Microwave Energy in Accelerating Reaction Rate of Solid-Assisted Solution Phase Synthesis

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Introduction

Solid-Assisted Solution Phase Synthesis (SASPS) is a technique where the target molecule is synthesized in solution and solid-supported molecules are used as reagents, catalysts or scavengers. Recently this technique has been getting a lot of attention as an alternative to solid phase organic synthesis (SPOS), since it offers many of the advantages of SPOS in terms of ease of reaction workup and product purification in addition to the advantages associated with traditional solution-phase chemistry (e.g. the ease of monitoring the progress of the reaction by simply applying LC-MS or TLC techniques). A disadvantage of this technique is the relative slow reaction rate, and many of these reactions are sluggish and require hours for complete conversion. The advent of Microwave-Assisted Organic Synthesis (MAOS) has helped accelerate these reactions and the technique is gaining rapid popularity as evidenced by the increasing number of publications on this topic. The polymer backbones are in general, stable at the high temperatures used with MAOS for the short periods of time required for most of these reactions. This technique is particularly well-suited for automation and can easily incorporate in-line purification protocols, such as reagent and byproduct scavenging and catch-and-release. This introduces the possibility of direct high-throughput synthesis of compounds with intrinsically high purities suitable for biological screening without the need for further purification.

A small library of aryl carboxamides[1] (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; increased diversity was added to these compounds by aryl-aryl bond formation using the MAOS Suzuki reaction. Also Si-TMA$(CO_3^{2-})_{0.5}$ (a silica-bonded equivalent of tetramethylammonium carbonate) was used for fast removal of excess carboxylic and boronic acids (used in excess to push these reactions to completion) (figure 1). This protocol can be employed in an automated drug design process.

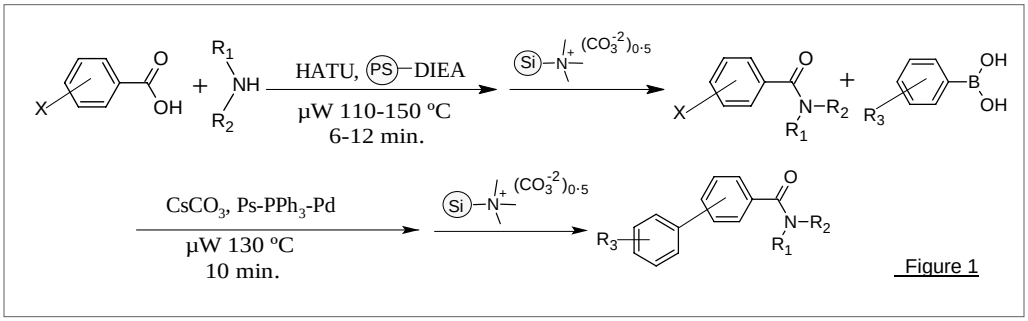


Figure 1

Amide synthesis: Polymer supported Carbodiimide (PS-Carbodiimide)[2] has been used for rapid synthesize of amides from carboxylic acids and amines within 5 minutes at 100 °C, using microwave irradiation followed by quick purification using Si-Carbonate (figure 2).

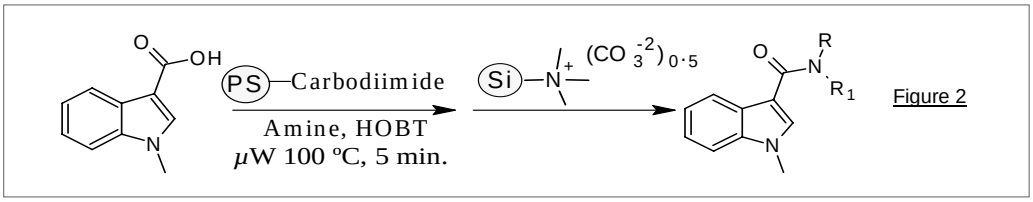
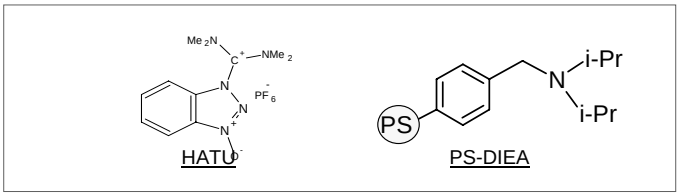
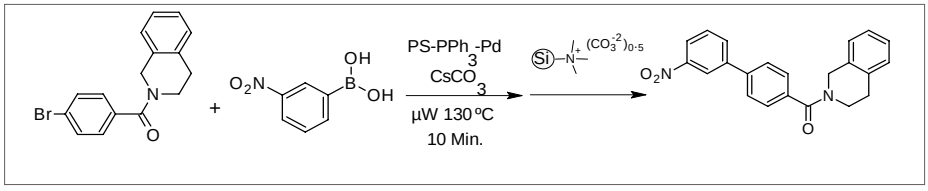


Figure 2

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.





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 that was used to push reaction to completion. Complete conversion to amide wasn't achieved in case of *N*-methyl aniline and benzyl aniline even at a higher temperature and longer reaction time (compounds 5 and 6). In these instances the un-reacted anilines were removed by filtering the reaction mixture through a short column of SCX (Si-benzenesulfonic acid)[4] and the resulting amides were used directly (without any further purification) in the next step (table1).

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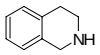
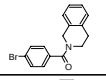
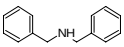
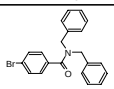
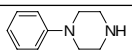
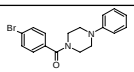
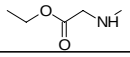
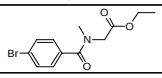
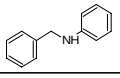
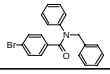
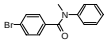
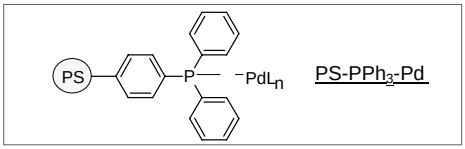
	Amine	Carboxamides	Condition	% Yield [a]	MS M+1 [b]
1			110 ºC, 6 min.	99	316
2			110 ºC, 6 min.	91	379.9
3			110 ºC, 6 min.	97	344.9
4			110 ºC, 6 min.	90	299.9
5			150 ºC, 12 min.	57	365.8
6			150 ºC, 12 min.	59	289.9

Table 1. Reactions were performed in the Biotage EMRYS™ Liberator microwave system in 2-5 mL reaction vials at 110-150 °C. [a] Yield and purity determined by LC/MASS with UV(220 and 254 nm). [b] LC/MASS was carried out on a XTerra® MS C18 3x50 mm, 3.5 µm, Mobile phase: A: 0.5 mM CH_3COONH_4 in 5% MeCN, B: 0.5mM CH_3COONH_4 in MeCN, Gradient: 10 to 100 B in 5 min. Micromass® ZQ Waters.

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



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).

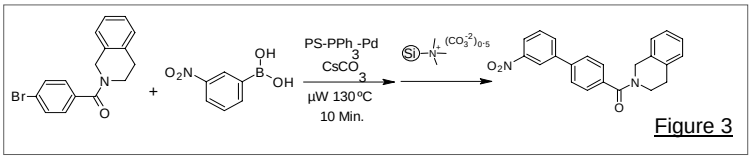


Figure 3

e amides (1-6) were reacted with 3-nitro , 4-methoxy, 4-methyl boronic acids to yield aryl carboxamides (7-14) (table 2).

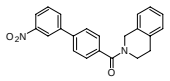
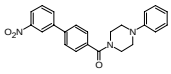
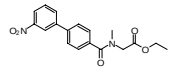
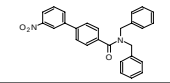
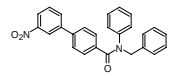
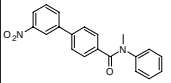
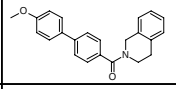
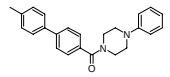
	Carboxamides	% isolated Yield [a]	MS M+1 [b]
7		99	359
8		89	388
9		85	344
10		96	423
11		95	409
12		97	333
13		99	344
14		99	356

Table 2. Reactions were performed in the Biotage EMRYS™ Liberator microwave system in 2-5 mL reaction vials at 130 °C for 10 min.. [a] Yield and purity determined by LC/MASS with UV(220 and 254 nm). [b] LC/MASS was carried out on a XTerra® MS C18 3x50 mm, 3.5 µm, Mobile phase: A: 0.5 mM CH_3COONH_4 in 5% MeCN, B: 0.5mM CH_3COONH_4 in MeCN, Gradient: 10 to 100 B in 5 min. Micromass® ZQ (Waters).

Conclusion

SASPS in conjunction with microwave heating has been employed for rapid and efficient preparation of a small library of aryl carboxamides through an amide and Suzuki synthesis. Excess carboxylic and boronic acids were effectively scavenged by Si-carbonate. This protocol is convenient for library generation since 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 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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