Microwave-assisted synthesis utilizing solid-supported reagents: A rapid and versatile technique in multi-step organic synthesis and purification

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Introduction

Bound reagents are functional polymers designed to perform synthetic transformations in same way as their solution counterparts. In this technique excess reagent and by-products remain attached to the solid, while product is in solution. Possible advantages of this technique are facile monitoring of reaction progress while reducing purification bottleneck. The disadvantage of this technique is the relative slow rate of reaction. Microwave irradiation has been used to overcome this problem and increase rate of reaction of solid-assisted solution phase synthesis. This presentation covers few examples of this technique in developing efficient and robust methods for the preparation of biologically interesting compounds, by using microwave heating in conjunction with PS-carbodiimide, PS-Ph_3Pd, PS-DIEA, Si-Carbonate, Si-Thiol, and Si-triamine.

Amide synthesis: Polymer supported Carbodiimide (PS-Carbodiimide)[1] has been used for rapid synthesize of amides from carboxylic acids and amines within 5 minutes using microwave irradiation followed by quick purification using Si-Carbonate (figure 1).

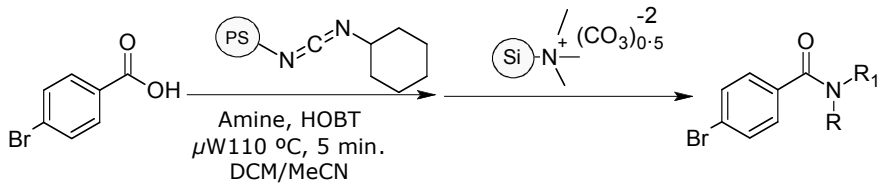
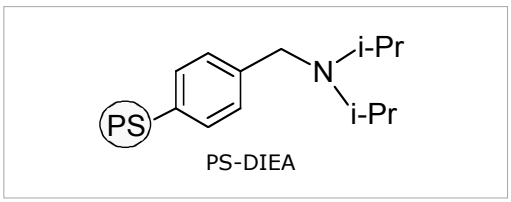


Figure 1

This technique is an excellent protocol for the synthesis of amides in high yield and purity from a broad range of primary amines with a variety of carboxylic acids. However, in case of less reactive aromatic amines low yield and purity of product has been reported. Acylation of secondary amines and anilines is usually a low yielding reaction which requires column chromatography for the separation of product from the reaction mixture. We have investigated a method for the synthesis and purification of amides from less reactive aromatic amines without the need for chromatography. Here we report the best yield and purity for the acylation of hindered amides and anilines employing a combination of 2-(7-Aza-1H-benzotriazole-1-yl)-1, 1, 3, 3-tetramethyluronium hexafluorophosphate (HATU)[3] with polymer bonded-tertiary amine, *N, N*-(diisopropyl) aminomethylpolystyrene (PS-DIEA)[4] using MAOS.



PS-DIEA

A small library of aryl carboxamides[2] (key pharmacophore elements in drug) was prepared in a rapid two-step SASPS in conjunction with microwave heating. The aryl carboxamides were prepared by amide synthesis reacting secondary amines and aniline with 4-bromobenzoic acid.

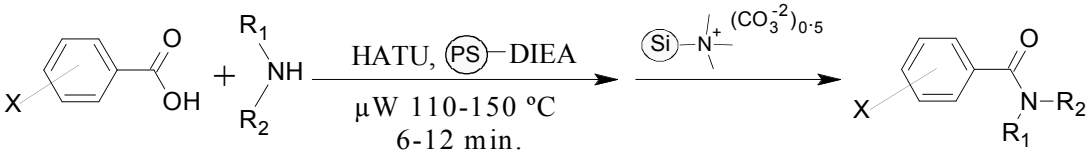
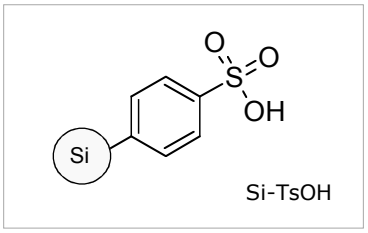
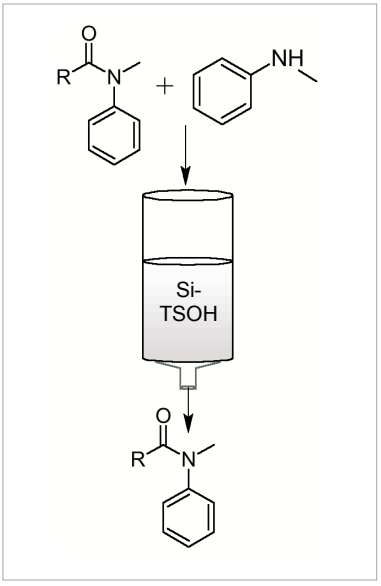


Figure 2

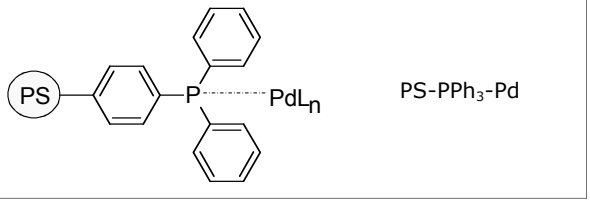
The combination of MAOS with HATU/ PS-DIEA resulted in higher purity and yield of these amides compared to PS-DCC/ HOBT or HATU/ DIEA under similar conditions. The final products were isolated from the reaction mixture by filtering through a short column of Si-Carbonate under gravity, which scavenged the excess 4-bromobenzoic acid.

Si-benzenesulfonic acid [3] has been used for fast removal of un-reacted hindered anilines such as *N*-methyl and benzyl aniline. In these instances the un-reacted anilines were removed by filtering the reaction mixture through a short column of Si-benzenesulfonic acid.





Aryl-aryl bond formation: Added diversity was introduced into these aryl carboxamides using microwave assisted palladium-catalyzed cross coupling (Suzuki reaction) using polystyrene bound triphenylphosphine palladium (PS-PPh_3-Pd)[4], the bound equivalent of the tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$)



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This bonded reagent has similar scope and reactivity to its small molecule counterpart with the added advantage of being air stable and, hence, easy to store and handle making them highly amenable for both routine and automated synthesis. The palladium levels in the products from PS-PPh_3-Pd catalyzed reactions were found to be in the 50-100 ppm range whereas $Pd(PPh_3)_4$ catalyzed reactions gave palladium levels in the 1000-1700 ppm range. Application of this reagent in conjunction with microwave heating has been reported for successful, rapid and efficient Suzuki reaction[5]. Here we report excellent yields and purities using PS-PPh_3-Pd/ $CsCO_3$ in EtOH/DME at 130 ºC (microwave) for 10 minutes. A simple filtration of the mixture through a short column of Si-TMA$(CO_3^{2-})_{0.5}$ afforded the final product in excellent yields and purity (figure 3).

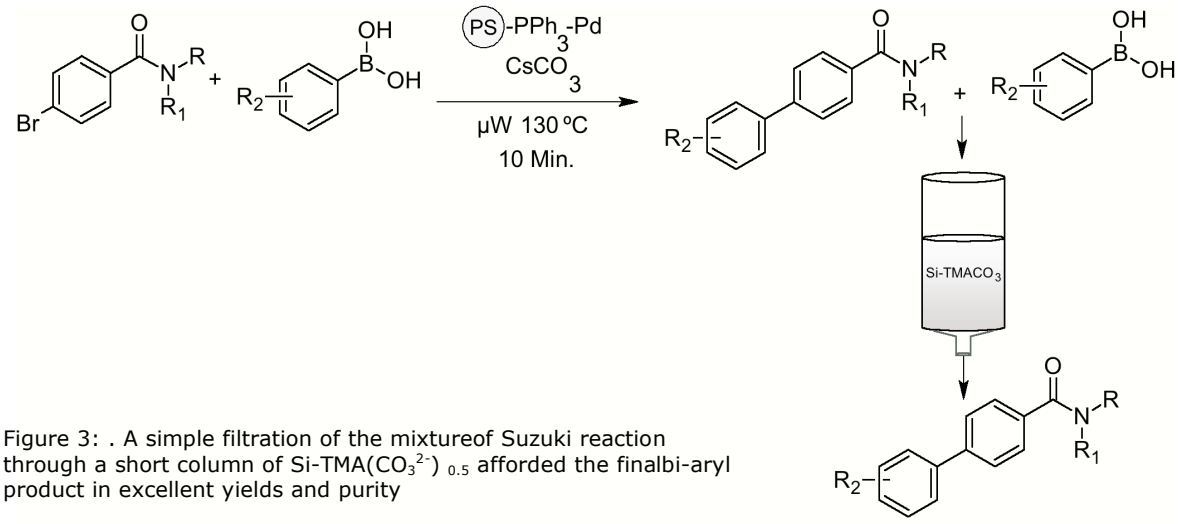
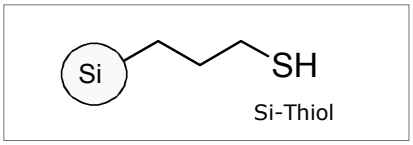
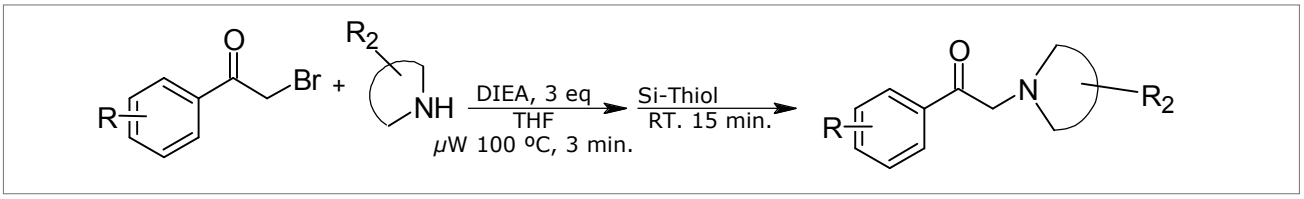


Figure 3: . A simple filtration of the mixtureof Suzuki reaction through a short column of Si-TMA$(CO_3^{2-})_{0.5}$ afforded the finalbi-aryl product in excellent yields and purity

Synthesis and clean–up of cyclic tertiary amines: An array of cyclic tertiary amines prepared by alkylating cyclic secondary amines with excess 2-bromo-acetophenones using DIEA as base in THF. For fast purification the excess 2-bromo-acetophenones was scavenged using Si-Thiol.

Si-Thiol is a silica-bonded equivalent of 1-propanethiol , This bounded reagents is useful for the covalent scavenging of alkyl, benzyl, and allyl halides as well as a variety of electrophiles, including acid chlorides, and isocyanates.





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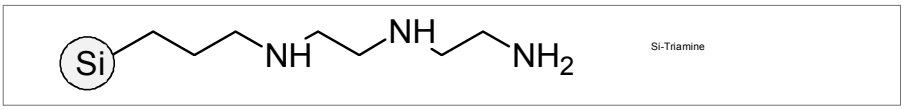
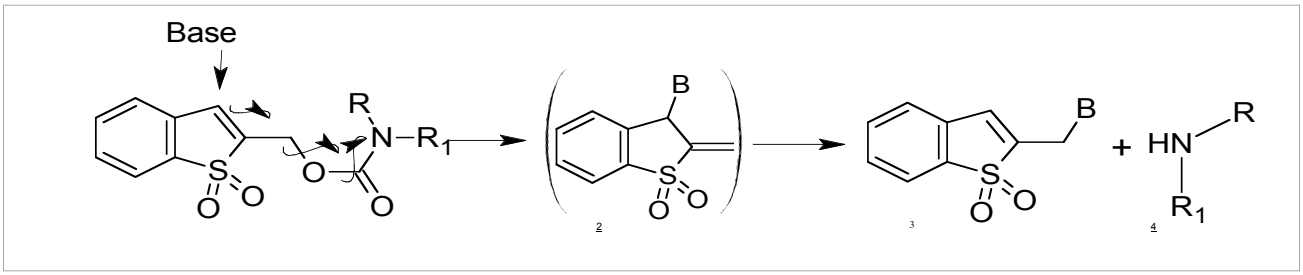
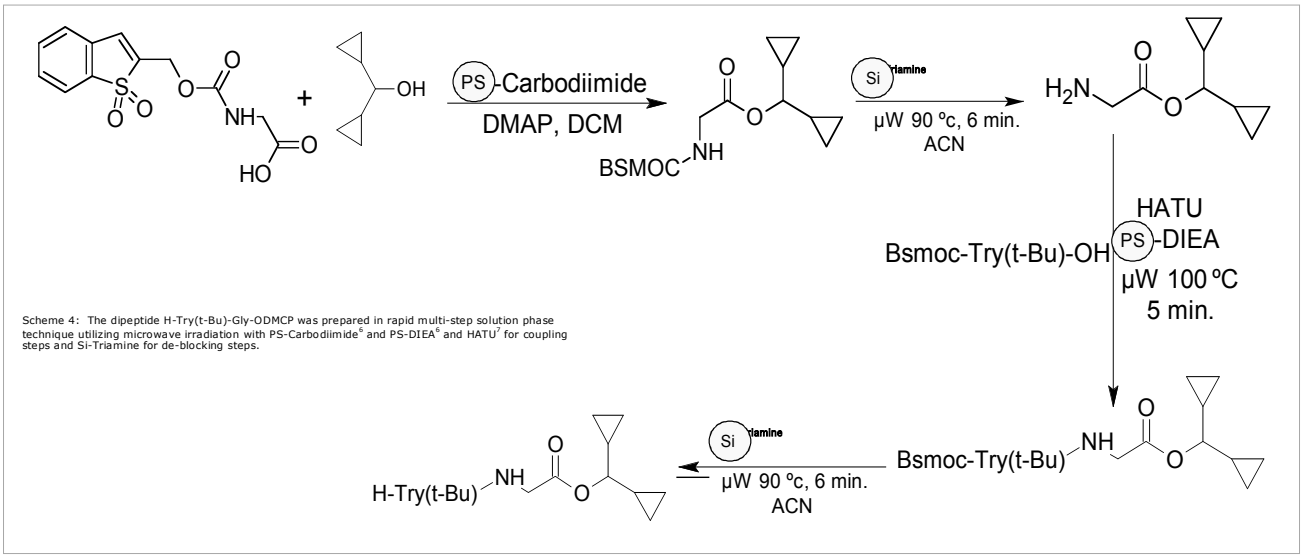
Simultaneous de-blocking and scavenging of 1,1-dioxobenzo[b]thiophene-2-ylmethyloxycarbonyl: 1,1-dioxobenzo[b]thiophene-2-ylmethyloxycarbonyl (Bsmoc)[i] (1) is a base sensitive amino protecting group used commonly in rapid solution phase peptide synthesis. Michael-like addition of the base to the Bsmoc thiophene ring results in cleavage of the Bsmoc-urethane bond, releasing the free amine (4) and a reactive intermediate (2) which rearranges to the stable by-product (3). Traditionally, the Bsmoc-urethane bond is cleaved upon stirring the Bsmoc-amine with tris(2-aminoethyl)amine (20 equiv) at room temperature for 15 minutes

followed by reaction workup, which involves several extractions with saturated NaCl. The use of ISOLUTE® Si-Triamine for Bsmoc- removal eliminates the aqueous extraction steps required for workup.







Scheme 4: The dipeptide H-Try(t-Bu)-Gly-ODMCP was prepared in rapid multi-step solution phase technique utilizing microwave irradiation with PS-Carbodiimide[6] and PS-DIEA[6] and HATU[7] for coupling steps and Si-Triamine for de-blocking steps.

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Conclusion

Solution phase synthesis employing solid supported reagents and scavengers in combination with MAOS has received greater importance and will become significant techniques in speeding up the drug development process, especially since in this protocol all aqueous washes and chromatography purification step have been eliminated.

References

1. Bettinetti, L.; LÖber, S.; Hübner, H.; Gmeiner, P., J*. Comb. Chem.* 200**5**, Vol. *7,* 309-316
2. Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721-4724
3.Carpino, L.A.; El-Faham, A.; *J. Am. Chem. Soc.;* **1995,** Vol. 117 No. 19, 5401-5402
4.Technical note and additional information available at **{** HYPERLINK "http://www.biotage.com/DynPage.aspx?id=800279#Polymer" **}**
5.Wang, Y.; Sauer, D, R. *Org. Lett.* **2004**, *6*, 2793-96

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