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Microwave-Assisted Synthesis Utilizing Supported Reagents: A Rapid and Efficient Acylation Procedure

Daryl R. Sauer,* Douglas Kalvin, and Kathleen M. Phelan

High-Throughput Organic Synthesis Group, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064-6113

daryl.r.sauer@abbott.com

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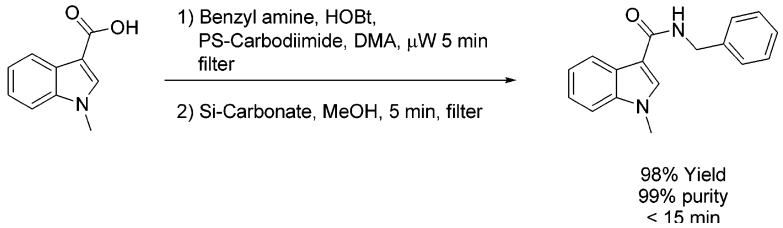
ABSTRACT



The application of microwave heating to a polymer-assisted solution-phase (PASP) synthesis technique has been utilized to develop a rapid and efficient protocol for the solution-phase synthesis of amides from either amine or carboxylic acid cores.

The use of polymer-supported reagents for the solution-phase synthesis of individual compounds or libraries of analogues has become an increasingly utilized tool for the preparation of molecules of biological interest.[1] One reason for this increase stems from the increased realization that PASP technology provides a convenient method of performing chemical transformations with minimal workup. In addition, an ever increasing array of commercially available polymer-supported reagents has become more readily available for both synthesis and purification[2] via solid-phase extraction (SPE) thereby making the technology more accessible.

In a high-throughput organic synthesis (HTOS) environment PASP synthesis is attractive since excess amounts of reagents can be used to enhance chemoselectivity and drive reactions to completion. This results in libraries being produced in higher purity, which is beneficial for the development of robust SAR in medicinal chemistry studies. This is also beneficial when subsequent modifications or additional purification is required. In addition, when using PASP chemistry techniques reactions can be easily monitored in real time by conventional methods. Last, PASP technologies are often suitable for automation, a highly desirable feature in a high-throughput laboratory.

The preparation of analogues and libraries via the formation of an amide bond, using both amine and carboxylic acid cores, is a staple in the repertoire of the medicinal chemist. In our efforts to develop robust, high-yielding, chemoselective transformations suitable for automated synthesis we have utilized the polymer-supported reagent PS-carbodiimide[3] to prepare libraries in which an amide bond is used to functionalize the molecule. An example of the conditions traditionally used in our laboratories is depicted in Scheme 1 as illustrated for the transformation of **1** to **2**.[4] Similar conditions have been reported for 1-hydroxybenzotriazole

(1) For recent examples see: (a) Senten, K.; Danieels, L.; Van der Veken, P.; De Meester, I.; Lambeir, A.-M.; Scharpe, S.; Haemers, A.; Augustyns, K. *J. Comb. Chem.* **2003**, *5*, 336−344. (b) South, M. S.; Dice, T. A.; Girard, T. J.; Lachance, R. M.; Stevens, A. M.; Stegeman, R. A.; Stallings, W. C.; Kurumbail, R. G.; Parlow, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2363−2367. (c) South, M. S.; Case, B. L.; Wood, R. S.; Jones, D. E.; Hayes, M. J.; Girard, T. J.; Lachance, R. M.; Nicholson, N. S.; Clare, M.; Stevens, A. M.; Stegeman, R. A.; Stallings, W. C.; Kurumbail, R. G.; Parlow, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2319−2325. (d) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1166−1170. (e) Vickerstaffe, E.; Warrington, B. H.; Ladlow, M.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 2419−2422. (f) Yun, Y. K.; Porco, J. A., Jr.; Labadie, J. *Synlett* **2002**, 739−742.

(2) (a) Flynn, D. L.; Devraj, R. V.; Naing, W.; Parlow, J. J.; Weidner, J. J.; Yang, S. *Med. Chem. Res.* **1998**, *8*, 219−243. (b) Flynn, D. L.; Devraj, R. V.; Parlow, J. J. *Curr. Opin. Drug Dis. Dev.* **1998**, *1*, 41−50. (c) Weidner, J. J.; Parlow, J. J.; Flynn, D. L. *Tetrahedron Lett.* **1999**, *40*, 239−242.

(3) Argonaut Technologies, http://www.argotech.com.

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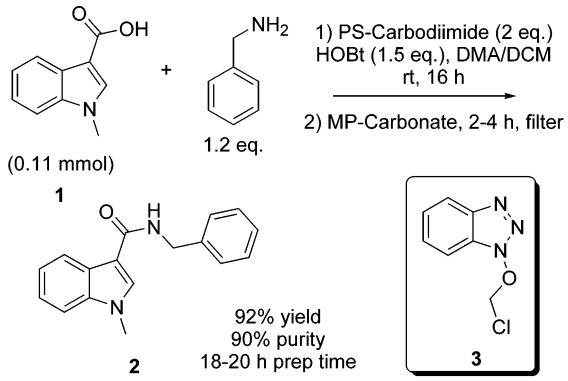
Scheme 1. Room Temperature Polymer-Assisted Acylation Protocol Utilizing PS-Carbodiimide and MP-Carbonate SPE



(HOBt) catalysis optimization studies,[5] design of experiment studies,[6] and analogue synthesis[1a−c,7] for SAR development. All of the synthetic conditions reported to date have been conducted at ambient temperature. We have found that when coupled with the use of SPE using the polymer-supported reagent MP-carbonate,[3] to sequester excess HOBt and any unreacted acid, the amide product can be isolated in good yield and purity.

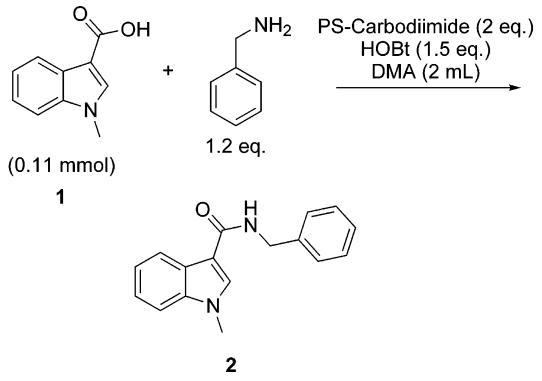
Microwave-assisted chemistry is also emerging as a powerful tool in combinatorial chemistry and drug discovery.[8] The combination of speed, control of reaction parameters, and automation makes this technology ideally suited for a high-throughput environment in which optimal reaction conditions are highly advantageous. With this in mind we sought to investigate the use of microwave-assisted chemistry to enhance the speed of the transformation described in Scheme 1. Initial experiments demonstrated that dichloromethane (DCM), commonly used for PASP chemistry due to its good resin swelling properties, would be incompatible to the heated reaction environment since it quantitatively alkylated HOBt when the reaction was conducted at even slightly elevated temperatures (i.e. 55 °C). This resulted in incomplete reactions due to the consumption of the catalyst HOBt as well as contamination of the desired amide by the resulting byproduct (**3**).[9] Therefore the use of DCM was terminated in this protocol and subsequent studies were performed in dimethylacetamide (DMA) or *N*-methylpyrrolidinone (NMP).

When using DMA as the reaction solvent it was found that at ambient temperature the reaction did not proceed to completion after 24 h (entries 1−4, Table 1); however, when heated in an oil bath the reaction was complete after 2 h at 55 °C and 15 min at 110 °C (entries 5 and 6, Table 1).

Under microwave heating conditions[10] it was found that the conversion of **1** to **2** could be accomplished quantitatively in 5 min at 110 °C (entry 7, Table 1). Attempts to conduct the reaction at 150 °C for 5 min (entry 8, Table 1), or longer, resulted in only partial conversion, presumably a consequence of the known thermal sensitivity of the *O*-acylisourea intermediates.[11]

It was also found that the use of HOBt was critical for reactions carried out at both ambient temperature and elevated temperatures as significantly reduced amounts of product were formed in its absence (Table 2). It has been

Table 1. Effect of Microwave Heating on the PASP PS-Carbodiimide Acyation Reaction



entry	time (min)	temp (°C)	conversion[d] (%)
1[a]	120	22	22
2[a]	240	22	49
3[a]	480	22	90
4[a]	1440	22	98
5[b]	120	55	100
6[b]	15	110	100
7[c]	5	110	100
8[c]	5	150	55

[a] Ambient temperature. [b] Oil bath. [c] Microwave. [d] Conversion by LC/MS with UV (220 and 254 nm) and ELSD detection.

Table 2. Effect of Added HOBt on PS-Carbodiimide Mediated Conversion of **1** to **2**[a]

entry	time (min)	temp (°C)	HOBt (equiv)	conversion[b] (%)
1	120	22	0	<5
2	120	22	1	20
3	60	55	0	<5
3	120	55	0	66
4	60	55	1	95
5	5	100 (μW)	0	0
6	5	100 (μW)	1	100

[a] Reaction conditions: 0.11 mmol of **1**, 1 equiv of benzylamine, indicated amount of HOBt, and 2 equiv of PS-carbodiimide in 2 mL of DMA at the time and temperature indicated. [b] Conversion determined by LC/MS with UV (220 and 254 nm) and ELSD detection.

(4) All synthetic compounds described were characterized by LC/MS, ^{1}H NMR, ^{13}C NMR, and HRMS.

(5) Lannuzel, M.; Lamothe, M.; Perez, M. *Tetrahedron Lett.* **2001**, *42*, 6703−6705.

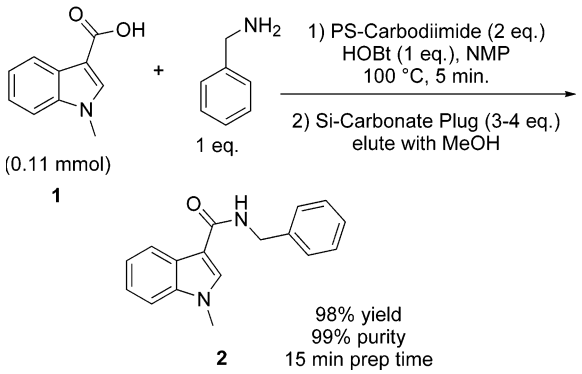
(6) Jamieson, C.; Congreve, M. S.; Emiabata-Smith, D. F.; Ley, S. V. *Synlett* **2000**, 1603−1607.

(7) South, M. S.; Dice, T. A.; Parlow, J. J. *Biotechnol. Bioeng.* **2000**, *71*, 51−57.

(8) (a) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (b) Kappe, C. O. *Curr. Opin. Chem. Bio.* **2002**, *6*, 314−320. (c) Dzierba, C. D.; Combs, A. P. *Annu. Rep. Med. Chem.* **2002**, *37*, 247−256. (d) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251−1283. (e) Blackwell, H. E. *Org. Biomol. Chem.* **2003**, *1*, 1251−1255.

reported that at ambient temperature 1.5 equiv of HOBt is required to drive the acylation reaction to completion;[5] however, under the microwave-assisted heating conditions employed in Scheme 2 the use of 1 equiv of HOBt proved sufficient to achieve complete conversion.

Scheme 2. Microwave-Accelerated Polymer-Assisted Acylation Protocol Utilizing PS-Carbodiimide and Si-Carbonate



The use of SPE is particularly well suited for this reaction since in many cases the only detectable material observed in the crude reaction mixture, other than product, was the added catalyst HOBt. In practice it was found that treatment of crude reaction mixtures with 3 equiv of MP-carbonate for 4 h completely sequestered the HOBt catalyst (Table 3)

Table 3. Solid-Phase Extraction Utilizing Polystyrene and Silica-Based Supports[a]

entry	SPE media	time (min)	HOBt removed[b] (%)
1	MP-carbonate	120	77
2	MP-carbonate	240	100
3	Si-carbonate	5	100

[a] Reaction conditions: See Table 2, entry 6. The reaction was then diluted with 2 mL of MeOH and shaken (200 rpm) with 3 equiv of the SPE reagent for the time indicated and filtered. [b] HOBt sequestration determined by LC/MS and verified by ^{1}H NMR.

resulting in the isolation of product in a highly pure state. This corresponds with previously reported studies involving MP-carbonate to scavenge HOBt.[5,12] We found that this process could be dramatically accelerated by taking advantage of the increased reagent surface area of silica gel-based SPE material vs MP-carbonate polystyrene resin. As shown in Table 3, the increased reaction kinetics achieved with use of Si-carbonate[13] reduces the time required to completely sequester HOBt to 5 min. The SPE step can be accomplished by shaking the reaction mixture with the Si-carbonate and filtering, or more conveniently, by passing the reaction mixture through a plug of the SPE material. This process greatly reduces the overall time required for the SPE phase of the protocol. In fact, by combining the microwave-assisted PASP chemistry with the silica-based SPE both synthesis and purification can be routinely accomplished in less than 15 min at the bench. In addition, as shown in Table 4 (entry 1), the products are isolated in high yield and purity. It should be noted that the speed and efficiency of the sequestration step allows for the use of a slight excess of the carboxylic acid component and the HOBt catalyst if desired. This ensures that sufficient quantities of reagents are available in the reaction mixture, an important consideration when compensating for the inherent variability associated with the use of automated reagent dispensing equipment.

Table 4. Solvent Effect on PS-Carbodiimide-Mediated Conversion of **1** to **2**[a]

entry	solvent	conversion (%)	temp (°C)	purity[b] (%)
1	NMP	100	100	>99
2	DMA	100	100	>97
3	DMA	100	120	94
4	DMA/DIEA	100	100	>97
5	DME	100	100	>97
6	CH_3CN	100	100	>97

[a] Reaction conditions: 0.11 mmol of **1**, 1 equiv of benzylamine, 1 equiv of HOBt, and 2 equiv of PS-carbodiimide in 2 mL of the solvent listed were heated for 5 min at the temperature indicated. The reaction was diluted with MeOH (4 mL) and filtered through 1 g of Si-carbonate (0.7 mmol/g loading). [b] Purity determined by LC/MS with UV (220 and 254 nm) and ELSD detection and verified by ^{1}H NMR.

While the use of NMP as a solvent affords products in very high purity (Table 4, entry 1), its high boiling point precludes its use in some high-throughput environments. The use of DMA is acceptable at 100 °C (Table 4, entry 2); however, at 120 °C or higher formation of a considerable amount (~6%) of the dimethylamide derivative was observed as an impurity (Table 4, entry 3). This byproduct results from the thermal decomposition of DMA to form dimethylamine and subsequent reaction with the core HOBt active ester. The addition of DIEA has no detrimental effect on the outcome of the reaction (Table 4, entry 4) and may be used to facilitate the reaction of amines that are available as salts. The reaction may also be carried out in dimethoxyethane (DME) or acetonitrile (Table 4, entries 5 and 6) to facilitate solvent evaporation. Our laboratory has found a combination of DMA:CH_3CN to be exceptionally useful as it solubilizes a wide variety of substrates and facilitates the course of the reaction.

For the scale of the reactions described herein it was found that a minimum of 2 mL of solvent was required to

(9) The reaction of DCM and HOBt has been observed at ambient temperature after extended periods of time: Ji, J.-G.; Zhang, D.-Y.; Ye, Y.-H.; Xing, Q.-Y. *Tetrahedron Lett.* **1998**, *39*, 6515−6516.

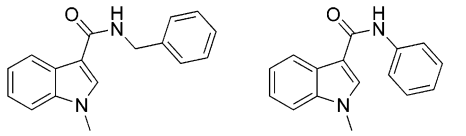
(10) All microwave reactions were performed on an Emrys Optimizer (Personal Chemistry, http://www.personalchemistry.com) without the use of continuous cooling. Wattage was automatically adjusted so as to maintain the desired temperature.

(11) Stadler, A.; Kappe, C. O. *Eur. J. Org. Chem.* **2001**, 919−925.

(12) Weidner, J. J.; Parlow, J. J.; Flynn, D. L. *Tetrahedron Lett.* **1999**, *40*, 239−242.

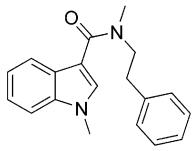
(13) SiliCycle, Inc., http://www.silicycle.com

Table 5. Microwave-Accelerated Polymer-Assisted Acylation Methodology[a] for the Preparation of Compounds **2** and **4**−**8**



2

4



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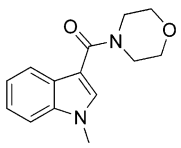

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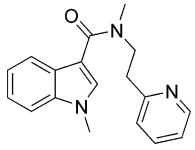

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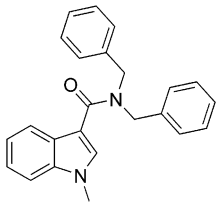

8

compd	yield (%)	purity[b] (%)	compd	yield (%)	purity[b] (%)
2	98	99	**6**	98	98
4	68[c]	100[c]	**7**	98	97
5	95	98	**8**	37[c]	100[c]

[a] Reaction conditions: 0.1 mmol of acid and amine, 1 equiv of HOBt, and 2 equiv of PS-carbodiimide in 2 mL of NMP heated to 100 °C for 5 min in the microwave. The reaction was then diluted with 4 mL of MeOH and filtered through 1 g of Si-carbonate (0.7 mmol/g loading) and washed with MeOH. [b] Purity was determined by LC/MS with UV (220 and 254 nm) and ELSD detection and verified by ^{1}H and ^{13}C NMR. [c] After purification by Si chromatography. While conversion to the HOBt ester was quantitative the ensuing amide formation proved to be the rate-limiting factor.

accommodate swelling of the PS-carbodiimide resin. Reactions were performed in Smith Process Vials designed for 2−5 mL solvent volumes. It was also found that the use of a stir bar facilitates suspension of the PS-carbodiimide resin and the mixing of reactions involving insoluble reagents. Due to the short reaction times, stirring does not promote significant mechanical degradation of the polymer support.

The scope of the reaction protocol (Scheme 2) is also quite general.[14] As shown in Table 5 the reaction conditions are amenable to primary, secondary, and aromatic amines. Significantly, less reactive amines, such as aniline and dibenzylamine, which give low (<10%) conversion at ambient temperature overnight, afford product in moderate yield in 5 min via the microwave-assisted protocol (Table 5, entries 4 and 8). As neither the amine nor acid component is required in excess amounts, the reaction protocol is also effective for amine cores thereby eliminating the need for separate acylation protocols for amine and acid derived libraries.

In summary, we have described a rapid, convenient, and high-yielding protocol for the preparation of amides from amines and carboxylic acids. The procedure utilizes commercially available reagents and equipment and is suitable for the preparation of individual analogues or automated library production. This procedure has become the method of choice for producing analogues for our High-Throughput Medicinal Chemistry efforts and has been used to prepare thousands of analogues from a variety of acid and amine cores.

Supporting Information Available: General experimental details as well as characterization data for compounds **2** and **4**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **General Procedure for the Preparation of Amides via Microwave Heating and Si−Carbonate SPE.** A Smith Process Vial (2−5 mL) was charged with a stir bar and 200 mg of PS-carbodiimide resin (1.2 mmol/g). To the vessel were added **1** (21 mg, 0.12 mmol) in NMP (0.7 mL), HOBt (16 mg, 0.12 mmol) in NMP (0.7 mL), and benzylamine (13 mg, 0.12 mmol) in NMP (0.7 mL). The reaction vessel was sealed and heated to 100 °C for 5 min in an Emrys Optimizer. After cooling the vessel was uncapped and the reaction mixture diluted with 2 mL of MeOH. The reaction mixture was transferred via pipet to a pre-packed column of Si-Carbonate (1 g, 0.7 mmol/g), which had been previously conditioned with MeOH, and the elutant collected via gravity filtration. The column was washed with MeOH (2 × 3 mL) and the solvent evaporated at reduced pressure to afford **2** (31 mg, 98%) as a white solid that was 98% pure by LC/MS analysis.