6,66 (t, 10-H), 7,51 (q, 9-

H), 7,94 (d, 11-H), 8,25 (d, 7-H), 8,93 (d, 4-H), 9,23 (d, 6-H), 11,2 (br. sign., N-H). Found: C 57,9; H 3,0; N 29,2. $C_{14}H_8N_6O_2$ requires: C 57,5; H 2,7; N 28,8. **6** was also obtained from **5** with malonodinitrile:

Malonodinitrile (0,26 g, 4 mmol) was added to the solution of **5** (1 g, 4 mmol) in 5 ml of water. The reaction mixture was stirred for 5 min at 15°C. The precipitate was filtered off and **6** (0,87 g, 74%) was obtained, m.p. 270-272°C (ethanol).

2-Amino-3-cyano-5-nitropyridine (7). Aniline (5,3 g, 57 mmol) was added to the solution of **2** (1 g, 3,8 mmol) in 15 ml of water. The reaction mixture was refluxed for 5 min, cooled and 5 ml of acetone was added. The precipitate was filtered off and 7 (0,4 g, 64%) was obtained, m.p. 242-244°C (DMF-water (1:1)), (Lit.[11] m.p. 242-244°C), M$^+$ 164. The cooled filtrate was adjusted to pH=1 with 25% HCl. The precipitate was filtered off and **11a** (0,38 g, 43%) was obtained, m.p. 156-157°C, (Lit.[10] m.p. 156°C), M$^+$ 248.

Compound 7 was obtained also from **2** and benzylamine or piperidine in the same manner. Yields are 64% for reaction of **2** with benzylamine, m.p.242°C, and 77% for reaction of **2** with piperidine, m.p. 242°C.

3-Nitro-5(H)-5-iminodipyrido[1,2-a:3,2-e]pyrimidine hydrochloride (17). 2-Aminopyridine (0,77 g, 8,18 mmol) was added to the solution of **1** (1 g, 5,54 mmol) in 20 ml acetonitrile. The reaction mixture was stirred for 3,5 h at 15°C. The precipitate was filtered off, washed with cold acetonitrile and **17** (1,3 g, 86%) was obtained, m.p. 256-258°C, M$^+$ 241. ^{13}C NMR (CD_3COOD): 111,3 (s, C_{4a}), 119,9 (d.d, $^1J_{CH}$=177,0 Hz, C_9), 125,8 (d.d, $^1J_{CH}$=175,5 Hz, C_7), 131,7 (d.tr, $^1J_{CH}$=195,3 Hz, C_{10}), 134,3 (d.d, $^1J_{CH}$=176,6 Hz, C_4), 146,1 (tr, Σ^2J=7,7 Hz, C_3), 146,2 (d.d, $^1J_{CH}$=170,2 Hz, C_8), 148,8 (m, ΣJ=25 Hz, C_{10a}), 151,3 (d.d, $^1J_{CH}$=201,4 Hz, C_2), 153,5 (m, ΣJ=17,3 Hz, C_{6a}), 160,7 (d, $^3J_{CH}$=3,8 Hz, C_5). Found: C 47,5; H 3,0; N 25,0. $C_{11}H_8ClN_5O_2$ requires: C 47,7; H 2,9; N 25,3.

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