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Reactivity switching on solid support: solid-phase synthesis of tertiary amines by reduction of tertiary amides with $LiAlH_4$

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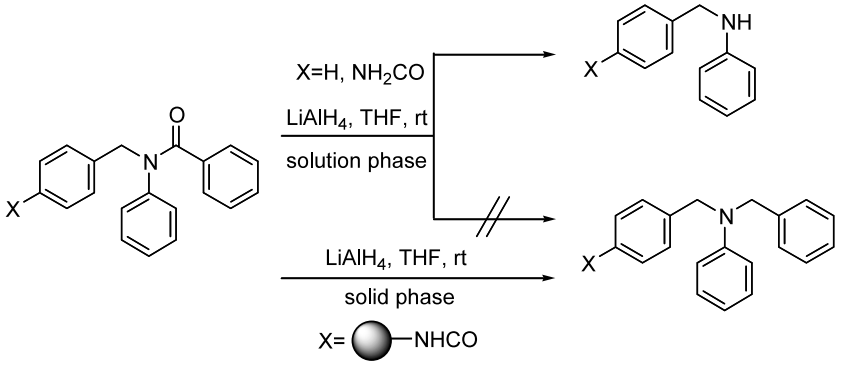
Abstract—Reactivity of $LiAlH_4$ was controlled by using solid-phase reaction conditions. Tertiary amides bound to gel-type polystyrene support were reduced with $LiAlH_4$ to give tertiary amines with satisfactory purity, whereas the reduction of similar tertiary amides in solution gave secondary amines as main products. Solid-phase synthesis of tertiary amine libraries was achieved by using this method.

Solid-phase synthesis has proved to be useful for library preparation of small organic molecules, since it helps in both expediting the preparation and increasing the diversity of the molecules.[1,2] In addition, solid-phase synthesis may enable new reactions which can not be effected by traditional solution synthesis. Reactions on solid-support generally proceed slowly in comparison to those in solutions owing to the low diffusion rate of reagents in polymer-support. We, therefore, expected that reactivity of reagents could be controlled by using solid-phase reaction conditions. In the present study, we found that tertiary amides (*N*-aryl-*N*-benzylbenzamides) bound to gel-type polystyrene support were reduced with $LiAlH_4$ to give tertiary amines, whereas the reduction of similar tertiary amides in solution generally gives secondary amines as main products.

Tertiary amines are an important class of compounds for the drug discovery process, due to their good intestinal absorption, CNS (central nervous system) penetration, and the potential for involvement of the tertiary nitrogen in ligand binding.[3] Several studies for the synthesis of tertiary amines on solid support have been reported.[4–19]

It is well known that reduction of primary and secondary amides affords the corresponding primary and secondary amines in good yields with $LiAlH_4$. Reduction of tertiary amides, however, generally gives secondary amines when the *N*-substituents are bulky.[20] In fact, the reduction of *N*-benzyl-*N*-phenylbenzamide with $LiAlH_4$ in solution gave benzylphenylamine as the sole product. On the other hand, the reduction of



Scheme 1.

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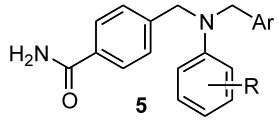
similar tertiary amides on solid-support (1% divinylbenzene cross-linked polystyrene resin, 100–200 mesh) afforded the corresponding tertiary amines as the main products (Scheme 1). The amide bond in Rink amide linker was not reduced under present conditions probably owing to the steric hindrance of benzhydryl group and/or polystyrene.

A new efficient route for the solid-phase synthesis of tertiary amines was then established via reduction of resin-bound *N*-aryl-*N*-benzylbenzamides with $LiAlH_4$ (Scheme 2). We introduced two points of diversity using readily available anilines and acyl chlorides. The reaction sequence began with deprotection of Fmoc-protected Rink amide resin (NOVABIOCHEM, Rink amide resin) **1** using a solution of 20% piperidine in DMF. 4-(Chloromethyl)benzoyl chloride was then coupled onto the resin to give the resin-bound benzyl chloride **2**. The chloride on resin **2** was substituted with anilines to give the resin-bound secondary amines **3**, which were coupled with acyl chlorides to give the resin-bound *N*-aryl-*N*-benzylbenzamides **4**. ESI-MS spectra of the synthetic intermediates (secondary amines **3** and tertiary amides **4**) cleaved from the resin by TFA showed that the reactions proceeded almost quantitatively. Reduction of the *N*-aryl-*N*-benzylbenzamides **4** on solid support was carried out by using $LiAlH_4$.[21] Since a small amount of arylbenzylamine was formed by the reduction, the resulting secondary amine was quenched by addition of succinyl chloride and triethylamine. The resin was then treated with 10% TFA in CH_2Cl_2. The reaction mixture was passed through anion-exchange resin (VARIAN BOND ELUT® Jr-PSA) and the eluate was concentrated in vacuo to give the desired tertiary amines. Both TFA and the *N*-succinylated secondary amines were easily removed by the anion-exchange resin. The yields and purities of tertiary amines are summarized in Table 1. When aniline and various benzoyl chlorides were used (entries 1–10), the desired tertiary amines were obtained in satisfactory yield (65–76%) and purity (79–90%) except for 4-bromobenzoyl chloride (54% purity). The low purity in the latter case was due to the formation of a debrominated product. Reduction of tertiary amides having a nitrobenzoyl moiety gave the secondary amine (entry 11).[22] Alkyl or methoxy substituents on the *N*-phenyl moiety did not influence the yield (59–72%) and purity (56–91%) (entries 12–23).

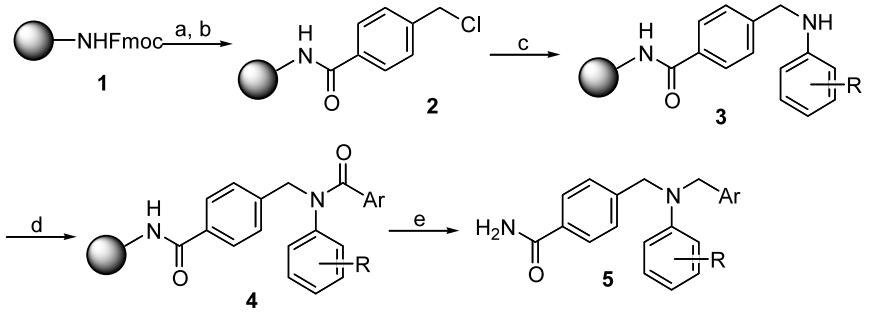
Reduction with $LiAlH_4$ in solid-phase synthesis is additionally advantageous in that the inorganic salt formed by the reduction can be readily removed by just filtration and washing with aqueous acetic acid and aqueous methanol.

Table 1. Yields and purities of tertiary amines



Entry	R	Ar	Yield (%)[a]	Purity (%)[b]
1	H	Phenyl	66	89
2	H	*p*-MeO-C_6H_4	71	79
3	H	*p*-Me-C_6H_4	72	81
4	H	*o*-Me-C_6H_4	76	84
5	H	*p*-F-C_6H_4	66	80
6	H	*p*-Br-C_6H_4	65	54 (22)[c]
7	H	4-Biphenyl	66	90
8	H	Naphthyl	66	84
9	H	2-Furyl	70	86
10	H	2-Thienyl	71	84
11	H	4-NO_2-C_6H_4	–	–[d]
12	2-Me	Phenyl	72	91
13	2-Me	*p*-MeO-C_6H_4	64	76
14	2-Me	*p*-Me-C_6H_4	69	81
15	4-Me	Phenyl	71	91
16	4-Me	*p*-MeO-C_6H_4	59	74
17	4-Me	*p*-Me-C_6H_4	60	88
18[e]	4-OMe	Phenyl	61	76
19[e]	4-OMe	*p*-MeO-C_6H_4	62	56
20[e]	4-OMe	*p*-Me-C_6H_4	62	71
21	4-*t*Bu	Phenyl	66	87
22	4-*t*Bu	*p*-MeO-C_6H_4	70	83
23	4-*t*Bu	*p*-Me-C_6H_4	69	85
24	4-Br	Phenyl	46	37 (24)[c]
25	4-Br	*p*-MeO-C_6H_4	49	46 (17)[c]
26	4-Br	*p*-Me-C_6H_4	49	44 (16)[c]

[a] Yield of crude product based on resin substitution.
[b] Purity was based on the peak area of HPLC of crude products as detected at 254 nm.
[c] Number in parentheses refers to the ratio of debrominated compound.
[d] Deacylated secondary amine was obtained.
[e] Alkylation of *p*-anisidine (Scheme 2, step c) was carried out at 50°C.



Scheme 2. *Reagents and conditions*: (a) 20% piperidine/DMF; (b) 4-(chloromethyl)benzoyl chloride, iPr_2EtN, CH_2Cl_2; (c) anilines, DMF, 80°C; (d) ArCOCl, Et_3N, CH_2Cl_2; (e) $LiAlH_4$, THF; succinyl chloride, Et_3N, CH_2Cl_2; 10% TFA in CH_2Cl_2.

In conclusion, a novel solid-phase synthesis of tertiary amines was effected through reduction of *N*-aryl-*N*-benzylbenzamides **4** with $LiAlH_4$. The present method allows facile introduction of diversity by the use of commercially available amines and acyl chlorides.

Acknowledgements

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21. The reduction of tertiary amides on solid support was carried out as follows: To the resin-bound *N*-aryl-*N*-benzylamides **4** (100 mg, 0.066 mmol) were added THF (1 ml) and $LiAlH_4$ (25 mg, 0.66 mmol). The mixture was agitated for 1 h at room temperature. The reaction mixture was quenched with AcOEt (0.5 ml) for 10 min and the mixture was filtered. To the resin was added MeOH:H_2O = 1:1 (1 ml) and the mixture was filtered, washed with AcOH:H_2O = 1:1 (3×1 ml), MeOH:H_2O = 1:1 (3×1 ml), MeOH (3×1 ml) and CH_2Cl_2 (3×1 ml). To the resin were added CH_2Cl_2 (1 ml), Et_3N (0.101 ml, 0.73 mmol) and succinyl chloride (0.036 ml, 0.33 mmol). The mixture was agitated for 2 h at room temperature. The reaction mixture was filtered, washed with CH_2Cl_2 (3×1 ml), pyridine (3×1 ml), MeOH:H_2O = 1:1 (1×1 ml), AcOH:H_2O = 1:1 (3×1 ml), MeOH:H_2O = 1:1 (3×1 ml), MeOH (3×1 ml) and CH_2Cl_2 (3×1 ml). The resin was treated with 10% TFA in CH_2Cl_2 (1 ml) and the mixture was agitated for 30 min at room temperature. The reaction mixture was passed through VARIAN BOND ELUT® Jr-PSA and eluted with 5% MeOH in CH_2Cl_2 to give the desired tertiary amines.
22. Reduction of tertiary amides having nitrobenzoyl moiety with $NaBH_3(OCOCF_3)$ gave the mixture of desired tertiary amines and starting materials.