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A New Cleavage Strategy for the Solid-Phase Synthesis of Secondary Amines

Paolo Conti, Dennis Demont, Jos Cals, Harry C.J. Ottenheijm and Dirk Leysen*

Department of Medicinal Chemistry, Scientific Development Group, NV Organon, PO Box 20, 5340 BH Oss, The Netherlands

Abstract: The clean and efficient cleavage of N-benzyl linked tertiary amines from a solid support (e.g. **4**) by treatment with α-chloroethyl chloroformate (ACE-Cl) / methanol to yield secondary amines **7** is described. This allows the solid-phase synthetic transformation of the secondary amine **2** into **7**. When the Merrifield resin **1** is used the N-tethered amine-polymeric matrix ensemble is stable towards a wide variety of reaction conditions. © 1997 Published by Elsevier Science Ltd.

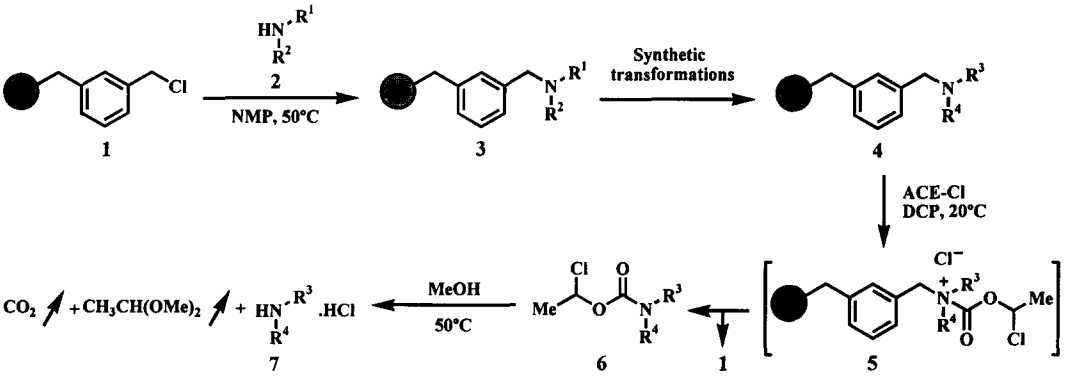
Combinatorial chemistry has the potential to prepare compounds faster than classical organic synthesis. Solid-phase chemistry is highly suited to combinatorial chemistry for reasons that include : easy work-up procedures, high yields by employing excess of reagents, and amenability to robotisation.[1,2] One of the disadvantages associated with solid-phase synthesis is the need for a "handle" to attach the small organic molecule to the resin an the need to use two additional synthetic steps for linkage and cleavage. Consequently, much attention has been paid to the development of linkers. Typically, this yielded functional groups such as carboxylic acids, alcohols, amines and amides in the product. Recently, new cleavage protocols were reported employing silicon-based linkers yielding -in a traceless fashion- a carbon-hydrogen bond.[3,4]

Many drugs contain a secondary or tertiary amine functionality, which alleviates the need for a traceless linker approach. A widely used method for the attachment of amines to resins is by linkage as benzyl carbamates. However, these carbamates are labile towards several reaction conditions, such as strong acids and several nucleophilic-, organometallic- and reductive reagents.[5] Other commonly used resins for the N-linkage of amines are of the trityl type.[6] However, these linkers are especially sensitive towards acidic conditions. Recently it was shown that tertiary amines can be prepared via solid-phase synthesis employing a concept that involves no linker to the resin other than the amine group itself.[7] Here we describe a release system for the preparation of secondary amines employing a related concept.

Our general protocol is depicted in scheme 1. A secondary amine **2** is ligated to a polymer-supported benzyl halide **1** yielding **3**. This in turn can undergo various synthetic transformations to give **4**. Cleavage

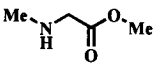
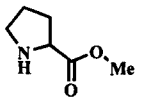
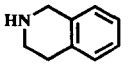
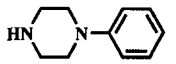
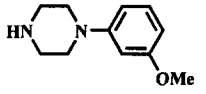
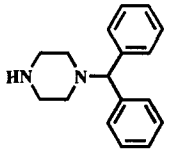
from the polymeric support was envisaged employing α-chloroethyl chloroformate (ACE-Cl). This would provide **6** and, subsequently, the desired, altered amine **7** in addition to volatile reagents.

This scheme is based on the following considerations. α-Chloroethyl chloroformate has been proven to be an efficient reagent for the selective debenzylation of tertiary amines.[8,9] The cleavage conditions employed are mild. The benzylic amine function **3** to be formed would enable us to use standard resins such as the Merrifield- [10], Wang- [11] and Sasrin- [12] resin. The Merrifield resin was viewed as particularly attractive due to its high stability towards a wide variety of reaction conditions.



Scheme 1. R^1, R^2, R^3, R^4= alkyl.

Table 1. Secondary amines used in route shown in scheme1.

Entry	Amine **2**	% yield[a]	% purity[b]
a		80	81
b		70	88
c		85	87
d		84	86
e		96	84
f		95	95

[a] All compounds gave satisfactory 200 MHz ^{1}H NMR spectra,

[b] Purity was determined by gas chromatography.

To realise the potential of scheme 1, the amines **2a-f** were studied (table 1). They were first coupled to the Merrifield resin, suspended in NMP. Some amines were added as their HCl salts, in which case DIPEA (20 equivalents) was added. The mixture was stirred for 17 hours at 50°C. The substitution level was > 0.6 mmol/g (> 85%).[13] To a suspension of the resin **3** in 1,2-dichloropropane [14], 10 eq. of α-chloroethyl chloroformate (ACE-Cl) was added and the resulting suspension was stirred at room temperature for 3 hours. The resin was filtered off and the filtrate evaporated to dryness. The residue was dissolved in methanol and the resulting solution was refluxed for 3 hours. The solvent was removed to yield the secondary amines **2** as their HCl-salts. The results are given in table 1.

These data clearly indicate that secondary amines **2a-2f** can be efficiently coupled to the Merrifield resin and cleaved in excellent yields using ACE-Cl ; treatment with refluxing methanol yields these amines as HCl salts in high purity. Of interest is also the selectivity observed in the synthesis of **2f**. This 1-(diphenylmethyl)piperazine is selectively cleaved from the resin without loss of the diphenylmethyl group [15].

In order to study the stability of the linking unit the following experiments were done. The resin, derivatised with arylpiperazine **2e**, was treated with 50% TFA/CH_2Cl_2, 99% TFA, KOtBu/THF or NaH/DMSO. No cleavage products were formed and the amine **2e** could be recovered in good yields by treatment with ACE-Cl / methanol. Furthermore, the feasibility of the conversion **3→4** was demonstrated as follows. Resin **1** was derivatised with 1-(2-cyanophenyl)piperazine. Subsequent reduction of the nitrile with $(CH_3)_2S.BH_3$ and cleavage with ACE-Cl / methanol afforded 1-(2-aminomethyl-phenyl)piperazine in 80% yield and 85% purity.[16]

After quaternisation of **4** with ACE-Cl, nucleophilic attack of the chloride anion at the benzylic carbon atom in **5** should lead towards the starting resin **1**. This regeneration of the Merrifield resin was shown as follows. Amine **2e** was coupled to the Merrifield resin and subsequently cleaved by treatment with ACE-Cl and methanol (96% yield); the resin which was filtered off was re-used in the same cycle yielding 85% of **2e**.

Subsequently, it was studied whether the cleavage protocol could also be applied using the Wang- and Sasrin resin. It was gratifying to find that phenylpiperazine **2e** was obtained in 80-85% yield and in 90-95% purity.

Finally, it was observed that cleavage can be induced by other chloroformates to yield the corresponding carbamates (see scheme 1). Treatment of **3e** with methyl chloroformate or vinyl chloroformate afforded the corresponding carbamates of **2e** in excellent yield (>80%) and purity (>98%). No cleavage was observed by treatment with acetyl chloride or benzoyl chloride.

In conclusion, reaction with ACE-Cl followed by treatment in refluxing methanol is an efficient and clean protocol for the cleavage of tethered, secondary amines **2** from a polymeric matrix. This protocol is remarkably selective; tethered primary amines (**4**, R^4=-H)are not cleaved and N-diphenylmethyl groups present in the ligand remain intact. If the Merrifield resin is used the N-tethered amine-polymeric matrix

ensemble is stable towards severe reaction conditions, thus allowing a diverse set of reaction conditions to be used to achieve modification in the amine moiety (**3**→**4**).

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13. The substitution level was determined by measuring the remaining chloride contents by a Schöninger combustion followed by ion chromatography with conductivity detection
14. The solvent originally described for this type of reaction, e.g. 1,2-dichloroethane, was replaced by 1,2-dichloropropane, in view of the reported carcinogenic, mutagenic and teratogenic activities of the former. Dichloromethane could also be used successfully.
15. This finding is in agreement with observations by Yang *et al* [9] who reported that in solution, treatment of piperazines bearing two different N-benzyl groups with ACE-Cl causes selective removal of one such group depending on electron-densities and sterical hindrance.
16. To 100 mg of the Merrifield resin, suspended in 3 ml of DMF, was added 130 mg of 1-(2-cyanophenyl)piperazine. After stirring the suspension for 17 hours at 50°C, the resin was filtered off and washed with ethanol and dichloromethane. The resin was dried, suspended in 3 ml of diglyme and treated with 0.1 ml of a 10M solution of $(CH_3)_2S.BH_3$ under an atmosphere of N_2. The suspension was heated for 17 h at 80°C, cooled to room temperature, treated with 1 ml of ethanol and heated for 3h at 80°C. The resin was filtered off, washed with ethanol, ethanol/dichloromethane and dichloromethane and suspended in 1,2-dichloropropane. A total of 0.1 ml of α-chloroethyl chloroformate (ACE-Cl) was added and the resulting suspension was stirred at room temperature for 3 hours. The resin was filtered off and the filtrate evaporated to dryness. The residue was dissolved in methanol and the resulting solution was refluxed for 3 hours. The solvent was removed to yield 1-(2-aminomethyl-phenyl)piperazine dihydrochloride.

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