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Synthesis, Chemistry, and Photochemistry of Methylcyanobutadiyne in the Context of Space Science

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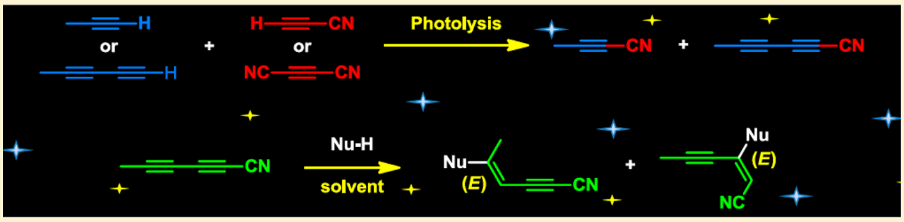

ABSTRACT: An alternative preparation of methylcyanobutadiyne (MeC_5N), a molecule present in the interstellar medium, was established in order to circumvent tedious steps from previous methods. The possibility of forming methylcyanoacetylene and MeC_5N by gas-phase photolysis was evaluated from relevant acetylene derivatives in the context of space science. The reactivity of MeC_5N toward simple nucleophiles was investigated. The exclusive formation of *E* adducts was observed, together with a solvent dependence for the regioselectivity of the addition.

■ INTRODUCTION

About 200 molecules have been detected in the interstellar medium (ISM) so far.[1] A wide range of compounds are present in different regions of space, ranging from small molecules like molecular hydrogen[2] to heavier molecules like fullerenes C_{60} and C_{70}.[3] An interesting family of molecules, the cyanopolyynes, is present in molecular clouds. The structure of cyanopolyynes consists of conjugated triple bonds substituted by a cyano group on one side and a hydrogen on the other side. The general formula of cyanopolyynes is $H-(C{\equiv}C)_n-CN$, and compounds with n ranging from 1 to 5 have been detected in the ISM.[4] Because of their high permanent dipole moment, they give strong signals in microwave spectroscopy, the method of choice for the detection of molecules in the ISM. Consequently, they are quite easily detected compared to other simple molecules, even when their abundance is not high.

Two methylated cyanopolyynes, for which the general formula is $Me-(C{\equiv}C)_n-CN$, have also been detected in the ISM ($n = 1-2$).[5]

Synthesis in the laboratory of only a few cyanopolyynes obtained in pure form has been achieved until now,[6] most probably because of the synthetic challenge that these unstable species represents.

The synthesis of cyanoacetylene has been known for more than 100 years and has been described by Moureu and Bongrand.[6a] It consists of preparing the corresponding amide and, in the next step, heating the latter in the presence of phosphorus pentoxide in order to obtain cyanoacetylene in pure form by removing it from the reaction mixture as it is formed. Later, Miller and Lemmon modified this procedure by adding sand to the mixture of amide and phosphorus pentoxide.[7]

Cyanoacetylene is considered to be a key compound in the field of the origins of life. Using HC_3N, different research groups have reported that it is possible to prepare amino acids,[8] nucleobases,[9] nucleosides,[10] and nucleotides[11] and to transform cyanoacetylene into a phosphorylating agent.[12] Cyanoacetaldehyde, which is prepared in almost quantitative yield from HC_3N in basic conditions,[9] is also an important compound in prebiotic chemistry and has been involved in the synthesis of compounds of prebiotic interest.[13]

Although HC_3N has retained a lot of attention in the community of scientists working on the origins of life and/or interstellar chemistry these last 50 years, the other cyanopolyynes have been much less studied, most probably because of the difficulty in synthesizing them at the hundreds of milligrams scale. In this work, we focused on methylcyanobutadiyne (MeC_5N) that has scarcely been studied so far. We report a new synthetic pathway that circumvents the tedious formation of 1,3-pentadiyne that was published a few years ago.[6d] The possibility of forming methylcyanobutadiyne as well as methylcyanoacetylene by photolysis in the gas phase has also been evaluated (the conditions used here are different from

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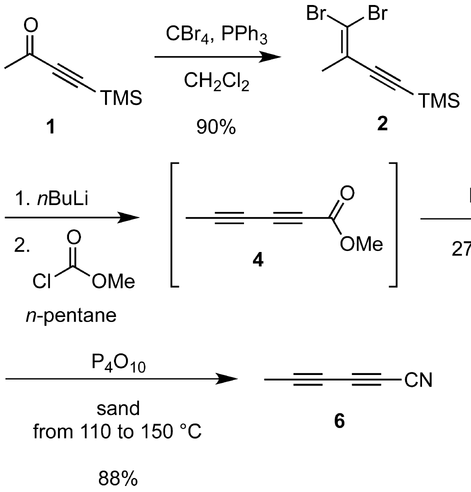
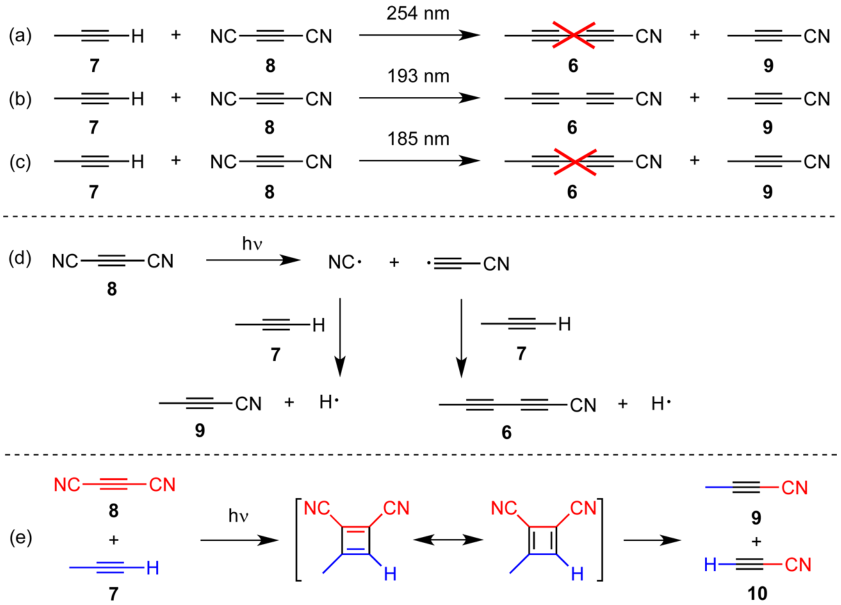
Scheme 1. Synthesis of Methylcyanobutadiyne 6



Scheme 2. Photolysis Experiments Using a Mixture of Propyne and Dicyanoacetylene and the Proposed Mechanisms[a]



[a]Conditions: (a–c) Photolysis experiments in the gas phase using binary mixtures of propyne (7) and dicyanoacetylene (8) at different wavelengths; (d) proposed radical pathways generating MeC_3N (9) and MeC_5N (6); (e) proposed cycloaddition pathway generating MeC_3N (9).

those of the ISM but could nevertheless give some interesting insights). Moreover, the reactivity of MeC_5N toward simple nucleophiles was investigated.

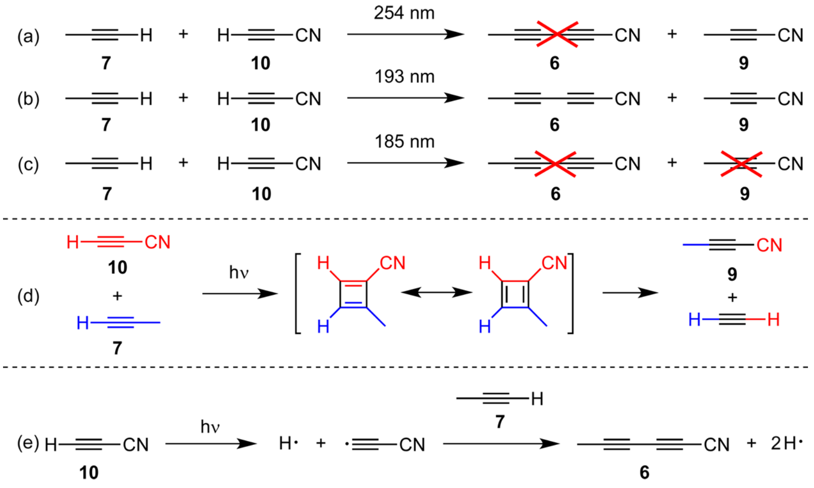
■ RESULTS AND DISCUSSION

Synthesis of MeC_5N. We have recently reported an efficient synthetic pathway for methylcyanobutadiyne.[6d] The synthesis involves the formation of 1,3-pentadiyne from commercially available 1,4-dichlorobutyne, following a modified procedure previously reported by Verkruijsse and Brandsma.[14] However, this step is tedious, and the reaction is very exothermic, which can induce safety issues in the laboratory.

To overcome this problem, another synthetic route was developed. The synthesis starts with the commercially available 4-(trimethylsilyl)-3-butyn-2-one **1**, which was reacted with carbon tetrabromide and triphenylphosphine, allowing thus the preparation of dibromoolefin **2** in 90% yield (Scheme 1).[15] Terminal alkyne **3** was obtained in 99% yield by reacting **2** with a solution of potassium hydroxide, allowing the deprotection of the triple bond.[16] Submitting **3** to the Fritsch–Buttenberg–Wiechell rearrangement led to the formation of 1,3-pentadiynyllithium that was then reacted with methyl chloroformate, affording ester **4**. It is important to notice that this compound could not be separated from methyl pentanoate, which is a byproduct from the reaction of *n*BuLi and methyl chloroformate. Nevertheless, this mixture was reacted with an aqueous solution of ammonia, leading to amide **5** in 27% yield from **3**. Finally, MeC_5N **6** was obtained in 88% yield by reacting amide **5** with an excess of phosphorus pentoxide in the presence of sand while heating the reaction mixture from 110 to 150 °C.

This alternative preparation of MeC_5N differs from the previous one[6d] by forming the ester **4** in another pathway and does not require the tedious synthesis of the thermally unstable 1,3-pentadiyne. Furthermore, one of the most significant improvements lies in the dehydration of amide **5**, obtained in

Scheme 3. Photolysis Experiments Using a Mixture of Propyne and Cyanoacetylene and the Proposed Mechanisms[a]



[a]Conditions: (a−c) Photolysis experiments in the gas phase using binary mixtures of propyne (**7**) and cyanoacetylene (**10**) at different wavelengths; (d) proposed cycloaddition pathway generating MeC_3N (**9**); (e) proposed radical pathway generating MeC_5N (**6**).

a yield higher than that previously published (88 vs 36%), by using an excess of phosphorus pentoxide. The overall yield of the sequence is 21% compared with our previously published sequence, which only reached 8%. Additionally, this procedure allows one to circumvent the one proposed by Kroto et al.,[6f] who used a stannylated precursor and cyanogen chloride, which are known to be toxic.

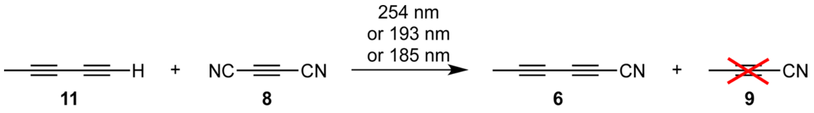
Particularly noteworthy is the thermal stability of MeC_5N compared to its parent compound cyanobutadiyne (HC_5N). Indeed, MeC_5N melts at 92 °C without decomposition, and HC_5N starts to decompose from −40 °C. The same trend was observed, to a lesser extent, between methylcyanoacetylene (MeC_3N) and HC_3N. Whereas the first one is stable at room temperature, the second one slowly decomposes at ordinary pressure and temperature conditions and must be kept in a freezer.

Photochemical Formation of MeC_3N and MeC_5N. The presence of "complex" molecules such as cyanopolyynes or fullerenes in the interstellar medium is quite puzzling, given the very low pressure and temperature conditions. The only reasonable source of energy available in molecular clouds is radiation. Therefore, we suppose that UV light (or shorter wavelength radiations) could be responsible for breaking bonds and thus generating radicals or simply exciting molecules and making them react more easily than in the ground state. To understand how MeC_5N could be formed in the medium, we submitted various binary mixtures of gases that are present or supposed to be present in this medium to a UV irradiation. We have already reported a preliminary study about the formation of trace amounts of MeC_5N under such conditions using a 193 nm irradiation.[6d] In order to gain more insights about the mechanism of formation of this compound, we have completed this study with an irradiation at 254 and 185 nm. In parallel, we tried to identify traces of MeC_3N in the same mixtures in order to collect information about the mechanism of formation of MeC_5N. All experiments were performed using 100 mbar of each gas at room temperature. These conditions are clearly far different from the genuine interstellar conditions, but they allow the new products to be formed in a decent time scale and detectable amounts. To evaluate the photochemical behavior of the different mixtures, three different irradiation conditions were used: one with a 254 nm irradiation, another using 254 and 193 irradiations, and a last one using 254, 193, and 185 nm irradiations. To simplify the way we distinguish these three conditions, only the shortest wavelength is specified in the following text.

The photolysis of propyne and dicyanoacetylene (which was synthesized according to a procedure from the literature[17]) at 254, 193, or 185 nm led to the formation of MeC_3N in each case, whereas MeC_5N was only formed at 193 nm (Scheme 2, eqs a−c). At 254 nm and shorter wavelengths, dicyanoacetylene can most likely undergo a homolytic bond cleavage of Csp−Csp single bond, forming a CN radical on the one hand and a C_3N radical on the other hand. Addition of a CN radical on propyne gives MeC_3N (as already described in other articles[18]), and addition of a C_3N radical gives MeC_5N (Scheme 2, eq d). However, particularly noteworthy is the formation of MeC_3N at each wavelength contrary to MeC_5N. In our previous report,[6d] we suggested that propyne could also lead to a propargylic radical below 193 nm that would inhibit the formation of MeC_5N. Nevertheless, MeC_3N was formed at 185 nm, which could suggest that the radical pathway might not be the only possible mechanism. Actually, we could also envisage a sequence of [2 + 2] cycloaddition−retroelectrocyclization that would allow for the formation of MeC_3N but not the formation of MeC_5N (Scheme 2, eq e). Such a mechanism has already been suggested for the reactivity of dicyanoacetylene with ethylene in similar experiments.[19]

When cyanoacetylene was used jointly with propyne, MeC_3N was observed at 254 and 193 nm (Scheme 3, eqs a and b) but not at 185 nm (Scheme 3, eq c). MeC_5N was only formed at 193 nm. According to the literature, cyanoacetylene does not undergo Csp−H cleavage upon irradiation at a wavelength longer than 240 nm.[20] Propyne does not absorb significantly at 254 nm;[21] therefore, a mechanism involving the formation of radical species cannot be invoked to describe the irradiation experiment at 254 nm. Nevertheless, at this wavelength, cyanoacetylene can be brought to its excited state and react with propyne in a cycloaddition reaction, forming a cyclobutadiene (Scheme 3, eq d).[18] The latter intermediate can rearrange into one molecule of MeC_3N and one molecule of acetylene after retroelectrocyclization. This observation tends

Scheme 4. Photolysis Experiments Using a Mixture of 1,3-Pentadiyne and Dicyanoacetylene



to confirm the possibility of a cycloaddition pathway that is parallel to a radical pathway (Scheme 3, eq d). Actually, MeC_5N was formed at 193 nm and cannot be formed by cycloaddition. Addition of a cyanoethynyl radical on propyne can lead to MeC_5N (Scheme 3, eq e). Neither methylcyanoacetylene nor methylcyanobutadiyne was observed at 185 nm when a mixture of propyne and cyanoacetylene was irradiated (Scheme 3, eq c). Since the absorption coefficient of propyne at 185 nm (about 110 amg^{-1} cm^{-1},[22] at 293 K)[20] is 10 times more important than that of cyanoacetylene (about 10 amg^{-1} cm^{-1}, at 293 K),[23] we suppose that the propargyl radical is mostly formed,[24] preventing thus the formation of MeC_3N and MeC_5N.

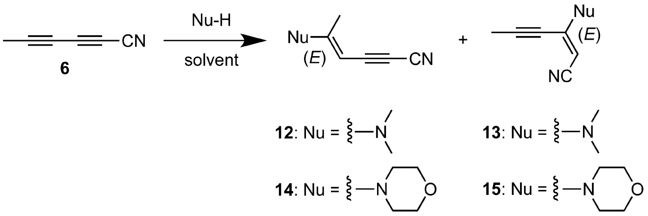
In order to complete these experiments, a mixture of 1,3-pentadiyne (detected in the interstellar medium in 1984[25]) and dicyanoacetylene was also subjected to photolysis (Scheme 4). Formation of MeC_3N was not observed at any of the three wavelengths, but in each case, trace amounts of MeC_5N were detected. These experiments indicate that C−C single bonds of 1,3-pentadiyne or C−C triple bonds from both compounds remain unchanged under these irradiation conditions. One can suppose that MeC_5N was probably formed by addition of CN radical on pentadiyne. However, a [2 + 2] cycloaddition−retroelectrocyclization cascade could also lead to MeC_5N. Furthermore, MeC_7N might have been formed by chain elongation during these experiments, but at the moment, we do not have any authentic sample of this compound, which would allow us to identify it easily out of a complex mixture. We are currently investigating the possibility to synthesize it in pure form in our laboratory.[26,27]

Addition of Nucleophiles on MeC_5N. The question "could life have emerged from space following a cascade of chemical processes that would have started outside the Earth" is still open. The Rosetta mission[28] as well as the study of the chemical composition of meteorites[29] attempts to answer this question, at least partially. In the same manner, numerous studies have shown that cyanoacetylene could have played a central role in the formation of building blocks of life on the Primitive Earth.[8−13]

Following this reasoning, we have investigated the reactivity of MeC_5N toward secondary amines as a preliminary study. Our previous study of the addition of nucleophiles on cyanobutadiyne showed the exclusive formation of the 1,6-addition products as a mixture of *Z*/*E* isomers.[6b,30] In the present work, MeC_5N has been treated with dimethylamine or morpholine in either methanol or tetrahydrofuran. For each experiment, 1 equiv of amine was added at room temperature; the compounds were reacted for 2 h, and the products were isolated after column chromatography. Even though these experiments are far from the Primitive Earth conditions with water as solvent, it was important to run these reactions because the reactivity of MeC_5N was completely unknown. This is the reason why investigating its reactivity with simple compounds was primordial as a first step.

The addition of dimethylamine or morpholine on MeC_5N in THF gave the corresponding 1,6-adducts **12** and **14** in 82 and 93% yields, respectively, as major products of this reaction. Formation of 1,4-adducts **13** and **15** was observed in trace amount according to ^1H NMR (Table 1, entries 1 and 2) but could not be isolated purely from these experiments. By simply changing the solvent, using methanol instead of THF, we observed the formation of a mixture of 1,4-addition and 1,6-addition products (Table 1, entries 3 and 4). For these experiments, the 1,4-addition products **13** and **15** were the major compounds and were obtained in 55 and 41% yields, respectively. This difference of reactivity while increasing the polarity of the solvent can be attributed to a difference of solvation of the dipolar activated complex, which is formed from neutral molecules.[31]

Table 1. Addition of Amines on MeC_5N (6)



entry	Nu−H	solvent	1,6-adducts (yield)	1,4-adducts (yield)
1	Me_2NH	THF	**12** (82%)	**13** (trace)
2	$O(CH_2{-}CH_2)_2NH$	THF	**14** (93%)	**15** (trace)
3	Me_2NH	methanol	**12** (28%)	**13** (55%)
4	$O(CH_2{-}CH_2)_2NH$	methanol	**14** (21%)	**15** (41%)

Compounds **12**−**15** were characterized by ^1H and ^{13}C NMR spectroscopy (HSQC, HMBC, and NOESY) as well as by high-resolution mass spectrometry. Structures of compounds **12** and **15** were also solved by X-ray crystallography.

Products of 1,4-addition on the one hand and products of 1,6-addition on the other hand were unambiguously distinguished by the characteristic ^{13}C carbon shifts of their methyl and cyano groups. Indeed, methyl groups ($\underline{CH_3}$−Csp) of compounds **13** and **15** have a 4.4 ppm chemical shift (Table 2, entries 3 and 5), which is consistent with the chemical shift of other methylacetylenic compounds such as compound **6** (4.7 ppm, Table 2, entry 1). Methyl groups ($\underline{CH_3}$−Csp^2) of compounds **12** and **14** are much more downfield shifted, reaching 18 ppm (Table 2, entries 2 and 4), and are analogous to enyne **18**,[32] for instance (18.5 ppm, Table 2, entry 8). Cyano groups also showed very characteristic chemical shifts. For compounds **13** and **15**, a signal at 121 ppm was observed, corresponding to a cyano group connected to a Csp^2 carbon (Table 2, entries 3 and 5), and was in the same range as compound **17**[33] (120.3 ppm, Table 2, entry 7). In the case of compounds **12** and **14**, a signal at 108 ppm was measured, which is typical of a cyano group directly connected to a carbon−carbon triple bond (Table 2, entries 2 and 4), fitting the chemical shifts measured for **6** and **16**,[6b] which are 105.5 and 107.6 ppm, respectively (Table 2, entries 1 and 6).

Additionally, absolute stereochemical determination of compounds **12**−**15** was evidenced by NOESY experiments.

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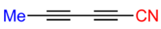
Table 2. Chemical Shifts of Methyl and Cyano Carbons for New Molecules 12−15 and Reported Molecules 6, 16, 17, and 18



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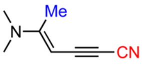

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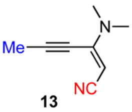

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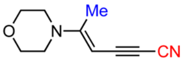

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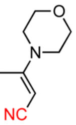

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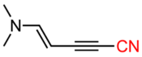

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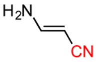

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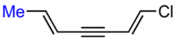

18

entry	compound	δ^{13}C methyl group $\underline{CH_3}$−Csp^2 or $\underline{CH_3}$−Csp (ppm)[a]	δ^{13}C cyano group (ppm)[a]
1	**6**	4.7	105.5
2	**12**	18.5	108.3
3	**13**	4.4	121.8
4	**14**	18.2	107.7
5	**15**	4.4	120.6
6	**16**		107.6
7	**17**		120.3
8	**18**	18.5	

[a] All ^{13}C spectra were recorded in CDCl$_3$.

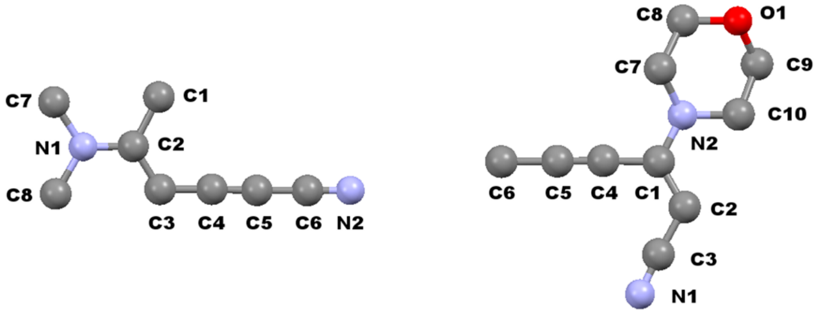

Figure 1. X-ray structures of compound **12** (left) and **15** (right). Hydrogen atoms were omitted for clarity.[35]

Each time, the exclusive formation of the *E* isomer was observed, most likely because it is less sterically hindered than the *Z* isomer and, therefore, is most likely to be formed.

X-ray-quality crystals were grown for compounds **12** and **15** by slow evaporation of *n*-pentane/acetone and chloroform solutions, respectively. They unambiguously confirmed the structures determined on the basis of ^{1}H and ^{13}C NMR spectroscopy.

The π-system of compound **12** is completely planar, showing good delocalization of electrons from the electron-donating dimethylamino group to the electron-withdrawing cyano group (Figure 1). As a consequence, conjugated single bonds are short: the C3−C4 single bond is 1.394(2) Å long, and C5−C6 is 1.365(2) Å, whereas nonconjugated single bonds are generally about 1.54 Å.[34] The C2−C3 double bond (1.379(2) Å) is slightly longer than a nonconjugated double bond, which is generally about 1.34 Å. The triple bond C4−C5 (1.214(2) Å) is less affected and is just slightly longer than a nonconjugated triple bond (*ca.* 1.18 Å).

Similar to that of compound **12**, the π-system of compound **15** is also mostly planar, with the torsion angle C4−C1−C2−C3 being 0.2°. The morpholine six-membered ring adopts a chair conformation. Delocalization of electrons from the nitrogen atom of the morpholine moiety toward the cyano group can be evidenced by carbon−carbon bond lengths. The length of C1−C2 double bond is 1.364(3) Å, which is slightly longer than a nonconjugated double bond, and the C2−C3 simple bond is 1.421(3) Å long, which is much shorter than a nonconjugated simple bond.

CONCLUSION

The alternative synthesis of MeC$_5$N described in this work makes this compound easily accessible for organic chemists. Additionally, the large improvement of the last step of the formation of this compound allows its preparation at the gram scale, which is also a fairly relevant point for further study of the latter, for spectroscopic purposes, and also extensive reactivity studies.

Photolysis experiments in the gas phase, using different binary mixtures of acetylenes, evidenced the formation of MeC$_5$N and MeC$_3$N in such conditions. The use of acetylenic derivatives detected in planetary atmospheres, in the interstellar medium, or simply assumed to be present in space but not detected yet allowed us to sharpen our understanding of the formation of these compounds in the gas phase. In particular, these experiments suggested that two different pathways could be at stake in our reaction conditions: cycloaddition and radical processes.

Addition of simple nucleophiles on MeC$_5$N, such as morpholine and dimethylamine, was also examined. Products of the 1,6-addition of amines on methylcyanobutadiyne were obtained as the exclusive addition products of these reactions in tetrahydrofuran, showing in each case only an *E* configuration for the newly formed double bond. Switching from tetrahydrofuran to methanol indicated the formation of the

1,4-addition products, also possessing systematically an *E* configuration. In these conditions, 1,4-addition products were found to be the major products.

In the frame of prebiotic chemistry, the relative stability of MeC_5N (which melts at 92 °C without decomposition) compared to that of its cyanopolyyne counterpart cyanobutadiyne HC_5N (which decomposes from −40 °C) is interesting and opens the possibility to envisage this compound as a carbon provider during the late heavy bombardment the Earth underwent 3.8 billion years ago, namely, just before the emergence of life on Earth on a geological time scale. Indeed, it could have survived the passage of carbonaceous meteorites (or comets) through the atmosphere which implies a quite important heating, depending on the size of the meteorite. If MeC_5N could have reached the Earth at that time, the question of its future in the conditions of the Primitive Earth remains open. Did it play any role in the formation of the building blocks of life? This is what we are currently investigating in our laboratory, as well as related compounds such as cyanohexatriyne (HC_7N) and methylcyanohexatriyne (MeC_7N). We are also interested in studying the physical properties of cyanopolyynes. With our collaborators, we were able to record the gas-phase infrared spectrum of MeC_5N, which gives a reference for its future detection and quantification in comets or planetary atmospheres.[36]

■ EXPERIMENTAL SECTION

General. Reactions were monitored by thin layer chromatography and visualized under UV irradiation at 254 nm and $KMnO_4$ staining solution. Compounds were purified by flash column chromatography using Geduran silica gel 60 (0.040−0.063 nm). NMR spectra were recorded on a 400 MHz spectrometer. Spectra were recorded in deuterochloroform referenced to $CHCl_3$ (^1H, 7.26 ppm) or $CDCl_3$ (^{13}C, 77.16 ppm) or deuteroacetone referenced to $(CD_3)(CD_2H)CO$ (^1H, 2.05 ppm) or $(CD_3)_2CO$ (^{13}C, 29.84). Chemical shifts (*d*) are reported in parts per million and coupling constants (*J*) are reported in hertz. The following abbreviations are used to describe multiplicity: s, singlet; br s, broad singlet; t, triplet. HRMS experiments were carried out on a Q-ToF spectrometer.

Photochemistry. Photolyses were performed using a low-pressure mercury lamp with a principal emission at 254 nm or another low-pressure mercury lamp with principal emissions at 254, 193, and 185 nm. Experiments were performed in 4 × 19 cm cylindrical cells of 240 cm^3, one in ordinary quartz, which absorbed most of the 185 nm irradiation, and one with a Suprasil window, which let 254, 193, and 185 nm wavelengths pass through. Therefore, there were three different kinds of irradiation experiments: one using the 254 nm wavelength (with the first lamp), another one using the 254 and 193 nm wavelengths (with the second lamp and the quartz cell), and a third one using the 254, 193, and 185 nm wavlengths (with the second lamp and the Suprasil cell). In a standard experiment, 100 mbar of each gas was used. At the end of the photolysis, the cell was connected to a vacuum line and the gaseous phase was condensed with a cosolvent on a cooling finger filled with liquid nitrogen. Analysis was performed by ^1H NMR spectroscopy. The presence of MeC_3N **9** and MeC_5N **6** was confirmed or invalidated by comparison of spectra before and after subsequent addition of an authentic sample in the NMR tube.

Crystallography. All measurements were made in the omega-scans technique on a diffractometer with graphite monochromatized Mo Kα radiation. The structure was solved by direct methods using the program SIR-97.[37] The non-hydrogen atoms were refined anisotropically by the full-matrix least-squares techniques using the program SHELXL97. All hydrogen atoms bonded to carbon atoms were located geometrically and treated using a riding model, with C−H = 0.95−1.00 Å and Uiso(H) = 1.2 or 1.5 Ueq(C).

Synthesis. *1,1-Dibromo-2-methylbut-1-en-3-yne (**3**).* Dibromoolefin **2** (3.63 g, 12.3 mmol) was dissolved in a mixture of THF (90 mL) and methanol (28 mL), and a solution of KOH (37 mL, 1 M) was added slowly. The reaction mixture was stirred at rt for 40 min. Then the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Compound **3** was obtained as a pale yellow oil in 99% yield (2.71 g, 12.1 mmol). The spectroscopic data were in accordance with those from the literature.[15]

*Hexa-2,4-diynamide (**5**).*[6d] A solution of compound **3** (4.90 g, 21.9 mmol) in dry *n*-pentane (110 mL) was placed into a three-neck flask under an argon atmosphere at −80 °C. *n*BuLi (31.5 mL of a 1.6 M solution in *n*-hexane, 50.4 mmol) was added dropwise. The temperature was maintained at −80 °C (solution A). The resulting solution was allowed to reach to −60 °C and was then cooled again to −80 °C. In parallel, a solution of methyl chloroformate (5.1 mL, 65.7 mmol) in dry *n*-pentane (180 mL) was placed into another three-neck flask. This solution (solution B) was cooled to −80 °C, and solution A was added dropwise to solution B. The resulting solution was allowed to reach rt. After being stirred overnight at rt, the solution was quenched with a saturated aqueous solution of ammonium chloride and extracted five times with diethyl ether. The organic layers were combined and washed with brine once. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, *n*-pentane/diethyl ether 95:5). 1.4 g of a mixture of compound **4** and methyl valerate in a ratio of 65/35 was obtained and used subsequently without further purification. Then, a 32% aqueous solution of ammonia (120 mL) was immersed in a liquid nitrogen bath. The flask was allowed to warm. When the aqueous solution became a liquid, a solution of the previous mixture of compound **4** and methyl valerate (1.4 g) in a minimum of methanol was added dropwise. After 1.5 h of stirring, the solution was evaporated. The residue was purified by column chromatography (SiO_2, gradient of elution with DCM/acetone from 10:0 to 9:1). Compound **5** was obtained as a white solid in 27% yield from **3** (619 mg, 5.78 mmol): ^1H NMR (400 MHz, $(CD_3)_2CO$) $\delta = 7.47$ (br s, 1H; NH), 7.04 (br s, 1H; NH), 2.02 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) $\delta = 153.7$, 83.0, 69.5, 68.6, 63.0, 3.8.

*Hexa-2,4-diynenitrile (**6**).* Compound **5** (1.30 g, 12.1 mmol) was placed in a flask containing P_4O_{10} (17.2 g, 60.7 mmol) and sand (17.2 g). The flask was placed under vacuum and gradually heated from 110 to 150 °C over 1.5 h. The product was collected in a trap immersed in a bath at −20 °C. Compound **6** was obtained as pure white powder in 88% yield (950 mg, 10.7 mmol): ^1H NMR (400 MHz, $CDCl_3$)[6d] $\delta = 2.05$ (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 105.5$, 82.0, 68.4, 63.1, 47.6, 4.7.

*Reactivity of MeC_5N with Dimethylamine in Methanol (Compounds **12** and **13**).* To a solution of methylcyanobutadiyne **6** (35 mg, 0.39 mmol) in methanol (1 mL) was added a solution of dimethylamine in methanol (0.205 mL, 2 M, 0.41 mmol). The reaction mixture was stirred at rt for 2 h. Then, the solution was concentrated in vacuo. Purification by flash chromatography (alumina, *n*-pentane/acetone 95/5) afforded compound **12** as a yellow-orange solid in 28% yield (14.8 mg, 0.11 mmol) and compound **13** (29 mg, 55%) as a colorless oil. Characterization of compound **12**: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 4.08$ (s, 1H), 2.93 (s, 6 H; NMe_2), 2.17 (s, 3 H; Me); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 164.7$, 108.3, 90.6, 68.7, 65.0, 40.2, 18.5; HRMS (ESI) *m*/*z* calcd for $C_8H_{10}N_2Na^+$ 157.07417 $[M + Na]^+$, found 157.0744. Crystal data: C_6H_5NO, $M = 134.18$ g mol^{-1}, $T = 140$ K, triclinic, space group = $P\overline{1}$, $a = 4.1693(5)$ Å, $b = 8.6870(10)$ Å, $c = 10.729(2)$ Å, $\alpha = 95.442(10)°$, $\beta = 90.247(10)°$, $\gamma = 95.864(10)°$, $V = 384.78\ (10)$ Å^3, $Z = 2$, $D_c = 1.158$ g cm^{-3}, absorption coefficient = 0.071 mm^{-1}, $F(000) = 144$, reflections collected = 2771, independent reflections = 1676 ($R_{int} = 0.0398$), data/restraints/parameters = 1676/0/94. Final *R* indices ($I > 2\sigma$): $R_1 = 0.0529$. *R* indices (all data): $wR_2 = 0.1622$, goodness-of-fit on F^2 of 1.065. Characterization of compound **13**: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 3.97$ (s, 1H), 2.95 (s, 6H; NMe_2), 2.10 (s, 3H; Me); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 147.1$, 121.8, 96.6, 72.4, 67.2, 40.1, 4.4; HRMS

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(ESI) m/z calcd for $C_8H_{10}N_2Na^+$ 157.07417 $[M + Na]^+$, found 157.0742.

*Reactivity of MeC_5N with Dimethylamine in THF (Compound **12**).* To a solution of methylcyanobutadiyne **6** (35 mg, 0.39 mmol) in THF (1 mL) was added a solution of dimethylamine in THF (0.20 mL, 2 M, 0.40 mmol). The reaction mixture was stirred at rt for 2 h. The solution was then concentrated in vacuo. Purification by flash chromatography (alumina, *n*-pentane/acetone 95/5) afforded compound **12** as a yellow-orange solid in 82% yield (43 mg, 0.32 mmol).

*Reactivity of MeC_5N with Morpholine in Methanol (Compounds **14** and **15**).* To a solution of methylcyanobutadiyne **6** (44 mg, 0.49 mmol) in methanol (1.5 mL) was added a solution of morpholine in methanol (1.0 mL, 0.5 M, 0.50 mmol). The reaction mixture was stirred at rt for 2 h. The solution was then concentrated in vacuo. Purification by flash chromatography (alumina, *n*-pentane/acetone from 95/5 to 85/15) afforded compound **14** as a yellow solid in 21% yield (18 mg, 0.10 mmol) and compound **15** as a white solid in 41% yield (35 mg, 0.20 mmol). Characterization of compound **14**: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 4.33$ (s, 1H), 3.72 (t, $^3J(H,H) = 5.0$ Hz, 4H; OCH_2), 3.20 (t, $^3J(H,H) = 5.0$ Hz, 4H; NCH_2), 2.15 (s, 3H; Me); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 164.3$, 107.7, 88.7, 72.0, 66.2, 65.6, 46.7, 18.2; HRMS (ESI) m/z calcd for $C_{10}H_{14}N_2O_2Na^+$ 217.0953 $[M + H_2O + Na]^+$, found 217.0957. Characterization of compound **15**: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 4.25$ (s, 1H), 3.72 (t, $^3J(H,H) = 5.0$ Hz, 4H; OCH_2), 3.29 (t, $^3J(H,H) = 5.0$ Hz, 4H; NCH_2), 2.11 (s, 3H; Me); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 147.1$, 120.6, 97.4, 72.0, 70.9, 65.9, 47.2, 4.4; HRMS (ESI) m/z calcd for $C_{10}H_{12}N_2ONa^+$ 199.08473 $[M + Na]^+$, found 199.0849. Crystal data: $C_{10}H_{12}N_2O$, M = 176.22 g mol^{-1}, $T = 150$ K, orthorhombic, space group $P2_12_12_1$, $a = 4.3708(2)$ Å, $b = 13.7544(5)$ Å, $c = 15.5815(5)$ Å, $\alpha = 90.0°$, $\beta = 90.0°$, $\gamma = 90.0°$, $V = 936.72$ (6) $Å^3$, $Z = 4$, $D_c = 1.250$ g cm^{-3}, absorption coefficient = 0.083 mm^{-1}, $F(000) = 376$, reflections collected = 6662, independent reflections = 2050 ($R_{int} = 0.0322$), data/restraints/parameters = 1676/0/127. Final R indices ($I > 2\sigma$): $R_1 = 0.0396$. R indices (all data): $wR_2 = 0.0920$, goodness-of-fit on F^2 of 1.047.

*Reactivity of MeC_5N with Morpholine in THF (Compound **14**).* To a solution of methylcyanobutadiyne **6** (45 mg, 0.51 mmol) in THF (2 mL) was added a solution of morpholine in THF (1.05 mL, 0.5 M, 0.525 mmol). The reaction mixture was stirred at rt for 2 h. The solution was then concentrated in vacuo. Purification by flash chromatography (alumina, *n*-pentane/acetone from 95/5 to 85/15) afforded compound **14** as an orange solid in 93% yield (83 mg, 0.47 mmol).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00205.

X-ray data for **12** (CIF)

X-ray data for **15** (CIF)

^1H and ^{13}C NMR data for compounds **5**, **6**, and **12−15** and thermal ellipsoid plots for the X-ray diffraction structures of compounds **12** and **15** (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Professor James P. Ferris (Rensselaer Polytechnic Institute).

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