Simultaneous Deprotection and Purification Based on Ionic Resin Capture: Application to Amide Formations and Grignard and Mitsunobu Reactions

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Abstract: Products containing Boc- or Tr-protected amines were caught directly out of reaction mixtures by simultaneous cleavage of the protecting group. By releasing the products with ammonia the corresponding free amines were obtained in high yields and purities. The broadly applicable method of simultaneous deprotection and purification based on ionic resin capture was applied for Grignard and Mitsunobu reactions as well as amide formations and show a high potential for multiparallel synthesis.

Key words: ion exchange, facile purification, Boc deprotection, Tr deprotection, combinatorial chemistry

A major challenge in parallel synthesis and especially in the production of combinatorial libraries is the purification of numerous intermediates and final compounds. Many purification and isolation methods lack a generic nature and can therefore not be used easily in the preparation of multifold products having very different properties. In multiparallel extractions, for instance, a certain number of the reaction mixtures usually show precipitates, do not give sufficient separations of the layers, or even result in emulsions. Chromatographical methods demand a much higher technical effort and need to be optimized carefully for each series of compounds. One possible solution is the application of scavengers to remove excess reagents or reactants, or to bind temporarily the product to the solid phase while the excess reagents and reactants are washed off, and finally to release the purified product – this is also known as polymer-assisted purification.1 The general principle was first described by Siegel et al. and involves the selective binding of a product from a reaction solution onto a solid phase, followed by washing of the solid phase to remove impurities.2 Recently, scavengers were applied in different multistep syntheses,3 and several novel scavenger types were developed4 and are now widely used in multiparallel synthesis.5 We report within this article a powerful and general expansion of this procedure to not only amide couplings but also Grignard and Mitsunobu reactions: intermediates or final products were bound to the resin and acid-labile tert-butyloxycarbonyl (Boc) or trityl (Tr) protecting groups were cleaved simultaneously.

Some examples of the cleavage of protecting groups by scavengers or ion exchangers are described in literature.6

In this article, a general method of ionic resin based purification combined with the simultaneous cleavage of an acid-labile protecting group, as depicted in Scheme 1, is reported.

Grignard Reactions

The corresponding Grignard reagents were added to 1-trityl-1H-imidazole-4-carbaldehyde (1) in THF (Table 1). The reaction mixture was quenched after one day with aqueous ammonium chloride and methanol. The products were caught by adding Bondesil SCX and shaking this mixture for three days at room temperature. This prolonged reaction time was necessary to get a complete trityl deprotection of the imidazoles. To remove excess reagents and side products, the Bondesil SCX was washed as described in Table 1. Finally, the product could by released from the scavenger by treatment with ammonia in methanol. The products with purities of 90% or better were isolated in good yields of 77–88%.

Mitsunobu Reactions

The corresponding alcohols 5 were coupled to 4-(1-trityl-1H-imidazol-4-yl)phenol (4) under classical Mitsunobu conditions (DIAD, PPh3, Table 2).
The products were caught by adding Bondesil SCX, formic acid, water and methanol and shaking this mixture for three days at room temperature. As mentioned for the Grignard reactions, the prolonged reaction time was necessary to get a complete trityl deprotection of the imidazoles. To remove excess reagents and side products, the Bondesil SCX was washed as described in Table 2. The products were released from the scavenger by treatment with ammonia in methanol and obtained with purities of 90% or more and in good yields of 79–84%.

### Amide Formations

The Boc-protected amino acids 7 were activated with HBTU (Table 3) and the amine 8 was added. After shaking for two days, Dowex 2X8-200 was added to remove HOBT as well as remaining amino acids.

Bondesil SCX and formic acid were added to the reaction mixture. After shaking for three days at room temperature, the products were completely bound to the resin and Boc-deprotected. To remove excess reagents and side products, the Bondesil SCX was washed as described in Table 3. The products were released from the scavenger by treatment with ammonia in methanol and obtained with purities of 85% or more and in good yields of 85–90%.

Applying this method, several discovery libraries (e.g., imidazole derivatives) consisting of overall more than 10000 members were prepared within Novartis.

In summary, we have demonstrated that the method of ionic resin capture, which allows the preparation of compounds in high yields by catching products out of reaction mixtures with acidic scavengers, cleaving simultaneously acid labile protecting groups, and finally releasing products with high purities, is a powerful method for multi-parallel synthesis. This method has been illustrated with different examples for Grignard and Mitsunobu reactions as well as amide formations.

Bondesil SCX (40 µM) was purchased from Varian. The starting materials were either purchased from various suppliers 8 or, in the case of 4, prepared in analogy to literature. 9 1H NMR and 13C NMR spectra were recorded on a Bruker Biospin 400 spectrometer. The high-resolution mass spectra were acquired on a Bruker APEXIII Ion Cyclotron Resonance Fourier Transform Mass Spectrometer equipped with an electrospray ion source operated in positive ion mode. Chemical shifts (δ) are given in parts per million relative to the NMR solvent signals (DMSO-d6: 2.5 and 39.51 ppm).

### Tables

#### Table 1 Deprotection and Purification Based on Ionic Resin Capture: Grignard Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Grignard reagent 2</th>
<th>Yield (%)</th>
<th>Product 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH2CH2MgBr (2a)</td>
<td>87</td>
<td>3a</td>
</tr>
<tr>
<td>2</td>
<td>n-PrMgCl (2b)</td>
<td>77</td>
<td>3b</td>
</tr>
<tr>
<td>3</td>
<td>PhMgBr (2c)</td>
<td>82</td>
<td>3c</td>
</tr>
<tr>
<td>4</td>
<td>EtMgBr (2d)</td>
<td>86</td>
<td>3d</td>
</tr>
</tbody>
</table>

a The reaction mixtures were shaken in grooved tubes for better mixing.

b Washing procedure: MeOH; 2 × toluene and MeOH; 3 × H2O; 3 × MeOH.

#### Table 2 Deprotection and Purification Based on Ionic Resin Capture: Mitsunobu Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol 5</th>
<th>Yield (%)</th>
<th>Product 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-(2-Dimethylaminoethoxy)ethanol (5a)</td>
<td>84</td>
<td>6a</td>
</tr>
<tr>
<td>2</td>
<td>2-Pyridin-3-yethanol (5b)</td>
<td>79</td>
<td>6b</td>
</tr>
<tr>
<td>3</td>
<td>2-Morpholin-4-yethanol (5c)</td>
<td>78</td>
<td>6c</td>
</tr>
<tr>
<td>4</td>
<td>1-(3-Hydroxypropyl)pyrrolidin-2-one (5d)</td>
<td>83</td>
<td>6d</td>
</tr>
<tr>
<td>5</td>
<td>2-Pyrrolidin-1-yl-ethanol (5e)</td>
<td>83</td>
<td>6e</td>
</tr>
</tbody>
</table>

a The reaction mixtures were shaken in grooved tubes for better mixing.

b Washing procedure: MeOH; 3 × toluene and MeOH; 3 × H2O; 3 × MeOH.
Deprotection and Purification Based on Ionic Resin Capture: Amide Formations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino acid 7</th>
<th>Amine 8</th>
<th>Yield (%)</th>
<th>Product 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc-phenylalanine (7a)</td>
<td>Benzylamine (8a)</td>
<td>90</td>
<td>9a</td>
</tr>
<tr>
<td>2</td>
<td>Boc-phenylalanine (7a)</td>
<td>1-Methylpiperezine (8b)</td>
<td>90</td>
<td>9b</td>
</tr>
<tr>
<td>3</td>
<td>Boc-phenylalanine (7a)</td>
<td>1,1-Dimethylethane-1,2-diamine (8c)</td>
<td>89</td>
<td>9c</td>
</tr>
<tr>
<td>4</td>
<td>N-Boc-tryptophan (7b)</td>
<td>1-Methylpiperezine (8b)</td>
<td>85</td>
<td>9d</td>
</tr>
<tr>
<td>5</td>
<td>N-Boc-tryptophan (7b)</td>
<td>1,1-Dimethylethane-1,2-diamine (8c)</td>
<td>88</td>
<td>9e</td>
</tr>
</tbody>
</table>

* The reaction mixtures were shaken in grooved tubes for better mixing.
* Washing procedure: MeOH; 3 × H2O; 3 × MeOH.

<table>
<thead>
<tr>
<th>1</th>
<th>(1H-Imidazol-4-yl)butan-1-ol (3b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR (400 MHz, DMSO-d6): δ = 8.99 (s, 1 H), 7.30 (s, 1 H), 4.67 (t, J = 6.6 Hz, 1 H), 1.56–1.84 (m, 2 H), 1.10–1.50 (m, 2 H), 0.89 (t, J = 7.5 Hz, 3 H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (100 MHz, DMSO-d6): δ = 137.7, 134.4, 115.4, 64.0, 38.8, 18.4, 14.0.</td>
<td></td>
</tr>
<tr>
<td>HRMS (ESI): m/z [M + H]+ calcd for C7H12N2O: 141.1179; found: 141.1178.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1</th>
<th>(1H-Imidazol-4-yl)phenylethanol (3c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR (400 MHz, DMSO-d6): δ = 9.01 (s, 1 H), 7.36–7.48 (m, 5 H), 5.88 (s, 1 H), 5.88 (s, 1 H).</td>
<td></td>
</tr>
<tr>
<td>13C NMR (100 MHz, DMSO-d6): δ = 142.0, 136.9, 134.5, 128.4, 127.8, 126.3, 115.7, 66.2.</td>
<td></td>
</tr>
</tbody>
</table>

Resium bromide (2a; 1.1 mL, 1.1 mmol, 1 M in THF) was added dropwise. Then, the mixture was shaken for 1 d at r.t. Sat. aq NH4Cl (5 mL), H2O (5 mL), MeOH (5 mL), and Bondesil SCX (3.1 g, loading: 0.79 mmol/g) were added and the mixture was shaken for 3 d at r.t. The Bondesil SCX was filtered off, washed with MeOH (20 mL), toluene (3 × 20 mL), MeOH (20 mL), H2O (3 × 20 mL), and MeOH (3 × 20 mL). A solution of NH3 in MeOH (7 M, 20 mL) was added to the residual Bondesil SCX and the suspension shaken for 2 d at r.t., filtered, and the solid washed with MeOH (10 mL). The combined filtrates were evaporated to give the product 3a (130 mg, 87%).

1H NMR (400 MHz, DMSO-d6): δ = 9.10 (s, 1 H), 7.54 (s, 1 H), 7.25–7.31 (m, 2 H), 7.14–7.23 (m, 3 H), 4.62–4.73 (m, 1 H), 2.55–2.77 (m, 2 H), 1.90–2.08 (m, 2 H).

1H NMR (400 MHz, DMSO-d6): δ = 153.8, 141.8, 137.3, 134.5, 128.7, 126.2, 115.6, 63.7, 38.3, 31.3.


Mitunobu Reactions; (2-{2-[4-(1H-Imidazol-4-yl)phenoxo]ethoxy}ethoxy)ethyl)dimethylamine (6a); Typical Procedure

4-(1-Trityl-1H-imidazol-4-yl)phenol (4; 100 mg, 0.25 mmol) was dissolved in THF (5 mL). 2-(Dimethylaminoethoxy)ethanol (5a; 45 mg, 0.34 mmol) and Ph,P (85 mg, 0.32 mmol) were added followed by DIAD (0.65 mL, 0.34 mmol) dissolved in THF (1 mL). The resulting mixture was shaken for 1 d at r.t. Bondesil SCX (1.04 g, loading: 0.79 mmol/g), H2O (1 mL), MeOH (5 mL) and HCO2H (1 mL) were added. The suspension was shaken for 3 d. The Bondesil SCX was filtered off and washed with MeOH (20 mL), toluene (3 × 20 mL), MeOH (20 mL), H2O (3 × 20 mL), and MeOH (3 × 20 mL). A solution of NH3 in MeOH (7 M, 15 mL) was added to the residual Bondesil SCX and the suspension shaken for 2 d at r.t., filtered, and the solid washed with MeOH (10 mL). The combined filtrates were evaporated to give the product 6a (58 mg, 84%).

1H NMR (400 MHz, DMSO-d6): δ = 9.07 (s, 1 H), 8.02 (d, J = 1.2 Hz, 1 H), 7.75 (d, J = 9.1 Hz, 2 H), 7.09 (d, J = 9.1 Hz, 2 H), 4.18–4.23 (m, 2 H), 3.75–3.88 (m, 4 H), 3.27–3.34 (m, 2 H), 2.81 (s, 6 H).

1H NMR (400 MHz, DMSO-d6): δ = 158.8, 158.0, 157.8, 134.8, 126.8, 115.1, 114.2, 68.7, 66.9, 64.4, 55.9, 42.6.


4-{2-[4-(1H-imidazol-4-yl)phenoxy]ethyl]morpholine (6c)
1H NMR (400 MHz, DMSO-d6): δ = 9.13 (s, 1 H), 8.06 (s, 1 H), 7.80 (d, J = 9.1 Hz, 2 H), 7.15 (d, J = 9.1 Hz, 2 H), 4.38–4.48 (m, 2 H), 3.86 (br s, 4 H), 3.55–3.68 (m, 2 H), 3.31–3.45 (m, 4 H).
13C NMR (100 MHz, DMSO-d6): δ = 158.4, 135.2, 132.9, 127.2, 119.1, 115.8, 114.9, 63.7, 62.6, 55.3, 52.1.

1-[3-[4-(1H-imidazol-4-yl)phenoxy]propyl]pyrrolidin-2-one (6d)
1H NMR (400 MHz, DMSO-d6): δ = 9.14 (s, 1 H), 8.06 (s, 1 H), 7.73 (d, J = 9.1 Hz, 2 H), 7.06 (d, J = 9.0 Hz, 2 H), 4.01 (t, J = 6.1 Hz, 2 H), 3.30–3.41 (m, 4 H), 2.20 (t, J = 8.8 Hz, 2 H), 1.84–2.01 (m, 4 H).
13C NMR (100 MHz, DMSO-d6): δ = 173.9, 159.2, 134.7, 132.6, 126.9, 120.7, 119.2, 115.1, 114.2, 65.6, 46.4, 30.4, 26.6, 17.5.

4-{4-(2-Pyrrolidin-1-ylethoxy)phenyl}-1H-imidazole (6e)
1H NMR (400 MHz, DMSO-d6): δ = 9.14 (s, 1 H), 8.06 (s, 1 H), 7.80 (d, J = 8.8 Hz, 2 H), 7.15 (d, J = 8.6 Hz, 2 H), 4.26–4.45 (m, 4 H), 3.55–3.70 (m, 4 H), 3.15–3.22 (m, 2 H), 1.77–2.15 (m, 4 H).
13C NMR (100 MHz, DMSO-d6): δ = 158.4, 134.8, 132.5, 126.9, 120.2, 115.4, 114.5, 63.4, 53.8, 52.7, 22.5.
HRMS (ESI): m/z [M + H]+ calcd for C16H22N4O: 258.1601; found: 258.1601.

Amide Formations; 2-Amino-N-benzyl-3-phenylpropionamide (9a); Typical Procedure
Boc-phenylalanine (7a; 250 mg, 0.94 mmol) was dissolved in THF (25 mL) and DMA (5 mL). HBTU (357 mg, 0.94 mmol) was added and the suspension was shaken for 2 d at r.t. The Dowex 2X8-200 (30 mL) was added to the residual Bondesil SCX and the suspension shaken for 2 d at r.t., filtered and the solid washed with MeOH (7 M, 25 mL). HBTU (357 mg, 0.94 mmol) was added and the suspension shaken for 45 min at r.t. Benzylamine (7a; 250 mg, 0.94 mmol) was dissolved in THF (25 mL) and Dowex 2X8-200 (2 g) were added and the suspension was shaken for 2 d at r.t. The Dowex 2X8-200 was filtered off and washed with MeOH (10 mL) and H2O (20 mL).
Bondesil SCX (3.9 g, loading: 0.79 mmol/g) was added to the combined filtrates and the suspension was shaken for 5 d at r.t. The Bondesil SCX was filtered off and washed with MeOH (20 mL), H2O (3 x 20 mL) and MeOH (3 x 20 mL). A solution of NHP, MeOH (7 M, 25 mL) was added to the residual Bondesil SCX and the suspension shaken for 2 d at r.t., filtered and the solid washed with MeOH (10 mL). The combined filtrates were evaporated to give the product 9a (215 mg, 83%).
1H NMR (400 MHz, DMSO-d6): δ = 8.84 (s, 1 H), 8.28 (s, 2 H), 7.17, 7.28 (m, 8 H), 7.04 (d, J = 7.3 Hz, 2 H), 4.26–4.36 (m, 1 H), 4.12–4.20 (m, 1 H), 4.00–4.09 (m, 1 H), 3.05 (br s, 2 H).
13C NMR (100 MHz, DMSO-d6): δ = 167.7, 138.1, 134.8, 129.5, 128.5, 128.2, 127.3, 127.0, 126.9, 53.6, 42.2, 36.9.
HRMS (ESI): m/z [M + H]+ calcd 265.1492; found: 255.1491.

2-Amino-1-(4-methylpyrrolizin-1-yl)-3-phenylpropan-1-one (9b)
1H NMR (400 MHz, DMSO-d6, 120 °C): δ = 7.31–7.41 (m, 3 H), 7.28 (d, J = 7.6 Hz, 2 H), 4.4–5.4 (br s, 2 H), 4.63 (t, J = 7.2 Hz, 1 H), 3.28–3.64 (m, 4 H), 3.14–3.23 (m, 1 H), 2.96–3.11 (m, 3 H), 2.72–2.90 (m, 2 H), 2.72 (s, 3 H).
13C NMR (100 MHz, DMSO-d6, 120 °C): δ = 159.0, 130.1, 129.0, 127.8, 118.2, 52.3, 42.5, 38.9, 37.3.

Acknowledgment
The authors thank the Novartis department for Analytical and Imaging Sciences for HRMS and NMR analyses.

References

(7) Bondesil SCX (purchased from Varian Deutschland GmbH, Darmstadt, Germany) was used since this silica-based scavenger has a high density that facilitates the settling after shaking in multiparallel fashion. The solvent can be removed therefore faster and more easily than with an organic-polymer-based ion-exchange resin.

(8) Grignard reagents were purchased from Rieke Metals Inc. (NE, USA; 2a) or Fluka Chemie GmbH (CH; 2b, 2c, 2c, 2d) as solutions in THF. Compound 1 and the alcohols 5b and 5d were supplied by ABCR GmbH & Co KG (Karlsruhe, Germany). All other reagents, Dowex 2X8-200 and solvents were purchased from Fluka Chemie GmbH (Buchs-CH).