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# Utilizing an Encapsulated Solution of Reagents to Achieve the Four-Component Synthesis of (Benzo)Thiophene Derivatives

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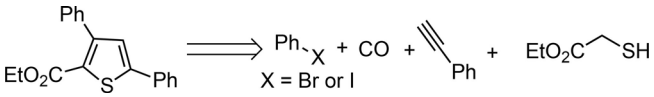
**Abstract:** Reagent capsules can help to resolve the compatibility problem of reagents in multicomponent processes. Herein we demonstrate a facile method for encapsulating smelly liquid chemicals and its application in a modular palladium-catalyzed carbonylative synthesis of multi-substituted thiophenes from terminal alkynes and aryl iodides as well as a palladium-catalyzed carbonylative synthesis of benzothiophene derivatives from aryl iodides and arylboronic acids. Here, the capsule plays a pivotal role in solving the issues on reaction condition incompatibilities and selectivity of multicomponent reactions as well as avoiding deactivation of the catalyst by releasing the reagents when the reaction temperature is raised. It greatly facilitates the development of highly-efficient multicomponent reactions and demonstrates a modular pathway to obtain functionalized molecules.

**Keywords:** carbonylation; encapsulated reagents; heterocycles; multicomponent reactions; palladium catalysis

Encapsulation is an ancient but important invention originally for precise and consistent dosing and delivery of medicines as well as for maintaining the stability of pharmaceuticals.[1] Nowadays the application of encapsulation has been extended from pharmacy to other realms,[2] for example, facilitating chemical research,[2a,b] and promoting the development of energy and material technology.[2c–g] In organic synthesis, the application and advantage of encapsulation are also emerging. By dispersing or encapsulating solid chemicals in paraffin wax, encapsulation helps to achieve the benchtop storage and delivery of air- or moisture-sensitive organometallic catalysts[3] and reagents.[4] It is expected to boost the popularization of glove-box-free synthesis[3] and advancement of organic chemistry teaching in the undergraduate laboratory.[5] Due to the fluidity of liquid chemicals and complexity of making paraffin capsules, neither dispersion into paraffin wax nor encapsulation by paraffin wax is the suitable solution to make capsules containing liquid chemicals. Recently a method of encapsulating liquid chemicals by embedding the compounds in crystalline matrices that form inclusion complexes of defined stoichiometry has been reported.[6] It makes toxic or malodorous liquid compounds easy to handle and dispense while but guarantees the immediate release of reagents in solution, but it always requires stoichiometric amounts of tetrakis(dimethoxyphenyl)adamantane. Therefore we sought to achieve the facile encapsulation and controlled release of liquid chemicals and excavate the potential of encapsulated liquid reagents in organic synthesis.

As one of the powerful tools in organic synthesis, the multicomponent reaction (MCR) can implement the continuous construction of multiple bonds and rapid generation of molecular complexity.[7] It provides an operationally effective and highly modular approach to obtain structurally diverse molecules through a process that combines three or more components in a single reaction vessel without isolating the intermediates or adding further reagents. Owing to the strict requirement of MCRs on reaction sequential order,[7c] MCRs involving four or more reagents are rather fewer than three-component reactions.[8] Apart from interrupting the original sequence, the addition of further components may also make the balance between selectivity and reactivity more subtle and elevate the probability of forming undesired side products. Moreover, the scenario would be further complicated with the participation of transition metal catalysts. The concerns over side-reactions, deactivation of catalyst and incompatibilities of reaction conditions between each step must be taken into consideration. Reagent capsules might be one of the

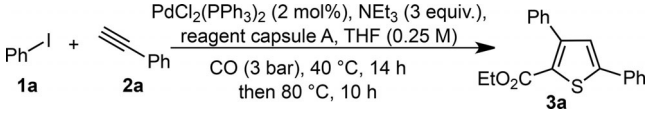
latent pathways to eliminate the issue of side reactions.[3] Based on our long-standing interest in developing highly efficient multicomponent reactions[9] and carbonylative synthesis of heterocycles,[10] we envisaged utilizing the combination of carbonylation[11] and Fiesselmann reaction[12] to achieve the four-component synthesis of multisubstituted thiophenes.[13] Ethyl 3,5-diphenylthiophene-2-carboxylate was selected as the exemplary product. By retrosynthetic analysis, the thiophene ring is disassembled to four moieties, aryl halides, carbon monoxide, phenylacetylene and ethyl thioglycolate (Scheme 1). Considering that the Fiesselmann reaction of ethyl thioglycolate with an alkynone intermediate would be the second step in this four-component process and the potential coordination of ethyl thioglycolate with a transition metal,[14] the foul-smelling ethyl thioglycolate liquid should be encapsulated and released from the capsule when the reaction temperature is raised. In order to predigest the preparation of reagent capsule and adapt the capsule to the liquid chemicals, the cheap and commercially available glass shell[15] is chosen to replace the paraffin capsule shell and capsule is sealed up with paraffin wax (see the Supporting Information for details).




**Scheme 1.** Retrosynthetic analysis of ethyl 3,5-diphenylthiophene-2-carboxylate.

The initial investigation was carried out with iodobenzene, phenylacetylene, reagent capsule containing ethyl thioglycolate and a palladium catalyst under a CO atmosphere. After investigation of the reaction parameters, it was found that the desired product **3a** was obtained in 65% yield by using $PdCl_2(PPh_3)_2$ with the help of the encapsulated ethanol solution of ethyl thioglycolate and DBU under 3 bar of CO in tetrahydrofuran solution[16] (Table 1). The molecular structure of product **3a** was confirmed by X-ray diffraction (Figure 1). With capsules that had been stored on the benchtop for two months, the product **3a** was still obtained in 64% yield, indicating that prolonged exposure to atmospheric oxygen and moisture does not reduce the efficacy of the capsule (entry 1). DBU, a stronger base than triethylamine, is crucial for the cyclization of the alkynone intermediate with ethyl thioglycolate (entry 2). Although ethanol can promote the Fiesselmann cyclization (entry 3), unencapsulated ethanol led to a significant diminution in the selectivity of the palladium-catalyzed carbonylative Sonogashira reaction (entry 4) and the side-product 1,2-diphenylethyne overwhelmed the product **3a**. Unencapsulated DBU has a similar negative effect on the reac-

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




| Entry | Variations from the standard conditions | Yield [%][b] |
|---|---|---|
| 1 | – | 65 (64)[c] |
| 2 | reagent capsule A without DBU | 0 |
| 3 | reagent capsule B[d] | 50 |
| 4 | EtOH in the reaction glass vial instead of in the capsule | 17 |
| 5 | DBU in the reaction glass vial instead of in the capsule | 0 |
| 6 | EtOH, ethyl thioglycolate and DBU without encapsulation | 0 |
| 7 | 1.50 mmol reaction scale | 64[e] |

[a] Reaction scale: 0.50 mmol (1.0 equiv. **1a**, 1.0 equiv. **2a**). The content of reagent capsule A is an EtOH (0.20 mL) solution of ethyl thioglycolate (0.55 mmol) and DBU (0.55 mmol).

[b] Yields of isolated products are given.

[c] With the reagent capsule A that had been stored on the benchtop for two months.

[d] The content of reagent capsule B is a THF (0.20 mL) solution of ethyl thioglycolate (0.55 mmol) and DBU (0.55 mmol).

[e] The shell of capsule is made from a glass Pasteur pipette. The content in one reagent capsule A is an EtOH (0.60 mL) solution of ethyl thioglycolate (1.65 mmol) and DBU (1.65 mmol). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. THF = tetrahydrofuran.

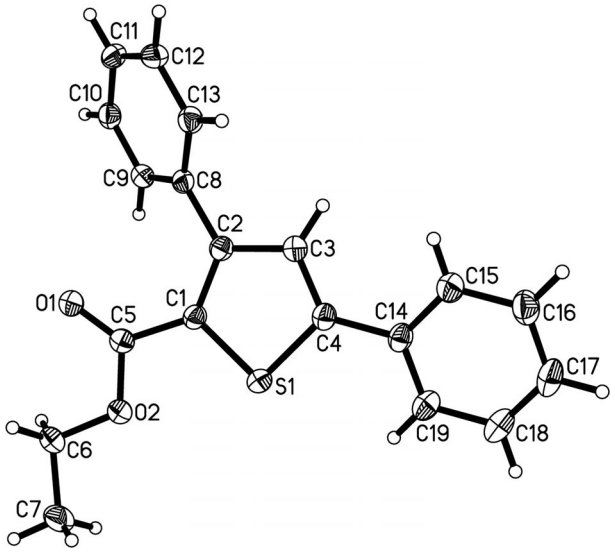
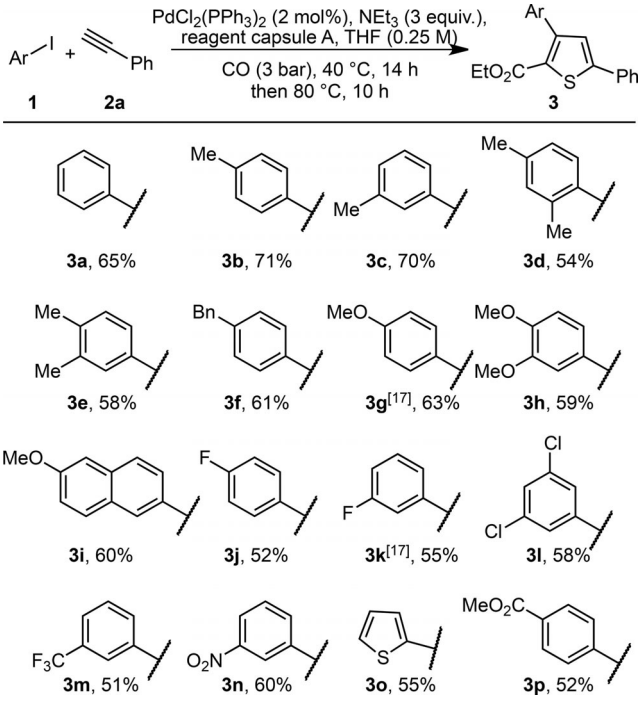



**Figure 1.** ORTEP diagram of **3a**.[17] Thermal ellipsoids set at 50% probability.

tion (entry 5). When EtOH, ethyl thioglycolate and DBU were all unencapsulated, neither the generation of 1,2-diphenylethyne or **3a** nor the conversion of **1a** was observed on GC (entry 6). This indicated that the palladium catalyst might be deactivated by ethyl thioglycolate. By trimming a commercially-available glass Pasteur pipette to make the shell of a capsule with a larger volume, the reaction scale can be enlarged (entry 7, see the Supporting Information for details).

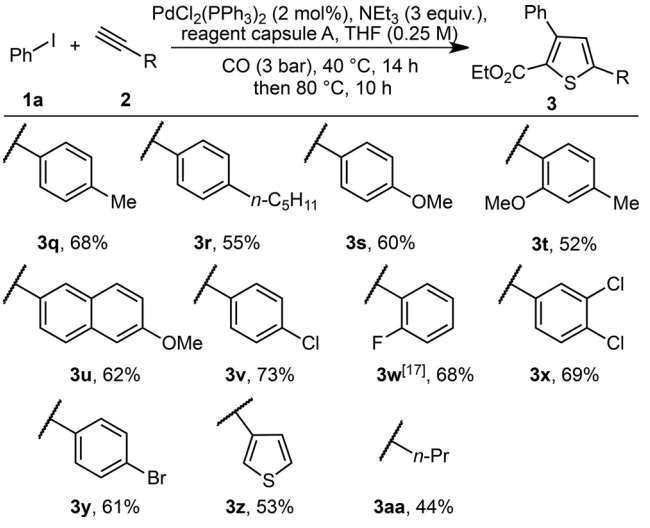
With the optimized protocol in hand, we investigated the scope of substrates with a range of substituted iodobenzenes (Table 2). Although the whole process involves Pd-catalyzed carbonylative Sonogashira reaction, 1,4-addition of thiol to alkynone and intramolecular condensation, moderate to good yields were achieved with various substituted iodobenzenes. With aryl iodides bearing electronically neutral groups (**3b**–**3f**), *para*- and *meta*-substituted substrates (**3b**, **3c**, **3e**, **3f**) can provided higher yields than the *ortho*-substituted substrate (**3d**). For both substrates with electron-donating groups on the *para*- and *meta*-position of phenyl ring or on the fused ring (**3g**–**3i**) and substrates with electron-withdrawing groups (**3j**–**3m**), the protocol also gave the desired products in moderate yields. Moreover nitro group, carboxylic ester and

**Table 2.** Palladium-catalyzed four-component reaction of phenylacetylene with substituted iodobenzenes.[a]




[a] Reaction scale: 0.50 mmol (1.0 equiv. **1**, 1.0 equiv. **2a**). Yields of isolated products are given. The content of reagent capsule A is the encapsulated EtOH (0.20 mL) solution of ethyl thioglycolate (0.55 mmol) and DBU (0.55 mmol).

**Table 3.** Palladium-catalyzed four-component reaction of iodobenzene with substituted phenylacetylene derivatives.[a]




[a] Reaction scale: 0.50 mmol (1.0 equiv. **1a**, 1.0 equiv. **2**). Yields of isolated products are given. Reagent capsule A is the encapsulated EtOH (0.20 mL) solution of ethyl thioglycolate (0.55 mmol) and DBU (0.55 mmol).

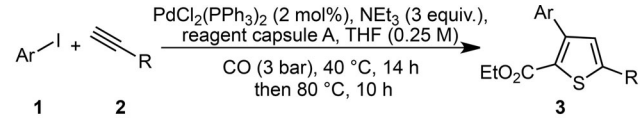
thiophene ring were able to survive under these reaction conditions (**3n**–**3p**).

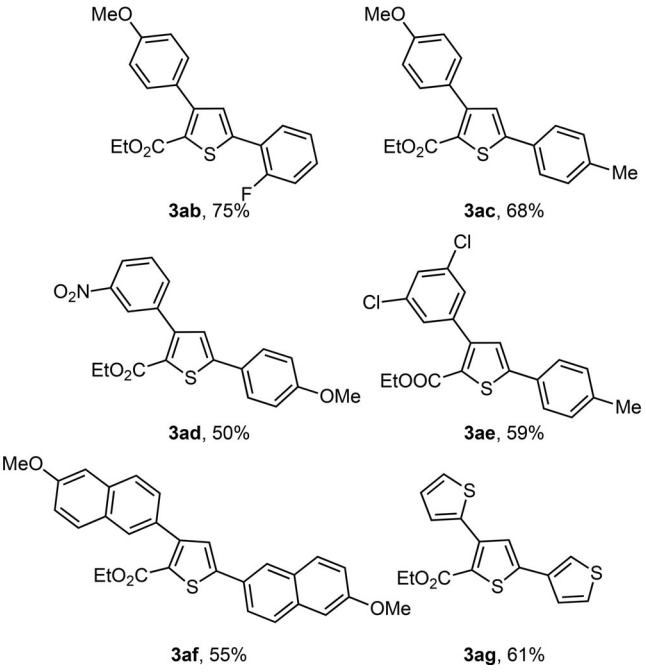
Then phenylacetylenes with different substitution patterns were tested as well (Table 3). Substituents in the *para*, *meta*, or *ortho* position, including methyl, methoxy, fluorine, and chlorine moieties, were all well tolerated (**3q**–**3x**). Because of the low temperature for carbonylation, there was no concern about the compatibility issue of a bromine substituent (**3y**). By employing 3-ethynylthiophene, the corresponding product with the skeleton of 2,3′-bithiophene was constructed (**3z**). Compared to those of arylacetylenes, the yield of the product from an alkylacetylene (**3aa**) is relatively lower.

The reaction was further extended to a number of ethyl 3,5-diphenylthiophene-2-carboxylates with substituents on both phenyl rings (Table 4). Moderated to good yields (**3ab**–**3af**) displayed the facility brought about by the reagent capsule in a rapid synthesis of highly functionalized molecules. This method was also able to be applied in synthesis of oligothiophene (**3ag**).

After adjusting the components of capsule, the capsule of ethyl thioglycolate was further applied in the preparation of a benzothiophene derivative (Table 5). With the aid of an encapsulated DMSO solution of ethyl thioglycolate, the four-component synthesis of ethyl 3-([1,1′-biphenyl]-4-yl)benzo[*b*]thiophene-2-carboxylate[18] was achieved as well. The structure of product **6** was also determined by X-ray diffraction.[17] To our delight, when the reaction scale was amplified 5 times, the yield was not significantly affected

**Table 4.** Synthesis of ethyl 3,5-diarylthiophene-2-carboxylate.[a]



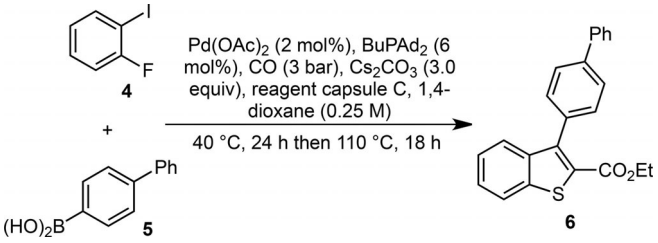




[a] Reaction scale: 0.50 mmol (1.0 equiv. **1**, 1.0 equiv. **2**). Yields of isolated products are given. Reagent capsule A is the encapsulated EtOH (0.20 mL) solution of ethyl thioglycolate (0.55 mmol) and DBU (0.55 mmol).

(entry 1). When polar DMSO was replaced by non-polar 1,4-dioxane, the aromatic nucleophilic substitution ($S_NAr$) turned to be sluggish (entry 2). Although DMSO can promote the $S_NAr$, unencapsulated DMSO made the undesired Suzuki cross-coupling dominant and no desired product was generated (entry 3). Similar to the scenario in the synthesis of ethyl 3,5-diphenylthiophene-2-carboxylate, no product or diaryl ketone intermediate was detected when both ethyl thioglycolate and DMSO were unencapsulated (entry 4).

In summary, a facile method of encapsulating liquid chemicals and an efficient four-component synthetic pathway to (benzo)thiophene derivatives that taking full advantage of encapsulated liquid reagents has been developed. The capsule plays a pivotal role in solving the issues on reaction conditions incompatibilities and selectivity of MCR as well as avoiding deactivation of the catalyst. It greatly facilitates the development of a highly-efficient multicomponent reaction and demonstrates a modular pathway to obtain functionalized molecules, which has the potential in readily preparing drug and material candidates.

**Table 5.** Synthesis of ethyl 3-([1,1′-biphenyl]-4-yl)benzo[*b*]-thiophene-2-carboxylate in the presence of reagent capsule.[a]




| Entry | Variations from the standard conditions | Yield [%] |
|---|---|---|
| 1 | – | 59 (56)[b] |
| 2 | reagent capsule D[c] | 40 |
| 3 | DMSO in the reaction glass vial instead of in the capsule | 0 |
| 4 | unencapsulated ethyl thioglycolate and DMSO | 0 |

[a] Unless otherwise stated, reaction scale: 0.50 mmol (1.0 equiv. **4**, 1.1 equiv. **5**). Yields of isolated products are given. The content of reagent capsule C is a DMSO (0.20 mL) solution of ethyl thioglycolate (0.55 mmol).

[b] Reaction scale: 2.50 mmol (1.0 equiv. **4**, 1.1 equiv. **5**). The shell of capsule is made from a glass Pasteur pipette. Reagent capsule C is a DMSO (0.6 mL) solution of thioglycolate (2.75 mmol).

[c] The content of reagent capsule D is a 1,4-dioxane (0.20 mL) solution of ethyl thioglycolate (0.55 mmol). DMSO = dimethyl sulfoxide.

## Experimental Section

### General Procedure

A 12-mL Wheaton® vial was charged with $PdCl_2(PPh_3)_2$ (7.1 mg, 0.01 mmol, 2 mol%), one reagent capsule A [encapsulated EtOH (0.20 mL) solution of ethyl thioglycolate (0.55 mmol) and DBU (0.55 mmol)] and a magnetic stirring bar (Supporting Information, Figure S11). Then under argon, a THF (2 mL) solution of iodobenzene (0.5 mmol), alkyne (0.5 mmol) and triethylamine (1.5 mmol) mixture was injected by syringe (Supporting Information, Figure S12). The vial (or several vials) was (were) placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under an argonr atmosphere. After flushing the autoclave three times with CO, a pressure of 3 bar CO was adjusted at ambient temperature. The reaction was performed at 40 °C (Note: avoid temperature rising too fast causing overheating above 45 °C) for 14 h. Then the temperature was elevated to 80 °C for 10 h. After the reaction had finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The reaction mixture was diluted with acetone (*ca.* 10 mL) and passed through a pad of Celite® once under reduced pressure. The filter cake was washed with additional acetone (*ca.* 15 mL). The filtrate was then collected and filtered through a pad of Celite® once more. After evap-

oration of the solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using *n*-pentane/AcOEt as eluent.

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[17] CCDC 1518303 (**3a**), CCDC 1518302 (**3g**), CCDC 1518301 (**3k**), CCDC 1518304 (**3w**) and CCDC 1518305 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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