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Synthesis of Primary Amines *via* Nucleophilic Addition of Organometallic Reagents to Aldimines on Solid Support

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Abstract: Resin-immobilized aldimines **5**, derived from the condensation of amine-functionalized Rink polystyrene resin with aldehydes, react with Grignard reagents, lithium reagents or $LiBH_4$ to afford a wide variety of primary amines in good to excellent yields upon trifluoroacetic acid cleavage. In this amine synthesis, Rink resin functions both as a solid support and as a NH protecting group.
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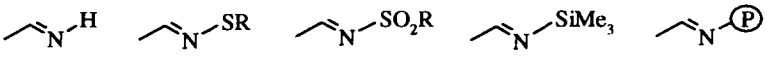
The rapid synthesis of a wide variety of compounds greatly facilitates the discovery of biologically active agents.[1,2] The ability to generate libraries of commercially unavailable primary amines is a valuable tool in this process since a large number of primary amines show biological activity.[3-5] Moreover, customized libraries of primary amines could be used as inputs for the preparation of further libraries.

Solution phase reactions of imines with Grignard and lithium reagents have been well documented.[6-8] Although, yields in some cases are not satisfactory due to relatively poor electrophilicity of the imine carbon, the reactions are well suited for the synthesis of secondary amines.[8,9] However, imines of ammonia **1** are easily hydrolyzed and undergo selfcondensation reactions,[6] thus to prepare primary amines, "masked" imine derivatives of ammonia, such as sulfenimines **2**,[10] sulfonimines **3**,[11,12] and *N*-trimethylsilylimines **4**,[13,14] have been developed. They react with organometallic reagents followed by the removal of the protecting group to give primary amines.

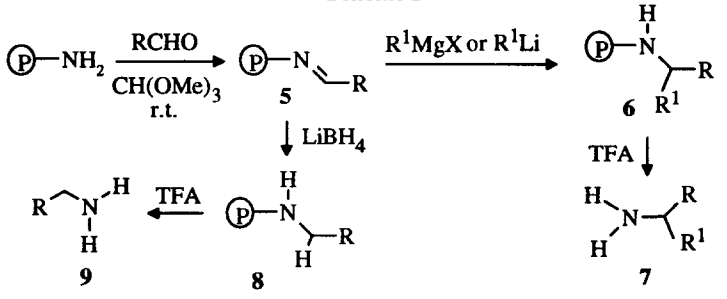


1 **2** **3** **4** **5**

Our interests in preparing combinatorial libraries *via* solid phase organic chemistry (SPOC) led us to devise a means to create primary amines. We found that none of the cited "masked" imines were suitable for SPOC.

We now report the efficient preparation of a wide range of primary amines in good to excellent yields *via* nucleophilic additions of organometallic reagents to resin-immobilized aldimines **5** on Rink resin, which functions both as a solid support and as an NH protecting group.

Scheme 1



Aldehydes were condensed with Rink amine resin in trimethyl orthoformate to give polymer-bound aldimines **5** according to the literature procedure.[15] Resin-immobilized aldimines **5** reacted with a range of Grignard reagents at 60 °C or lithium reagents at -78 °C to 20 °C, to give the corresponding primary amines **7a-n** in good yield and purity in most cases after TFA cleavage (Table 1).[16] Aldimines derived from both electron-rich (entries 2 and 3) and electron-deficient (entries 4, 5, 6, 7, 8, 10, 11, 13, 16) aldehydes worked well.

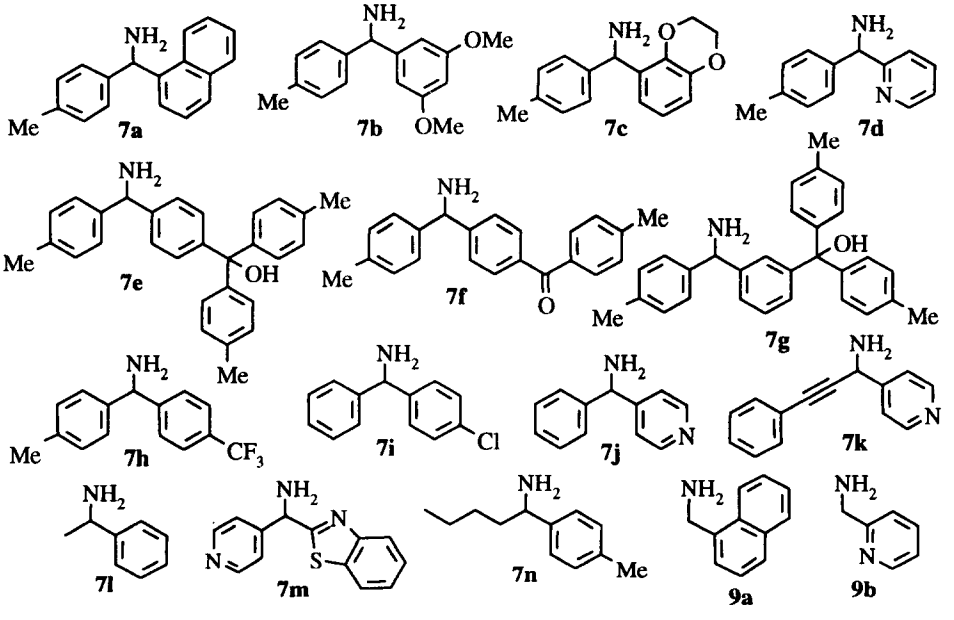


Table 1. Preparation of Primary Amines **7a-n** and **9a,b**

entry	aldehyde	organometallic or $LiBH_4$	product	yield [17] (%)	purity [18] (%)
1	1-naphthaldehyde	4-MeC_6H_4MgBr	**7a**	89	92
2	1,5-dimethoxybenzaldehyde	4-MeC_6H_4MgBr	**7b**	99	93
3	1,4-benzodioxan-6-carboxaldehyde	4-MeC_6H_4MgBr	**7c**	89	84
4	2-pyridinecarboxaldehyde	4-MeC_6H_4MgBr	**7d**	100	87
5	4-carboxybenzaldehyde	4-MeC_6H_4MgBr	**7e**	65	100
6	4-cyanobenzaldehyde	4-MeC_6H_4MgBr	**7f**	94	78
7	3-carboxybenzaldehyde	4-MeC_6H_4MgBr	**7g**	55	100
8	4-trifluoromethylbenzaldehyde	4-MeC_6H_4MgBr	**7h**	100	73
9	4-chlorobenzaldehyde	PhMgBr	**7i**	99	90
10	4-pyridinecarboxaldehyde	PhMgBr	**7j**	82	78
11	4-pyridinecarboxaldehyde	PhC≡CMgBr	**7k**	45	65 [a]
12	benzaldehyde	MeMgI	**7l**	91	89
13	4-pyridinecarboxaldehyde	2-lithiobenzothiazole	**7m**	100	42 [a]
14	4-methylbenzaldehyde	*n*-BuLi	**7n**	64	69
15	1-naphthaldehyde	$LiBH_4$	**9a**	74	86
16	2-pyridinecarboxaldehyde	$LiBH_4$	**9b**	100	100

[a] The balance consists of unidentified impurities.

Interestingly, treatment of the aldimine derived from 4-cyanobenzaldehyde with 4-methylphenylmagnesium bromide (entry 6), gave amine **7f** *via* nucleophilic addition of the Grignard reagent to both the imine and the cyano functionalities. Similar reactions of aldimines from 3-carboxybenzaldehyde (entry 7) and 4-carboxybenzaldehyde (entry 5) led to **7g** and **7e**, respectively, *via* addition of 4-MeC_6H_4MgBr to the imine groups and double addition to the carboxy groups.

Lithium borohydride was also reacted with polymer-bound aldimines **5** to provide primary amines **9a** and **9b** in good yield and purity after THF cleavage.[16]

In summary, nucleophilic addition of Grignard reagents and lithium reagents to aldimines on solid support potentially permits the rapid synthesis of the primary amine library, which illustrates the synthetic value of **5** as polymer-bound "masked" imine derivatives of ammonia. Most of the amines prepared in Table 1 are not commercially available. Most of the crude amine products are of sufficient purity to be used in subsequent reactions. Attempts to extend this method to enolizable aldehydes failed.

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16. **General Procedure for the Preparation of Amines 7a-n, 9a,b.** (i) To 2 bags[19] of resin **5** (loading 0.47 mmol/g, 100 mg/bag, 100-200 mesh) under N_2 was added an appropriate Grignard reagent (1 *M* in Et_2O, 15 mL), and dry toluene (15 mL). The mixture was stirred at 60 °C for 24 h (for **7a-l**); (ii) To 2 bags of resin **5** in THF (30 mL) at -78 °C under argon was added an appropriate lithium reagent (1.6 *M*, 12.5 mL). The bags were kept at -78 °C to 0 °C for 24 h and then at 20 °C for an additional 7 h (for **7m,n**); (iii) To 2 bags of resin **5** in THF (30 mL) was added $LiBH_4$ (15 mmol, 0.33 g). The mixture was stirred at 70 °C for 5 h (for **9a,b**). The bags were washed with water (3 × 40 mL), MeOH (3 × 40 mL), DCM (40 mL), MeOH (40 mL), DCM (40 mL), MeOH (40 mL), and dried in a vacuum desicator overnight. A bag of the resulting resin **6** was shaken with TFA (5%, 1 mL) and H_2O (5%, 1 mL) in DCM (18 mL) at rt for 5 h. At 0 °C, the mixture was neutralized with NaOH (aq. 20%) until basic. The organic layer was separated. The bag was washed with DCM (3 × 20 mL) and each extract was sequentially poured into the aqueous layer in the separation funnel to extract the product. The combined organic extracts were dried over anhydrous sodium sulfate and the solvent evaporated to give the corresponding amine. Amines **7a-n** and **9a,b** were characterized by their ^1H NMR spectra and mass spectra. For prior methods for the addition of Grignard reagents and alkyl lithiums to resin bound imines, see: a) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999. b) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1979. c) For the additon of silyl enol ethers to imines, see Kobayashi, S.; Moriwaki, M.; Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahetron Lett.* **1996**, *37*, 7783.
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