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COMMUNICATION

Synthesis of 2-amidoindenone derivatives through an ynamide carbosilylation / Houben-Hoesch cyclization 2-step sequence.

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In this manuscript we report the efficient and selective two-step synthesis of various 3-silyl-2-amidoindenones from easily accessible ynamides. This sequence involves a regio- and stereo-selective silylcyanation followed by a Houben-Hoesch type cyclization. Thanks to post-transformations, various 3-substituted 2-amidoindenones could be obtained.

1-Indenone derivatives can be frequently found in natural molecules and represent an important scaffold in pharmaceuticals and agrochemicals.¹ Therefore, general synthetic routes towards such molecular structures have been intensively investigated over the last decades.² However, when we consider the synthesis of indenones bearing a heteroatom in position 2, the number of available methods drops dramatically and the reported strategies are often very limited in terms of functionalization in position 3. Quite surprisingly, given the prevalence of nitrogen-based functionalities in bioactive molecules, the number of available methods to access 2-aminoindenones is remarkably low.^{14–16} Among the reported syntheses we can cite the reaction of *o*-alkynylbenzoyl cyanides with carboxylic acids developed by the group of Murakami³ (Figure 1–A) and the gold-catalyzed oxidation of 1-(2-alkynylphenyl)ketones investigated by Liu and coworkers⁴ (Figure 1–B). Recently, two direct annulation strategies using ynamides as partners have been reported. The first one, described by the Sahoo group, involves a key step of cobalt-catalyzed C-H activation in ortho position of arylthioamides⁵ (Figure 1–C). The second one, reported by our group, relies on a palladium-catalyzed Larock-type annulation of *o*-iodo-benzaldehydes⁶ (Figure 1–D). Notably, both methods, whereas efficient and practical, appeared to be limited to aryl-ynamides and so ending in 3-aryl-2-amidoindenones. In summary, although the reported methods to access 2-aminoindenone derivatives present

various synthetic possibilities, they also show limitation regarding the substituent diversity on the final indenones, especially on position 3, and, in some cases, in terms of regioselectivity. To address both issues, we have designed a new strategy to access selectively versatile 3-silyl-2-amidoindenones (Figure 1–E). This two-step approach involves the silylcyanation of various ynamides functionalized with a nucleophilic ring followed by a cyclization through an intramolecular Houben-Hoesch type reaction. The resulting 2-amidoindenones are substituted in position 3 by a TMS group that can be then converted into other functional groups.

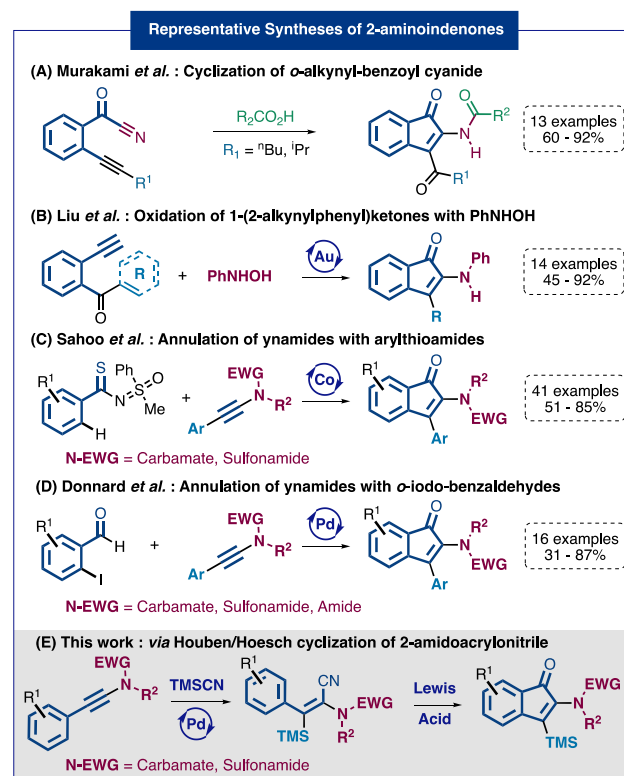


Fig. 1 Selected synthetic routes to access 2-aminoindenones.

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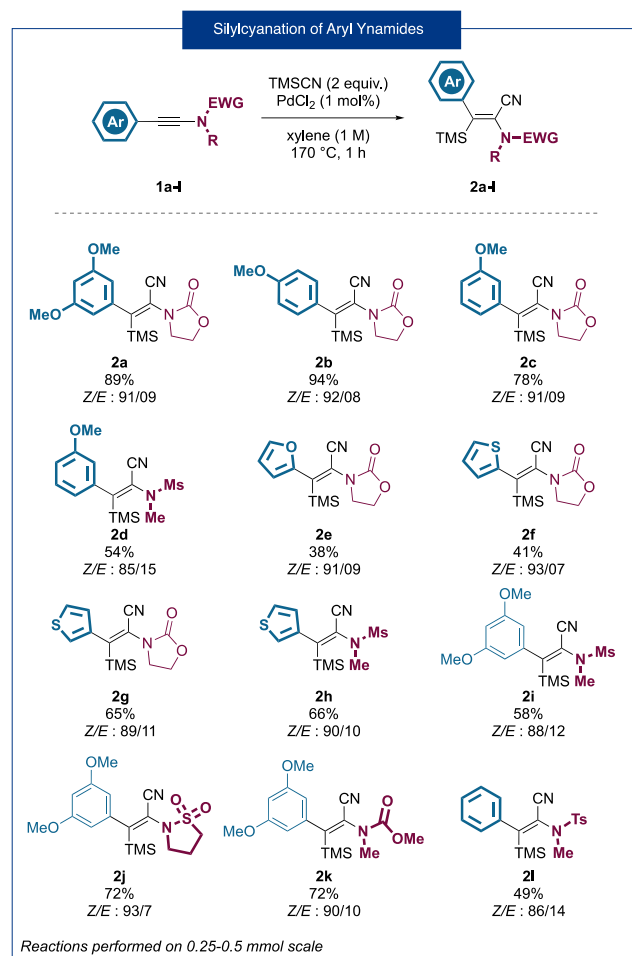


Fig. 2 Silylcyanation of ynamides bearing an electron-rich aromatic substituent.

As a starting point for our research, using an ynamide silylcyanation reaction previously developed in our group,⁷ we synthesized variously substituted 2-amido-acrylonitrile derivatives bearing nucleophilic aromatic rings in the 3-position (**Figure 2**). Overall, a total of 12 products **2a – 2l** were obtained in good to very good yields and high stereoselectivities (*Z/E* ratios around 90:10). In the case of heteroaromatic-substituted ynamides (**2e – 2h**) a slight erosion of the yields (41 – 66 %) could be observed and, in the case of the furan substituted product **2e**, a decreasing of the stereoselectivity. In the same ways, ynamides bearing a *N*-methylsulfonamide substituent (**2d**, **2h**, **2i**, **2l**) were obtained in lower yields ranging from 49% to 66%. In most cases, the products were obtained in an inseparable *Z/E* mixture which was used as such for the following cyclization step. Considering that only the *Z* isomer can lead to the desired ring closing, we envisaged that isomerization could potentially take place during the cyclization step, leading to complete conversion of the mixture to the desired indenones. Once this set of substrates in hand, we began the optimization of the Houben-Hoesch type cyclization step, using compound **2a** as a substrate, by studying the influence of several parameters such as the solvent, the temperature,

the time of reaction and the nature of the Lewis acid (**Table 1**).

Table 1. Optimization of the Houben-Hoesch cyclization.

Entry	Lewis Acid (equiv.)	Solv.	t (h)	Conv. Z-2a (%)	¹ H NMR Ratio ^a 3a/4a	¹ H NMR Yield ^b (%) 4a
1	BF ₃ ·OEt ₂ (0.5)	Tol.	15	66	74/26	58
2	BF ₃ ·OEt ₂ (1.0)	Tol.	15	81	73/27	75 (72) ^c
3	AlCl ₃ (1.0)	Tol.	15	0	-	0
4	BiCl ₃ (1.0)	Tol.	15	66	92/8	38
5 ^d	TiCl ₄ (1.0)	Tol.	15	84	97/3	62
6	FeCl ₃ (1.0)	Tol.	15	66	62/38	52
7	BF ₃ ·OEt ₂ (1.0)	THF	15	66	97/3	63
8	BF ₃ ·OEt ₂ (1.0)	ACN	15	62	96/4	47
9	BF ₃ ·OEt ₂ (1.0)	DCE	15	67	94/6	50
10 ^e	BF ₃ ·OEt ₂ (2.0)	Tol.	15	85	100/0	84
11 ^e	BF ₃ ·OEt ₂ (2.0)	Tol.	24	100	100/0	91 (91)
12 ^f	BF ₃ ·OEt ₂ (2.0)	Tol.	24	33	100/0	24

Reactions were performed on 0.1 mmol scale; ^a ¹H NMR ratio before SiO₂ mediated hydrolysis ^b ¹H NMR yield with respect to the *Z* isomer of the *Z/E* mixture, after SiO₂ mediated hydrolysis, with CH₂BrCl as internal standard, ^c isolated yield in parentheses, ^d reaction performed at 25 °C, ^e 2nd equiv. added at t = 5 h, ^f reaction performed at 50 °C.

Inspired by the work of Compaigne and Mais,⁸ the reaction was first carried out with 50 mol% of BF₃·OEt₂ in toluene at 80 °C for 15 h. Gratifyingly, the expected product was obtained as a 74:26 mixture of indenimine **3a** and indenone **4a**. A subsequent hydrolysis of the mixture in a suspension of silica in chloroform led to the desired product **4a** in a decent 58% yield (**Entry 1**). Notably, unlike our expectations, no isomerization of the starting acrylonitrile was observed as the *E* isomer was completely recovered at the end of the reaction in the initial proportions. The use of 1 equivalent of the Lewis acid allowed an increase of the isolated yield to 72%, but the conversion remained incomplete (81%) (**Entry**

2). Other Lewis acids (**Entries 3-6**) gave lower yields with various **3a/4a** ratios, except for aluminum trichloride that showed no conversion of starting material (**Entry 3**). A slight decrease in yield was observed when carrying out the reaction in other solvents (**Entries 7-9**). Finally, the addition of a second equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ after 5 h of reaction was required to achieve full conversion and, after hydrolysis, afford indenone **4a** in a 91% isolated yield after 24 h as 15h led to uncomplete conversion (**Entries 10-11**). Notably, the use of 2 equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ directly from the beginning of the reaction gave significantly lower yields. An attempt to reduce the temperature of the reaction led to a significant decrease in conversion (33% after 24 h).

With these optimized conditions defined, we then turned our attention to the scope of the cyclization reaction (**Figure 3-A**). Notably, similarly to **3a**, some of the indenimine intermediates could be isolated and characterized. When required, the latter were hydrolyzed quantitatively to the corresponding indenones. The indenimine higher stability in some cases can potentially be explained by higher electron density coming from richer aromatic rings and/or more electron-donating amido groups (sulfonamides). Predictably, no conversion of substrate **2b**, bearing a less nucleophilic *p*-methoxyphenyl, was observed. Whereas the mono-methoxylated *m*-methoxyphenyl acrylonitrile **2c**, bearing an oxazolidinone as nitrogen moiety, led to a modest 27% and a 70:30 mixture of regioisomers, the analogous substrate **2d** bearing a sulfonamide led to a significant increase both in yield and selectivity. This trend could be observed in most examples involving sulfonamide substrates (**4h-4j**) and could be explained by the more electron-donating nature of sulfonamides compared to carbamates. A substrate bearing a furan as nucleophilic ring did not lead to the targeted cyclopenta[*b*]furan-6-one **4e** but only to the isomerized product *E*-**2e**. An explanation could be a coordination of the furan moiety to the Lewis acid depleting it in electrons. Remarkably, substrates **2f-2h** bearing a thiophene all led to corresponding products **4f-4h** in good to very good yields (62–86%), providing access to unprecedented compounds with scaffolds very rarely described in the literature^{5,9} (especially cyclopenta[*b*]thiophen-6-one derivatives such as **4g** and **4h**). These results are all the more interesting as they represent, as far as we know, the first examples of Houben-Hoesch reaction involving thiophene rings. Moreover, the reaction was compatible with various substitutions on the nitrogen moiety of the starting material leading to the targeted indenones (**4i-4k**) in very good yields (77%–93%). Although, substituted by a sulfonamide, an acrylonitrile lacking a nucleophilic aryl substituent (**2l**) did not undergo the cyclization under our conditions. In an attempt to reach dibenzotropone derivatives using our strategy, we synthesized the 2-amido-acrylonitrile **2m** bearing an electron-rich biaryl substituent. Unfortunately, this substrate appeared completely inert under our cyclization conditions (**Figure 3-B**). Interestingly, the desilylated amido-acrylonitrile **2a'** did not react under our Houben-Hoesch conditions. A potential explanation for this difference in reactivity with the analogous silylated substrate could be a stabilizing silicon effect of the arenium intermediate formed during the cyclization (**Figure 3-C**).¹⁰

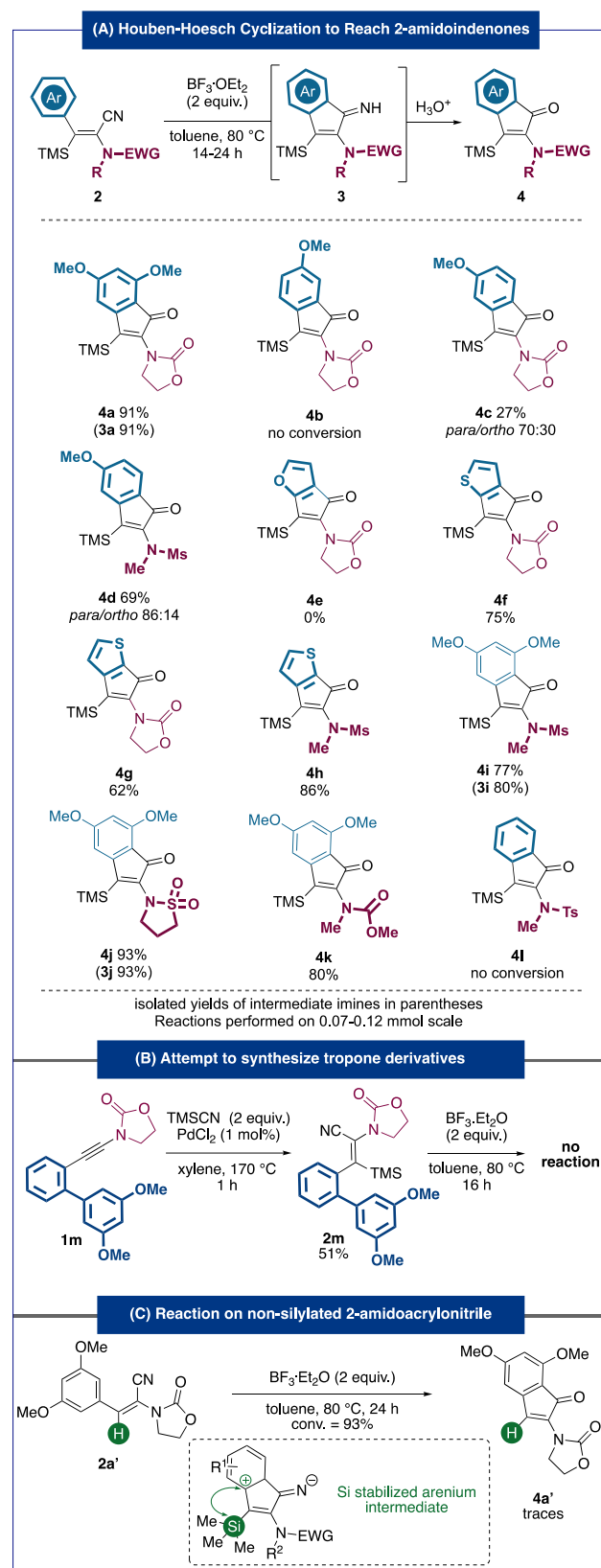


Fig. 3 Scope and limitations of the methodology to access 2-amidoindenones.

Finally, the resulting 2-amido-indenones were then valorised through various post-functionalization reactions (**Figure 4**).

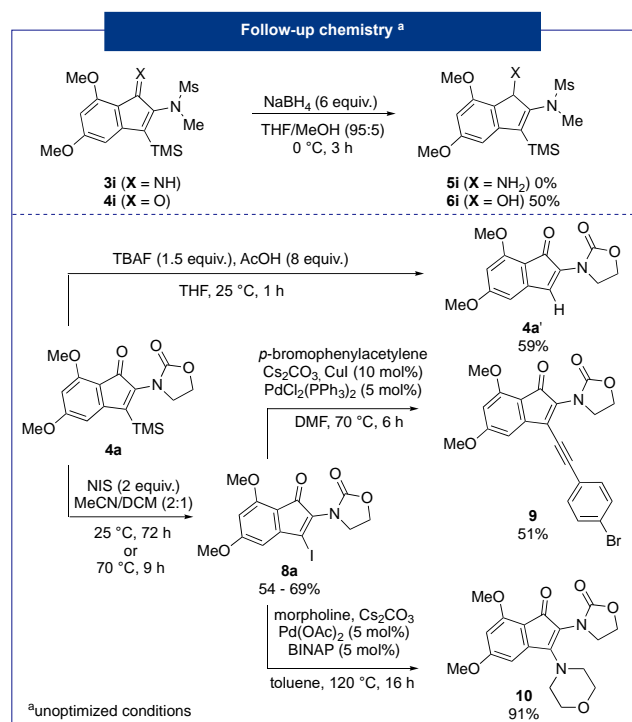


Fig. 4 Follow-up chemistry on 3-silyl-2-aminoindenones **4a** and **4i**.

First, carbonyl reduction of indenone was carried out using sodium borohydride as the reducing agent¹¹ and afforded the corresponding alcohol **6i** in a good 50% yield. Conversely, an attempt to reduce the imine **3i** led only to desilylation of the starting substrate. Transformations of the silicon group were then investigated. First, a protodesilylation reaction using TBAF in THF with an excess of acetic acid led to the indenone **4a'** in 56% yield. Then, an iododesilylation reaction was envisaged to access a versatile 3-iodo-indenone **8a** that could be then functionalized through various cross-coupling reactions.¹² Using NIS as electrophilic source of iodine, the desired product was obtained in a good 69% yield after 72 h at 25 °C. Notably, increasing the temperature to 70 °C allowed to form the desired product in only 9 h, but in a significantly lower 54% yield. The iodinated derivative **8a** was then engaged into two typical palladium-catalyzed cross-coupling reactions, namely an alkynylation and an amination. Firstly, a Sonogashira reaction in the presence of *p*-bromophenylacetylene was carried out.¹³ The product **9** was obtained in a moderate 51% yield. This can be explained by a portion of overreaction leading to a second coupling on the bromo-aryl moiety linked to the alkynyl moiety. Secondly, a Buchwald-Hartwig coupling with morpholine was carried out and yielded the desired 2,3-diaminoindenone **10** in an excellent 91% yield.¹⁴ In conclusion, we have been able to regioselectively access versatile 3-silyl-2-amido-indenones through a 2-step sequence involving a silylcyanation of ynamides followed by an intramolecular Houben-Hoesch reaction. In some cases, 2-amido-indenimine intermediates were isolated and indenones bearing a heteroatom such as a thiophene were obtained with very good yields. The resulting products were

finally valorised through a reduction of the carbonyl function. The vinylsilane function was also valorised through protodesilylation and iododesilylation reactions. Finally, an iodinated derivative was subjected to Sonogashira and Buchwald-Hartwig cross-coupling reactions with good to excellent yields.

Conflicts of interest

There are no conflicts to declare.

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