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Expedient synthesis of secondary amines bound to indole resin and cleavage of resin-bound urea, amide and sulfonamide under mild conditions

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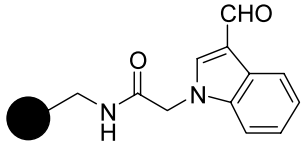
Abstract—Highly efficient, new protocols for the attachment of primary amines to indole aldehyde resin using $Ti(O^iPr)_4$–$NaBH_4$ and $CH(OMe)_3$–$NaBH_3CN$–HOAc are reported. Mild cleavage conditions for the release of urea, amide and sulfonamide products from the solid support using 1% trifluoroacetic acid (TFA) are developed.

The electron-rich alkoxybenzaldehyde resins[1] are valuable linkers for the attachment of various primary amines by reductive amination reactions. Reaction of the resin-bound secondary amine intermediates with a variety of electrophiles allows solid-phase synthesis of amides, sulfonamides and ureas. The products are released from the solid support by acid-mediated cleavage of the *N*-alkoxybenzyl bond and do not carry any evidence of resin attachment. The synthesis offers easy introduction of two diversity points in succession. Accordingly, the conception is highly attractive in light of nitrogen-based library generation as a wide range of primary amines, acid chlorides, acid anhydrides, carboxylic acids, sulfonyl chlorides and isocyanates are commercially available. However, the utility[2] of alkoxybenzaldehyde linkers has significant limitations as both the nature of the primary amine and the electrophile influence the reaction efficiency. Moreover, strong acidic conditions (>90% TFA) required for cleavage of the products from the solid support often compromise product purity due to potential leaching from the resin upon exposure to TFA.

To address these shortcomings, Estep et al. has recently described[3] an indole aldehyde resin **1** and demonstrated its broad application in the syntheses of amides, sulfonamides, ureas, guanidines and carbamates. Nonetheless, the reported procedure for reductive amination of the resin **1** was sluggish that required the sequential use of tetramethylammonium triacetoxyborohydride in dichloroethane for 16 h followed by sodium cyanoborohydride in methanol for 6 h. The resin-bound products were typically released from the solid support with a 50% solution of TFA in dichloromethane.



1

In the context of our efforts on functionalized resin development, we sought to enhance the efficacy of the indole resin **1** by developing new, expedient protocols for the attachment of primary amines and milder cleavage conditions for release of the products from the solid support. In connection with our ongoing investigations on reductive amination reactions, we have earlier reported a versatile, mild method for the reductive amination of carbonyl compounds using titanium isopropoxide and sodium borohydride.[4] In an effort to expand the utility of this reagent combination in solid-phase organic synthesis, we report here its novel application in the reductive amination of the resin **1**, leading to a highly efficient, expedient protocol for the attachment of various primary amines. Alternatively, we developed another expedient method for attaching primary amines to the indole resin **1** using sodium cyanoborohydride and trimethyl orthoformate (TMOF).[5] In both of the cases, the reactions were rapid

Keywords: indole aldehyde resin; primary amines; reductive amination.

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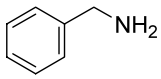
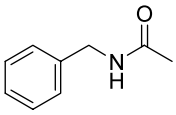
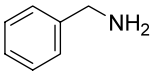
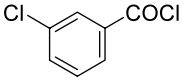
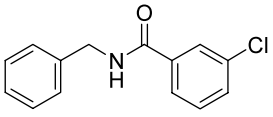
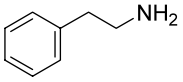
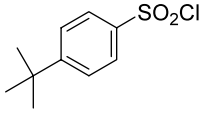
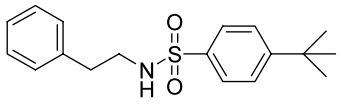
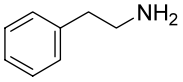
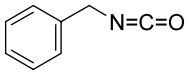
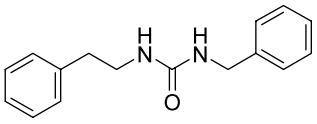
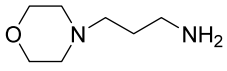
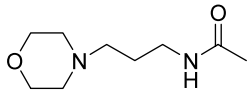
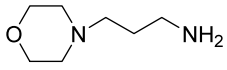
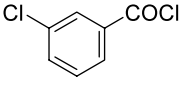
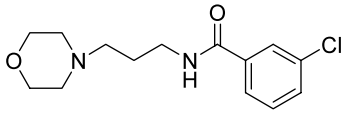
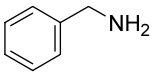
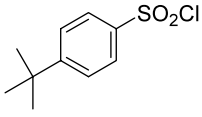
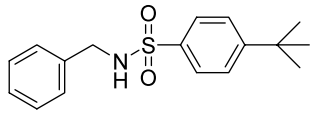
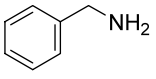
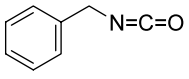
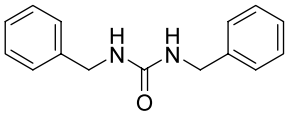
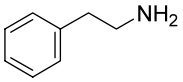
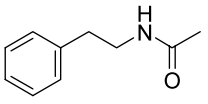
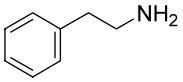
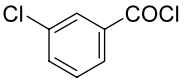
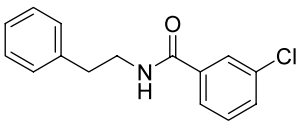
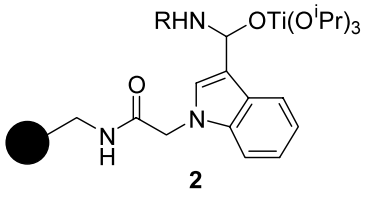
Table 1. Synthesis of urea, amide and sulfonamide from indole aldehyde resin

Entry	Primary Amine	Electrophile	Product[c]	Purity (%)[d]	Yield (%)[e]
1[a]		MeCOCl		100	98
2[a]				96	97
3[a]				97	86
4[a]				100	96
5[a]		MeCOCl		95	89[f]
6[a]				95	92[f]
7[b]				98	84
8[b]				100	96
9[b]		MeCOCl		100	95
10[b]				96	88

[a] $Ti(O^iPr)_4$-$NaBH_4$ method was used. [b] TMOF-$NaBH_3CN$-HOAc method was used. [c] All products were characterized by their ^1H NMR spectral analysis. [d] Purities refer to crude products as determined by HPLC analysis. [e] Yields refer to isolated mass yields based on the initial loading of the indole resin **1** (0.93 mmol/g). [f] Isolated as TFA salt.

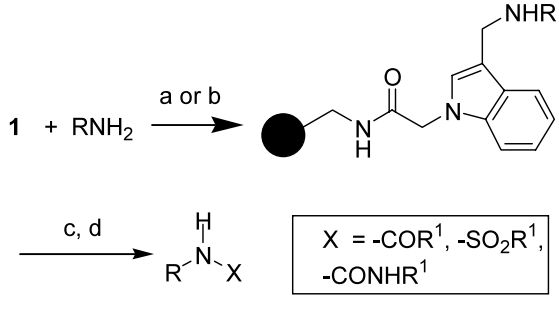
with complete conversion in 6 h. We have found that the product amides, sulfonamides and ureas can be cleaved from the solid support under very mild reaction conditions by using as low as 1% TFA in dichloromethane at room temperature. The synthesis is outlined in Scheme 1.

The scope of the resin-bound secondary amine synthesis was assessed on a set of primary amines using both of the reductive amination methods. With $Ti(O^iPr)_4$–$NaBH_4$, a mixture of the indole resin **1**,[6] the primary amine and $Ti(O^iPr)_4$ in anhydrous THF was stirred at ambient temperature for 4 h to allow the formation of the intermediate titanium(IV) complex **2**.[4] The complete consumption of the aldehyde group in the resin **1** was indicated by a qualitative 2,4-dinitrophenylhydrazine (DNP) test of the beads. Absolute ethanol was then added followed by $NaBH_4$, and the resulting mixture stirred for a further period of 2 h at room temperature.[7] The resin-bound secondary amines were isolated by filtration followed by washing with THF, MeOH and DCM. The reactions were performed under standard anhydrous conditions and we have not encountered any problem with precipitated titanium oxides as reported earlier.[8]



2

With TMOF–$NaBH_3CN$, a mixture of the resin **1**, TMOF, and the primary amine in THF was stirred at room temperature for 4 h. $NaBH_3CN$ and a catalytic amount of acetic acid were then added and the resulting mixture was further stirred for 2 h.[9] The resulting polymer-bound secondary amines obtained from both of the methods were found to be compatible to a variety of reaction conditions leading to the synthesis of resin-bound amides,[10] sulfonamides[10] and ureas.[11] Cleavage of the products from the support were effected under very mild conditions by using as low as 1% (v/v) TFA in dichloromethane (DCM) at ambient temperature.[12] These conditions are much milder than the cleavage protocols reported in the literature. The results for a set of primary amine, acid chloride, sulfonyl chloride and isocyanate are summarized in Table 1. In all cases, the crude products were analyzed by HPLC and had 95–100% purity. The products were characterized by their ^1H NMR spectra[13] and comparison with those reported in the literature.[3] The isolated yields were excellent, based on the initial loading of the indole resin **1** (0.93 mmol/g). Unlike the reported protocols for cleavage using strong acidic conditions, the present method offers clean release of the products without any contamination from leaching of the resin.



Scheme 1. *Reagents and conditions*: (a) i. RNH_2, $Ti(O^iPr)_4$, THF, rt, 4 h, ii. abs. EtOH, rt, 2 h. (b) i. RNH_2, TMOF, THF, rt, 4 h, ii. HOAc, $NaBH_3CN$, rt, 2 h. (c) R^1COCl, NEt_3 or R^1SO_2Cl, NEt_3 or R^1NCO, DCM, rt, 14 h. (d) 1% v/v TFA (4 equiv.), DCM, rt, 4 h.

In summary, we have reported new, expedient methods for the attachment of primary amines to indole-aldehyde resin **1** using $Ti(O^iPr)_4$–$NaBH_4$ and $CH(OMe)_3$–$NaBH_3CN$–HOAc. We have demonstrated that the product amide, sulfonamide and urea can be released from the solid support under very mild conditions using 1% TFA in dichloromethane. In view of the facile, high-yielding conversions, the protocols described herein should find wide application in nitrogen-based library synthesis.

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4. For examples, see: (a) Bhattacharyya, S. *Tetrahedron Lett*. **1994**, *35*, 2401; (b) Bhattacharyya, S. *J. Org. Chem*. **1995**, *60*, 4928; (c) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, 1079; (d) Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527; (e) Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781.
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6. Indole-aldehyde resin, PS-Indole-CHO was obtained from Argonaut Technologies.
7. $Ti(O^iPr)_4$–$NaBH_4$ method: A mixture containing the resin (0.5 g, 0.46 mmol) in THF (4 ml), $Ti(O^iPr)_4$ (1.0 mmol) and the primary amine (1.0 mmol) was agitated at rt for 4 h. Then, a solution of $NaBH_4$ (2 ml, ca. 0.75 M) in absolute EtOH was added and the resulting mixture stirred for a further period of 2 h. The supernatant liquid was drained off and the resin washed with THF (8 mL×2), MeOH (8 mL×3) and DCM (8 mL×2).

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9. TMOF–$NaBH_3CN$ method: A mixture of PS-Indole-CHO resin (0.5 g, 0.46 mmol), THF (2 mL), TMOF (2 mL) and the primary amine (1.0 mmol) was agitated at ambient temperature for 4 h. Then, a solution of $NaBH_3CN$ (1.0 mL, 1 M) in THF and acetic acid (0.1 mL) were added. The resulting mixture was stirred for 2 h. The supernatant liquid was drained off and the resin washed with THF (8 mL×2), MeOH (8 mL×3) and DCM (8 mL×2).
10. To a suspension of the resin-bound secondary amine (0.1 g) in DCM (2 mL) and triethylamine (1 mL) was added an acid chloride/sulfonyl chloride (0.5 mmol). The resulting mixture was agitated overnight at ambient temperature. The supernatant liquid is drained off and the resin washed with DMF, MeOH and DCM.
11. To a suspension of the resin-bound secondary amine (0.1 g) in DCM (2 mL) was added an isocyanate (0.5 mmol). The resulting mixture was agitated overnight at ambient temperature. The supernatant liquid is drained off and the resin washed with DMF, MeOH and DCM.
12. The resin-bound product was suspended in 1% (v/v) TFA (3 mL, ca. 4 mol equiv.) and the mixture agitated at ambient temperature for 4 h. The color of the resin became deep purple. The supernatant liquid was collected and the resin was washed with DCM (2×2 mL). The combined solution was concentrated to afford pure products in excellent yields. All products were characterized by ^1H NMR spectral analysis.
13. Representative ^1H NMR spectra of the products derived from 2-phenethylamine: Amide (entry 9): δ ($CDCl_3$, 300 MHz): 2.02 (s, 3H), 2.84 (t, 2H, $J=6$ Hz), 3.58 (q, 2H, $J=6$ Hz), 5.77 (br s, 1H), 7.18–7.4 (m, 5H). Sulfonamide (entry 3): δ ($CDCl_3$, 300 MHz): 1.4 (s, 9H), 2.8 (t, 2H, $J=6.5$ Hz), 3.18–3.32 (m, 2H), 4.42 (br s, 1H), 7.04–7.12 (m, 2H), 7.2–7.38 (m, 3H), 7.5 (d, 2H, $J=8$ Hz), 7.7 (d, 2H, $J=8$ Hz). Urea (entry 4): δ ($CDCl_3$, 300 MHz): 2.8 (t, 2H, $J=7$ Hz), 3.4 (t, 2H, $J=7$ Hz), 4.26 (s, 2H), 7.06–7.4 (m, 10H).