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A Facile Synthesis of ($^{15}N_2$) Malononitrile

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SUMMARY

The first synthesis of doubly ^{15}N-labelled malononitrile is described and its spectral properties are provided. A highly pure ($^{15}N_2$) malononitrile is obtained in a facile and simple two-step synthesis which include reaction of diethyl malonate with 25% $^{15}NH_4OH$ at room temperature overnight to form ($^{15}N_2$)-malonodiamide in 84% yield, and dehydration of the latter by $POCl_3$ in acetonitrile to ($^{15}N_2$) malononitrile (75%). The choice of reagents, and simple solutions for work-up, are discussed.

Key Words: ($^{15}N_2$)-malonodiamide; ($^{15}N_2$) malononitrile

INTRODUCTION

Malononitrile is a useful building block for the synthesis of numerous heterocycles (1). Recent applications of malononitrile include the preparation of: pyrazoles (2), pyridines and pyrimidines (3), thiophenes (4), tetrahydrofolic acid analogues (5), condensed pyridazinones (6), and fused pyrrole rings (7).

Nitrogen containing heterocycles are ubiquitous in biological systems. ^{15}N labelling is a useful tool for studying, by NMR, possible H-bonds between the heterocycle, and certain amino acid residues in the protein binding site, and even the type of the H-bond (acceptor or donor). This application is based on the fact that H-bonding interactions cause changes that can be clearly monitored by ^{15}N-NMR spectroscopy, due to its large range of chemical shifts (900 ppm) and its large sensitivity to structural and environmental changes (8). Furthermore, the chemical

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shift of ^{15}N changes drastically upon protonation, and provides a route for determining pKa values of the heterocycle nitrogens (9).

In spite of the vast use of malononitrile in the synthesis of heterocycles of biological importance, there is no documentation of the preparation of doubly ^{15}N-labeled malononitrile. The only reports on ^{15}N-labeled malononitrile refer to mono-labelling (10).

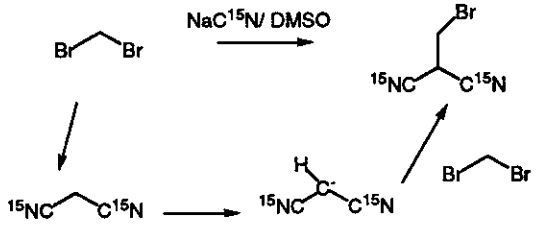
Here we describe a facile and simple synthesis of highly pure ($^{15}N_2$) malononitrile and provide its spectral properties.

^{15}N-labelling requires a minimal number of synthetic steps and high efficiency, due to the high cost of the labelled reagents. Therefore, a standard synthetic procedure for the preparation of malononitrile in four steps from chloroacetic acid (11), was rejected. Other procedures, involving only one step with the labelled reagent, were found to be unsuitable for small-scale laboratory synthesis. Thus, the preparation of malononitrile from acetonitrile and cyanogen chloride requires heating to 700-1000 °C (12). Likewise, the preparation from a diester of malonic acid and ammonia, over silica gel, takes place in the gas phase at 400 °C (13). Other procedures, such as the reaction of acrylonitrile (14) or ketene (15) with ammonia in the presence of oxygen, result in low yields. Preparations with hazardous reagents such as the reaction of diazoacetonitrile with HCN (16), are also not desired.

The inherent properties of malononitrile, which is an exceptionally reactive compound and a weak cyanocarbon acid (1), limit considerably the reaction and work-up conditions. Thus, the use of acids or bases should be avoided to prevent dimerization of the product. Ketones and aldehydes cannot be used as solvents since they react readily with malononitrile to form alkylidenemalononitriles. Likewise, methanol and ethanol are not suitable solvents, since in the presence of acid they form orthoesters from malononitrile. Work-up of a reaction mixture containing malononitrile poses additional complexities. Malononitrile may be hydrolyzed to malonic acid in dilute HCl, and to malonodiamide with NH_4OH (1). In addition, it is not stable on silica gel, and its isolation by extraction is also difficult due to its solubility in water.

RESULTS AND DISCUSSION

A short synthesis of malononitrile from readily available starting materials in an inert solvent, was sought. A symmetric reaction of dibromomethane with $NaC^{15}N$ in DMSO in the presence of catalytic amount of NaI, yielded 1-bromo-2, 2-dicyanoethane as the main product (Scheme 1). The latter is due to proton abstraction from the malononitrile product by the basic cyanide ion, and subsequent reaction of the carbanion with dibromomethane.

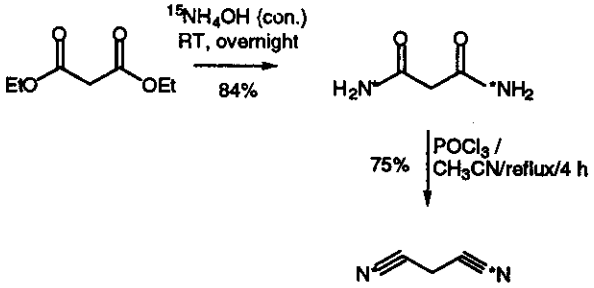


Scheme 1.

The proposed optimal synthesis of ($^{15}N_2$) malononitrile is described in Scheme 2. This is a short two-steps preparation from readily available reagents involving a simple work-up, and leading to relatively high yields and purity. Reaction of diethyl malonate with 25% NH_4OH at room temperature overnight formed malonodiamide in 84% yield. Diethyl malonate was a superior starting reagent compared to malonyl dichloride. The latter, under the reaction conditions, led to the formation of a mixture of malonodiamide and monomalonic acid monoamide or to dimethyl malonate in methanolic ammonia. Formation of monomalonic acid monoamide is minimized by addition of excess $^{15}NH_4OH$ to diethyl malonate. Due to the cost of $^{15}NH_4OH$, an excess of 1.75 eq per ester group was found optimal. The small amount of the side-product was removed from malonodiamide based on solubility differences in EtOH.

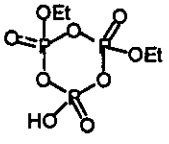
In the second step ($^{15}N_2$) malonodiamide was dehydrated to give malononitrile. The use of various tri- and pentavalent phosphorous compounds is described in the literature for dehydration of amides. Yields range from low, with tris(diethylamino)phosphine (17), to medium with PCl_5 (18) or $POCl_3$ (11c). Furthermore, with these reagents, phosphorus impurities are found in the product even after distillation (11c).

Attempts to use P_2O_5 as a dehydrating agent in the solid phase (10a), in a sublimator, proved inefficient since only a small amount of sublimate is obtained in each run. Moreover, ^{31}P NMR proved the presence of phosphorous contamination in the sublimate. Alternatively, we used $POCl_3$ in acetonitrile, which was found a superior solvent to dichloroethane (11c). In acetonitrile, the reaction time was shorter and the yield was higher. When higher numbers of equivalents of $POCl_3$ were used, the dehydration yield improved, however, more phosphorous side-products were formed. Two equivalents of $POCl_3$ led to an optimal yield.



Scheme 2.

Surprisingly, chloroform soluble phosphoric esters were obtained as side-products in this reaction. ^1H NMR spectrum of one of the products indicated the presence of an ethyl ester group (4.48, dq, 1.50, dt). A singlet at 1 ppm was seen in ^{31}P NMR spectrum and a mass of 296 was measured. On the basis of these data the putative cyclic phosphate ester, **1**, is proposed. This side-product could neither be fully characterized, nor could the origin of the ethyl group be explained.



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Phosphoric ester products complicated the isolation and purification of ($^{15}N_2$) malononitrile, since both are chloroform soluble. Silica gel column separation caused decomposition of malononitrile, and distillation was impractical for the small amounts of labelled product. A pure product was eluted with water from an anion exchanger (Sephadex DEAE-A25) column, however the yields were low. The best

method leading to >98% pure product was sequential extraction of ($^{15}N_2$) malononitrile. Chloroform was added to dissolve phosphoric esters and malononitrile was extracted with a basic aqueous solution, which was subsequently neutralized, NaCl saturated, and extracted with $CHCl_3$.

Exploitation of ($^{15}N_2$) malononitrile for the synthesis of natural and unnatural heterocycles is currently investigated in our laboratory.

EXPERIMENTAL

General. NMR spectra were measured on a Bruker DPX-300 instrument, 330.1, 75.5, and 30.4 MHz for ^1H, ^{13}C, and ^{15}N, respectively. ^{15}N NMR spectra were recorded with CH_3NO_2 ($\delta = 0$ ppm) as an external standard. Products were characterized on an Autospec-E Fision VG high resolution Mass Spectrometer. $^{15}NH_4OH$ was purchased from Cambridge Isotope Laboratories Inc.

($^{15}N_2$) Malonodiamide

Diethyl malonate (1.5 mL, 9.89 mmol) was added to 5.8 N $^{15}NH_4OH$ (5.0 mL) and the mixture was stirred at room temperature overnight. The product could be visualized on tlc by staining with $KMnO_4$ solution. The tlc plate turns purple and malonodiamide is seen as a yellow stain, Rf 0.52, isopropanol: NH_4OH 3:1. The solvent was evaporated and the white residue was washed with ethanol. The solid was collected and dried to give ($^{15}N_2$) malonodiamide (609 mg, 59%) as a white solid, in >99% purity. When the reaction is performed with 7 N NH_4OH yield was 84% (872 mg), mp 170-172 °C (20). ^1H NMR (D_2O): δ = 3.33 (br. s). ^{13}C NMR (D_2O): δ= 42.78 (t, $^2J_{CN}$ = 7.2 Hz, CH_2), 172.70 (d, $^1J_{CN}$ = 16.9 Hz, C=O). ^{15}N NMR (D_2O): δ=-267.2. MS CI/NH_3 m/z: 122 (MNH_4^+), 105 (MH^+).

($^{15}N_2$) Malononitrile

Phosphoryl chloride (0.36 mL, 3.93 mmol) was added to a stirred suspension of ($^{15}N_2$) malonodiamide (200 mg, 1.92 mmol) in dry acetonitrile (4 mL). After reflux for 4 h, the solution was filtered and evaporated. The product could be visualized on tlc by staining with $KMnO_4$ solution. The tlc plate turns purple and malononitrile is seen as a yellow stain, Rf 0.58, $CHCl_3$: MeOH 9:1. The oily residue was dissolved in chloroform and

extracted two times with a saturated solution of Na_2CO_3. The combined aqueous phase was neutralized with a 10% HCl, NaCl was added till a saturated solution was obtained. The aqueous phase was extracted with chloroform (6x20 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed, to yield ($^{15}N_2$) malononitrile as a yellow oil (98 mg, 75%) in >98% purity. ^{1}H NMR (D_2O): δ =3.62 (t, $^3J_{N,H}$ = 1.6 Hz). ^{13}C NMR (D_2O): δ =8.68 (t, $^3J_{C,N}$ = 3 Hz, CH_2), 109.01 (d, $^1J_{C,N}$ = 17.3 Hz, CN). ^{15}N NMR (D_2O): δ = -124.6 (t, $^3J_{N,H}$ = 1.6 Hz). MS EI m/z: 67 ($M\text{-}H^+$).

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