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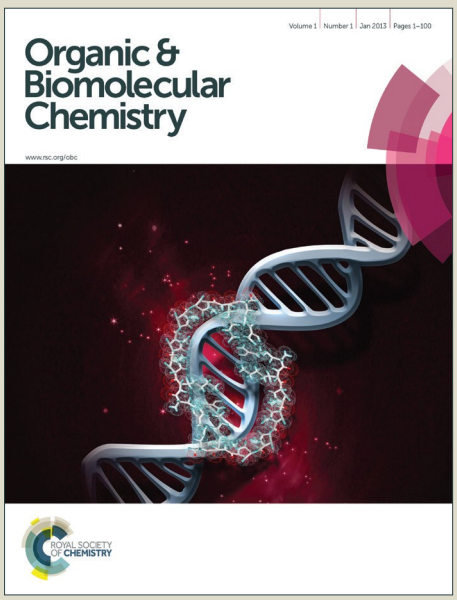

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ARTICLE

Synthesis of 3-substituted isoindolin-1-ones via a tandem desilylation, cross-coupling, hydroamidation sequence under aqueous phase-transfer conditions

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A simple and expedient method for the synthesis of 3-methylene-isoindolin-1-ones **4** under aqueous phase-transfer conditions has been developed. Starting from 2-iodobenzamides **1** and (silyl)alkynes, the products are obtained in high yields and short reaction times (30 min) with the use of inexpensive $CuCl/PPh_3$ catalyst system in the presence of n-Bu_4NBr (TBAB) as a phase-transfer agent. Terminal alkynes are conveniently "unmasked" upon *in-situ* desilylation under the reaction conditions. Alkynes possessing heterocyclic moieties were also found as amenable substrates. Furthermore, a one-pot process starting from 2-iodobenzamides **1,** aryl halides (bromides or iodides) and trimethylsilylacetylene (TMSA) as a convenient acetylene surrogate was also shown to be feasible under Pd/Cu catalysis.

Introduction

Isoindolin-1-ones are preeminent amongst the heterocyclic scaffolds found in both naturally occurring products[1] as well as designed medicinal agents.[2] They possess many biological activities varying from antihypertensive,[3] antipsychotic,[4] anesthetic[5] to anxiolytic, antiviral,[6] and antileukemic[7] effects (Figure 1).

Accordingly, several methods for their preparation have been developed, some of which include the Wittig reaction of phtalimide derivatives with phosphorous ylides,[8] organometallic reagents[9] or benzylic radical donors[10] and subsequent dehydration of the obtained 3-hydroxy-isoindolinone. A condensation of aldehydes with a preassembled phosphorylated derivative (prepared in three steps) via a Wittig-Horner reaction was also reported by Couture and coworkers.[11] A more recent approach involves the Pd catalyzed elimination-cyclization-Suzuki coupling sequence.[12] However, the preparation of the required *o*-gem-dibromovinylbenzamides is not straight forward (Scheme 1, path A).

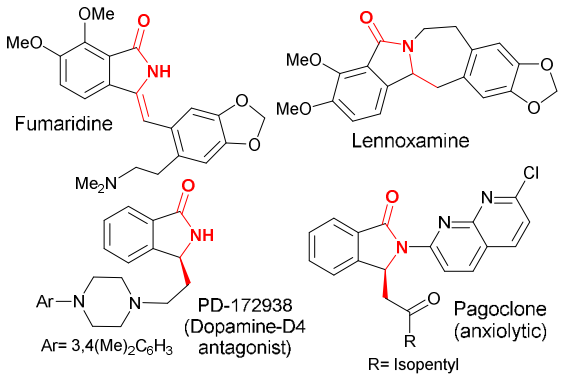

Fig. 1 Structure of some biologically relevant isoindolin-1-ones

An alternative strategy for the assembly of the target molecules was first introduced by Kondo *et al*. in which an *o*-alkynylbenzamide was subjected to a Pd catalyzed oxidative cyclization-alkoxycarbonylation sequence to obtain 3-[(alkoxycarbonyl)methylene]-isoindolin-1-ones in modest yields (55%).[13] Very recently, Fustero and coworkers,[14] disclosed a Pd catalyzed aminocarbonylation approach for the asymmetric synthesis of fluorinated isoindolinones and in 2008 Alper and coworkers[15] delineated an elegant four component approach in which an *o*-alkynylbenzamide was the likely key intermediate. In fact, due to their ease of access, *o*-alkynylbenzamide moieties have been exploited by several groups to access unsaturated isoindolinones upon treatment with strong bases.[16] However, this approach suffers from lack of regio- and stereoselectivity (*6-endo-dig* cyclization product, isoquinolin-1(2*H*)-ones, could also be obtained in some cases).

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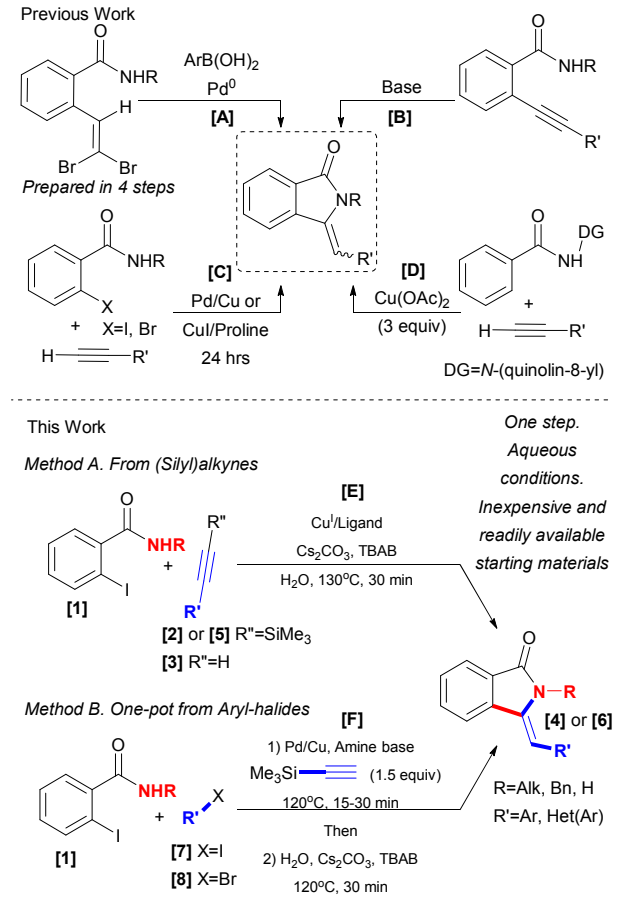
In addition, the need to pre-synthesize and isolate the necessary *o*-alkynylbenzamides has rendered these protocols less practical (Scheme 1, path B).

To circumvent these limitations, several tandem cross-coupling cyclization sequences have appeared in the literature. Starting from *o*-halobenzamides (X= Br or I) and terminal alkynes, several Pd/Cu,[17] Pd,[18] and Cu[19] catalyzed/meditated protocols have been reported (Scheme 1, path C). Among these methods, reports using inexpensive copper-based catalysts are quite attractive. Nevertheless, these methods still require the use of organic media and/or long reaction times (24-36 h).



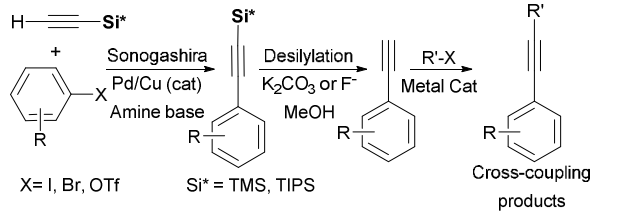
Scheme 1. Selected methods for the synthesis of 3-methylene-Isoindolinone and present work.

Recently, an important protocol was reported by You and coworkers[19c] in which *N*-(quinolin-8-yl)benzamides were cross-coupled with terminal alkynes under oxidative conditions mediated by a Cu(II) salt. While this method has the advantages of direct C–H bond functionalization, it is nonetheless, exclusively applied to benzamides bearing *N*-(quinolin-8-yl) directing group, which is not easily removable. In addition to long reaction times (24 h), super-stoichiometric amounts of $Cu(OAc)_2$ (3 equiv) were required to achieve good yields (Scheme 1, path D).

Since the pioneering work by Hiyama[20] and Denmark,[21] owing in part to their stability, non-toxicity and natural abundance of silicon, much attention has been paid to the organic chemistry of organosilicon compounds (silanes and silanols), particularly to their utilization in metal catalyzed cross-coupling reactions and accordingly, several publications have emerged.[22,23]

While several reports on the synthesis of 3-methylene-isoindolin-1-ones **4** via tandem cross-coupling cyclization sequences utilizing terminal alkynes **3** have been reported,[17-19] the use of silylated derivatives **2** (TMS), to the best of our knowledge, has not been reported thus far. Herein, we describe a triple tandem desilylation cross-coupling hydroamidation approach for the synthesis of 3-methylene-isoindolin-1-ones **4** under aqueous phase-transfer conditions from (silyl)alkynes (Scheme 1, path E). A one-pot protocol starting from Ar-X (X = I, Br) is also disclosed (Scheme 1, path F).

Alkynylsilanes are conveniently and inexpensively accessed by the Sonogashira[24] coupling of Aryl-X (X = I, Br, Cl, OTf)[25] with easy-to-handle trialkylsilylacetylene derivatives $R_3Si–C{\equiv}CH$ TMSA (R = Me) or TIPSA (R = iPr) which serve as convenient liquid acetylene surrogates. Terminal alkynes are then "unmasked" upon treatment with inorganic base or fluoride in a protic solvent and can be further subjected to cross-coupling conditions (Scheme 2).



Scheme 2. Iterative trialkylsilylalkyne synthesis, deprotection and cross-coupling

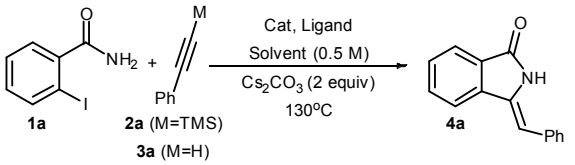
The use of alkynylsilanes **2** directly[26] as coupling partners significantly simplifies this three-step procedure, dramatically enhances the reaction scope, as well as avoids dependence on commercial sources for terminal alkynes. Additionally, the use of alkynylsilanes could provide a fertile ground for the development of one-pot or multicomponent protocols (*vide infra*). Furthermore, alkynylation of several aryl electrophiles (Cl, OTf, OMs, OPO_3Et_2)[27] with TMSA has been recently shown to proceed under metal-free conditions, thus, making the use of **2** considerably more attractive.

Results and discussion

Although direct transmetalation from silicon to copper to form Cu(I) acetylides has been shown to proceed without the need of an external activator,[25e,28,29] our optimization studies were focused on the use of phenylacetylene **3a** which would form upon *in-situ* deprotection of the corresponding silyl derivative **2a** in a protic solvent. Several combinations of solvent, copper source and bases were screened to identify suitable reaction

conditions for the desired transformation, and the results are summarized in Table 1.

Table 1. Optimization of the reaction conditions.[a]

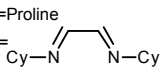


1a **2a** (M=TMS) **3a** (M=H) **4a**

Entry	Alkyne	Solvent	Cat (Equiv)	Ligand (Equiv)	Rxn Time	Yield (%)
1[b]	3a	MeOH	$CuCl_2$ (0.2)	L_1 (0.2)	24 hrs	60
2	3a	H2O[c]	$CuCl_2$ (0.2)	L_2 (0.2)	30 min	52
3	3a	H2O[c]	$Cu(OTf)_2$ (0.2)	L_2 (0.2)	30 min	57
4	3a	H2O[c]	CuI (0.1)	L_2 (0.2)	30 min	47
5	3a	H2O[c]	CuBr (0.1)	L_2 (0.2)	30 min	52
6	3a	H2O[c]	CuCl (0.1)	L_1 (0.2)	30 min	52
7	3a	H2O[c]	CuCl (0.1)	L_2 (0.2)	30 min	65
8	3a	H2O[c]	CuCl (0.1)	L_3 (0.2)	30 min	60
9	3a	H2O[c]	CuCl (0.1)	L_4 (0.2)	30 min	50
10	3a	H2O[c]	CuCl (0.1)	L_5 (0.2)	30 min	46
11	3a	H2O[c]	CuCl (0.1)	L_6 (0.2)	30 min	59
12	**3a**	**H2O[c]**	**CuCl (0.1)**	**L_2 (0.3)**	**30 min**	**70**
13	3a	H2O[c]	CuCl (0.1)	none	30 min	40
14[d]	3a	H2O[c]	CuCl (0.1)	L_2 (0.3)	30 min	63
15[e]	3a	H2O[c]	CuCl (0.1)	L_2 (0.3)	30 min	58
16[f]	3a	H2O[c]	CuCl (0.1)	L_2 (0.3)	30 min	n.d
17[g]	3a	H2O[c]	CuCl (0.1)	L_2 (0.3)	30 min	n.d.
18[h]	**2a**	**H2O[c]**	**CuCl (0.1)**	**L_2 (0.3)**	**30 min**	**70**

L_1 Salicilic acid L_2=PPh_3 L_3=Proline

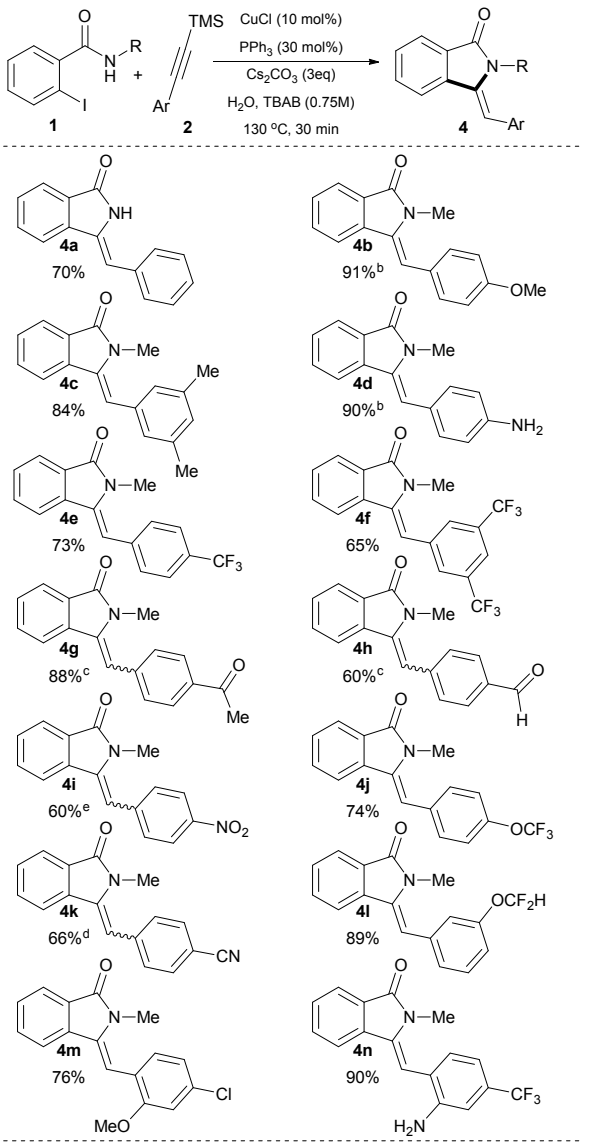
L_4=1,10-Phenantroline L_5=$P(Cy)_3$ L_6=



[a]Reaction conditions: 0.5 mmol of **1a**, 1.5 equiv. of alkyne Cs_2CO_3 (2 equiv), ligand and solvent (1mL, degassed) were placed in a crimp top vial, sealed and heated at 130 °C for the indicated time. Isolated Yields are shown. Average of 2 consecutive runs [b]Reaction was performed at 80 °C. [c]n-Bu_4NBr (0.75 M) was added. [d]K_2CO_3 (2 equiv) was used. [e]K_3PO_4 was used (2 equiv) [f]n-Bu4NBr (0.5 M) was used [g]Reaction was performed at 100 °C. [h]3 equiv. of Cs_2CO_3 were used.

Initial screening was performed utilizing 10 mol% of $CuCl_2$, salicylic acid (20 mol%) as a ligand and Cs_2CO_3 (2 equiv) as a base. Since protodesilylation is known to proceed under basic, protic media, MeOH was first tried as a reaction medium and it was found to be a suitable solvent affording **4a** in 60% yield after 24 h at 80 °C (Table 1, entry 1).[30] To our delight, the use of water as a solvent significantly enhanced the kinetics of the reaction affording **4a** in 52% yield in only 30 minutes at 130 °C, using *n*-tetrabutylammonium bromide (TBAB) as a phase-transfer agent (Table 1, entry 2). When $Cu(OTf)_2/PPh_3$ system was used, the yield of **4a** was slightly enhanced to 57% (Table 1, entry 3). Further screening revealed that among the cuprous salts studied, CuCl was superior (Table 1, entries 4-6) and PPh_3 was better than salicylic acid as a ligand affording **4a** in a 65% isolated yield (Table 1, entry 7). Several other N-N, N-O and P ligands were also studied, but their use did not lead to any major improvements (Table 1, entries 8-11).

Table 2. Triple tandem desilylation-cross-coupling-heterocyclization of alkynylsilanes **2** with iodobenzamides **1**[a]



[a]Reaction conditions: 0.5 mmol of **1b**, silylalkyne **4** (1.5 equiv), Cs_2CO_3 (3 equiv), n-tetrabutylammonium bromide (TBAB, 0.75 M), CuCl (10 mol%), PPh_3 (30 mol%) in 1 mL of H_2O (degassed) were heated at 130 °C for 30 min in a crimp top vial under N_2. [b]Reaction time = 40 min. [c]Z/E ratio = 2 [d] Z/E ratio = 1.2 [e]Z/E ratio = 0.2

Increasing the loading of PPh_3 to 30 mol% significantly improved the yield of **4a** (70%), while its absence resulted in a noticeable decrease in yield (40%), emphasizing the importance of PPh_3 in the present reaction (Table 1, entries 12-13). Efforts to further optimize the conditions by changing the base were met with rather limited success (Table 1, entries 14-15). Additionally, the use of TBAB as a phase-transfer agent was found an essential component of the present protocol.

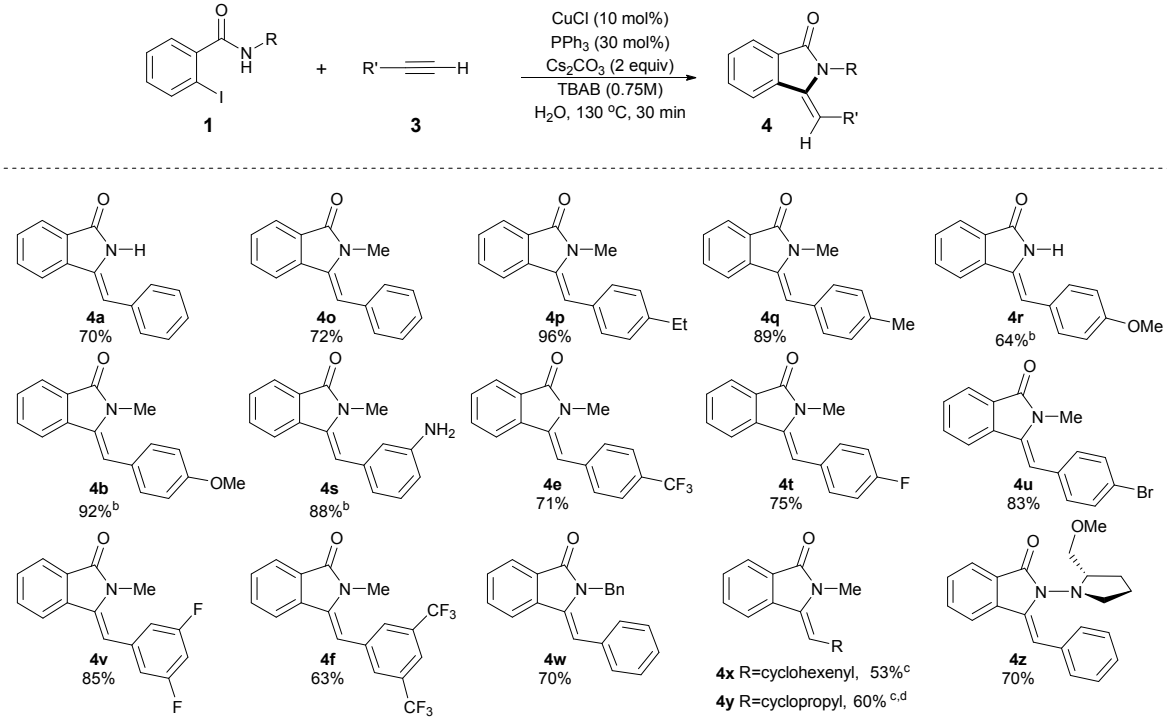
Lower concentrations of TBAB or lower reaction temperature led to incomplete conversion of starting materials (Table 1, entries 16-17). As expected, when **2a** was used in the presence of 3 equiv of Cs_2CO_3 under otherwise identical conditions, it underwent *in-situ* desilylation[31] followed by a cross-coupling hydroamidation sequence without compromising the yield (Table 1, entry 18).[32] With these optimized conditions in hand, parallel studies were performed using both trimethylsilyl alkynes **2** (Table 2) as well as commercially available terminal alkynes **3** (Table 3) under aqueous phase-transfer conditions.

The scope of the process with respect to (silyl)alkynes was found to be broad and allowed access to the target molecules with a varied range of functionalities in good to excellent isolated yields (60-96%). Alkynylsilanes possessing electron-donating as well as electron-withdrawing groups were found suitable substrates, with electron donating groups giving generally higher yields. Accordingly, 4-MeO and 4-NH_2 derivatives **4b** and **4d** (Table 2), were obtained in high yields (91% and 90% respectively), albeit under slightly longer reaction times (40 min). These results are in accordance with the effect of reduced electrophilicity of the corresponding *o*-alkynylbenzamide intermediate possessing electron-donating moieties.[33]

With the exception of **4g**, **4h**, **4i** and **4k**, which possess strong electron-withdrawing groups (–COMe, –CHO, –NO_2 and –CN respectively) exclusive *Z*-configuration around the exocyclic double bond was revealed by NOESY experiments in all products obtained. Furthermore, *Z*-configuration was unambiguously determined by X-ray crystallography of **4a** and **4y**.[34] It is worth mentioning that medicinally attractive CF_3, OCF_3 and OCF_2H-substituted isoindolin-1-ones **4e**, **4f, 4j** and **4l** were obtained in good yields and as single *Z*-isomers.

For products **4a, 4b**, **4e** and **4f**, as can be seen by comparison of Tables 2 and 3, the use of either silylalkyne or terminal alkynes afforded the products in similar isolated yields, with silylalkynes requiring 3 equiv of base. Noticeably, unprotected N–H functionality was readily incorporated, providing amino-substituted isoindolin-1-ones in a very high yield without competitive C–N bond formation (Table 2, **4d, 4n** and Table 3, **4s**). Silylalkynes with *ortho* substituents were also smoothly converted into the corresponding products in good yields (Table 2, **4m** and **4n**). Remarkably, for the *ortho*-NH_2 substituted silylalkyne **2n,** the competitive cyclization to form the corresponding indole[16b,35] was completely suppressed and the corresponding isoindolinone **4n** was isolated in 90% yield with exclusive *Z*-selectivity.

Table 3. Tandem cross-coupling, hydroamidation of 2-iodobenzamides **1** with terminal alkynes **3** under aqueous phase-transfer conditions.[a]



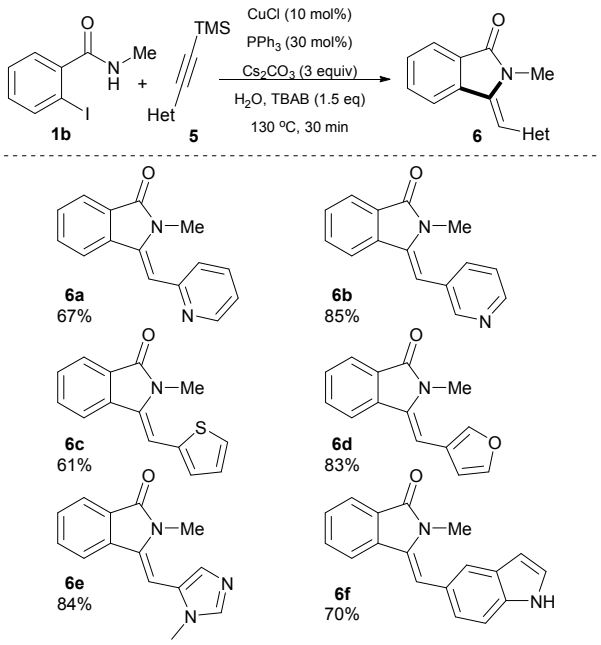
[a]Isolated yields, average of two runs are shown. Reactions conditions: 0.5 mmol 2-Iodobenzamide derivatives **1**, 1.5 equiv of terminal alkyne **3**, CuCl (10 mol%), PPh_3 (30 mol%), Cs_2CO_3 (2 equiv), n-tetrabutylammonium bromide (TBAB, 0.75 M) in 1 mL of H_2O (degassed) were heated at 130 °C for 30 min. [b]Reaction time = 40 min [c]3 equiv of alkyne were used. [d]Reaction time was 90 min.

The use of halo-substituted (F, Cl and Br) substrates is notable as it allows the potential for further product functionalization by subsequent transition metal catalyzed coupling processes (Table 2, **4m** and Table 3, **4t**, **4u** and **4v**). The acetyl and formyl functionalities were also readily incorporated in good yields without competitive 1,2-addition, albeit with a decrease in *Z*-selectivity (*Z/E* ratio = 2, Table 2, **4g**, and **4h**). In the case of 4–cyano substituted silylalkyne **2k**, the corresponding product was obtained in 66% isolated yield also with a decreased *Z*-selectivity (*Z/E* ratio = 1.2, Table 2, **4k**). Similarly, NO_2-substituted silylalkyne **2i** was smoothly converted into product in 60% yield, however with a reverted stereoselectivity (*Z/E* ratio = 0.2).[36] Aliphatic alkynes 1-ethynylcyclohex-1-ene **3x** and ethynylcyclopropane **3y** were utilized successfully in this process, providing products **4x** and **4y** in slightly diminished yields of 53% and 60%, respectively, after 90 min (Table 3). Although the decreased yields obtained with aliphatic alkynes represent a drawback in the present protocol, these results clearly highlight the 5-*exo*-selectivity of the process as evidenced by X-ray crystallographic studies of **4y**.[34] Investigation of *N*-substituted amide coupling partner showed the high tolerance of N–Me, N–Bn as well as free N–H functionalities, albeit the latter delivers slightly reduced yields of product (**4a** and **4r** in 70% and 64% yield, respectively). Furthermore, (*S*)-1-amino-2-methoxymethylpyrrolidine, SAMP-derived benzamide **1z,** provided the corresponding enantiomerically enriched isoindolinone **4z** in 70% isolated yield (Table 3), which could potentially allow for subsequent asymmetric transformations.

In pursuit of medicinally relevant isoindolin-1-ones scaffolds, we decided to explore the possibility of employing heteroaryl silylalkyne substrates **5** and the results are shown in Table 4. Gratifyingly, the present protocol successfully enabled the preparation of a series of heterocyclic alkyne-derived isoindolin-1-ones **6** in good yields. For example, 2-pyridyl as well as 3-pyridylsilylalkynes afforded **6a** and **6b** in 67% and 85% yield, respectively. Furthermore, 2-thienyl- and 3-furanyl-derived trimethylsilylacetylenes were smoothly converted into products affording isoindolinones **6c** and **6d** in good yields (61% and 83%, respectively) with exclusive *Z*-configuration. Other nitrogen heterocycles such as *N*-Me-imidazole and 1*H*-indole were also well tolerated and afforded **6e** and **6f** in 84% and 70% isolated yields, respectively. In this case, it is important to point out that competitive *N*-arylation[37] of the indole moiety, a process known to be catalyzed by copper, was completely absent under our reaction conditions, thus, further emphasizing the tolerance of our method for this type of N–H heterocycles.

As mentioned earlier, the direct use of alkynylsilanes as coupling partners could enable the development of one-pot or multicomponent processes. Accordingly, we investigated the possibility to access the target molecules by this protocol (Scheme 3 and 4). Towards this end, we performed the reaction of TMSA, 2-iodo-N-methylbenzamide **1b** and 4-(trifluoromethoxy)iodobenzene **7j** in a multicomponent

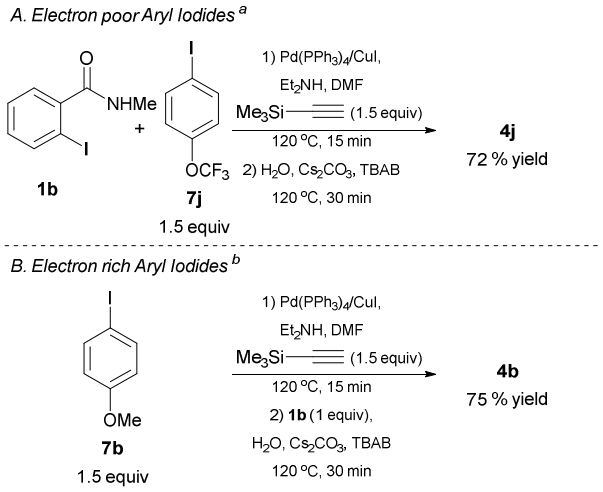
Table 4. Triple tandem desilylation, cross-coupling, hydroamidation of heteroaromatic silyl-acetylenes with **1b**[a]



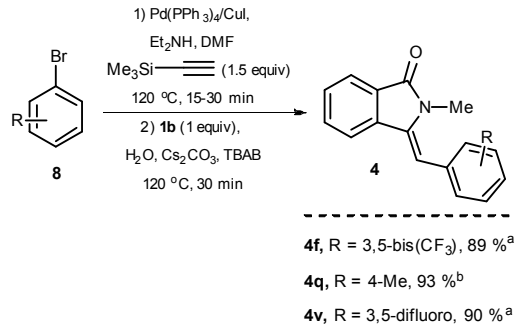
[a]Reaction conditions: 0.5 mmol of **1b**, heteroaryl silylalkyne **5** (1.5 equiv), Cs_2CO_3 (3 equiv), n-tetrabutylammonium bromide (0.75 M), CuCl (10 mol%), PPh_3 (30 mol%) in 1 mL of H_2O (degassed) were heated at 130 °C for 30 min in a crimp top vial under N_2.

fashion using $Pd(PPh_3)_4$ (3 mol%) and CuI (10 mol%) as co-catalysts in DMF/Et_2NH system.[38] After heating this mixture at 120 °C for 15 min, simple addition of aqueous Cs_2CO_3, TBAB and further heating for 30 min, led to the isolation of **4j** in a 72% yield (Scheme 3, Conditions A). In the case of electron rich aryl iodides such as 4-iodoanisole **7b**, best results were obtained by adding **1b** in the second step, along with aqueous carbonate and TBAB[39] (Conditions B). These preliminary results (although not yet optimized) clearly emphasize the importance of using alkynylsilanes to facilitate this and other consecutive cross-coupling processes, thus, enabling the creation of molecular complexity in a single operational step from readily available aryl electrophiles and TMSA as a convenient acetylene surrogate.

Because of the inexpensive nature and greater atom-economy exhibited by aryl bromides **8** when compared to their aryl iodide counterparts, we explored the possibility of utilizing this type of coupling partner in a one-pot protocol. Gratifyingly, under conditions analogous to the ones used for electron rich aryl iodides, the reaction of **8f**, **8q** or **8v** with TMSA under Pd/Cu catalysis, followed by addition of **1b**, led to the clean formation of the corresponding isoindolin-1-ones **4f**, **4q** and **4v** in yields superior to the ones obtained with the preformed alkynes. The simple and straightforward nature of this protocol clearly highlights the advantages of utilizing TMSA in a one-pot process (Scheme 4).



Scheme 3. One-pot preparation of Isoindolin-1-ones from 1b, TMSA and aryl iodides.‡



Scheme 4. One-pot preparation of Isoindolin-1-ones from 1b, TMSA and aryl bromides.‡‡

Conclusions

In summary, we have developed an inexpensive, fast and efficient CuCl/PPh_3-catalyzed method for the synthesis of 3-methylene-isoindolin-1-ones **4** from 2-iodobenzamides **1** and silyl **2** or terminal **3** alkynes. Salient features of this protocol include the utilization of aqueous phase-transfer conditions and very short reaction times (30 min), affording the products with exclusive *Z*-configuration, with few exceptions. In addition, Br- Cl-, COMe-, CHO-, NH_2-, CN- and NO_2-substituents were well tolerated, thus, enabling further synthetic transformations. Furthermore, heteroaryl silylalkynes **5** are suitable substrates including the ones bearing unprotected N–H functionality. Preliminary results demonstrated the feasibility of a one-pot process with the use of $Pd(PPh_3)_4$/CuI co-catalyst system starting from **1b**, TMSA and electron-rich as well as electron-poor aryl iodides **7** and aryl bromides **8**. These results represent a successful example of a process combining the elements of pot, atom and step economy[40] (PASE); characteristics which significantly simplify the synthesis of 3-methylene-isoindolin-1-ones and other heterocyclic frameworks while significantly contributing to the principles of green chemistry. The extension of this one-pot protocol to other halo-benzamides or other electrophiles such as Ar-OTf should also be possible and such studies are currently underway in our laboratories.

Acknowledgements

Support by the Loker Hydrocarbon Research Institute and Mexico's Consejo Nacional de Ciencia y Tecnologia, CONACYT is gratefully acknowledged.

Notes and references

‡ Scheme 3 reaction conditions. Conditions A: **1b** 0.5 mmol (1 equiv), aryl iodide derivative **7** (1.5 equiv), TMSA (1.5 equiv), $Pd(PPh_3)_4$ 3 mol%, CuI 10 mol%, DMF (1 mL), Et_2NH (1 mL), were placed in a crimp-top vial, sealed under argon and heated at 120 °C for 15 min. Then 1 mL of an aqueous solution (degassed) of Cs_2CO_3 (3 equiv) and TBAB (0.75 M) was added and heating was continued for 30 min. Conditions B: For electron rich aryl iodides, same as above but **1b** 0.5 mmol (1 equiv) is added after the first step in 1 mL of H_2O (degassed), along with Cs_2CO_3 (3 equiv) and TBAB (0.75 M). TMSA = trimethylsilylacetylene TBAB = n-tetrabutylammonium bromide.

‡‡ Scheme 4 reaction conditions: Aryl bromide derivative **8** (1.5 equiv), TMSA (1.5 equiv), $Pd(PPh_3)_4$ 3 mol%, CuI 10 mol%, DMF (1 mL), Et_2NH (1 mL), were placed in a crimp-top vial, sealed under argon and heated at 120 °C for (a) 15 min or (b) 30 min. Then **1b** 0.5 mmol (1 equiv), 1 ml of an aqueous solution (degassed) of Cs_2CO_3 (3 equiv) and TBAB (0.75 M) was added and heating was continued for 30 min. Catalyst loadings are based on limiting reagent **1b**. TMSA = trimethylsilylacetylene TBAB= n-tetrabutylammonium bromide. See supporting information for full experimental and characterization details.

1 G. Blasko, D. J. Gula, M. Shamma, *J. Nat. Prod*., 1982, **45**, 105.
2 T. R. Belliotti, W. A. Brink, S. R. Kesten, J. R. Rubin, D. J. Wustrow, K. T. Zoski, S. Z. Whetzel, A. E. Corbin, T. A. Pugsley, T. G. Heffner, L. D. Wise, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1499.
3 Y. Kato, M. Takemoto, K. Achiwa, *Chem. Pharm. Bull*., 1993, **41,** 2003.
4 (a) M. Linden, D. Hadler, S. Hofmann, *Hum. Psychopharmacol*. 1997, **12**, 445; (b) Z.-P. Zhuang, M.-P. Kung, M. Mu, H. F. Kung, *J.Med. Chem*. 1998, **41**, 157; (c) M. H. Norman, D. J. Minick, G. C. Rigdon, *J. Med. Chem.* 1998, **39**, 149.
5 Japanese Patent 5,946,268, 1984; *Chem.Abstr*. 1984, **101**, 54922.

6 (a) I. Pendrak, S. Barney, R. Wittrock, D. M. Lambert, W. D. Kingsbury, *J. Org. Chem*. 1994, **59**, 2623; (b) E. De Clercq, *J. Med.Chem*. 1995, **38**, 2491.
7 (a) E. C. Taylor, P. Zhou, L. D. Jennings, Z. Mao, B. Hu, J.-G. Jun, *Tetrahedron Lett*. 1997, **38**, 521; (b) C. Riedinger, J. A. Endicott, S. J. Kemp, L. A. Smyth, A. Watson, E. Valeur, B. T. Golding, R. J. Griffin, I. R. Hardcastle, M. E. Noble, J. M. McDonnell, *J. Am. Chem. Soc*. 2008, **130**, 16038.
8 H. Peters, W. Flitsch, *Tetrahedron Lett.*, 1969, **15**, 1161.
9 (a) E.-C. Wang, H.-F. Chen, P.-K. Feng, Y.-L. Lin, M.-K. Hsu, *Tetrahedron Lett.*, 2002, **43**, 9163; (b) Y. Kato, M. Takemoto, K. Achiwa, *Chem. Pharm. Bull.*, 1993, **41**, 2003.
10 M. Freccero, E. Fasani, A. Albini, *J. Org. Chem.*, 1998, **58**, 1740.
11 A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron*, 1997, **53**, 10313.
12 C. Sun, B. Xu, *J. Org. Chem.*, 2008, **73**, 7361.
13 Y. Kondo, F. Shiga, N. Murata, T. Sakamoto, H. Yamanaka, *Tetrahedron*, 1994, **50**, 11803.
14 (a) P. Barrio, I. Ibáñez, L. Herrera, R. Román, S. Catalán, S. Fustero, *Chem. Eur. J*. 2015, **21**, 11579. For other aminocarbonylation protocols see: (b) D. Marosvölgyi-Haskó, A. Takács, Z. Riedl, L. Kollár, *Tetrahedron*, 2011, **67**, 1036; (c) M. Fujioka, T. Morimoto, T. Tsumagari, H. Tanimoto, Y. Nishiyama, K. Kakiuchi, *J. Org. Chem.*, 2012, **77**, 2911; (d) R. Mancuso, I. Ziccarelli, D. Armentano, N. Marino, S. V. Giofre, B. Gabriele, *J. Org. Chem.*, 2014, **79**, 3506; (e) Y. Xu, W. Hu, X. Tang, J. Zhao, W. Wu, H. Jiang, *Chem. Commun. (Camb).*, 2015, **51**, 6843.
15 H. Cao, L. Mcnamee, H. Alper, *Org. Lett.*, 2008, **10**, 5281.
16 (a) Y. Koseki, S. Kusano, T. Nagasaka, *Tetrahedron Lett.*, 1998, **39**, 3517; (b) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron*, 2003, **59**, 1571; (c) C. Kanazawa, M. Terada, *Chem. Asian J.*, 2009, **4**, 1668; (d) G. Bianchi, M. Chiarini, F. Marinelli, L. Rossi, A. Arcadi, *Adv. Synth. Catal.*, 2010, **352**, 136; For a phase-transfer promoted cyclization see: (e) J. Hu, L. Liu, X. Wang, Y. Hu, S. Yang, Y. Liang, *Green Sustain. Chem.*, 2011, **01**, 165; (f) A. Bubar, P. Estey, M. Lawson, S. Eisler, *J. Org. Chem.*, 2012, **77**, 1572; (g) D. Y. Li, K. J. Shi, X. F. Mao, Z. Le Zhao, X. Y. Wu, P. N. Liu, *Tetrahedron*, 2014, **70**, 7022.
17 (a) M. W. Khan, N. G. Kundu, *Synlett*, 1997, 1435; (b) N. G. Kundu, M. W. Khan, *Tetrahedron*, 2000, **56**, 4777.
18 (a) M. Hellal, G. D. Cuny, *Tetrahedron Lett.*, 2011, **52**, 5508. (b) S. Sarkar, S. Dutta, R. Dey, S. Naskar, *Tetrahedron Lett.*, 2012, **53**, 6789.
19 (a) L. Li, M. Wang, X. Zhang, Y. Jiang, D. Ma, *Org. Lett.*, 2009, **11**, 1309; (b) J. Pan, Z. Xu, R. Zeng, J. Zou, *Chinese J. Chem.*, 2013, **31**, 1022. (c) J. Dong, F. Wang, J. You, *Org. Lett.*, 2014, **16**, 2884; For a Cu-catalyzed decarboxylative protocol starting from alkynyl carboxylic acids as alkyne sources see: (d) A. Gogoi, S. Guin, S. K. Rout, G. Majji, B. K. Patel, *RSC Adv.* 2014, **4**, 59902.
20 (a) Y. Hatanaka, T. Hiyama, *J. Org. Chem.*, 1988, **53**, 918; (b) Y. Hatanaka, K. Matsui, T. Hiyama, *Tetrahedron Lett.*, 1989, **30**, 2403.
21 S. E. Denmark, D. Wehrli, *Org. Lett.*, 2000, **2**, 565.
22 (a) S. E. Denmark, S. A. Tymonko, *J. Org. Chem.*, 2003, **68**, 9151;. (b) S. Chang, S. H. Yang, P. H. Lee, *Tetrahedron Lett.*, 2001, **42**, 4833; (c) S. E. Denmark, L. Neuville, M. E. L. Christy, S. A. Tymonko, *J. Org. Chem.*, 2006, **71**, 8500; (d) E. Alacid, C. Najera, *J. Org. Chem.*, 2008, **73**, 2315.
23 For accounts and review articles see: (a) Y. Hatanaka, T. Hiyama, *Synlett*, 1991, 845; (b) Y. Nakao, T. Hiyama, *Chem. Soc. Rev.*, 2011, **40**, 4893; (c) S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.*, 2002, **35**, 8359 (d) S. E. Denmark, J. D. Baird, *Chem. Eur. J.*, 2006, **12**, 4954.
24 Although not uniformly used in the literature, the term "Sonogashira reaction" strictly refers to the Pd/Cu co-catalyzed C(sp)-C(sp2) coupling. Other types of alkynylation protocols are also available, in fact, a decade prior to the discovery of Sonogashira reaction, Stephens and Castro developed a protocol using stoichiometric amounts of copper acetylides. Reactions catalyzed by copper only should be referred to as catalytic "Castro-Stephens reactions", whereas the Pd only protocols should be referred to as "Heck–Cassar coupling". For a brief review on alkynylation catalyzed by different metals see: H. Plenio, *Angew. Chem. Int. Ed. Engl.*, 2008, **47**, 6954.
25 (a) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis (Stuttg).*, 1980, 627; (b) M. Erdelyi, A. Gogoll, *J. Org. Chem.*, 2001, **66**, 4165; (c) M. S. Mohamed Ahmed, A. Sekiguchi, K. Masui, A. Mori, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 160; (d) G. Zengin, *Asian J. Chem.*, 2007, **19**, 3063;. (e) Y. Nishihara, K. Ikegashira, A. Mori, T. Hiyama, *Chem. Lett.*, 1997, 1233. For reviews see: (f) R. Chinchilla, C. Najera, *Chem. Rev.*, 2007, **107**, 874; (g) E. Negishi, L. Anastasia, *Chem. Rev.*, 2003, **103**, 1979.
26 Y. Nishihara, S. Noyori, T. Okamoto, M. Suetsugu, M. Iwasaki, *Chem. Lett.*, 2011, **40**, 972.
27 S. Protti, M. Fagnoni, A. Albini, *Angew. Chem. Int. Ed,.* 2005, **44**, 5675.
28 Y. Nishihara, K. Ikegashira, A. Mori, T. Hiyama, *Tetrahedron Lett.*, 1998, **39**, 4075.
29 Y. Nishihara, K. Ikegashira, K. Hirabayashi, J. Ando, A. Mori, T. Hiyama, *J. Org. Chem.*, 2000, **65**, 1780.
30 Reaction was conducted in a crimp top vial. Due to methanol's high volatility, further enhancement of the reaction rate by increasing the reaction temperature was not pursued.
31 The similar reaction rates for silyl and terminal alkynes, suggests that *in-situ* deprotection is the dominant pathway, although direct transmetalation from silicon to copper cannot be ruled out.
32 Only 2 equivalents of base were insufficient to achieve higher yields.

33 Shorter reaction times led to the isolation of a mixture of isoindolinone and the uncyclized *o*-alkynylbenzamide derivative.
34 See supporting information for details. Crystallographic information files have been deposited in the Cambridge Crystallographic Data Centre. CCDC numbers of products are **4a**: 1427402 and **4y**: 1426924.
35 G. W. Kabalka, L. Wang, R. M. Pagni, *Tetrahedron*, 2001, **57**, 8017.
36 The results of the *Z/E* ratio in this series are in perfect alignment with the electron withdrawing ability of the corresponding functional groups as judged by their σ(para) values. However, the *p*-CF_3 substituted product **4e** deviates from this trend. We attribute this observation to the decreased coordination of –CF_3 to the copper Lewis acid. Coordination of moieties containing stronger Lewis basic sites most likely enhances the electron withdrawing ability of such functional groups.
37 J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 11684.
38 Catalyst loadings mentioned are based on the limiting reagent **1b.**
39 If **1b** is present in the first step, the product **4b** could also be obtained, albeit in a decreased yield of 52% along with significant amounts of 1,2-bis(4-methoxyphenyl)ethyne, resulting from the competitive cross-coupling of **2b** with **7b.**
40 P. a. Clarke, S. Santos, W. H. C. Martin, *Green Chem.*, 2007, **9**, 438.