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Pierre Hansjacob, Frédéric R Leroux, Morgan Donnard. Zinc-Catalyzed Hydrocyanation of Ynamides and Photoisomerization, a General and Selective Access to E and Z Trisubstituted Alpha-Enamidonitriles. *Chemistry - A European Journal*, 2023, pp.e202300120. 10.1002/chem.202300120 . hal-04051662

HAL Id: hal-04051662

<https://hal.science/hal-04051662>

Submitted on 30 Mar 2023

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Zinc-Catalyzed Hydrocyanation of Ynamides and Photoisomerization, a General and Selective Access to *E* and *Z* Trisubstituted α -Enamidonitriles.

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Abstract: The fully regio and stereoselective Zn-catalyzed hydrocyanation of ynamides is reported and represents a general access to various trisubstituted *E*- α -enamidonitriles. The catalyst-free photoisomerization selectively yields the energetically comparable *Z*-stereoisomer. Finally, the synthetic potential of these new α -enamidonitriles was evaluated through the synthesis of original heterocycles.

Introduction

For decades, acrylonitriles have been recognized for their synthetic utility in various fields such as pharmaceuticals, agrochemicals, or materials.¹ Within this family of compounds, amino-acrylonitriles have emerged over the years as versatile and valuable building blocks for the synthesis of heterocycles. However, while β -enamidonitriles (*i.e.* 3-amino-acrylonitriles) have been extensively studied both in terms of synthesis and application,² α -enamidonitriles (bearing the amino group in position 2) have been much less studied. These captodative enamines,³ despite a real synthetic potential, suffers from a lack of versatile generic synthesis methodologies to access them. If we now consider the case of α -enamidonitriles (2-amidoacrylonitriles), the observation is then accentuated by the very rare descriptions of their syntheses which are almost exclusively based on a sequence involving the formation of amido-acetonitriles followed by a condensation with aldehydes (first reported by Fleury⁴ and then generalized by Takahashi⁵) (Figure 1).⁶ Notably, this approach remains mainly limited to the use of aromatic aldehydes and is therefore rather restricted in scope. Moreover, this methodology consistently suffers from a lack of stereoselectivity. Recently, during our studies on captodative enamides,⁷ our group reported the first general access to tetrasubstituted α -enamidonitriles by means of a palladium-catalyzed silylcyanation of ynamides.⁸ However, these overcrowded scaffolds may represent a drawback for some subsequent transformations such as Michael-type additions for instance. If we also reported the protodesilylation of these tetrasubstituted α -enamidonitriles to easily obtain the corresponding trisubstituted products, this approach requires two different synthetic steps (including two purifications) starting from the corresponding ynamides,⁹ which we believe is unsatisfactory (Figure 1). In addition, depending on the substitution of the ynamides, different major stereoisomers of the C=C are obtained. For these reasons, we have decided to develop a practical and straightforward synthesis of trisubstituted α -enamidonitriles via

the regio- and stereo-selective hydrocyanation¹⁰ of ynamides using a relatively safe cyanide source (Figure 1).

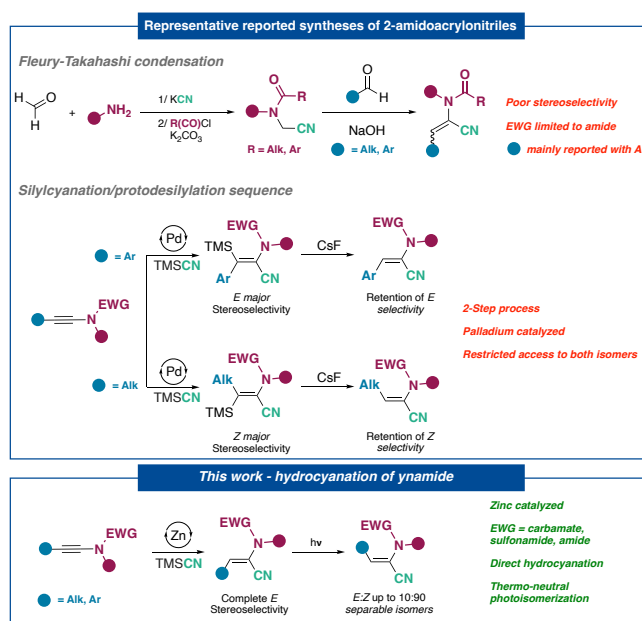


Figure 1. Comparison of strategies to reach trisubstituted α -enamidonitriles.

Results and Discussion

Interestingly, while investigating this silylcyanation reaction, we identified the competitive direct hydrocyanation reaction (Table 1, entry 1) using TMSCN as cyanide source and leading to the *E*- α -enamidonitrile **2a** in a 22% yield. We then determined that this direct approach,^{11,12} HCN-free and using a safe source of cyanide, could be of high interest and therefore we started our investigations to optimize the reaction conditions. First, we studied various catalysts (Table 1, entries 2-9) to evaluate their effect on different parameters such as the regio- and the stereoselectivity, the formation of the silylcyanated product **3a** as well as the direct hydration of the starting ynamide **1a** (a side product frequently obtained while using a Lewis acid with ynamides). Then a catalytic loading of 30 mol% was determined as the most productive both in terms of yield and selectivity (Table 1, entry 10). If other solvents appeared to be suitable for this transformation (MeCN and 1,4-dioxane), the reaction appeared to be less efficient and additionally led to a mixture of hydro- and silyl-cyanation products (Table 1, entries 12 and 13). The

reaction proved to be less productive at lower temperatures (**Table 1, entry 14**) and the use of other sources of cyanide such as K_4FeCN_6 or acetone cyanhydrine did not yield to the targeted acrylonitrile **2a** (**Table 1, entries 15 and 16**). Finally, we performed two control reactions. The first one, without catalyst, led only to the hydration of the ynamide (**Table 1, entry 17**). The second one was performed using our optimized conditions with $ZnBr_2 \cdot 2H_2O$ as the catalyst. Since $ZnBr_2$ is highly hygroscopic and considering that the reagent was not stored or weighed in a glovebox, it is realistic to consider the hydrated salt as the real catalyst of the reaction. In this case, the reaction gave similar results to those obtained with $ZnBr_2$ (82% yield, full stereoselectivity; **Table 1, entry 18**).

Table 1. Optimization of the reaction conditions.

Entry	Cat. (mol%)	CN source	Ratio ^[a] 2a:3a:4a	Yield ^[b] 2a (%)
1	$PdCl_2$ (1)	TMSCN	40:60:0	22
2	$AgOTf$ (20)	TMSCN	35:65:0	16
3	$AlCl_3$ (20)	TMSCN	42:18:40	19
4	CuI (20)	TMSCN	0:100:0	0
5	$Bi(OTf)_3$ (20)	TMSCN	69:31:0	20
6	$Zn(OTf)_2$ (20)	TMSCN	27:73:0	23
7	$ZnCl_2$ (20)	TMSCN	-	traces
8	$ZnBr_2$ (20)	TMSCN	92:8:0	71
9	$ZnCN_2$ (20)	TMSCN	-	traces
10	$ZnBr_2$ (30)	TMSCN	100:0:0	87
11 ^[c]	$ZnBr_2$ (30)	TMSCN	-	0
12 ^[d]	$ZnBr_2$ (30)	TMSCN	73:27:0	34
13 ^[e]	$ZnBr_2$ (30)	TMSCN	82:18:0	56
14 ^[f]	$ZnBr_2$ (30)	TMSCN	90:10:0	48 ^[g]
15	$ZnBr_2$ (30)	K_4FeCN_6	-	0
16	$ZnBr_2$ (30)	$Me_2C(OH)CN$	0:0:100	0
17 ^[h]	No catalyst	TMSCN	0:0:100	0
18	$ZnBr_2 \cdot 2H_2O$ (30)	TMSCN	100:0:0	82

[a] Determined by 1H NMR of the crude mixture; [b] Isolated yield; [c] DMF as solvent; [d] MeCN as solvent; [e] 1,4-dioxane as solvent; [f] at 110 °C; [g] incomplete conversion after 12h (55%); [h] reaction performed in the presence of 1 equiv. of water.

Using these optimized conditions (*i.e.* $ZnBr_2$ 30 mol%, TMSCN 2 equiv., 130°C, xylene [1M], 12 h), we then evaluated the scope and limitations of this hydrocyanation reaction (**Figure 2**). With pleasure, we noticed that the reaction was particularly tolerant to

various substitutions on the aryl moiety of the ynamides. Thus, electron-donating or electron-withdrawing groups in the *para* or *meta* position led to the corresponding hydrocyanated products in overall good yield and full stereo- and regioselectivity (**2b-d, 2f**). Of note, in the case of a product bearing an electron-withdrawing group such as **2e**, the yield was lower due to its relative instability. In contrast, the stereoselectivity of the reaction seems to be particularly dependent on steric hindrance. As a representative example, the *ortho*-tolyl substituted substrate **1g** led to the desired product **2g** in a good yield of 56% but with a partially reversed *E/Z* selectivity (35:65). Nicely, an heteroaromatic substitution such as a 3-thiophenyl group led to the desired product **2h** in 61% yield.

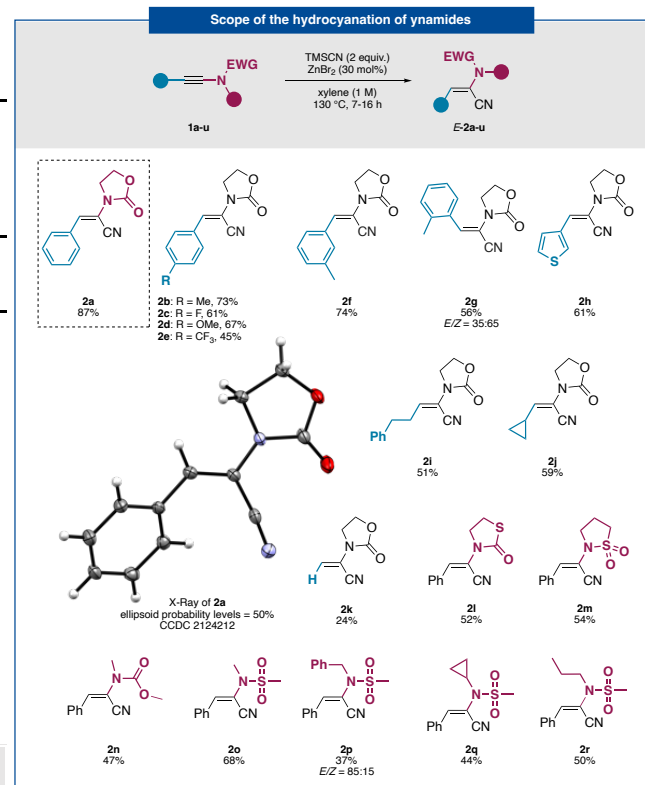


Figure 2. Zinc catalyzed *E*-selective hydrocyanation of ynamides **1** and X-ray analysis of **2a**.

Primary (**2i**) and secondary (**2j**) alkyl groups substituted on the alkyne gave approximately similar results with full *E*-selectivity and yields of 51% and 59% respectively. Due to the relative instability of the formed product **2k**, the terminal ynamide **1k** led stereoselectively to the desired product in 24% yield after purification. Then we had a look on the influence of the substitution at the nitrogen part of the ynamides on the course of the reaction. In terms of electron withdrawing groups, if a thiazolidinone (**2l**), a sultam (**2m**), a methoxycarbonyl (Moc) (**2n**) or a mesyl (Ms) (**2o**) group were well tolerated as the targeted products were obtained with yields of 52%, 54%, 47% and 68% respectively. Changing the alkyl chain on NMs substrates to more hindered ones such as a benzyl (**2p**), a cyclopropyl (**2q**) or a propyl (**2r**) decreased the yield of the transformation and even lightly eroded the stereoselectivity in the case of the benzylated substrate (**1p**).

A first hypothesis regarding the mechanism, similar to the hydrohalogenation of ynamides reported by Iwasawa *et al.*,¹³ was the hydrolysis of TMS-CN by residual water in the medium leading to the *in-situ* formation of HCN. As the reaction did not work in presence of additional water without Zn catalyst (**Table 1, entry 17**), it appears that the reaction follows another pathway. A second hypothesis, was the potential *in situ* formation of Zn(CN)₂,¹⁴ from the reaction between TMS-CN and ZnBr₂, which could then undergo a carbocation on the ynamide. Since our attempt to carry out the reaction using Zn(CN)₂ as a catalyst led only to trace amounts of product (**Table 1, entry 9**), this possibility was quickly ruled out. Based on literature precedents, a reasonable hypothesis that could be considered is the activation of ynamides with a Lewis acid (here ZnBr₂) to form the corresponding zinc keteniminium intermediate **I**.¹⁵ Subsequent attack by a cyanide anion (potentially coming from TMS-CN hydrolysis) on the opposite side of the metal could then take place to form a zinc vinyl intermediate **II**. To determine if the hydrolysis of TMS-CN was carried out by residual water in the medium, we tested the standard reaction with an addition of 1 equiv. of D₂O. In that case, no traces of the product resulting from deuterium incorporation was detected. Thus, the most reasonable hypothesis regarding the origin of water seems to be the zinc salt (ZnBr₂·2H₂O). Finally, the last step of the catalytic cycle could be a protodemetalation leading to the targeted product **2**. This assumption is in perfect agreement with the erosion of selectivity observed in the case of congested ynamide **1g**. Conversely, keteniminiums bearing an ethylbenzene substituent on the alkyne are known to cyclize readily^{15,16} but we never observed the corresponding product in reactions with ynamide **1i** which did not allow us to make a definitive indisputable decision on the mechanism (**Figure 3**).

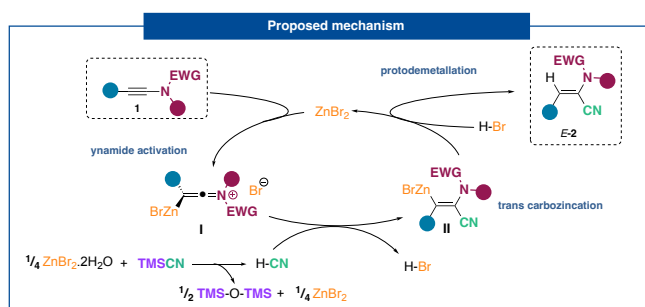


Figure 3. Tentative mechanism of the hydrocyanation.

Having demonstrated the relative tolerance of this transformation leading to trisubstituted *E*- α -enamidonitriles with various functional groups, we then decided to study the *E* to *Z* photoisomerization¹⁷ of compounds **2** to have a complete strategy to reach each isomer at will under mild metal-free conditions (**Figure 4**). Nicely, the isomerization, without additional catalyst or sensitizer in chloroform under UV LEDs (1x 52 W, 390 nm), of various selected substrates bearing substituted aryl (**2a**, **2d**, **2e**), heteroaryl (**2h**) or even alkyl (**2i**) groups as well as different nitrogen moieties such as thiazolidone (**2l**), sultam (**2m**), Moc (**2n**) or Ms (**2o**, **2q**) electron withdrawing groups all led to the isomerized *Z* products in good yields (51-80%) (**Figure 4**). However, the isomerization of enamidonitrile *E*-**2j** bearing a cyclopropyl group led only, without degradation, to a 1:1 mixture

of *E* and *Z* isomers. Notably, attempts to increase the ratio of isomerization of all substrates, such as the addition of a photosensitizer (riboflavin or benzophenone), change of solvent (CH₃CN, DCM) or wavelength (2x 40 W, 450 nm) did not give better results.

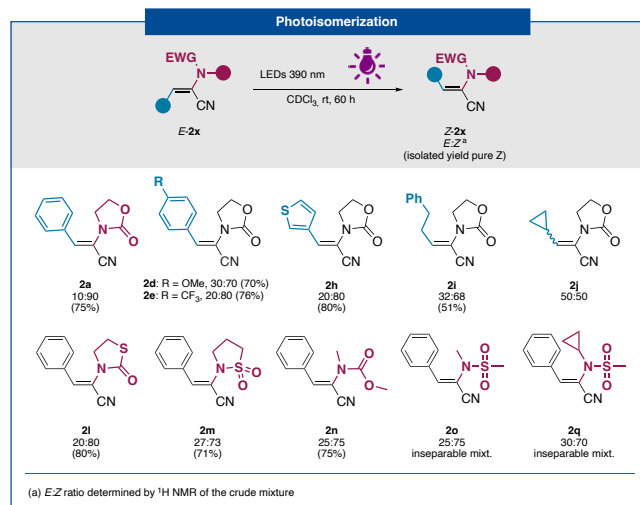


Figure 4. Catalyst-free *contra-* or *neutral-*thermodynamic photoisomerization of *E*-**2** to *Z*-**2**.

Then we decided to investigate the origin and the selectivity of the photoisomerization process. To start with, a rapid computational study of our model substrate **2a** at the DFT level of theory (geometrical optimization: TPSS-D3/def2-TZVP; single point energy: PWPB95-D3/def2-TZVP; please see SI for more details) allowed us to determine that this photoisomerization is close to thermo-neutral (*E*-**2a**→*Z*-**2a**, $\Delta G_{298} = 0.5 \text{ kcal.mol}^{-1}$). Inspired by the enlightening recent work by Gilmour *et al.* on 2,2-disubstituted acrylonitriles,¹⁸ this isomerization can be potentially explained by the difference of photo-excitability between the *E* and the *Z* isomers (**Figure 5**). Indeed, a UV-vis absorption spectrum of **2a** pure two isomers shows: 1/ a hypsochromic shift of the wavelength of maximum absorption between *E*-**2a** ($\lambda_{\text{max}} = 300 \text{ nm}$) and *Z*-**2a** ($\lambda_{\text{max}} = 285 \text{ nm}$); 2/ a fourfold decrease of the molar absorptivity between *E*-**2a** and *Z*-**2a** (see SI). It follows that if the *E*-isomer can reach a triplet state in which isomerization can take place, the small portion formed of *Z*-isomer does not absorb enough energy to return to the triplet state and therefore does not isomerize back to the *E* configuration. Thus, in the course of time, according to Le Chatelier's principle, the isomerization equilibrium is shifted towards the *Z* isomer yet similar in energy to the *E* one. Interestingly, the difference of molar absorptivity between *E*-**2a** and *Z*-**2a** can potentially be rationalized thanks to the DFT geometry optimization (TPSS-D3/def2-TZVP)¹⁹ that shows significative differences between both isomers in the dihedral angle between the olefin C=C and the aromatic ring (*E*-**2a** = 0.5° vs *Z*-**2a** = 28°) and in the less extend in the one between the olefin and the N-(CO) bond of the oxazolidinone (*E*-**2a** = 25° vs *Z*-**2a** = 36°). Consequently, these two configurations (*E*-**2a** being significantly less twisted than *Z*-**2a**) which could explain the difference in light absorption observed (**Figure 5**). Finally, a TD-DFT (BLYP/def2-TZVP) investigation (see SI) showed that if a small difference in energy (0.9 kcal.mol⁻¹) between the two isomers for the first singlet (S₀→S₁) excitation (*E*-**2a** = 83.8 kcal.mol⁻¹ vs *Z*-**2a** = 84.7

kcal.mol⁻¹) can be seen, the difference for the first forbidden ($S_0 \rightarrow T_1$) excitation ($E-2a = 54.1$ kcal.mol⁻¹ vs $Z-2a = 58.2$ kcal.mol⁻¹) is more significant (4.1 kcal.mol⁻¹).

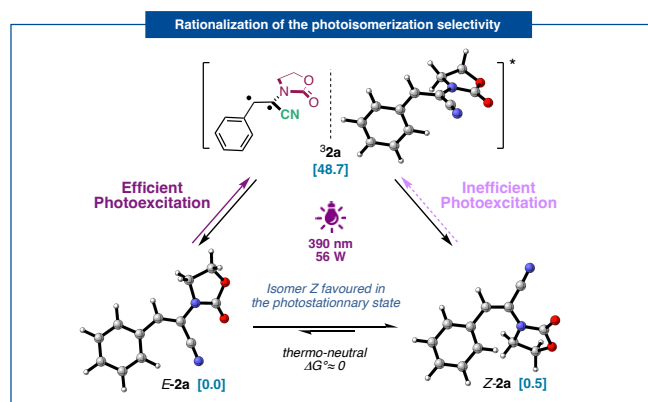


Figure 5. Potential rationalization for the thermo-neutral photoisomerization of $E-2a$ to $Z-2a$ through 32a (structures minimized by DFT (TPSS-D3/def2-TZVP)). [$\Delta G_{298}^{\ddagger}$ kcal.mol⁻¹] (PWPB95-D3/ TPSS-D3/def2-TZVP).¹⁹

Finally, to evaluate the synthetic potential of these building blocks, we then performed various transformations selectively involving each of its functionalities (**Figure 6**). After having demonstrated that our methodology could be applied on a gram scale (52% yield for $E-2a$), we first evaluated the synthetic possibilities on the alkene moiety of this new compound. A classical bromination with NBS led to the corresponding β -bromo- α -enamidonitrile derivative **5a** in a good 71% yield but with a significant erosion of the C=C double bond configuration ($E/Z = 40:60$).²⁰ A copper-catalyzed trifluoromethylation using Togni II reagent led to the tetrasubstituted fluorinated 2-amido-acrylonitrile **6a** as a single E isomer in a 46% yield.²¹ Then, we decided to use our new enamidonitriles as precursors for valuable heterocycles. First, compound $E-2n$ bearing a Moc electron-withdrawing group on the nitrogen was treated with 4 equivalents of sodium methoxide and led to hydantoin **7n** in a good 76% yield and a ratio E/Z of 60:40.²² We finally looked at compound $E-2o$, bearing this time a mesyl group as electron withdrawing group on the nitrogen, that could be deprotonated²³ thanks to the use of a Grignard reagent as base to subsequently cyclize to form in 67% yield the completely original β -amino-sultam derivative $E-8o$ with an excellent retention of the C=C double bond configuration. Nicely, the same reaction applied to the other stereoisomer $Z-2o$ led to the stereopure β -amino-sultam $Z-8o$ in similar yield (70%) (**Figure 6**).

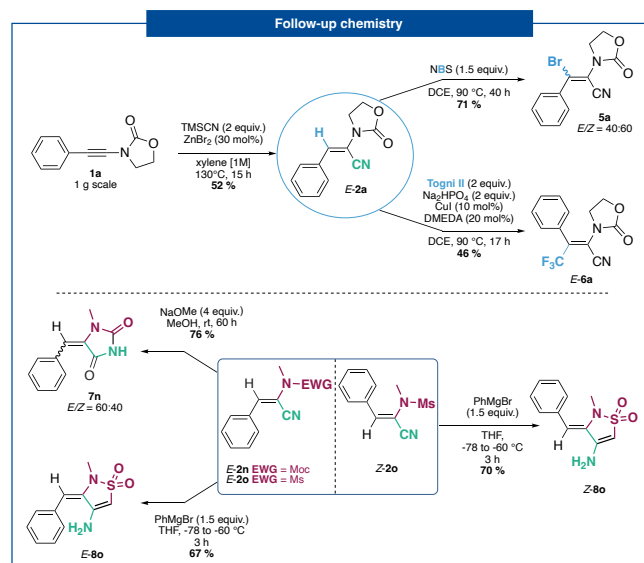


Figure 6. Follow-up chemistry.

Conclusion

In summary, we have developed a direct, general, and selective access to trisubstituted E - α -enamidonitriles. This strategy is based on the first stereo and regioselective hydrocyanation of ynamides and is catalyzed by abundant, inexpensive and low toxicity zinc(II) bromide. The reaction is tolerant to various substitutions but the stereoselectivity appears sensitive to the steric hindrance in the case of high congestion around the alkyne. We have then shown that Z - α -enamidonitriles can be subsequently obtained by simple catalyst-free photoisomerization under a 390 nm irradiation (LEDs). Although close to thermo-neutral, this isomerization could be rationalized, thanks to a concordant combination of experimental and computational studies by DFT, by the difference in excitability between the two isomers shifting the equilibrium towards the Z configuration. Remarkably, if the reaction is efficient with aromatic substituted substrates, it is almost as effective with alkyl substituted ones. Finally, the synthetic utility of these original compounds has been explored thanks to various post-transformations including heterocycle syntheses.

Experimental Section

General procedure for the hydrocyanation of ynamides (1) to form 2-amidoacrylonitriles (2)

A 2 mL sealed was charged with ynamide **1** (0.1-0.8 mmol, 1 eq) and zinc bromide (30 mol%) under Ar. Xylene (1M) was first added, and then TMSCN (0.4-1 mmol, 2 eq). The rubber septum was replaced by a septum-cap under argon. The mixture was stirred in a pre-heated oil bath at 130 °C for 7-17h. After complete consumption of starting ynamide indicated by TLC, the reaction mixture was cooled to room temperature, filtrated over a pad of celite with dichloromethane, evaporated and directly purified by flash column chromatography over silica gel to give the desired hydrocyanated compound **2**.

General procedure for the photoisomerization of E-2 to Z-2

A quartz-NMR tube was charged with hydrocyanated compound **E-2** and dissolved in CDCl₃ (0.1–0.2 M) under Ar. The tube was capped and placed 6 cm away from a purple Kessil PR160L UV-LED (1x 52 W, 390 nm, average intensity: 352mW/cm²) and irradiated for 60 h. *E/Z* ratio was determined by ¹H NMR of the crude mixture. Purification of the reaction mixture by flash column chromatography over silica gel gave the desired hydrocyanated compound **Z-2**.

Acknowledgements

The authors thank the CNRS and the University of Strasbourg for financial support. PH is grateful to the French ministry for research and higher education for a PhD fellowship. Lilian Wisson (PhD student in our team at the University of Strasbourg) is thanked for UV/vis measurements. The authors thank Dr. E. Wasielewski and Mr. M. Chessé, respective managers of the NMR and Analytical platforms and facilities of LIMA (UMR7042 CNRS-Unistra-UHA), who contributed, by their technical and scientific support, to the achievement of this research project. We thank Nathalie Gruber (Uni. Strasbourg) and Corinne Bailly (Uni. Strasbourg) for X-Ray analyses. The authors would like to acknowledge the High-Performance Computing Center of the University of Strasbourg for supporting this work by providing scientific support and access to computing resources. Part of the computing resources were funded by the Equipex Equip@ Meso project (Programme Investissements d'Avenir) and the CPER Alsacalcul/Big Data.

Keywords: Ynamide • Hydrocyanation • Acrylonitrile • Enamide • Photoisomerization

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