Increasing the Selectivity of Silica-based Cation Exchange Sorbent for the Work-up of Reaction Mixtures using Derivatization Purification Techniques

Chemistry Data Sheet

This Chemistry Data Sheet describes the use of derivatization techniques to separate aliphatic secondary amines from aliphatic tertiary amines using the strong cation exchange sorbent, ISOLUTE® SCX-2.

Standardized procedures developed for target compound purification by reagent scavenging and catch and release SPE techniques utilize the strong cation exchange sorbent, ISOLUTE SCX-2. The sulfonic acid functionality in ISOLUTE SCX-2 binds compounds with basic functionality. This allows isolation of basic target compounds from reaction mixtures, followed by release of the purified product with methanol/ammonia. Although this is a powerful method of separating basic compounds from non-basic impurities, it is not possible to differentiate between, for example, a compound with a secondary amine and a compound with a tertiary amine using ISOLUTE SCX-2.

Separation of secondary and tertiary amines is a common problem facing organic chemists. Common reactions such as alkylations, dealkylations, deprotections and reductive aminations can provide such mixtures.

It is possible to enhance the selectivity of the catch and release process with ISOLUTE SCX-2 using a derivatization purification technique (DPT) that utilizes selective modification of the basicity of secondary amines by derivatization. This is a complementary approach to the use of solution-phase scavenger resins for selective removal of components (e.g. polystyrene based isocyanate resins, PS-Isocyanate and MP-Isocyanate from Biotage). The advantage of the DPT approach with ISOLUTE SCX-2 is that it allows flow-through processing using columns or plates.

Capacity of ISOLUTE SCX-2 Columns

The configuration of the column required is dependent on the amount of compound to be purified, ISOLUTE SCX-2 columns can be used to purify approximately 20-50 mg of basic compound (molecular weight 350 amu) per gram of sorbent, under ideal conditions. If the reaction mixture contains any potential interfering species (cations, etc.), these must be taken into account and the size of the column should be carefully selected to ensure sufficient capacity.

Chemical Data

Base Material: Silica, 50 µm
Functional Group: Propylsulfonic acid
Capacity: 0.6 mmol/g
Counter Ion: Proton

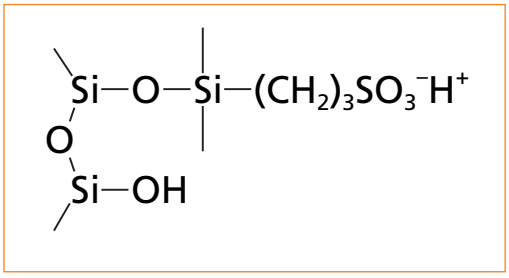

***Figure 1**. Structure of ISOLUTE SCX-2 bonded phase*

Biotage

Derivatization Purification Techniques - Separation of Secondary and Tertiary Amine Mixtures

This Chemistry Data Sheet describes the use of derivatization techniques to separate aliphatic secondary amines from aliphatic tertiary amines using the strong cation exchange sorbent, ISOLUTE SCX-2. The secondary amine is selectively derivatized, rendering it non-basic, allowing separation from the tertiary amine. There are two possible derivatization routes:

1. Acetylation of the secondary amine only with excess acetic anhydride (added directly to the crude reaction mixture) **(Figure 2).**

2. Treatment of the reaction mixture with excess Boc_2O in DCM, forming a carbamate with the secondary amine only. In this case, the secondary amine can also be subsequently recovered following the catch & release by simple removal of the Boc group using TFA (**Figure 3**).

Acetylation of Secondary Amine to Produce an Acetamide

1 Incomplete alkylation reaction yields secondary and tertiary amines

2 Addition of excess (2-fold) acetic anhydride converts the secondary amine to an acetamide (non-basic). The tertiary amine remains unchanged

3 Employing ISOLUTE SCX-2 column in catch and release mode isolates the tertiary amine

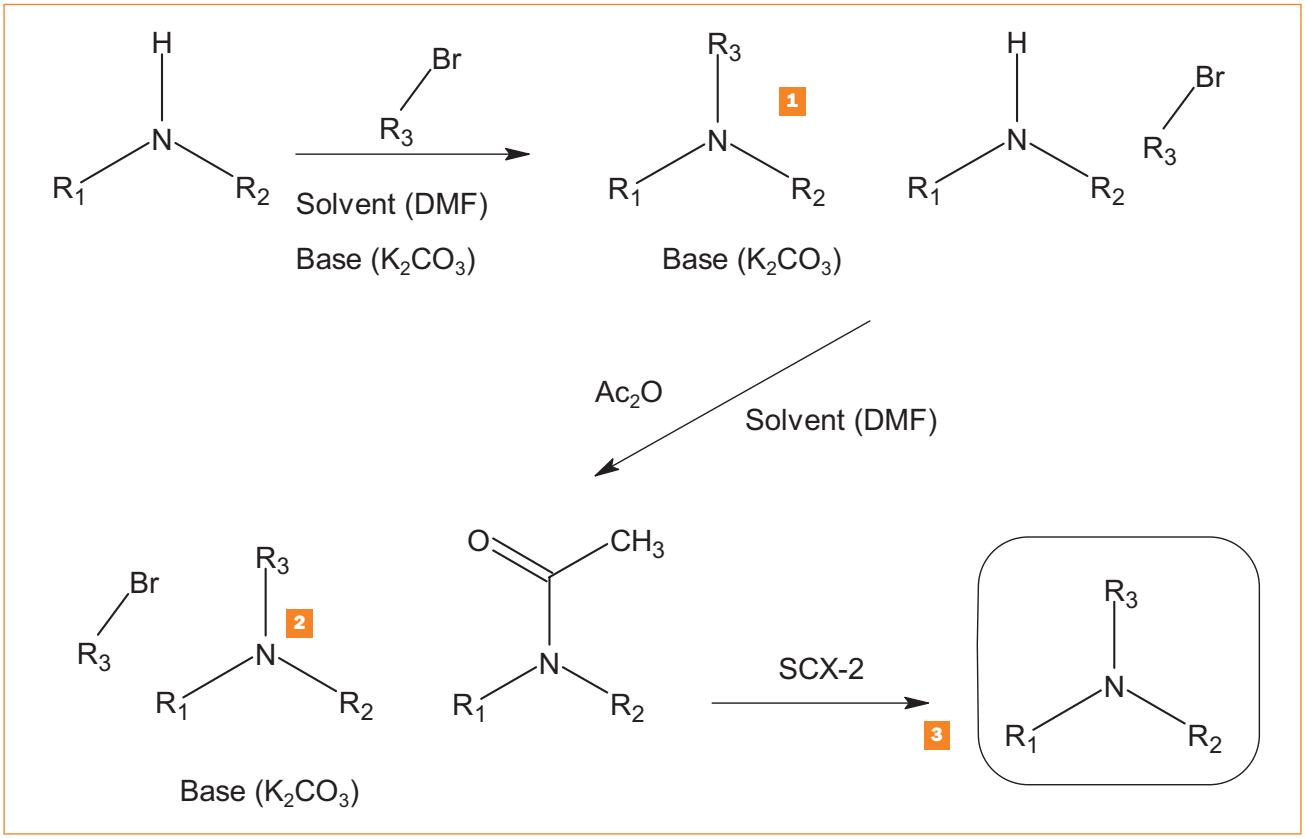

Figure 2. *Typical alkylation work-up: acetylation of the secondary amine with acetic anhydride*

General Precedure

1. Add acetic anhydride (2 equivalents with respect to the starting amine) to the crude alkylation reaction mixture and leave to stand at room temperature for 10 minutes
2. Follow the purification method below:
   - i) Dilute the mixture with methanol (1:1, v/v)
   - ii) Condition the ISOLUTE SCX-2 column with methanol (2 bed volumes*)
   - iii) Load reaction mixture onto the top frit of the column, under gravity
   - iv) Elute acetamide with methanol (2 bed volumes*)
   - v) Elute tertiary amine with 2 M ammonia in methanol (2 bed volumes*), under gravity
   - vi) Concentrate the ammonia/methanol fraction to yield the pure tertiary amine

* 100 mg of sorbent has a bed volume of 125 µL

Note: The concentration of strongly basic metal ions present must be taken into account when deciding on which sorbent mass to use. If sufficient capacity is not available then breakthrough of the amine will result.

Yields are difficult to quantify as conversions to the tertiary amine differ from reaction to reaction. Generally, excellent correlation between the recovery and the % conversion can be seen.

Treatment of Secondary Amine with BOC to Produce a Carbamate

1. Separation by ISOLUTE SCX-2 column yields the amine mixture
2. Treatment with excess (2-fold) Boc_2O in DCM effects instantaneous carbamate formation with the secondary amine, rendering it non-basic. The tertiary amine remains unchanged.
3. Employing ISOLUTE SCX-2 column to catch the tertiary amine, while the Boc-amine is eluted with methanol. The tertiary amine is recovered by elution with 2M ammonia/methanol
4. The Boc-protected secondary amine is deprotected with TFA. The secondary amine can be recovered as its TFA salt by treatment with TFA. ISOLUTE SCX-2 column in catch and release mode can then be employed again to liberate the free base

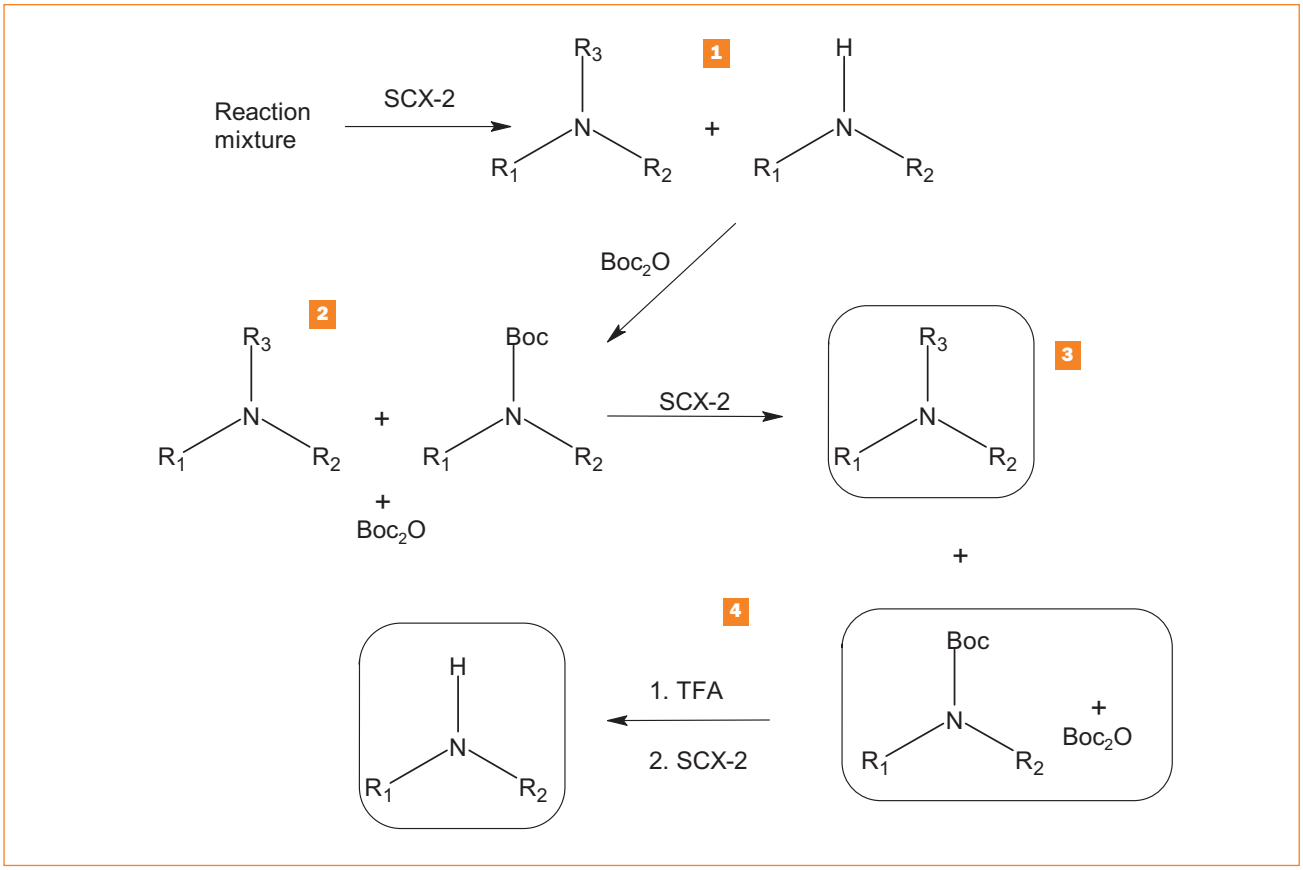

Figure 3. *Treatment with Boc_2O in DCM, to form a carbamate with the secondary amine*

General Precedure

1. Purification step #1: isolate the secondary and tertiary amines from the reaction mixture
   - i Dilute the crude reaction mixture with methanol (1:1, v/v)
   - ii Condition an ISOLUTE SCX-2 column with methanol (2 bed volumes*)
   - iii Apply dilute reaction mixture to the column, under gravity
   - iv Rinse with methanol (2 bed volumes*)
   - v Elute amines with 2 M ammonia in methanol (2 bed volumes*)
   - vi Concentrate the ammonia/methanol fraction to yield the secondary and tertiary amine mixture
2. Derivatization step: dissolve in dichloromethane. Add Boc_2O (2 eq with respect to the starting secondary amine) and allow to stand for 10 minutes
3. Purification step #2: purify the tertiary amine
   - i Dilute the amine mixture with methanol (1:1, v/v)
   - ii Condition an ISOLUTE SCX-2 column with methanol (2 bed volumes*)
   - iii Apply diluted reaction mixture to the column, under gravity
   - iv Elute the Boc-protected secondary amine with methanol (2 bed volumes*)
   - v Elute tertiary amine with 2 M ammonia in methanol (2 bed volumes*)
   - vi Concentrate the ammonia/methanol fraction to yield the pure tertiary amine
   - vii Concentrate the methanol fraction to yield the secondary amine carbamate and any residual Boc_2O
   - viii Treat with trifluoroacetic acid/water (95:5, v/v), followed by concentration to yield the pure secondary amine as the trifluoroacetate salt
4.
   - i Purification step #3: liberate the secondary amine
   - ii Dissolve the trifluoroacetate salt in methanol
   - iii Condition an ISOLUTE SCX-2 column with methanol (2 bed volumes*)
   - iv Apply dilute reaction mixture to the column, under gravity
   - v Rinse with methanol (2 bed volumes*)
   - vi Elute secondary amine with 2 M ammonia in methanol (2 bed volumes*)
   - viii Concentrate the methanolic ammonia fraction to yield the pure secondary amine

*100 mg of sorbent has a bed volume of 125 µL

Note: The concentration of any strongly basic metal ions present must be taken in to account when deciding on which sorbent mass to use. If sufficient capacity is not available analyte breakthrough will occur.

Yields are generally quantitative based on the starting amine mixtures.

These procedures are suitable for purification of amines at mg and multiple g amounts. Scale up the SPE method as appropriate.

Thanks to Ian Clemens at the Synthetic Technologies Group, Lilly Research Laboratories, Erl Wood, UK.

For information on the use of ISOLUTE SCX-2 for the extraction of basic compounds from organic synthesis reaction mixtures, see Purification of Basic Products from Synthesis Mixtures Using ISOLUTE SCX-2 Columns (Chemistry Data Sheet **TN121**). This technical note also lists the range of column configurations available for this application.

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