Pergamon

Tetrahedron Letters, Vol. 38, No. 11, pp. 1895-1898, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00245-1

Solid Phase Synthesis of Ureas of Secondary Amines via Carbamoyl Chloride

Gary T. Wang*, Yuanwei Chen, Sheldon Wang, Richard Sciotti and Thomas Sowin

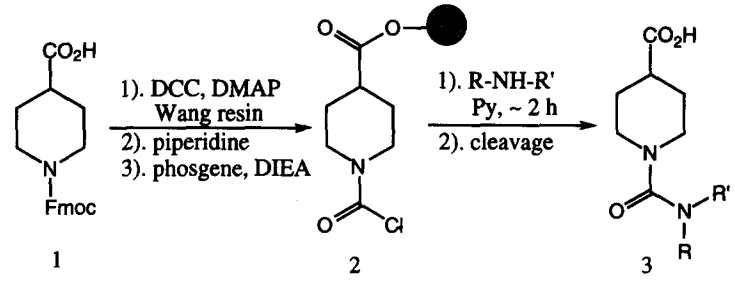
Department of Combinatorial Chemistry, Pharmaceutical Discovery
Abbott Laboratories, Abbott Park, IL 60064

Abstract:. Secondary amines attached to a solid support such as the Wang resin can be converted to the corresponding carbamoyl chlorides by treatment with phosgene or triphosgene. Further reaction of the resulting carbamoyl chlorides with primary or secondary amines affords ureas in high yield and chemical purity.

Solid phase organic synthesis, carried out either in combinatorial mode (mix and split synthesis) or parallel synthesis mode, is gaining wide acceptance as a way to increase the synthetic through-put in order to accelerate lead generation and optimization in drug discovery.[1] One of the remaining obstacles toward further progress is to expand the boundary of solid phase synthesis by developing new chemistry and extending known solution chemistry to solid phase. Rapid progress is being made in this area.[2-3] Recently, our work in solid phase synthesis of combinatorial libraries required formation of ureas of a secondary amine on solid support. Previously, Hutchins and Chapman described solid phase synthesis of ureas of primary amines on solid support via *p*-nitrophenylcarbamate intermediate.[4] However, this method does not work for secondary amines since *p*-nitrophenylcarbamates derived from secondary amines do not react with primary or secondary amine nucleophiles under normal conditions. Additionally, Burgess and coworkers reported the solid phase synthesis of ureas of primary amines on solid support via isocyanate intermediates.[5] Herein, we report that ureas of secondary amines on solid support can be formed in high yield and chemical purity through the intermediacy of carbamoyl chlorides.

We chose isonipecotic acid to demonstrate the feasibility of this chemistry (Scheme). Fmoc-protected isonipecotic acid **1** was coupled to *p*-benzyloxybenzyl alcohol resin (Wang resin) using dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine (DMAP) following the standard protocol.[6] The carbamoyl chloride **2** was then prepared according to the following procedure. In a typical experiment, Wang resin with Fmoc-isonipecotic acid (6.0 g, ~0.46 mmole/g) was treated with 50 mL of 20% piperidine in CH_2Cl_2 for 1 h, filtered, and then washed with CH_2Cl_2, DMF and CH_2Cl_2. The resin was then mixed with 9.0 mL of diisopropylethylamine and 30 mL of CH_2Cl_2 and the resulting slurry was added slowly to a cooled (0 °C) solution of phosgene (20% in toluene, 17.0 mL, 10 equiv. Caution: toxic).[7] After 10 min at 0 °C, the mixture

Scheme

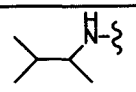
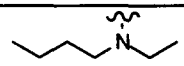
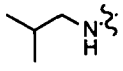
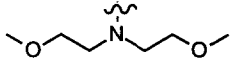
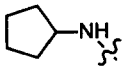
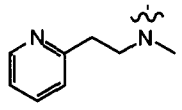
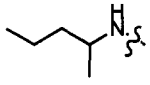
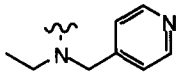
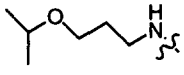
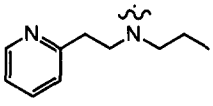
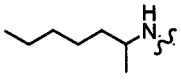
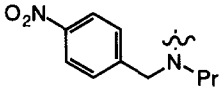
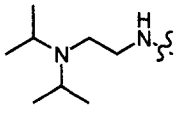
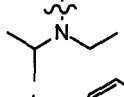
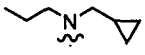
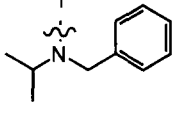
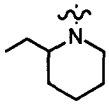
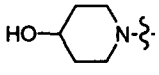
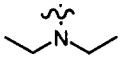
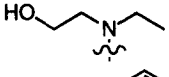
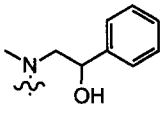
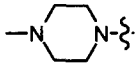
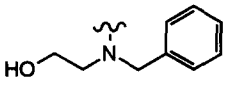


was shaken at ambient temperature for 2 h. The resin was then filtered and washed with CH_2Cl_2, *N*-methyl pyrrolidone (NMP), CH_2Cl_2, and dried.

Next, the reaction of the carbamoyl chloride resin **2** with a group of 24 representative amines was investigated on an automated multiple peptide synthesizer.[8] Thus, 80-100 mg of resin **2** was placed in each of the reaction vessels and mixed with 1.0 mL of CH_2Cl_2, 10 equivalents of the desired amine, and 10 equivalents of pyridine. After mixing for 2 h, the solution was drained and the resin was washed with CH_2Cl_2, NMP and CH_2Cl_2 (all automated). The resin was then treated with 80% trifluoroacetic acid in CH_2Cl_2 (1.5 mL for each reaction) for 1 h to effect cleavage. The solutions were then vacuum dried to yield the desired ureas, which were characterized by HPLC, mass spectroscopy and ^1H NMR. Expected molecular ions (M+H, or $M+NH_4^+$) were observed for all the products, in most case as the base peak. For HPLC analysis, an evaporative light scattering detector (ELS)[9] was used since many ureas synthesized (Table) contain no chromophores, rendering UV-detection ineffective.

In general, reaction of the carbamoyl chloride resin **2** with amines gives ureas in high yield and purity (Table), with the reactivity of the amine being the main determinant of the result. Essentially all mono-functional, primary aliphatic amines tested (entry 1-7) lead to formation of the disubstituted ureas (3, R'=H) in high yield (~100%) and >90% purity, even for relatively sterically hindered isopropyl-type amines (entry 1, 4, and 6). Anilines or severely hindered aliphatic primary amines such as *tert*-butyl amine give poor results. With secondary amines, steric hindrance becomes a more significant factor. Thus, unhindered secondary amines (entry 8-18) gives results that are even better than typical primary amines, whereas more sterically hindered secondary amines lead to inferior results (entry 19 and 20). Finally, reaction of unprotected β-hydroxyamines with the carbamoyl chloride resin **2** give rather poor results, presumably due to the poor nucleophilicity of β-hydroxyamines (entry 22-24). In model studies, alcohols did not react to any significant extent with the carbamoyl chloride resin. Consistent with this result, reaction of 4-hydroxypiperidine with resin **2** gave the corresponding urea very cleanly (entry 21).

Table: HPLC Purity of 3 Synthesized via Carbamoyl Chloride in Solid Phase

Entry	Amine	HPLC Purity	Entry	Amine	HPLC Purity
1		95.8%	13		100%
2		94.1%	14		100%
3		96.0%	15		100%
4		96.6%	16		93.5%
5		100%	17		100%
6		97.6%	18		100%
7		99.9%	19		87.0%
8		94.7%	20		70.2%
9		95.9%	21		100%
10		94.6%	22		55.0%
11		100%	23		68.5%
12		100%	24		57.0%

The methodology of solid phase urea formation described in this paper provides a simple and effective way to prepared ureas when a secondary amine is attached to the resin. We have applied this procedure to a number of different substrates including pyrrolidines and tetrahydroisoquinolines on solid support in both parallel synthesis as well combinatorial synthesis, all with satisfactory results.

References:

1. Reviews: (a). Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144-154. (b) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132-143. (c). Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233-1251. (d). Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P.A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385-1401.
2. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600
3. Hermkens, P. H. H.; Ottenheilm, H. C., Rees, D. *Tetrahedron* **1996**, *52*, 4527-4559.
4. (a) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055-4058. (b) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 2583-2586.
5. Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 907-909.
6. We thank Dr. Doug Kalvin for a sample of Fmoc-isonipecotic acid.
7. The reaction has also been performed successfully using triphosgene following a slightly different procedure. To preswelled resin (50-100 mg) in DCM (1-2 mL) at room temperature was added diisopropylethyl amine (10 equivalents) followed by triphosgene (3 equivalents). The reaction was allowed to shake for 1-1.5 hours then drained, washed with DCM (4X), then dried under vacuum.
8. An Advanced ChemTech Model 396 multiple peptide synthesizer was used. This instrument allows 96 parallel reactions with 60 individual monomers (starting materials).
9. The signal of evaporative light scattering detection is independent of the absorption spectrum of the analyte. Elfakir, C.; Lafosse, M.; Dreux, M. *J. Chromatography* **1990**, *513*, 354-359.

(*Received in USA* 12 *November* 1996; *accepted* 29 *January* 1997)