Pergamon

Tetrahedron Letters 43 (2002) 7221–7223

TETRAHEDRON LETTERS

A single vessel protocol for the efficient formation of amide bonds from esters and lactones

Noriyuki H. Kawahata, Jeseca Brookes and Gergely M. Makara*

NeoGenesis Pharmaceuticals, Inc., 840 Memorial Drive, Cambridge, MA 02139, USA

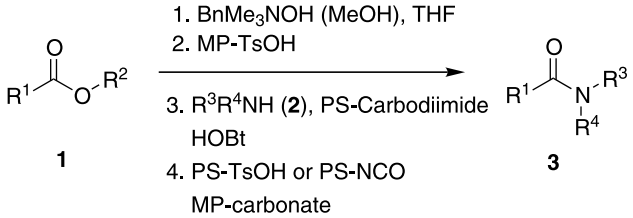
Received 1 July 2002; accepted 7 August 2002

Abstract—A single vessel solution phase protocol for the formation of amide bonds from esters or lactones has been developed. The process involves hydrolysis of the ester or lactone followed by amide bond formation utilizing resin-bound carbodiimide. Excess reagents and reactants are sequestered using polymer-supported scavengers to yield the desired products in high yields and purities without the need for extraction or chromatography.

The recent development of a variety of reagents attached to solid supports has brought about the expansion of the synthetic methodologies that can be used to populate compound collections.[1] The application of solution phase synthetic techniques towards combinatorial chemistry has allowed for the rapid development of combinatorial libraries possessing several advantages over those synthesized using solid phase techniques.[2] During development, these reactions can be easily monitored and do not require cleavage for unambiguous characterization of intermediates. A more efficient use of reactants is realized in solution phase chemistry as solid phase reactions often rely on excess reagents to drive the reaction to completion. Additionally, the diversity of the reactants in solution phase combinatorial chemistry is not limited by the cleavage conditions required to release the desired product from the solid support.

A large number of methodologies and reagents have been developed for the formation of amide bonds on solid phase.[3] The number and functional diversity of carboxylic acids and amines often make amide bond formation a diversification step of choice for the expansion and diversity of combinatorial libraries. The incorporation of amides in the middle of a synthetic scheme typically requires a carboxylic acid that is often protected as an ester. A recent report described the conversion of an ester or lactone to an amide using DIBAL–amine complexes.[4] Although this method is efficient and provides the desired products in high yields, the use of DIBAL limits the diversity of the functional groups that can exist on either the amine or the carboxylic acid components. The conversion of 2,2,2-trihaloethyl esters to amides using phosphorous(III) reagents was also accomplished in one-pot.[5] However, for this procedure to be effective, the 2,2,2-trihaloethyl ester would have to be synthesized due to the lack of a diverse set of commercially available trihaloesters. It is important to note that both of the above procedures utilize a chromatographic step to achieve high purities. Therefore, a flexible method that can be readily applied to the efficient syntheses of a large number of compounds in parallel without need for chromatographic purification was sought.

The use of esters as a starting point necessitated a hydrolysis protocol that would allow for an efficient sequestration of the by-products and excess reactants. Tetraalkylammonium hydroxides have previously been shown to affect the hydrolysis of esters.[6] Gratifyingly, it was found that both aliphatic and aromatic esters were readily hydrolyzed in THF at 50°C (Scheme 1). Treatment of the crude reaction mixture with polymer-bound



Scheme 1. One-pot formation of amide bonds utilizing polymer bound reagents and scavenging agents.

Keywords: polymer-supported; scavenger; parallel; ester; amide.

* Corresponding author. Fax: 617-868-1515; e-mail: gregm@neogenesis.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01657-X

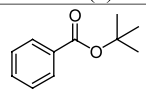
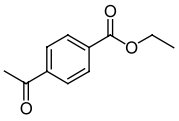
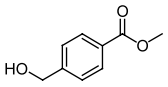
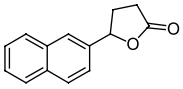
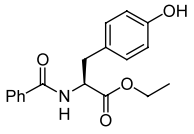
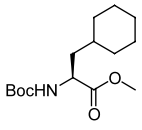
toluenesulfonic acid (MP-TsOH)[7] followed by filtration and concentration of the filtrate yielded the corresponding carboxylic acids in high yields and purities (data not shown).

In an effort to eliminate the filtration, washing and concentration steps prior to the amide-bond formation, the subsequent reaction was carried out in the same well by adding the amine, 1-hydroxybenzotriazole (HOBt) and polymer-bound carbodiimide resin[8,9] to the mixture (Scheme 1). Although the amides were formed with the carbodiimide resin alone, addition of HOBt significantly increased the final product yields and purities. The reaction was allowed to stir overnight at ambient temperature. The excess amine was scavenged using more MP-TsOH. Macroporous polymer-bound carbonate resin (MP-carbonate)[10] was used to extract HOBt[11] and any remaining carboxylic acid. Fortuitously, THF was found to be an appropriate solvent for both steps. Filtration and concentration yielded the desired products in high yields and purities.

The scope of the hydrolysis step was examined by treating a range of esters to the above conditions. The reactions were monitored by TLC and HPLC–MS, and the results are summarized in Table 1. Several of the coupling reactions incorporated an aromatic amine (**3b**,**d**,**f**,**h**) as well as a more reactive alkyl amine (**3a**,**c**,**e**,**g**,**i**,**j**).[12] Aryl esters, including the more hindered *tert*-butyl ester (**3a**,**b**) were cleanly hydrolyzed at 50°C in THF overnight and gave the subsequent amides at ambient temperatures. The method was tolerant to the presence of ketone and hydroxyl functional groups (entries **3c**–**f**). A butyrolactone (entry **3g**,**h**) was opened and reacted to give the corresponding lactams (as opposed to acyclic amides) with primary amines or anilines. Coupling chiral amines to acids derived from the hydrolysis of aliphatic esters (entries **3i**,**j**) at elevated temperatures resulted in the formation of two diastereomers (6.5:1). This is most likely the result of epimerization of the asymmetric center adjacent to the original ester as only one product was detected when an achiral amine was coupled to the subsequent carboxylic acid. Epimerization in the basic milieu was significantly reduced (10:1 diastereomeric ratio) by lowering the temperature of the hydrolysis step to 4°C. It is noteworthy that hydrolysis of aryl esters was incomplete at ambient temperatures but no remaining ester was detected with the more labile alkyl esters

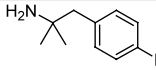
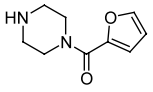
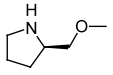
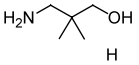
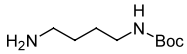
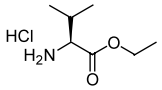
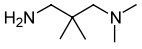
A family of amines was also successfully incorporated using this methodology as illustrated in Table 2. A hindered amine (**3k**), secondary amines (**3l**,**m**), Boc-protected amine (**3o**), and an amine containing a hydroxy group (**3n**) gave the desired amides in high yields and purities. Importantly, amines bearing an ester functionality (**3p**) gave the desired product in good yields. Thus, the quaternary ammonium hydroxide became completely deactivated by sequestration with MP-TsOH. This finding opens the avenue to the potential production of polyamides after a simple filtration. If the amine contains an ester moiety, the THF filtrate can conceivably be subjected to the same procedure to lead to

Table 1. Synthesis of amides (**3a**–**f**, **3i**,**j**) and lactams (**3g**,**h**) from a series of esters

Entry	Ester (**1**)	Amine[a]	Yield[b]	Purity[c]
3a		A	89%	99%
3b		B	98%	99%
3c		A	97%	95%
3d		B	93%	94%
3e		A	90%	95%
3f		B	82%	92%
3g[d]		A	89%	93%
3h[d]		B	96%	98%
3i[e]		C	88%	99%
3j[f]		C	75%	99%

[a] Amine A: 4-methylbenzylamine, B: *p*-anisidine, C: α-methylbenzylamine. [b] Isolated yield after filtration and concentration. [c] As determined by ELSD-HPLC of the desired ion. [d] Product is the corresponding lactam, no acyclic amide was detected. [e] Hydrolysis was performed at 4°C, 10:1 diastereomeric ratio (6.5:1 diastereomeric ratio at room temperature) was obtained. [f] Hydrolysis was performed at ambient temperatures, diastereomeric ratio was not determined due to poor resolution of isomers.

Table 2. Synthesis of amides (**3**) from a series of amines (**2**) and methyl 4-bromobenzoate

Entry	Amine (**2**)	Yield[a]	Purity[b]
3k		98%	99%
3l		98%	99%
3m		96%	99%
3n		93%	99%
3o		94%	99%
3p[c]		93%	98%
3q[d]		96%	99%

[a] Isolated yield after filtration and concentration. [b] As determined by ELSD-HPLC of the desired ion. [c] An equivalent amount of DIPEA was added for the coupling step and treated with twice the amount of TsOH resin during the scavenging step. [d] In this case, the excess amine was sequestered using PS-NCO.

diamides. Amine hydrochloride salts were incorporated by the addition of an equivalent of DIPEA during the coupling step and an equivalent amount of MP-TsOH for the scavenging step. The application of amines with basic groups (**3q**) is also tolerated by sequestering the excess amine with polymer-bound isocyanate (PS-NCO)[13] resin rather than MP-TsOH. The electrophilic sequestrant is required because the acidic resin would also sequester the product.

In conclusion, a single vessel conversion of esters to amides has been accomplished using polymer-supported reagents and scavengers. Our method also demonstrates how resin-bound reagents can be utilized to effectively carry out processes ordinarily requiring more rigorous purification.[14] The lack of filtration between the hydrolysis and amide bond-forming steps simplifies the application of this sequence towards parallel synthetic techniques. Development of hydrolysis conditions free of racemization of amino acids is currently under investigation in our laboratories.

References

1. (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815; (b) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S. *J. Am. Chem. Soc.* **1997**, *119*, 4874–4881.
2. Flynn, D. L. *Med. Res. Rev.* **1999**, *19*, 408–432.
3. Albericio, F.; Kates, S. A. In *Solid-Phase Synthesis*; Kates, S. A.; Albericio, F., Eds.; Marcel Dekker: New York, 2000; pp. 275–330.
4. Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, *42*, 9039.
5. Hans, J. J.; Driver, R. W.; Burke, S. D. *J. Org. Chem.* **1999**, *64*, 1430.
6. Kataky, R.; Nicholson, P. E.; Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1990**, 321.
7. Macroporous 30–60 mesh, Aldrich.
8. PS-Carbodiimide, 100–200 mesh, Argonaut Technologies.
9. Parlow, J. J.; Mischke, D. A.; Woodward, S. S. *J. Org. Chem.* **1997**, *62*, 5908.
10. MP-Carbonate, 18–52 mesh, Argonaut Technologies.
11. Weidner, J. J.; Parlow, J. J.; Flynn, D. L. *Tetrahedron Lett.* **1999**, *40*, 239–242.
12. Typical procedure (**3k**): Methyl 4-bromobenzoate (0.02 mmol) was dissolved in THF (1 mL) and benzyltrimethylammonium hydroxide (0.04 mmol, 20% in MeOH) was added. The solution was heated (55°C) for 18 h. The mixture was cooled to rt and MP-TsOH (0.05 mmol) was added. The mixture was agitated at rt for 3 h. The reaction was diluted with THF (0.5 mL) and α,α-dimethyl-3-(*p*-F-phenyl)ethylamine (0.1 mmol) and 1-hydroxybenzotriazole (0.04 mmol) were added. PS-carbodiimide (0.08 mmol) was then added and the mixture was agitated for 18 h at rt. MP-carbonate resin (0.12 mmol) and MP-TsOH (0.12 mmol) resin were added and the mixture was agitated for 8 h. The mixture was filtered and the resin was washed with THF (1.5 mL). The filtrate was concentrated to give **3k** (6.5 mg, 98%) in high purity (99% determined by ELSD-HPLC of the desired ion).
13. PS-Isocyanate, 100–200 mesh, Argonaut Technologies.
14. Parlow, J. J. *Tetrahedron Lett.* **1995**, *36*, 1395.