Multicomponent Reactions

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Palladium-Catalyzed Carbonylative Four-Component Synthesis of Thiochromenones: The Advantages of a Reagent Capsule

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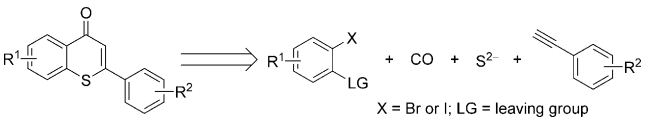
Abstract: *Multicomponent reactions, especially those involving four or even more reagents, have been a long-standing challenge because of the issues associated with balancing reactivity, selectivity, and compatibility. Herein, we demonstrate how the use of a reagent capsule provides straightforward access to synthetically valuable thiochromenone derivatives by a palladium-catalyzed carbonylative four-component reaction. To the best of our knowledge, this is the first example of applying a capsule to prevent catalyst poisoning and undesired side reactions of the multicomponent reaction.*

Purification processes probably are the most time-consuming, cost-ineffective, and waste-producing manual operations in modern organic synthesis. However, to improve compatibility and to ensure that the consecutive reaction proceeds smoothly, the purification of intermediates seems to be inevitable. As an advancement of this conventional "stop-and-go" synthetic approach, multistep one-pot strategies, which are more compact, less time-consuming, and less waste-generating, can dramatically improve synthetic efficiency.[1] In this respect, significant progress has been achieved in the area of multicomponent reactions (MCR),[2] as illustrated by various examples of three-component reactions.[3] Upon addition of further components, the balance between selectivity and reactivity will become more subtle, and more undesired side products may be formed. Furthermore, the participation of transition-metal catalysts would further complicate this scenario. The possibility of catalyst poisoning and side reactions triggered by the catalyst must be taken into consideration. Hence, straightforward MCRs with transition-metal catalysts and four or even more reagents are still under development and have remained an arduous challenge.[4]

As one of the most important inventions in pharmacy, the use of capsules represents a reproducible method for the precise and consistent dosing and delivery of medicines as well as for maintaining the stability of pharmaceuticals.[5a,b] In the meantime, capsules have also been applied within the realm of energy and functional materials.[5c-e] Recently, simple and practical techniques for reagent encapsulation were introduced to substantially minimize the inconvenience of dispensing air- or moisture-sensitive compounds in the glove box, enabling the bench-top storage of air- or moisture-sensitive reagents,[6] and were selected as one of 2015's most notable chemistry research advances.[7] This award proves the enormous potential of reagent capsules in organic synthesis. Therefore, based on our long-lasting interest in developing highly efficient multicomponent reactions[8] and carbonylative syntheses of heterocycles,[9] we intended to take advantage of reagent capsules to overcome the barriers encountered in the development of multicomponent reactions.

Thiochromone, the thio homologue of the core constituent of the natural product class of flavones, constitutes the skeleton of numerous biologically or pharmaceutically active compounds.[10] Furthermore, the oxidized variants of thiochromen-4-ones are used as human cytomegalovirus protease inhibitors[11] and photolabile protecting groups for phosphate compounds.[12] Aside from various classical pathways entailing cyclization by condensation or addition,[13] only a limited number of transition-metal-catalyzed syntheses of thiochromones have been reported.[14] The previously reported methods generally suffer from drawbacks related to synthetic efficiency, availability or diversity of the substrates, regioselectivity, and functional-group compatibility. In theory, our proposed carbonylative four-component one-pot reaction is a fairly efficient pathway that provides the desired products from commercially available odorless materials with a reduced number of manual operations (Scheme 1).[15] The



Scheme 1. Retrosynthetic analysis of thiochromenones.

reaction is expected to proceed by a carbonylative Sonogashira coupling followed by an aromatic nucleophilic substitution (S_NAr)/conjugate addition tandem reaction. Quick and irreversible poisoning of the transition-metal catalyst by the sulfur species[16] and potential side reactions with sulfide or its hydrate could pose problems that must not be neglected.

The initial investigation was carried out with 1-fluoro-2-iodobenzene, phenylacetylene, and sodium sulfide nonahydrate as the substrates and a palladium catalyst under CO atmosphere. After screening various reaction conditions, including palladium precursors, ligands, solvents, and reaction temperatures, the desired product could still not be detected (Figure 1 a). Upon analyzing the reaction mixture and isolat-

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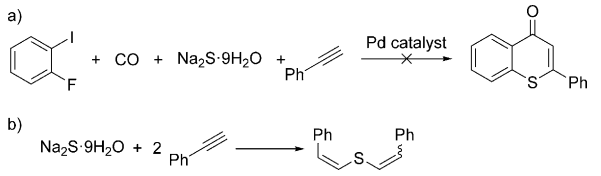


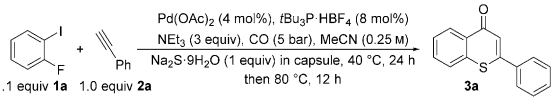
Figure 1. a) Desired thiochromenone synthesis. b) Addition reaction between $Na_2S·9H_2O$ and phenyl acetylene.

ing a side product, we found that the inhibitory effect of the sodium sulfide nonahydrate is not only due to the widely recognized poisoning of transition-metal catalysts by sulfide anions,[17] but also to the addition of sodium sulfide nonahydrate to phenyl acetylene.[18] The side reaction can rapidly (usually <6 h) consume all phenylacetylene at low temperature (40–90 °C) and give a mixture of the *cis*/*cis* and *cis*/*trans* isomers of bis(2-phenylvinyl)sulfide (Figure 1b).

To address the challenges of the four-component carbonylative synthesis of thiochromenones and overcome the problems associated with the use of sodium sulfide nonahydrate, a paraffin wax capsule for the controlled release of $Na_2S·9H_2O$ was conceived and prepared. After investigating various reaction parameters, we finally succeeded in isolating the desired thiochromenone product in 68% yield using the capsule containing $Na_2S·9H_2O$ in combination with $Pd(OAc)_2$/tBu_3P under 5 bar CO with a time-controlled temperature regulator (Table 1). Conversely, when $Na_2S·9H_2O$ was employed without the capsule, no desired product, but only side product bis(2-phenylvinyl)sulfide, was generated (entry 2). Reducing the ligand loading or replacing tBu_3P with other monodentate phosphine ligands decreased the yield (entries 3–5). Among various solvents, MeCN proved to be the most suitable medium (entries 6–9). Several other commonly applied inorganic and organic bases were not able to achieve higher yields than NEt_3 (entries 10–13). For the leaving group, fluorine showed better reactivity in the S_NAr process than the chlorine, bromine, and methoxy counterparts (entries 14–16).[19] Notably, when $Mo(CO)_6$ was used as a non-gaseous CO precursor, the desired product was still formed in moderate yield (entry 17).[20]

With the optimized reaction conditions in hand, we examined the scope of the reaction with a range of acetylenes (Table 2). As the process combines three reactions, the substitution and electronic effects are difficult to be clearly attributed. With most substituted phenylacetylenes with electronically neutral or electron-donating or -withdrawing groups (**3b**–**3i** and **3k**), moderate to good yields were achieved. On the other hand, the yields obtained with phenylacetylene derivatives with a strongly electron-withdrawing group (EWG) in the *para* position (**3j**), an EWG in the *ortho* position (**3l**), or two EWGs (**3m**) were lower. Moderate yields of the desired products can also be achieved with aliphatic alkynes (**3n** and **3o**). Notably, when ethynyl-

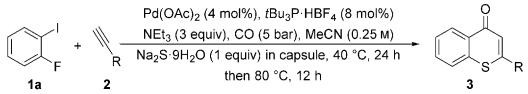
Table 1: Selected results of the optimization of the reaction conditions.[a]

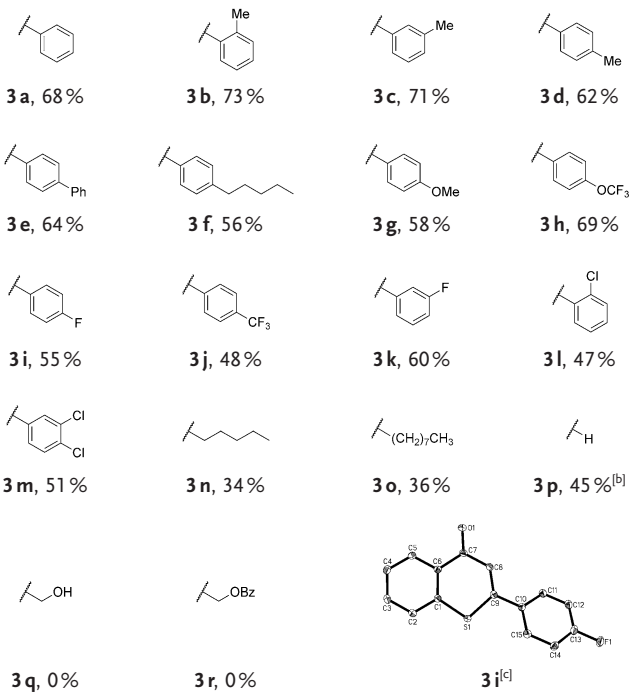


Entry	Variations from the standard conditions	Yield [%][b]
1	–	68
2	$Na_2S·9H_2O$ without a paraffin wax capsule	0
3	$tBu_3P·HBF_4$ (6 mol%) instead of $tBu_3P·HBF_4$ (8 mol%)	58
4	nBuPAd$_2$ instead of $tBu_3P·HBF_4$	45
5	$PdCl_2(PPh_3)_2$ (2.5 mol%) instead of $Pd(OAc)_2$ and $tBu_3P·HBF_4$	6
6	DMF instead of MeCN	29
7	DMA instead of MeCN	33
8	toluene instead of MeCN	0
9	DMSO instead of MeCN	0
10	K_2CO_3 (2.0 equiv) instead of NEt_3	10
11	Cs_2CO_3 (2.0 equiv) instead of NEt_3	0
12	DIPEA instead of NEt_3	22
13	DBU instead of NEt_3	0
14	1-chloro-2-iodobenzene instead of **1a**	51
15	1-bromo-2-iodobenzene instead of **1a**	32
16	1-iodo-2-methoxybenzene instead of **1a**	28
17	$Mo(CO)_6$ (1.0 equiv) in a sealed tube instead of 5 bar CO in an autoclave	55

[a] Reaction scale: 0.50 mmol. [b] Yields of isolated products are given. Ad = adamantyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, DMA = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

Table 2: Palladium-catalyzed four-component reaction of 1-fluoro-2-iodobenzene with various acetylenes.[a]





[a] Reaction scale: 0.50 mmol (1.1 equiv **1a**, 1.0 equiv **2**). Yields of isolated products are given. [b] Ethynyltrimethylsilane was employed. [c] Molecular structure of **3i**.[22] Thermal ellipsoids set at 30% probability; hydrogen atoms omitted for clarity.

trimethylsilane was employed, owing to the water contained within $Na_2S{\cdot}9H_2O$, the product was further hydrolyzed, and 4*H*-thiochromen-4-one was generated as the final product (**3p**). Functionalized terminal alkynes, such as propargyl alcohol and propargyl benzoate (**3q** and **3r**), failed to generate the corresponding thiochromenones, which may be due to the isomerization of propargyl alcohol and propargyl benzoate catalyzed by the palladium catalyst.[21]

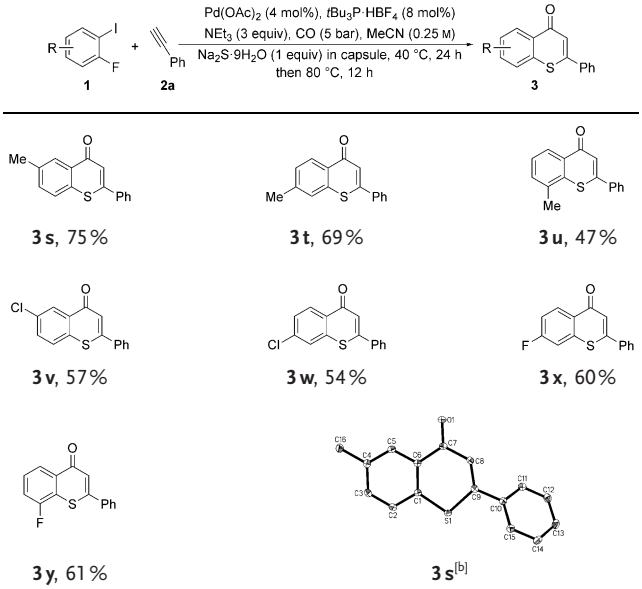
ortho-Fluoroiodobenzenes with different substitution patterns were tested as well (Table 3). Substituents in the *para*, *meta*, or *ortho* position, including methyl, fluorine, and chlorine moieties, were all well tolerated (**3s**–**3x**). The decreased yield of **3u** is due to the steric hindrance of the methyl group during nucleophilic substitution.

Furthermore, several disubstituted 2-aryl-4*H*-thiochromen-4-ones were prepared by this new method. Starting from commercially available substituted phenylacetylenes and substituted 1-fluoro-2-iodobenzenes, moderate to good yields were achieved under the standard reaction conditions (Table 4).

The preparation of 3-iodo-2-phenyl-4*H*-thiochromen-4-one, a derivative of our product, was carried out as well. In the presence of iodine and cerium(IV) ammonium nitrate (CAN), the desired compound was isolated in 91% yield (Scheme 2). This product is ready for further derivatization by transition-metal-catalyzed coupling reactions, and the obtained 2,3-disubstituted thiochromenones have potential applications in pharmaceutical lead optimization.[23]

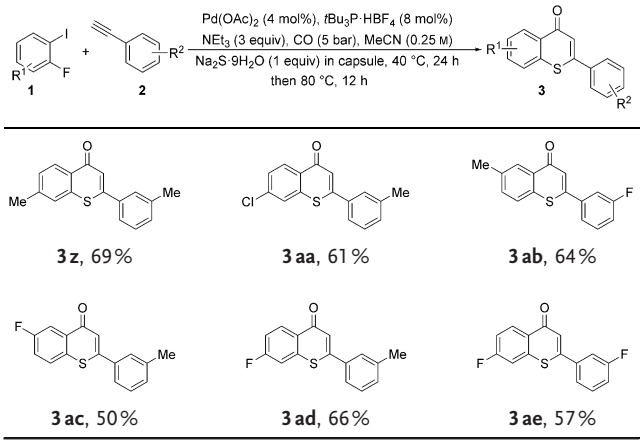
In summary, an efficient palladium-catalyzed carbonylative method for preparing thiochromenones in a four-component reaction that makes use of an reagent capsule has been developed. The reagent capsule was essential to solving problems related to the poisoning of the transition-metal catalyst as well as the compatibility of the various reagents in the one-pot process. It also helped to reduce the total number of manual operations, rendering the purification of intermediates unnecessary, and greatly facilitated the development of a highly efficient, environmentally friendly multicomponent reaction. To the best of our knowledge, this is the first example of applying a reagent capsule for preventing catalyst poisoning and undesired side reactions in a multicomponent reaction.

Table 3: Palladium-catalyzed four-component reaction of substituted 1-fluoro-2-iodobenzenes with phenylacetylene.[a]

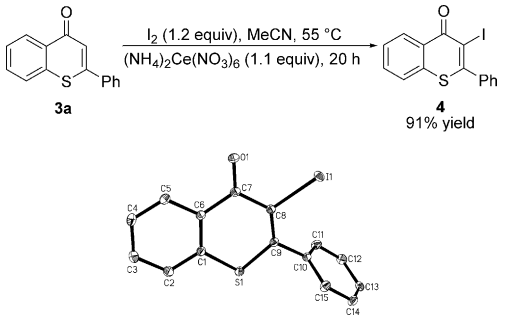


[a] Reaction scale: 0.50 mmol (1.1 equiv **1**, 1.0 equiv **2**). Yields of isolated products are given. [b] Molecular structure of **3s**.[22] Thermal ellipsoids set at 30% probability; hydrogen atoms omitted for clarity.

Table 4: Palladium-catalyzed four-component reaction of substituted 1-fluoro-2-iodobenzenes and substituted phenylacetylene derivatives.[a]



[a] Reaction scale: 0.50 mmol (1.1 equiv **1**, 1.0 equiv **2**). Yields of isolated products are given.



Scheme 2. Top: Synthesis of 3-iodo-2-phenyl-4*H*-thiochromen-4-one. The yield is that of isolated **4**. Bottom: Molecular structure of **4**;[22] hydrogen atoms omitted for clarity.

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