Addition of Diamines to Methylthiopyridones

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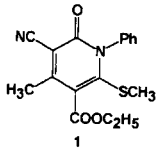
Received September 28, 1993

Thiopyridone derivatives react with diamines: ethylenediamine, 1,3-propylenediamine and 1,4-butylenediamine to produce bicyclic addition compounds. Ethanolamine reacts with thiopyridone derivatives to afford only open chain adducts. Diethylenetriamine and 2-(2-aminoethylamino)ethanol in reaction with thiopyridones yielded seven membered ring tricyclic derivatives. The procedures described here constitute a relatively simple method to prepare these novel heterocycles.

J. Heterocyclic Chem., **31**, 393 (1994).

Introduction.

Pyrido[1,2-*a*]pyrimidines belong to a class of organic compounds that are extensively studied because of their potential biological activity [1]. Some of them have been found to possess valuable pharmacological activity [2].

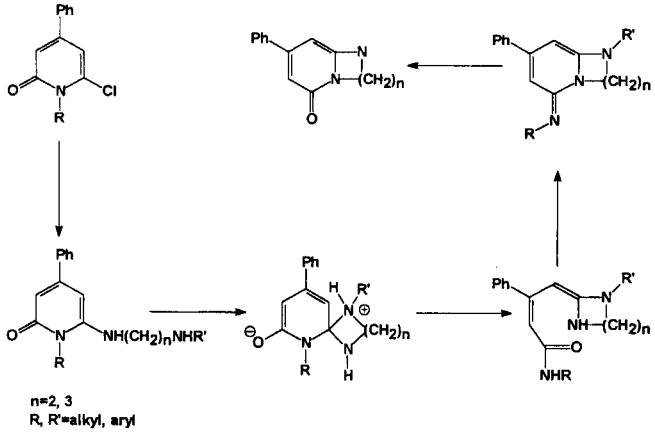


1

Figure 1

They are also used as synthetic intermediates and as additives to photographic materials and dyes [1]. One convenient reaction pathway leading to these compounds was described by Kubo *et al.* [2-4]. According to these reports, 6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidines were obtained in a reaction of 1,3-diaminopropane with derivatives of 1,2-dihydro-6-chloropyridyl-2-oxopyridines. In a similar reaction, ethylenediamine gave imidazo[1,2-*a*]-pyrimidine. In both cases, these reactions begin with nucleophilic displacement of a halogen followed by pyridone ring opening. Next, rearrangement and condensation resulted in formation of the second heterocyclic ring (Scheme I) [1]. Taking into consideration these results and the fact that the pyridone **1** can be readily synthesized [5], we felt that **1** would make a convenient starting material for the syntheses of pyrido[1,2-*a*]pyrimidine, imidazo[1,2-*a*]pyridine and pyrido[1,2-*a*][1,3]diazepine derivatives. This assumption is supported by the following two properties of **1**: First, its thiomethoxy group would be expected to function as a better leaving group when compared to the chlorine atom used in Scheme I and second, the strongly electron withdrawing cyano and carboethoxy groups on the pyridine ring should promote reaction by stabilizing any negative charge that builds up during the course of the reaction. Moreover, the carboethoxy group, present in close proximity to the thiomethoxy moiety, should provide a valuable electrophilic reactive site in the molecule. In addition, through reactions of **1** with diethylenetriamine and 2-(2-aminoethylamino)ethanol, we have been able to prepare compounds **8** and **9** which represent, to our knowledge, members of two new classes of heterocyclic compounds.

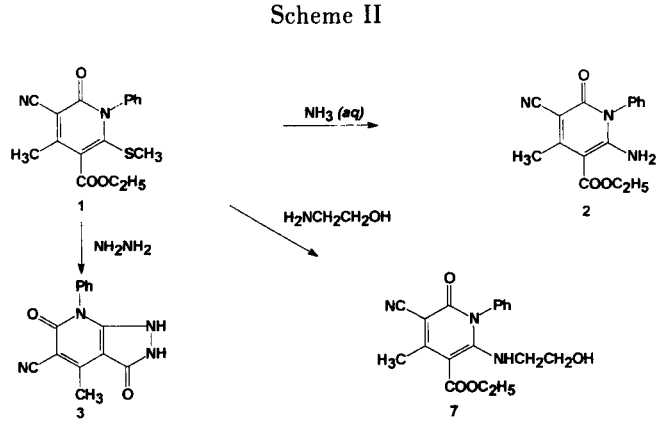
Scheme I



Results and Discussion.

To investigate the ability of the thiomethoxy group of **1** to undergo nucleophilic substitution and the possibility of a subsequent heterocyclic ring closure involving the thiomethoxy and ethoxycarbonyl groups, experiments with ammonia and hydrazine were carried out first. In the reaction of ammonia with **1** a substitution product **2** was obtained indicating that indeed the thiomethoxy group is

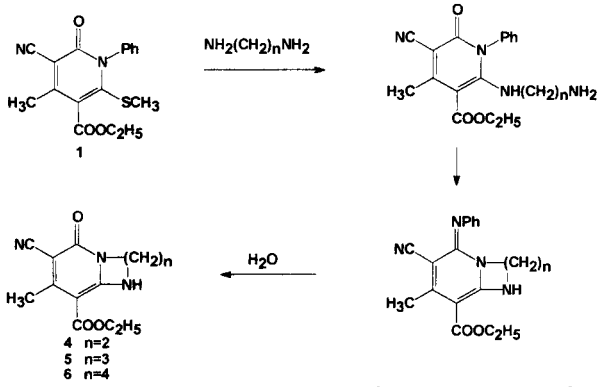
Scheme II



capable of undergoing ready substitution. Using hydrazine as the simplest diamine-like-nucleophile in reaction with **1**, the cyclic product, **3**, resulted (Scheme II). The structures of compounds **2** and **3** were both fully supported by their ir, ^{1}H-nmr, ^{13}C-nmr, and mass spectra.

Next, we looked into the reaction of **1** with diamines containing varying numbers of methylene units. Reaction of **1** with ethylenediamine, 1,3-propylenediamine and 1,4-butylenediamine gave compounds **4, 5** and **6** respectively (Scheme III).

Scheme III



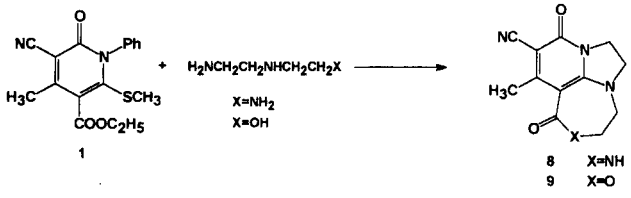
The structures of compounds **4-6** were determined on the basis of their ir, ^{1}H-nmr, ^{13}C-nmr and mass spectra. A characteristic (C ≡ N) band around 2210 cm^{-1} is present in the ir spectra of all three of the compounds. The conjugated ester carbonyl function can be identified by the ir bands within the range ν = 1667-1717 cm^{-1}; the endocyclic amide carbonyl groups of **4-6** appear at ν = 1645-1657 cm^{-1} and the N-H group stretching bands appear close to ν = 3240-3390 cm^{-1}. The ^{1}H-nmr and COSY experiments allow the following signal identification: N-C*H*$_2$, δ 4.05-5.31; N*H*-CH$_2$, δ 3.51-3.78; N-CH$_2$-C*H*$_2$-CH$_2$-N, δ 1.99-2.07. The methyl group on the pyridine ring appears as a singlet in these compounds resonating between δ 2.50-2.60.

The ^{13}C-nmr spectra of compounds **4-6** consist of up to seven signals corresponding to the six doubly and one triply bonded carbon atoms, and the appropriate number of CH$_2$ group signals. Mass spectra of compounds **4-6** show intense molecular ion peaks (100% relative abundance) in all cases. In addition, each shows characteristic peaks corresponding to loss of an ethoxy group [M-45]$^+$ and loss of a molecule of ethanol [M-46]$^+$.

In contrast to the diamine additions, ethanolamine reacted with **1** to give an open chain adduct, **7**, which was found to be thermally stable and did not cyclize even upon prolonged heating at 200° (Scheme II). The structural identification of compound **7** was aided in part by the COSY spectrum which showed coupling between a broad triplet at δ 8.48 corresponding to one proton and the signal at δ 2.68 which was identified as coming from the NH-CH$_2$ methylene protons. The downfield shifted signal at δ 3.47 was assigned to the CH$_2$-OH group. The ir spectrum of **7** shows a characteristic hydroxyl group absorbance at 3405 cm^{-1}. Two carbonyl absorbance bands are present at 1650 and 1673 cm^{-1}, and a cyano group absorbance is present at 2222 cm^{-1}. The mass spectrum of compound **7** shows a molecular ion peak at m/z 341. There are also peaks corresponding to loss of ethanol, and a characteristic fragment at m/z 119 corresponding to the phenylisocyanate fragment present in the pyridine ring of **7**.

Addition of diethylenetriamine and 2-(2-aminoethylamino)ethanol to **1** produced tri-fused ring compounds **8** and **9** respectively (Scheme IV). ^{1}H- and ^{13}C-nmr, COSY, ir and

Scheme IV



mass spectra provide sufficient information to permit structure elucidation of compounds **8** and **9**. The coupled N-CH$_2$-CH$_2$-N ethylene protons of the five membered ring of compounds **8** and **9** appear within the range δ 3.81-4.14 as a set of two deformed triplets in the ^{1}H-nmr. The group of signals at δ 3.33-3.48 in the spectrum of **8** represent a closely coupled set of four protons on the seven membered ring. The COSY, experiment of **8** shows that the two protons corresponding to the signal at δ 3.33 are coupled to the amide proton at δ 8.11. The corresponding signals in compound **9** are well resolved and can be identified as coming from the O-C*H*$_2$-CH$_2$-N group (δ 4.56) and from the O-CH$_2$C*H*$_2$-N group (δ 3.73). The ^{13}C-nmr spectra of compounds **8** and **9** show five signals that can be correlated with the five aliphatic carbon atoms present in both molecules and seven downfield shifted (δ 90.6-166.1) signals corresponding to the sp^2 and sp (C ≡ N) hybridized carbon atoms. The ^{13}C-nmr signals that correspond to the two adjacent CH$_2$ carbons of the diazepine ring of **8** are identified unambiguously by the proton-carbon HETCOR experiment. The carbon attached to the amide nitrogen resonates at δ 38.0, whereas the neighbouring carbon's chemical shift was found to be δ 52.7. This signal assignment is also supported by the ^{13}C-nmr spectrum of **9** where the signal at δ 38.0 is replaced by the downfield shifted O-CH$_2$ carbon signal at δ 63.9. The ir spectra of compounds **8** and **9** contain two carbonyl absorbance bands each at ν = 1655 cm^{-1}, 1642 cm^{-1} and 1657 cm^{-1}, 1692 cm^{-1} respectively. The presence of a cyano group in both compounds can be associated with a characteristic sharp absorption band at ν = 2210 cm^{-1}. In addition, the ir spectrum of compound **8** shows an amide, N-H stretching absorption at

ν = 3266 cm^{-1}. Finally, the mass spectra of compounds **8** and **9** confirm the proposed structures by showing abundant molecular ion peaks (100% relative abundance) at the m/z values of 244 and 245. Interestingly the peak at m/z 215 that is present in the mass spectra of both compounds was shown by collisionally activated decomposition (CAD) experiments to exhibit identical fragmentation irregardless of its origin. This result allows us to assume that the m/z 215 peak corresponds to the loss of a CH_2NH fragment from compound **8** or a formaldehyde unit from compound **9** thus leading to the same fragment ion in each case. This, in turn, confirms the close structural relationship between compounds **8** and **9**.

Conclusion.

Summarizing, the pyridone derivative **1** reacts with diamines: ethylenediamine, 1,3-propylenediamine and 1,4-butylenediamine to give compounds **4, 5** and **6** respectively. Ethanolamine and **1**, however, afforded only the open chain adduct **7**. Diethylenetriamine and 2-(2-aminoethylamino)ethanol in reaction with **1** yielded, (probably through a process similar to that outlined form the synthesis of **4-6**, with a subsequent seven membered ring closure) compounds **8** and **9**. The procedures described here constitute a relatively simple method to the two new classes of heterocycles represented by compounds **8** and **9**.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Mattson 4020 Galaxy ft/ir as potassium bromide pellets. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker AC 300 spectrometer in deuteriochloroform or DMSO-d_6 (TMS was added as internal standard). Mass spectra were obtained using a Finnigan TSQ-45 Quadrupole Mass Spectrometer. Compound **1** was prepared as described previously [5].

Preparation of 6-Amino-3-cyano-5-ethoxycarbonyl-4-methyl-1-phenyl-1,2-dihydropyridin-2-one (**2**).

A solution of 0.30 g of **1** in 10 ml of ethanol was added to a solution of 20 ml of 35% ammonia and the mixture was stirred overnight. The mixture was then diluted with 100 ml of distilled water and recrystallized from ethanol yielding a colorless solid, mp 244-245°, yield 81%; ^{1}H-nmr (deuteriochloroform): δ 1.40 (t, 3H), 2.73 (s, 3H), 4.34 (q, 2H), 7.23-7.65 (m, 5H); ^{13}C-nmr (DMSO-d_6): δ 14.2 (CH_3CH_2O), 22.6 (CH_3), 61.1 (CH_3CH_2), 90.0 (91.0), 117.3, 128.9, 130.1, 130.6, 134.1, 156.5, 159.1, 159.9, 167.0; ms: m/z 297 (100%, M^+), 119 (5.0%, $PhNCO^+$), 77 (19.0%, Ph^+); ir: ν 3320, 3181 (NH_2), 2211 (C≡N), 1676 (C=O), 1643 (C=O).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.66; H, 4.99; N, 14.12.

Preparation of 5-Cyano-4-methyl-7-phenyl-2,3,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine-3,6-dione (**3**).

A mixture of sodium ethoxide (prepared from 0.14 g of sodium and 15 ml of absolute ethanol) 0.32 g of hydrazine dihydrochloride and 0.25 g of **1** was stirred for 1 hour at room temperature and then refluxed for an additional hour. The solvent was removed under reduced pressure and the crude product was collected and washed with two 10 ml portions of water. The crude product was recrystallized from *N,N*-dimethylformamide yielding a colorless crystalline solid, mp above 330° dec, yield 49%; ^{1}H-nmr (DMSO-d_6): δ 2.61 (s, 3H), 3.0-5.0 (broad s, 1H), 7.41-7.61 (m, 5H); ^{13}C-nmr (DMSO-d_6): δ 16.9 (CH_3), 116.4, 128.2, 129.1, 129.5, 134.1, 156.6, 159.6; ms: m/z 266 (100.0%, M^+), 77 (66%, Ph^+); ir: ν 3100-3300 (NH), 2222 (C≡N), 1663 (C=O), 1649 (C=O).

Anal. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.87; H, 3.66; N, 20.90.

Synthesis of 6-Cyano-8-ethoxycarbonyl-7-methyl-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridin-5-one (**4**).

A mixture of 0.45 g of **1** and 2.00 g of ethylenediamine was stirred at room temperature for 12 hours and then at 110° (oil bath) for an additional hour. An excess of the amine was removed *in vacuo* (1.0 Torr) and the crude solid product was recrystallized form DMF yielding a colorless crystalline solid 232-233°, yield 89%; ^{1}H-nmr (DMSO-d_6): δ 1.28 (t, 3H), 2.53 (s, 3H), 3.78 (m, 2H), 4.05 (t, 2H), 4.25 (q, 2H), 8.74 (s, 1H); ^{13}C-nmr (DMSO-d_6): δ 14.3 (CH_3CH_2O), 21.5 (CH_3), 42.9 (CH_2), 43.7 (CH_2), 60.4 (CH_3CH_2O), 90.0, 91.0, 117.2, 156.4, 158.0, 160.8, 164.7; ms: m/z 247 (100%, M^+), 202 (31.7%, M^+-C_2H_5O·), 201 (91.8%, M^+-C_2H_5OH); ir: ν 3386 (N-H), 2216 (C≡N), 1717 (C=O), 1657 (C=O).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.23; H, 5.13; N, 16.90.

Synthesis of 7-Cyano-9-ethoxycarbonyl-8-methyl-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (**5**).

A mixture of 0.35 g of **1** and 1.5 g of 1,3-propylenediamine was stirred for 12 hours at room temperature and then 1 hour at 100°. An excess of the amine was removed *in vacuo* (1.0 Torr). The crude product was recrystallized from a mixture of ethanol/*N,N*-dimethylformamide (10:1 v/v), yielding a colorless solid, mp 177-178°, yield 72%; ^{1}H-nmr (deuteriochloroform): δ 1.38 (t, 3H), 2.07 (m, 2H), 2.62 (s, 3H), 3.51 (m, 2H), 4.07 (t, 2H), 4.30 (q, 2H), 10.35 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 13.9 (CH_3CH_2O), 17.9 (CH_3), 22.1 (CH_2), 38.8 (CH_2), 39.9 (CH_2), 60.7 (CH_3CH_2O), 87.7, 91.8, 117.4, 153.5, 157.5, 158.8, 166.7; ms: m/z 261 (100%, M^+), 215 (91.7%, M^+-C_2H_5OH); ir: ν 3238 (N-H), 2211 (C≡N), 1667 (C=O), 1649 (C=O).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.75; H, 5.76; N, 15.97.

Preparation of 8-Cyano-10-ethoxycarbonyl-9-methyl-1,2,3,4,5,7-hexahydropyrido[1,2-*a*][1,3]diazepin-7-one (**6**).

A mixture of 0.25 g of **1** and 0.27 g of 1,4-butylenediamine was stirred at 140° (oil bath) for two hours. An excess of the amine was removed *in vacuo* (1.0 Torr) and the remaining oily residue was dissolved in 30 ml of distilled water and extracted with three 30 ml portions of chloroform. The combined chloroform extracts were dried over magnesium chloride, filtered and evaporated under reduced pressure. The crude product was recrystallized from a small amount of ethanol yielding a colorless solid, mp 157-158°, yield 48%; ^{1}H-nmr (deuteriochloroform): δ 1.38 (t, 3H), 1.99 (m, 2 x 2H), 2.60 (s, 3H), 3.60 (m, 2H), 4.31 (m, 2 x 2H), 9.78 (t, 1H); ^{13}C-nmr (deuteriochloroform): δ 14.2 (CH_3CH_2O), 23.2 (CH_3), 23.8 (CH_2), 24.7 (CH_2), 45.3 (CH_2), 45.5 (CH_2), 61.5 (CH_3CH_2O), 94.1, 94.9, 116.7, 159.5, 160.1, 168.3; ms: m/z 275 (100%, M^+), 230 (16.5%, M^+-C_2H_5O·), 229 (15.8%, M^+-C_2H_5OH); ir: ν 3273, (N-H);

2210, (C≡N); 1670, (C=O); 1645, (C=O).

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.92; H, 6.13; N, 15.13.

Synthesis of 3-Cyano-5-ethoxycarbonyl-6-(2-hydroxyethyl)amino-4-methyl-1-phenyl-1,2-dihydropyridin-2-one (**7**).

A mixture of 0.30 g of **1** and 0.22 g of 2-aminoethanol was refluxed in 5 ml of methyl cellosolve for two hours. The liquid components of the mixture were removed *in vacuo* (1.0 Torr) and the crude solid product was recrystallized from ethanol. The resultant colorless solid had, mp 176-177°, yield 64%; ^{1}H-nmr (deuteriochloroform): δ 1.39 (t, 3H), 2.59 (s, 3H), 2.68 (m, 2H), 3.47 (t, 2H), 4.34 (q, 2H), 7.27-7.53 (m, 5H), 8.48 (broad t, 1H); ^{13}C-nmr (deuteriochloroform): δ 14.2 (*C*H$_3$CH$_2$O), 22.3 (*C*H$_3$), 47.6 (*C*H$_2$), 60.4 (*C*H$_2$), 61.8 (*C*H$_2$) 91.8, 96.1, 116.6, 129.0, 129.8, 129.9, 135.7, 156.1, 159.6, 160.1, 167.7; ms: m/z 341 (10.3%, M$^+$), 296 (10.0%, M$^+$-CH$_2$CH$_2$OH), 264 (23.2%, M$^+$-C$_6$H$_5$), 119 (9.31, PhNCO$^+$), 77 (100.0%, Ph$^+$); ir: ν 3405 (O-H, N-H), 2222 (C≡N), 1673 (C=O), 1650 (C=O).

Anal. Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.11; H, 5.61; N, 12.19.

Synthesis of 2-Cyano-1-methyl-5,6,8,9,10,11-hexahydro-3*H*-pyrido[3,2,1-*ij*]-1,3a,6-triazaazulene-3,11-dione (**8**).

A mixture of 0.30 g of **1** and 0.38 g of triethylenediamine was refluxed in 5 ml of methyl cellosolve for two hours. A similar yield was obtained when a fourfold excess of the amine was stirred with 0.30 g of **1** at 100° for 3 hours. Upon removal of the amine *in vacuo* and trituration with ethanol a crude solid product was formed. The crude product was recrystallized from ethanol yielding a white crystalline solid, mp 327-328°, yield 74%; ^{1}H-nmr (DMSO-d$_6$/deuteriochloroform (1:1 v/v)): δ 2.43 (s, 3H), 3.33-3.48 (m, 4H), 3.81 (t, 3H), 4.01 (t, 2H), 8.11 (t, 1H); ^{13}C-nmr (DMSO-d$_6$/-deuteriochloroform (1:1 v/v)): δ 21.0 (*C*H$_3$), 38.0 (NH*C*H$_2$CH$_2$N), 42.2 (*C*H$_2$), 50.3 (*C*H$_2$), 52.7 (NHCH$_2$*C*H$_2$N), 90.6, 94.7, 117.0, 151.0, 157.9, 162.0, 166.1; ms: m/z 244 (100.0%, M$^+$), 215 (30.7%, M$^+$-CH$_2$NH); ir: ν 3266 (N-H), 2209 (C≡N), 1656 (C=O), 1642 (C=O).

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.22; H, 5.00; N, 23.04.

Synthesis of 2-Cyano-1-methyl-5,6,8,9-tetrahydro-3*H*,11*H*-pyrido-[3,2,1-*ij*]-6-oxa-1,3a-diazaazulene-3,11-dione (**9**).

A mixture of 0.30 g of **1** and 0.38 g of 2-(2-aminoethylamino)-ethanol was refluxed in 5 ml of methyl cellosolve for two hours. The liquid components of the mixture were removed under reduced pressure. A crude product was recrystallized from ethanol yielding a colorless solid, mp 239-240°, yield 54%; ^{1}H-nmr (DMSO-d$_6$/deuteriochloroform (1:1 v/v)): δ 2.51 (s, 3H), 3.73 (t, 2H), 3.92 (t, 2H), 4.41 (t, 2H), 4.56 (t, 2H); ^{13}C-nmr (DMSO-d$_6$/deuteriochloroform (1:1 v/v)): δ 21.5 (*C*H$_3$), 43.0 (*C*H$_2$), 50.2 (*C*H$_2$), 50.3 (*C*H$_2$), 63.9 (*C*H$_2$), 79.4, 90.9, 116.9, 152.3, 158.0, 163.4, 165.8; ms: m/z 245 (100%, M$^+$), 215 (27.2%, M$^+$-CH$_2$O); ir: ν 2211 (C≡), 1692 (C=O), 1657, (C=O).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.78; H, 4.34; N, 16.89.

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