Organic Syntheses

Copper-catalyzed Cyanation of Alkenyl Iodides

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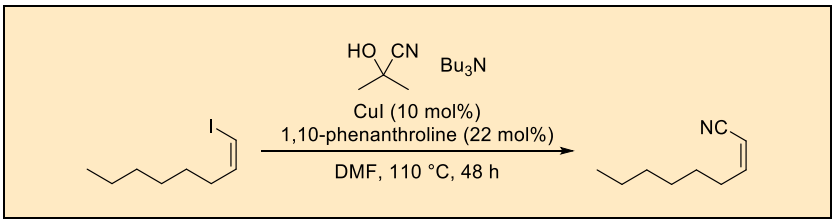

Procedure

Acetone cyanohydrin is highly toxic and must be handled in a well-ventilated fume hood. The aqueous waste solutions should not be in contact with acids and, where permitted, must be treated with excess commercial Clorox® bleach. All glassware and apparatus that comes into contact with it must be washed with commercial Clorox® bleach. All spills around balances or work areas should be immediately cleaned up and the area washed down with bleach.

A. *(Z)-Non-2-enenitrile (**2a**).* A 50-mL, double-necked, oven dried, round-bottomed flask equipped with an octagonal Teflon®-coated magnetic stir bar (0.8 mm x 3.8 cm) is successively charged with (*Z*)-1-iodooct-1-ene **1a** (13.7 g, 57.5 mmol) (Note 1), copper(I) iodide (1.1 g, 5.8 mmol, 0.1 equiv) (Note 2), and 1,10-phenanthroline (2.3 g, 12.8 mmol, 0.2 equiv) (Note 3). The lateral neck of the flask is equipped with a rubber septum and the top neck of the flask with a water-cooled condenser fitted with a gas inlet (Figure 1).

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The flask is then evacuated under vacuum (2 mmHg) and backfilled with argon three times. *N*,*N*-Dimethylformamide (70 mL) (Note 4) is added via a syringe through the septum and the mixture is stirred for 5 min at room temperature before successively adding tri-*n*-butylamine (17.8 mL, 74.7 mmol, 1.3 equiv) (Note 5) and acetone cyanohydrin (6.3 mL, 69 mmol, 1.2 equiv) (Note 6) via a syringe through the septum. The septum is replaced by a glass stopper and the resulting slurry (Note 7) is heated in a pre-heated oil bath at 110 °C (bath temperature) and kept under vigorous stirring for 48 h (Note 8) (Figure 2). The reaction mixture is then allowed to cool to room temperature, diluted with diethyl ether (150 mL) (Note 9), vacuum filtered through a one-half inch pad of Celite® on a 150-mL medium porosity sintered glass filtration funnel and rinsed with diethyl ether (150 mL) before being diluted with water (300 mL) and transferred to a 1-L separatory funnel. The organic layer is separated and the aqueous layer is extracted with diethyl ether (3 x 100 mL). The combined organic layers are successively washed with water (200 mL) and brine (200 mL), dried over 30 g of anhydrous magnesium sulfate, vacuum filtered through a 150-mL medium porosity sintered glass filtration funnel, and concentrated by rotary evaporation (25 °C, 350 mmHg then 40 mmHg when most of the solvent has been evaporated) to

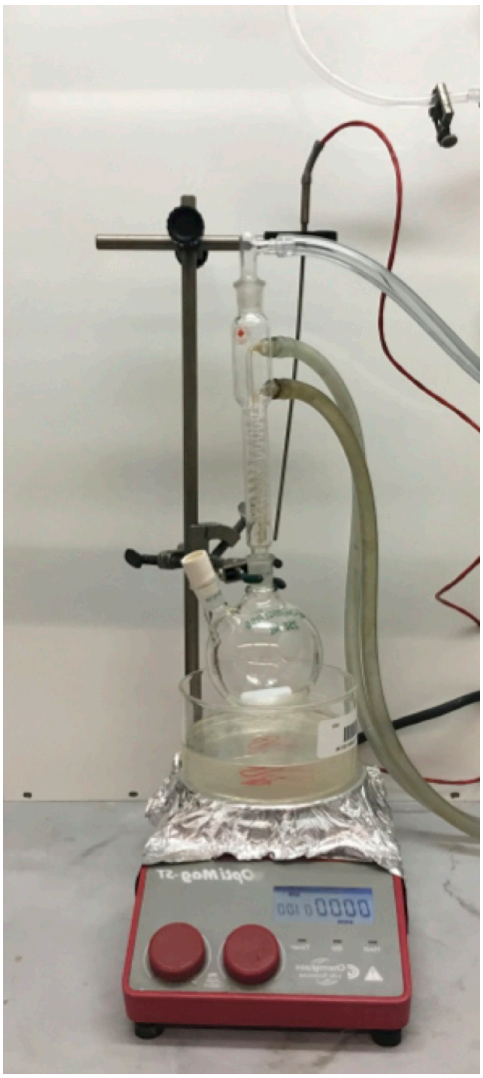

Figure 1. Reaction Apparatus

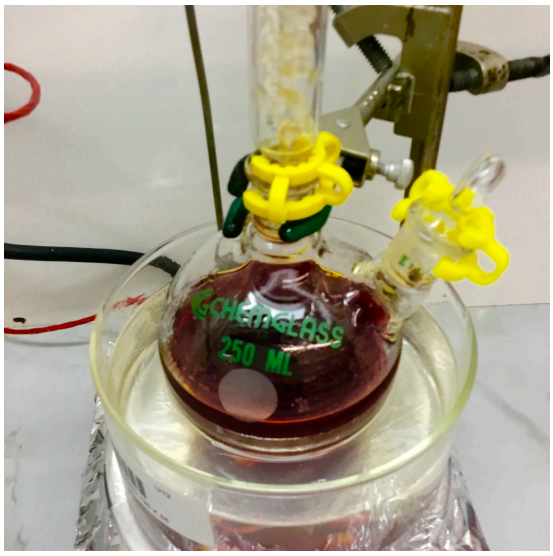

Figure 2. Reaction mixture after heating to 110 °C turns deep red/orange

give 11.2-12.1 g of a brown oil. The product is dissolved in cyclohexane (10 mL) (Note 10) and charged on a column (5 x 40 cm), which is packed with a slurry of 200 g of silica gel (Note 11) in 500 mL of cyclohexane. The column is first eluted with 500 mL of cyclohexane. At that point, fraction collection (~35-mL fractions) is begun, and elution is continued with 500 mL of 2% EtOAc-cyclohexane (98:2 cyclohexane:EtOAc) (Note 12) and then 1250 mL of 3% EtOAc-cyclohexane (97:3 cyclohexane:EtOAc). The desired

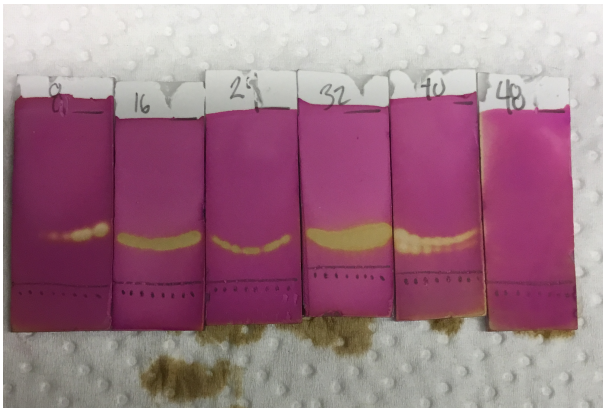

Figure 3. TLC of fractions collected during column chromatography

product is obtained in fractions 3–40 (Notes 13 and 14) (Figure 3), which are concentrated by rotary evaporation (30 °C, 100 mmHg then 15 mmHg when most of the solvent has been evaporated). The resulting oil is dried under vacuum (3 mmHg, 2 h) (Note 15) to afford (*Z*)-non-2-enenitrile (**2a**) (6.3 g, 80%) as a pale yellow oil (Notes 16, 17, 18, 19, 20, and 21).

Notes

1. Synthesized according to Yang, D.; Cwynar, V. A.; Hart, D. J.; Madanmohan, J.; Lee, J.; Lyons, J.; Caffrey, M. *Org. Synth.* **2012**, *89*, 183–201.
2. Copper iodide (99.999%) was purchased from Sigma-Aldrich and used as received. The yield was not significantly changed when switching to 98% copper iodide (purchased from Sigma-Aldrich and used without purification).
3. Anhydrous 1,10-phenanthroline (99%) was purchased from Alfa-Aesar and used as received.
4. *N*,*N*-Dimethylformamide (reagent grade, >99%) was purchased from Fisher and purified by distillation over calcium hydride under argon at 0.06 mmHg. The yield was not significantly changed when switching to 99.8% extra dry *N*,*N*-dimethylformamide stored over molecular sieves (purchased from Acros Organics and used without purification). The Checkers used the latter source of *N*,*N*-dimethylformamide.
5. Tri-*n*-butylamine (99%) was purchased from Sigma-Aldrich. It was purified by distillation over calcium hydride under argon at 0.06 mmHg and stored under argon in a flask covered with aluminum foil to protect it from the light. The Checkers used 20 mL of the amine over 2.8 g of CaH for the distillation.
6. Acetone cyanohydrin (99%) was purchased from Sigma-Aldrich and used as received.
7. The reaction mixture turns to dark orange at this stage and then back to brown upon heating.
8. TLC analysis was performed on Merck aluminum silica gel plates 60 F_{254}. Reaction conversion was ascertained using the following procedure. The reaction mixture was spotted directly on the TLC plate, which was eluted with 4% EtOAc-cyclohexane (96:4 cyclohexane:EtOAc), and visualized with $KMnO_4$ stain after heating:

starting material **1a** (R_f = 0.7, a $KMnO_4$ active spot); product **2a** (R_f = 0.22, a $KMnO_4$ active spot). The $KMnO_4$ stain was prepared using 1.5 g of $KMnO_4$ and 10 g of K_2CO_3 dissolved in 150 mL of deionized water and 5.0 mL of a 5% weight NaOH solution. The Checkers prepared their $KMnO_4$ stain according to the procedure of Pirrung, M. C. "The Synthetic Organic Chemist's Companion." **2007**, Wiley, p. 171.

9. Diethyl ether (reagent grade, >99%) was purchased from VWR and used as received.
10. Cyclohexane (analytical reagent grade, >99.9%) was purchased from Fisher and distilled before use to remove non-volatile residues.
11. Silica gel Geduran® Si60 particle size 40-63 μm was purchased from Merck.
12. Ethyl acetate (analytical reagent grade, >99.9%) was purchased from Fisher and distilled before use to remove non-volatile residues.
13. The presence of the product **2a** is visualized by TLC analysis on Merck aluminum silica gel plates 60 F_{254} (R_f = 0.22, 96:4 cyclohexane:EtOAc, a $KMnO_4$ active spot).
14. Minor amounts of the unconjugated isomer, (*E*)-non-3-enenitrile, can be detected by TLC analysis on Merck aluminum silica gel plates 60 F_{254} (R_f = 0.20, 96:4 cyclohexane:EtOAc, a $KMnO_4$ active spot). All fractions for which TLC analyses indicate that the intensity of the spot corresponding to this byproduct was less important than the intensity of the spot corresponding to **2a** were collected. The Checkers found that collecting *only* the spots containing product **2a** gives 68% isolated yield of product without the undesired unconjugated product.
15. The product being volatile, drying it under higher vacuum or for longer times results in significant losses of product. During one run, the Checkers rinsed the test tubes containing product with ethyl acetate (5 mL each) to ensure complete product collection. Upon concentration, the Checkers found that this added ethyl acetate could not be removed completely without significant loss of the product on high vacuum. Rinsing the test tubes is not recommended.
16. (*Z*)-Non-2-enenitrile **2a** has the following physical properties: IR (ATR) 2957, 2930, 2859, 2220, 1621, 1465, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 6.9 Hz, 3H), 1.23–1.39 (m, 6H), 1.40–1.52 (m, 2H), 2.42 (dq, *J* = 7.6, 1.3 Hz, 2H), 5.30 (dt, *J* = 10.9, 1.3 Hz, 1H), 6.48 (dt, *J* = 10.9, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 28.2, 28.7, 31.5, 31.9, 99.4, 116.1, 155.3; ESIHRMS *m*/*z* calcd for $C_9H_{16}N^+$ $[M+H]^+$ 138.1277, found 138.1278.

17. Purity 97.1% *wt.* by quantitative ^{1}H NMR assay using ethylene carbonate as an internal standard. The Checkers found that the product could be obtained without contamination from the unconjugated alkene byproduct in chromatographic fractions 3 – 32 accounting for 68% yield. The purity refers to the total combined yield (79-80%) of product **2a** plus its unconjugated isomer.
18. The product contains 2-3% *wt.* of the unconjugated isomer, (*E*)-non-3-enenitrile, as determined by ^{1}H NMR analysis.
19. The product has a rather unpleasant smell and should therefore be handled in a well-ventilated fume hood.
20. The product was stored under argon at –20 °C and found to be stable for more than a year at this temperature.
21. A second run of the reaction provided 6.2 g (79%) of the product in 97.7% purity as assessed by Q NMR with ethylene carbonate as the internal standard.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment

and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

Alkenyl nitriles, commonly called acrylonitriles, are important building blocks and intermediates in organic synthesis where they have been used in an impressive number of transformations involving the activated alkene, the nitrile or both. They are in addition found in various natural products, the most famous examples probably being hemi-phorboxazole A[2] or calyculin A,[3] and compounds from the pharmaceutical industry such as trilostane (Modrenal®),[4] a steroidal alkenyl nitrile used for the treatment of Cushing's disease and breast cancer, or rilpivirine (Edurant®), a non-nucleoside reverse transcriptase inhibitor used for the treatment of HIV infections.[5]

The classical synthesis of acrylonitriles typically rely on Wittig,[6] Horner-Wadsworth-Emmons[7] or Peterson[8] olefination reactions. While these reactions are in general efficient and high yielding, they are often restricted to the preparation of one of the *E* or *Z* isomer and/or yield mixtures of these isomers whose separation is in general troublesome. Other standard techniques available to access these building blocks include the dehydration of conjugated amides or oximes,[9] Heck-type reactions[10] or cross-metathesis,[11] just to mention the methods that are the most commonly used for the synthesis of conjugated nitriles.[12] While extensively used, these routes however still have major limitations in terms of scope, yields and *E*/*Z* selectivity, the last point being in general the main issue. An interesting solution to this problem lies in the metal-catalyzed cyanation of alkenyl halides. Indeed, their *E* and *Z* isomers can be easily prepared by a range of robust and reliable methods such as the Takai[13] or Stork-Zhao[14] olefinations of aldehydes, Brown's hydroboration of iodoalkynes followed by protonolysis[15] or the homologation/elimination sequence from benzyl

halides and diiodomethane.[16] Provided that the stereochemistry of the double bond can be preserved during the cross-coupling, the cyanation of alkenyl halides could provide an interesting, general and stereocontroled route to acrylonitriles.

While this approach had already been investigated before we started our studies, most catalytic systems based on nickel,[17] cobalt[18] or palladium[19] are often limited to the preparation of aryl-substituted alkenyl nitriles, lack generality and/or require expensive complexes and ligands. A general, stereospecific and robust cyanation of alkenyl halides was therefore still an unmet challenge, which prompted us to develop the copper-catalyzed cyanation we reported in 2014 and that is discussed below.[20]

The cyanation of alkenyl iodides was found to be best performed using a catalytic system similar to the one developed by Taillefer for the cyanation of aryl halides[21,22] based on the combination of copper(I) iodide (10 mol%) and 1,10-phenanthroline (20 mol%) in DMF at 110°C for 16-48 hours. The best source of cyanide was found to be acetone cyanohydrin,[23] which decomposes quantitatively to acetone and cyanide in the presence of a base, tributylamine in our case. A slight excess (1.2 and 1.3 equivalents of the former and the latter, respectively) was shown to be sufficient for full conversion and, while a slow addition of the base is usually required in metal-catalyzed cross-coupling reactions involving acetone cyanohydrin in order to minimize the amount of cyanide present in solution and therefore avoid catalyst poisoning, all the base could be added at the beginning of the reaction in our case without significant catalyst deactivation.

Representative examples of this copper-catalyzed cyanation of alkenyl iodides are shown in Table 1.[20] As evidenced by these results, the procedure was found to be suitable for the preparation of a wide range of alkenyl nitriles, substituted not only with aryl groups but also with alkyl chains. The presence of substituents close to the reacting center was not detrimental since 1-substituted and 2,2-disubstituted 1-alkenyl-iodides were conveniently transformed to the corresponding conjugated nitriles under the reaction conditions. Importantly, the configuration of the double bond was fully retained, which therefore enabled the cyanation of Z-iodoalkenes without noticeable isomerization of the double bond. Benzyl and silyl ethers, acetals and acetates were shown to be stable under the reaction conditions, and an aromatic bromide was also found to be compatible. While most alkenyl iodides were found to be reactive under our standard reaction conditions, the corresponding bromide were, however, found to be totally inert and recovered at the end of the reaction.

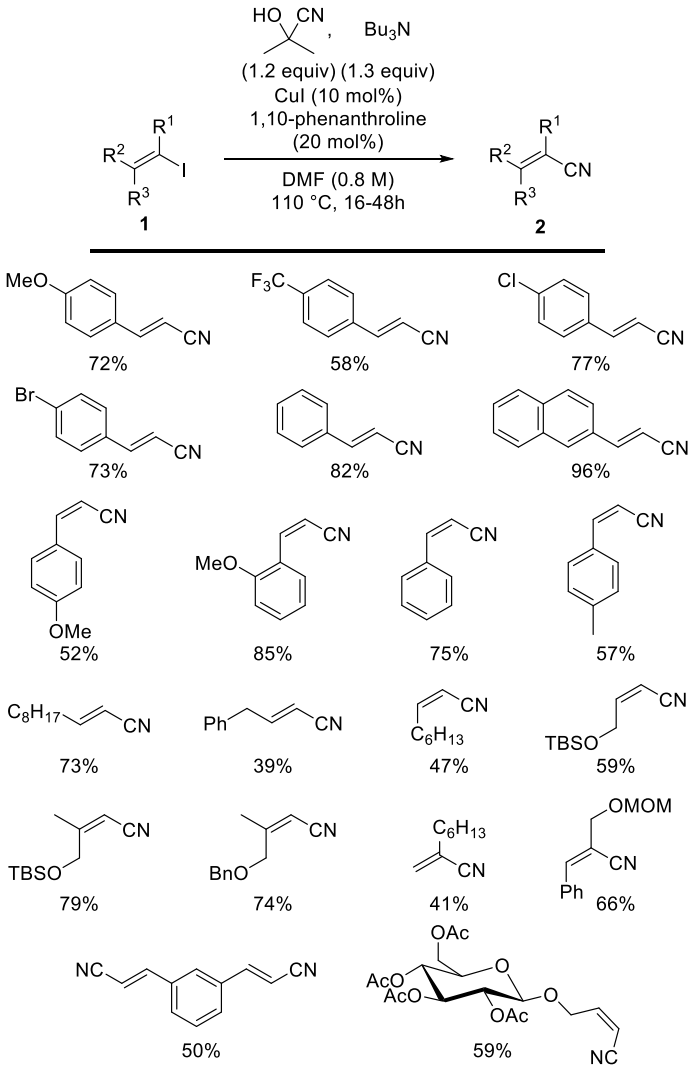

Table 1. Copper-catalyzed cyanation of alkenyl iodides

In summary, a general and practical copper-catalyzed vinylic version of the Rosenmund-von Braun cyanation reaction was developed and provides an efficient entry to both *E*- and *Z*- polysubstituted alkenyl nitriles. The

cyanation of (*Z*)-1-iodooct-1-ene described in this procedure is illustrative of this reaction which can be conveniently performed on a multi-gram scale.

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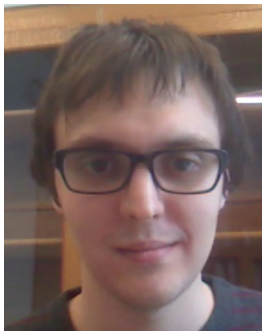
Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*Z*)-Non-2-enenitrile: 2-Nonenenitrile, (2*Z*)-; (40856-15-3)
(*Z*)-1-Iodooct-1-ene: 1-Octene, 1-iodo-, (1*Z*)-; (52356-93-1)
Copper(I) iodide: Copper iodide; (7681-65-4)
1,10-Phenanthroline; (66-71-7)
Tri-*n*-butylamine: 1-Butanamine, *N*,*N*-dibutyl-; (102-82-9)
Acetone cyanohydrin: Propanenitrile, 2-hydroxy-2-methyl-; (75-86-5)

Antoine Nitelet was born in Charleroi in 1990 and studied chemistry at the Université Libre de Bruxelles. In 2012, he joined the group of Prof. Gwilherm Evano as a master student and obtained a F.R.I.A. Ph.D. fellowship in 2013. His work focuses on the development of new copper-catalyzed cross-coupling reactions involving alkenyl halides and their application to the synthesis of natural products.

Sara Zahim was born in Tanger in 1986 and studied chemistry at the Université Libre de Bruxelles. In 2011, she joined the groups of Profs. Gwilherm Evano and Ivan Jabin as a master student and obtained a F.R.I.A. Ph.D. fellowship in 2012. Her work focuses on the development of new methods for the selective functionalization of calix[6]arenes and their application to the design of new molecular receptors and new ligands for metal-catalyzed reactions.

Cédric Theunissen was born in Brussels in 1989 and studied chemistry at the Université Libre de Bruxelles. In 2012, he obtained his master thesis, under the supervision of Prof. Cécile Moucheron, which focused on the synthesis of new ruthenium complexes designed to interact with DNA in an anti-cancer approach. He then joined the group of Prof. Gwilherm Evano and obtained a F.R.I.A. Ph.D. fellowship. His work focuses on the development of new copper-mediated transformations and on the study of the reactivity of ynamides.

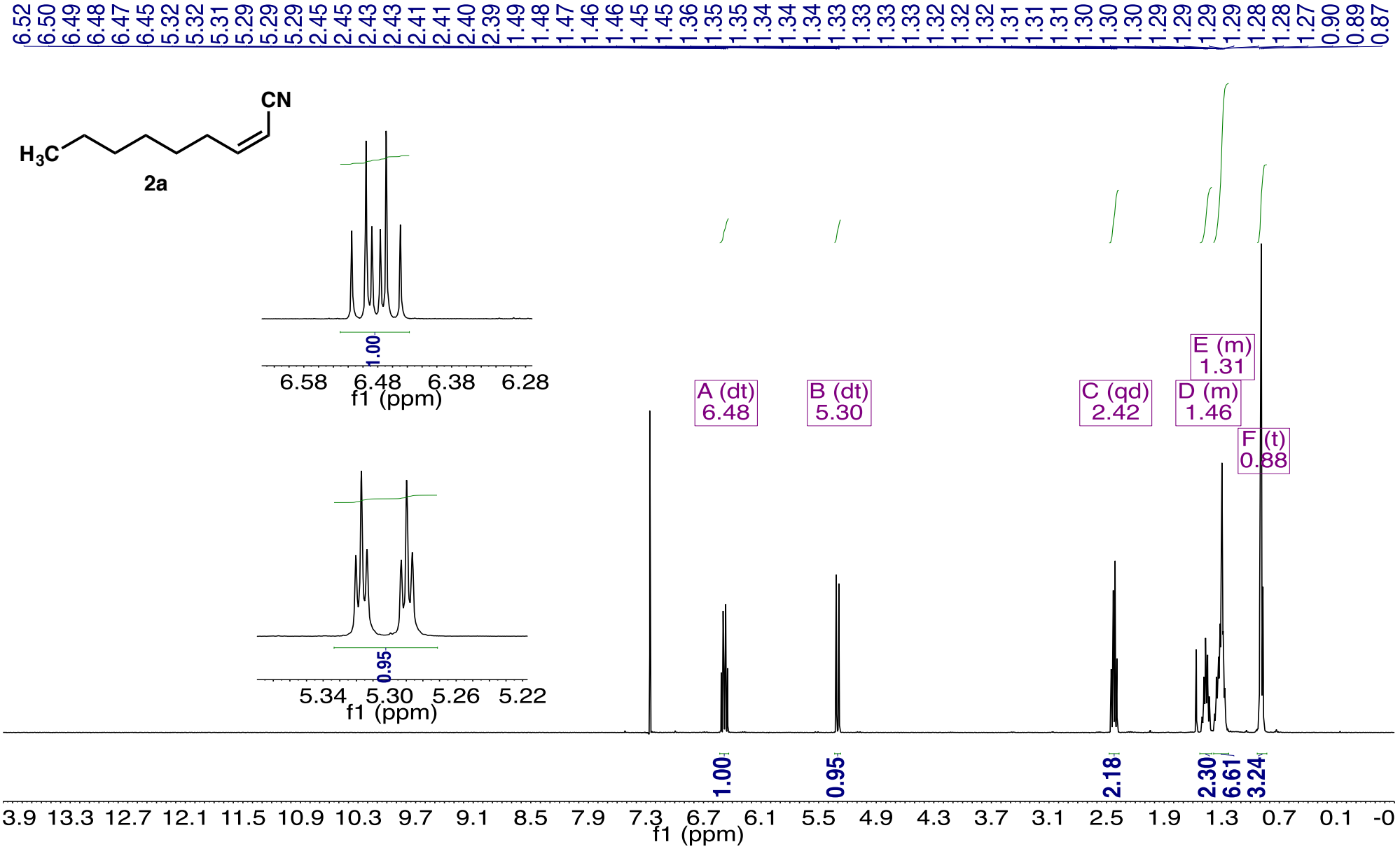


Alexandre Pradal was born in 1987 in Maisons-Laffitte (France) and received his Ph.D. in 2012 under the supervision of Drs. Véronique Michelet and Patrick Toullec with whom he worked on electrophilic carbocyclization and asymmetric cycloisomerization reactions of 1,n-enynes in the presence of platinum and gold catalysts. He then joined the group of Prof. Gwilherm Evano at the Université Libre de Bruxelles as a postoctoral researcher where he worked on the copper-catalyzed cyanation of alkenyl iodides. He next moved to the University of Nottingham as a postdoctoral researcher in the group of Prof. Christopher Moody, working on the total synthesis of diazonamide A and is currently working with Prof. Vincent Dalla at the Université du Havre.

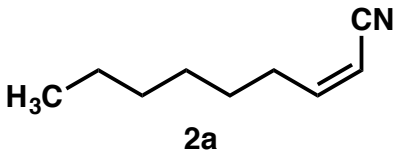
Gwilherm Evano studied chemistry at the Ecole Normale Supérieure in Paris and received his Ph.D. from the Université Pierre et Marie Curie in 2002 under the supervision of Profs. François Couty and Claude Agami. After postdoctoral studies with Prof. James S. Panek at Boston University, he joined the CNRS at the University of Versailles in 2004. He then moved to the Université Libre de Bruxelles as associate professor in 2012. He has coauthored 80 publications and 10 book chapters with research interests in developing copper-mediated transformations and the chemistry of heteroatom-substituted alkynes as well as the total synthesis of natural and/or biologically relevant products.

Sidney Wilkerson-Hill was born in Kinston, North Carolina in 1988 and studied chemistry at North Carolina State University. In 2015, Sidney received his Ph.D. under the supervision of Prof. Richmond Sarpong at the University of California, Berkeley where his research focused on using cycloisomerization reactions to access natural product scaffolds. He is currently a UNCF-Merck postdoctoral fellow in the group of Prof. Huw Davies at Emory University in Atlanta, GA where his research focuses on developing novel reactions using *N*-sulfonyltriazoles and rhodium tetracarboxylate catalysts.

^{1}H NMR for (*Z*)-non-2-enenitrile **2a**



^{13}C NMR for (*Z*)-non-2-enenitrile **2a**



2a