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Access to Functionalized Thienopyridines via a Reagent-Capsule-Assisted Coupling, Thiolation and Cyclization Cascade Sequence

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Thienopyridines and related heterocycles were prepared in a straightforward manner in moderate to good yields and under mild conditions by the palladium-catalysed cross-coupling of *ortho*-fluorinated iodopyridines and terminal alkynes, followed by a reagent-capsule-assisted thiolation cyclization process. By applying paraffin wax capsules to prevent catalyst poisoning and undesired side reactions, the separation and purification processes were reduced.

The Sonogashira cross-coupling reaction is a well-recognized, powerful method for the preparation of arylalkynes and enynes through Csp-Csp^2 bond formation[1]with applications in pharmaceuticals, natural products and molecular organic materials.[2] Due to the compatibility of palladium and copper catalysts, when direct used these acetylene synthons in subsequent translation, the purification of these acetylene products appears to be unavoidable, thereby increasing the manual operations and time consumed. Paraffin capsules present an alternative solution to this problem. Particularly, in multi-component reactions based on the Sonogashira cross-coupling reaction, the reagent may affect the palladium and copper catalysts and the terminal alkyne encapsulated in the paraffin wax capsules.[3] During the completion of the cross-coupling reaction, raising the temperature can melt the paraffin capsule, releasing reagents and leading to subsequent reactions. Therefore, reagent encapsulation can not only protect against air- and moisture-sensitive reagents but also reduce the amount of required separation and purification processes.

The development of sustainable and efficient methodologies for the synthesis of thienopyridines and related heterocycles is crucial in modern organic synthesis due to their wide biological activities and pharmaceutical applications.[4] For example, DRAK2 [5] was reported as drug target for treatment of autoimmune diseases. Research by Boschelli and co-workers identified a thieno[3,2-*b*]pyridine-based drug candidate as Src kinase inhibitors.[6] The thieno[3,2-*d*]pyrimidine core was also utilized by Folkes and co-workers, who reported a new class of orally bioavailable inhibitor for the treatment of cancer, such as **3**.[7] Despite the importance of thienopyridines, synthetic methodologies for their production remain limited, and the provision various of these heterocycle compounds may represent a bottleneck for further studies and application in medicinal chemistry. The transition metal-catalysed cyclization of 3-aminothiophene derivatives is the most general and versatile synthetic methodology for the preparation of thienopyridine heterocycles.[8]

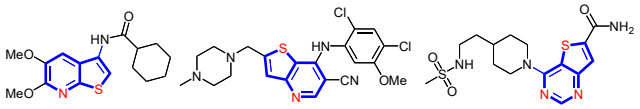

Figure 1 Pharmaceutically active compounds containing the thienopyridine core.

Our success in preparing benzo[*b*]furans and benzo[*b*]thiophenes using $Na_2S•9H_2O$ as a thiol surrogate encouraged us to employ related chemistry for the preparation of thienopyridine derivatives.[9] To the best of our knowledge, the sole attempt to involve ethynylpyridine in the formation of thienopyridine was made by Queiroz and co-workers, who obtained only 2-(hetero)aryl thienopyridines in good yields.[10] However, the utility of the above reactions is limited by their harsh conditions, and aliphatic alkynes do not react in this chemistry. Using *ortho*-fluoroiodopyridines as model substrates, we initially considered employing $Na_2S·9H_2O$ in DMSO as the solvent at 130 °C, following the procedure described by Queiroz and co-workers. In the presence of $Na_2S·9H_2O$, this reaction produced 2-phenylthieno[2,3-*b*]pyridine **3a** in 23% yield in 12 hours at 130 °C, but also gave the unexpected 2-phenylfuro[2,3-*b*]pyridine **4a** in 69% yield

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(Figure 2) (see supporting information). [11] Alternatively, we envisioned that the weakly nucleophilic thiol surrogate is essential in this thiolation cyclization process. Gratifyingly, the yield of 2-phenylthieno[2,3-*b*]pyridine **3a** was improved to 88% when EtOC(S)SK was employed as the thiol surrogate. In view of our on-going research to develop new methods in heterocycle synthesis[12], herein, we report an efficient and flexible synthetic protocol for the synthesis of thienopyridine and related heterocycles, utilizing a strategy consisting of palladium-catalysed sequential coupling, in situ thiolation and *S*-cyclization.

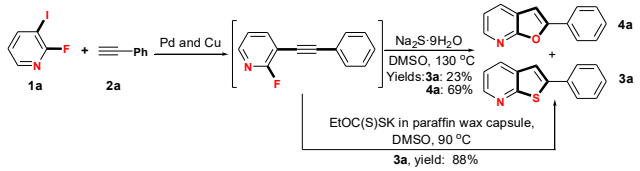
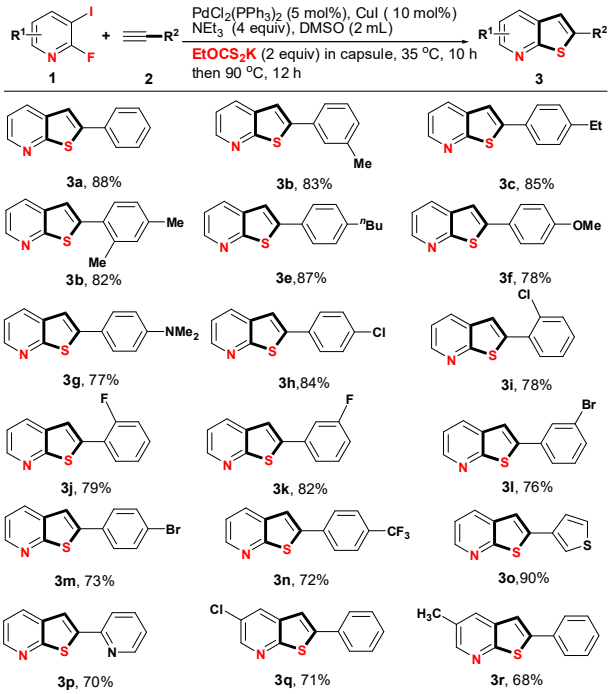


Figure 2: Synthesis of thieno[2,3-b]pyridines.

Furthermore, simple and practical techniques for paraffin encapsulation technology have been introduced in organic synthesis, especially for moisture- or air-sensitive compounds[13] and multicomponent reactions.[14] Encouraged by these results, we investigated the substrate scope of palladium-catalysed coupling, thiolation and cyclization reactions using a reagent-capsule-assisted method. As shown in Scheme 1, both electron-deficient and electron-rich arylalkynes reacted with *ortho*-fluoroiodopyridines to give the corresponding thieno[2,3-*b*]pyridine products in moderate to good yields (Scheme 1). Functional groups, including alkyl, OMe, NMe_2, F, Cl, Br, CF_3 and pyridine, can be well tolerated. Notably, we found that the *ortho* substituents of the benzyl group did not affected the coupling and annulation reaction (Scheme 1, **3i** and **3j**). When 2-fluoro-3-iodopyridine and 2-fluorophenylacetylene were used as reaction substrates, the 2-fluoro moiety on pyridine served as the leaving group and gave 2-(2-fluorophenyl)thieno[2,3-*b*]pyridine **3j** as the sole product. Substrates bearing heterocycles such as 3-thienyl or 2-pyridyl groups could also form the corresponding thieno[2,3-*b*]pyridine products **3o** and **3p** in moderate to good yields. *Ortho*-fluoroiodopyridines with different substitution patterns were tested as well. Substituents, including Me and Cl, were well tolerated (Scheme 1, **3q** and **3r**).

To extend the substrate scope, we used aliphatic alkynes to investigate the possibility of this transformation (Scheme 2). First, when *ortho*-fluoroiodopyridine was used as the substrate, a wide variety of aliphatic alkynes were screened and gave thieno[2,3-*b*]pyridine products in good yields. The reaction of non-1-yne provided a slightly higher yield than that of ethynylcyclopentane (Scheme 2, **3s**-**3u**). We were pleased to find that the internal C≡C triple bond was good tolerated under the optimization conditions (Scheme 2, **3v**). Notably, the reaction of octa-1,7-diyne with *ortho*-fluoroiodopyridine afforded 2-(3-(thieno[2,3-*b*]pyridin-2-yl)propyl)thieno[2,3-*b*]pyridine **3w** in 76% yield. Furthermore, the presented method was not limited to the use of arylalkyne derivatives as

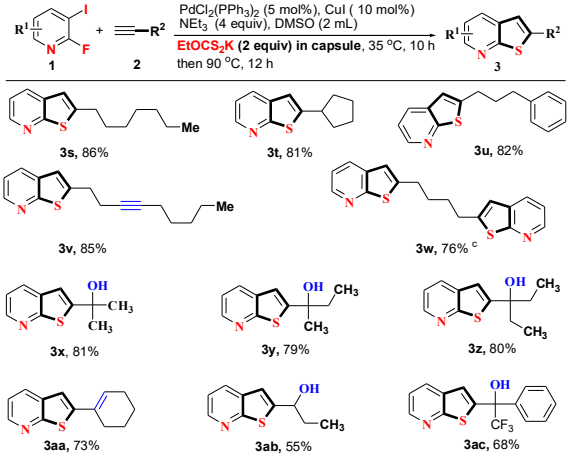
Scheme 1 Synthesis of 2-(hetero)arylthieno[2,3-*b*]pyridines [a,b]



[a] Reaction conditions: fluoroiodopyridine **1** (1.0 mmol), terminal alkyne **2** (1.3 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N (4.0 mmol), EtOC(S)SK (2.0 mol) in paraffin wax capsule, DMSO (2 mL) at 35 °C for 10 h, then 90 °C for 12h. [b] Yields are given for isolated products.

substrates, although the use of arylalkynes and aliphatic alkynes appeared to facilitate the process, given that alkynols afforded 2-(thieno[2,3-*b*]pyridin-2-yl)propan-2-ol derivatives in slightly lower yields than when using the arylalkyne systems.

Scheme 2 Synthesis of 2-alkylthieno[2,3-*b*]pyridines [a,b]

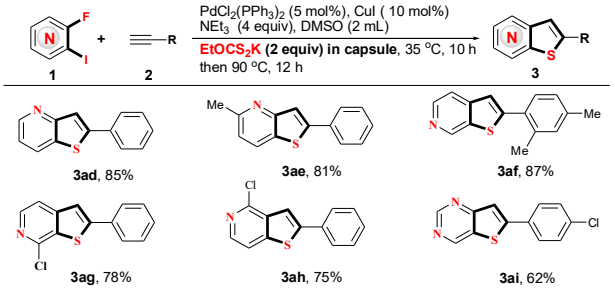


[a] Reaction conditions: fluoroiodopyridine 1 (1.0 mmol), terminal alkyne 2 (1.3 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N (4.0 mmol), EtOC(S)SK (2.0 mol) in paraffin wax capsule, DMSO (2 mL) at 35 °C for 10h, then 90 °C for 12h. [b] Yields are given for isolated products. [c] octa-1,7-diyne (0.65 mmol) was used.

When *ortho*-fluoroiodopyridine was used, a wide variety of propargyl alcohols were successfully employed in this process (Scheme 2, **3x**-**3ac**). Notably, when 1-ethynylcyclohexanol was employed as the substrate, the unexpected dehydration product **3aa** was obtained in 73% yield. Additionally, pent-1-yn-3-ol also reacted with *ortho*-fluoroiodopyridine to afford 1-(thieno[2,3-*b*]pyridin-2-yl)propan-1-ol **3ab** in moderate yields. Importantly, substrates bearing a CF_3 group at the tertiary alcohol were compatible with this reaction, and the coupling/cyclization product **3ac** was generated in 68% yield.

Next, several sulfur- and nitrogen-containing heterocycles were prepared using this method (Scheme 3). Starting from commercially available *ortho*-fluorinated iodopyridines and terminal alkynes, moderate to good yields were achieved. Thieno[3,2-*b*]pyridines (**3ad** and **3ae**)[15], thieno[2,3-*c*]pyridines (**3af** and **3ag**)[16], thieno[3,2-*c*]pyridines (**3ah**)[17] and thieno[3,2-*d*]pyrimidines (**3ai**)[7] were readily prepared via the sulfur reagent-capsule-assisted cyclization reaction. 4-F- and 2-Cl-substituted pyridines afforded the Cl-substituted product **3ah** as the sole product in standard condition. Interestingly, 5-fluoro-4-iodopyrimidines were converted into thieno[3,2-*d*]pyrimidines **3ai** in moderate yields. This practical reagent encapsulation method might be useful for further exploration of the total synthesis of thieno[3,2-*d*]pyrimidine-based pharmaceuticals and natural products.[18]

Scheme 3 Synthesis of high substituted thiophenes[a,b]

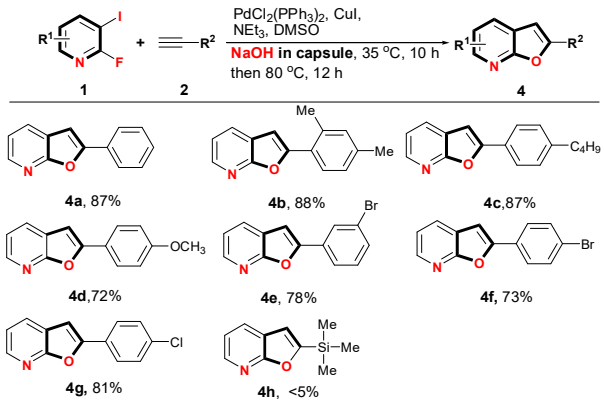


[a] Reaction conditions: fluoroiodopyridine **1** (1.0 mmol), terminal alkyne **2** (1.3 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N (4.0 mmol), EtOC(S)SK (2.0 mol) in paraffin wax capsule, DMSO (2 mL) at 35 °C for 10 h, then 90 °C for 12h. [b] Yields are given for isolated products.

Finally, the transformation of *ortho*-fluoroiodopyridine and terminal alkynes to the 2-arylfuro[2,3-*b*]pyridines derivatives is highly efficicent under a reagent-capsule-assisted annulation process. As shown in Scheme 4, the reagent-capsule-assisted substitution and *O*-cyclization syntheis of furo[2,3-*b*]pyridine derivatives in moderate to good yields. Unfortunately, the reaction with ethynyltrimethylsilane only affords chaotic system in strong alkali condition.

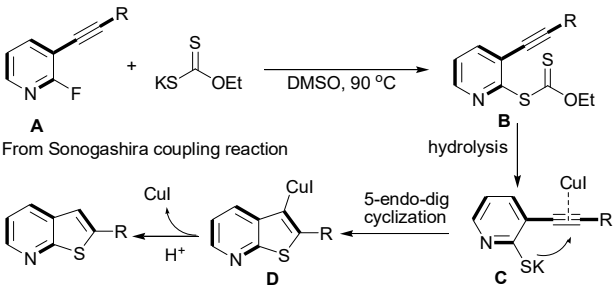
The postulated reaction mechanism for the synthesis of thienopyridines is proposed in Scheme 5. Initially, there will be a nucleophilic substitution of *ortho*-fluorinated iodopyridines **A** with EtOC(S)SK provide intermediate **B**[9]**.** The corresponding pyridyl thiolate **C** is *in situ* generated through the hydrolysis of **B**[19], which then undergoes intramolecular cyclization generates thienopyridine products with the aid of CuI.

Scheme 4 Synthesis of 2-arylfuro[2,3-*b*]pyridines[a,b]



[a] Reaction conditions: flouroiodopyridine **1** (1.0 mmol), terminal alkyne **2** (1.3 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N (4.0 mmol), DMSO (2 mL) and paraffin wax capsule (NaOH (2.0 mmol) at 35 °C for 10 h, then 80 °C for 12 h. [b] Yields are given for isolated products.

Scheme 5 Proposed mechanism for the cyclization reaction



In conclusion, an efficient and practical palladium-catalysed cross-coupling, thiolation and cyclization method for preparing functionalized thienopyridines and related heterocycles in a one-pot synthetic process that makes use of a reagent capsuleis was reported. This coupling and cyclization method displays a variety of substrate scope and well tolerance of functional groups. The use of reagent encapsulation methods helped reduce operational procedure and purification of intermediates, especially greatly promoting the development of environmentally friendly multicomponent reaction.

Acknowledgements

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