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$TiCl(O^iPr)_3$ and $NaBH(OAc)_3$: an efficient reagent combination for the reductive amination of aldehydes by electron-deficient amines

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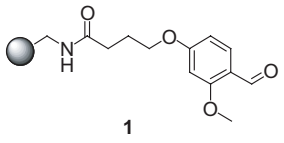
Abstract—Sodium triacetoxyborohydride, $NaBH(OAc)_3$ with tri-isopropoxytitanium chloride, $TiCl(O^iPr)_3$ is a useful reagent combination for reductive amination. Electron-deficient amines and heteroaromatic amines such as 2-aminopyrimidine and 2-aminothiazole can be reductively alkylated at room temperature to afford the corresponding secondary amines in good yields.

Reductive amination of aldehydes and ketones is an important reaction that is used extensively in organic synthesis. The two-step transformation proceeds via the formation of an imine that is reduced to the corresponding amine by a variety of reducing agents, including $NaBH_3CN$, $NaBH(OAc)_3$,[1] $NaBH_4$, decaborane[2] and $PyBH_3$.[3] In some cases, the condensation of the amine with a carbonyl compound is promoted by the use in situ of Lewis acids such as $ZnCl_2$, $TiCl_4$[4] and $Ti(O^iPr)_4$.[5–7]

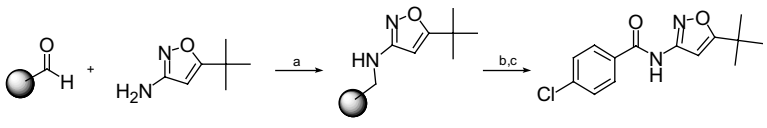


1

Figure 1. Aldehyde linker.

Reductive amination of aldehydes and ketones is also commonly used in solid phase chemistry for the formation of the C–N bond.[8–10] A number of sulfonamide and amide libraries have been generated on solid support by the reductive amination of a resin bound aldehyde followed by reaction of the resulting secondary amines with an electrophile.[11–15] These literature reports suggest that the reaction is best performed with alkylamines or electron rich anilines.

Part of our current work is concerned with the design and solid phase synthesis of libraries directed against a variety of anticancer targets. To increase diversity in the amine set, we attempted the reductive amination of a resin bound aldehyde linker (Fig. 1) with electron-deficient anilines and heterocyclic amines, for example, 2-aminopyrimidine, and 2-aminothiazole. Yields were poor under a variety of conditions and it should be noted that literature reports regarding the solid phase



Scheme 1. Solid phase reductive amination of 1 with 3-amino-5-*tert*-butylisoxazole. Reagents and conditions: (a) see text; (b) 4-chlorobenzoyl chloride (10 equiv), $^iPrNEt_2$ (10 equiv), DMAP (1 equiv), CH_2Cl_2, 16 h, rt; (c) 20% TFA/CH_2Cl_2, 1 h, rt.

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Table 1. Solid phase reductive amination of **1** with 3-amino-5-*tert*-butylisoxazole

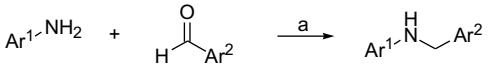
Entry	Method	Yield[a] (%)	Purity[b] (%)
1	5% AcOH/DMF/$NaBH(OAc)_3$	53	20
2	Decaborane/MeOH	45	65
3	$Ti(O^iPr)_4/NaBH(OAc)_3$,	43	90
4	$TiCl(O^iPr)_3/NaBH(OAc)_3$	66	92

[a] Percent yield refers to weight of crude product based on the theoretical loading of the resin.
[b] LC–MS purity.

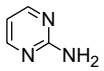
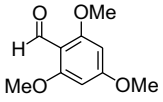
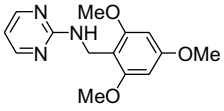
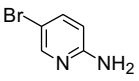
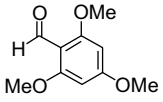
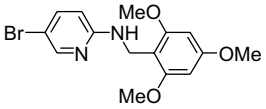
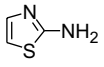
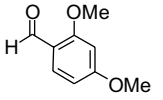
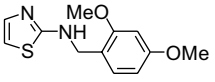
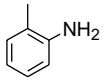
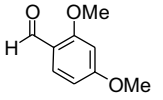
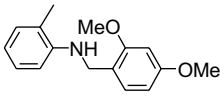
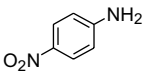
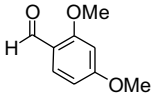
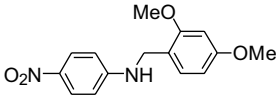
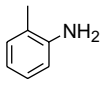
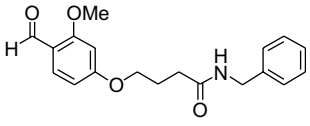
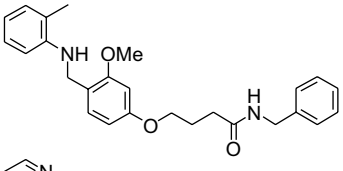
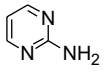
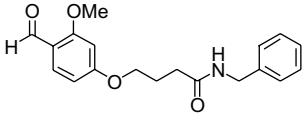
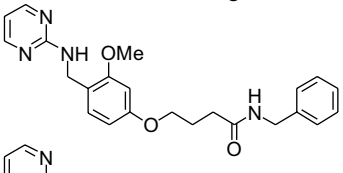
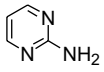
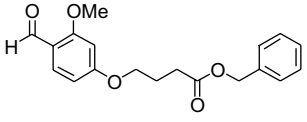
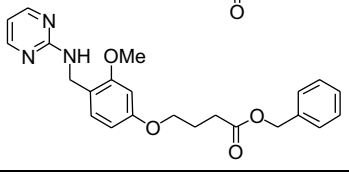
reductive amination of aldehyde linkers with deactivated anilines or heteroaromatic amines are rare.[15] A systematic investigation to identify the optimal conditions for this type of reaction was therefore undertaken. Initial reaction conditions were investigated on the solid phase using 3-amino-5-*tert*-butyl isoxazole and commercially available 4-(4-formyl-3-methoxyphenoxy)butyryl resin (Scheme 1). The resin bound amine was treated with 4-chlorobenzoyl chloride to give an amide that could be cleaved of the resin with 20% trifluoroacetic acid (TFA) in CH_2Cl_2. The products were then analysed by LC–MS to determine purity (Scheme 1, Table 1).

Initial efforts to find a workable system for the reductive amination of linker **1** with 3-amino-5-*tert*-butyl isoxazole using $NaBH(OAc)_3$ with 5% AcOH in DMF gave poor yields and purity (Table 1, entry 1). Decaborane in methanol has been used for the successful reductive amination of aldehydes with anilines in solution phase, but did not give satisfactory results on solid phase (Table 1, entry 2). $Ti(O^iPr)_4/NaBH(OAc)_3$ has also been shown to be effective for solid phase reductive amination, but in this case, gave low yields (Table 1, entry 3). It was hypothesised that replacing one of the

Table 2. Solution phase reductive amination of aldehydes



Conditions: a) $TiCl(O^iPr)_3$, CH_2Cl_2, room temp, 5 min., then $NaBH(OAc)_3$, room temp, 16 h

Entry	Amine	Aldehyde	Product	Yield (%)
1				59
2				43
3[16]				72
4				79
5				89
6				68
7				50
8				61

isopropoxide ligands with a chlorine atom would increase the Lewis acidity of the reagent and facilitate the condensation of the amine with the aldehyde. Indeed, use of $TiCl(O^iPr)_3$ and subsequent treatment with $NaBH(OAc)_3$ gave higher yields and excellent purity (Table 1, entry 4).

Encouraged by these preliminary results on solid phase, a closer investigation of $TiCl(O^iPr)_3$ in solution was undertaken. Using 3-amino-5-*tert*-butylisoxazole as the amine component and 2,4-dimethoxybenzaldehyde, as a model for linker **1**, imine formation was monitored by ^1H NMR spectroscopy following the disappearance of the C*H*O signal at $\delta = 10.2$. When 1 equiv of aldehyde and 1.1 equiv of the amine were shaken with 1.1 equiv of $TiCl(O^iPr)_3$ in $CDCl_3$ for 5 min the intensity of the aldehyde signal was reduced by ca. 50%, and a new singlet appeared at $\delta = 9.1$ corresponding to the expected imine. Prolonged shaking at room temperature for up to 24 h did not significantly change the ratio of aldehyde to imine, but addition of 1.1 extra equivalents of $TiCl(O^iPr)_3$ caused the compete disappearance of the aldehyde peak in the ^1H NMR spectra within 5 min. Addition of $NaBH(OAc)_3$ then effected complete reduction of the imine.

The scope for performing reductive amination in situ was then explored using 2.2 equiv of $TiCl(O^iPr)_3$, $NaBH(OAc)_3$ and 1.1 equivalent of amine. Under these conditions it was possible to reductively aminate electron rich aldehydes with deactivated heterocyclic amines, such as 2-aminopyridine and 2-amino-5-bromopyridine (Table 2, entries 1 and 2). Likewise, the reaction proceeded in good yields with sterically hindered 2-aminotoluene (Table 2, entry 4) or with deactivated 4-nitroaniline (Table 2, entry 5). Both ester and amide functionalities were tolerated under the reaction conditions (Table 2, entries 6–8). Yields of 50–89% were achieved.

In conclusion, we have found that $TiCl(O^iPr)_3$ in combination with $NaBH(OAc)_3$ is a useful system for the reductive amination of aldehydes with a variety of electron-deficient amines. These reaction conditions are currently being evaluated on the solid phase and will be reported in future communications.

Acknowledgements

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References and notes

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16. Representative procedure: Synthesis of (2,4-dimethoxybenzyl)-thiazol-2-yl-amine (Table 2, entry 3): To a stirred solution of 2-aminothiazole (0.110 g, 1.1 mmol, 1.1 equiv) and 2,4-dimethoxybenzaldehyde (0.166 g, 1.0 mmol, 1 equiv) in anhydrous CH_2Cl_2 (3 mL) was added $TiCl(O^iPr)_3$ (0.524 mL, 2.2 mmol, 2.2 equiv) in one portion under argon. The solution was stirred for 5 min before the portionwise addition of freshly ground $NaBH(OAc)_3$ (1.05 g, 5 mmol, 5 equiv) (caution: exothermic reaction and evolves gas) and three drops of AcOH. The reaction mixture was stirred for an additional 6 h, then poured into saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (4×10 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica (Et_2O–CH_2Cl_2; v/v 1:1) to give 181 mg (79%) of the title compound as a white solid; mp: 115–117 °C; ν_{max} (thin film)/cm^{-1} 3390 (NH), 1155 (OMe); ^1H NMR ($CDCl_3$, 250 MHz): δ 3.80 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 4.38 (s, 2H, C*H*$_2$), 6.46 (m, 3H, thiazole, Ph H-3, and Ph H-5), 7.10 (d, $J = 3.6$ Hz, 1H, thiazole), 7.22 (d, $J = 8.0$ Hz, 1H, Ph H-6); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 45.6, 55.4, 55.4, 98.7, 103.8, 106.3, 118.3, 130.2, 139.0, 158.6, 160.7, 170.5; Found C, 57.29; H, 5.65; N, 10.84; $C_{12}H_{14}N_2O_2S$ requires C, 57.58; H, 5.64; N, 11.19.