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Efficient synthesis of tertiary amines from secondary amines

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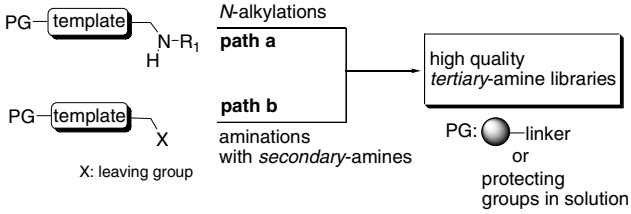
Abstract—Reliable N-alkylations of secondary amines have been developed. By using DIAD and TPP (or PS-TPP) a variety of secondary amines can be converted to the corresponding tertiary amines in good to excellent yields with diverse alkylhalides; no formation of quaternary amine salts are observed. These protocols are amenable to combinatorial chemistry libraries, and are also useful for the syntheses of secondary amines by an acid lysis of the cleavable tertiary amino resins.

We recently validated that menaquinone A (MenA),[1] the sixth enzyme in menaquinone biosynthesis, is a novel tuberculosis (TB)-drug target. In the discovery of MenA inhibitors, we observed that a tertiary amine in the molecule is a critical functional group to exhibit high affinity against MenA enzyme.[2] Although X-ray crystal structure of MenA has not been available, however, analysis of the amino acid sequence of MenA was revealed that MenA is likely to have five transmembrane segments and has highly conserved Asp (D) which would be located in the inner-plasma membrane as being predicted by using a prediction program (Sosui).[3] Therefore, it was speculated that tertiary amine functional group in the inhibitor molecules would increase affinity by forming an ionic interaction with Asp residue(s) in the binding site.[4]

In an attempt to deliver target-specific library for the development of MenA inhibitors, we recognized that no reliable method of the synthesis of tertiary amines that can diversify secondary amines both in solution and solid phase has been available in literatures. Especially high-throughput synthesis on polymer-support requires complete conversions (near quantitative yields) with diverse structure of building blocks. Therefore, secondary amines in combinatorial libraries have never been utilized in generating a library of tertiary amine containing small molecules (path a in Scheme 1). On the contrary, successful aminations of alkyl halides with



Scheme 1. Synthesis of tertiary amine libraries in solution or solid phase.

secondary amine to form tertiary amines vary depending on the nucleophilicity of secondary amine and leaving aptitude of R–X (path b in Scheme 1). In addition, the generation of tertiary amine in path b requires diverse structures of low-molecular-weight secondary amine building blocks, which, however, has been limited by the lack of availability from commercial sources. Nonetheless, two pathways in Scheme 1 would serve as complementary manner to generate libraries of tertiary amine molecules.[5]

We have encountered difficulty in using direct N-alkylation methods published in literatures for the synthesis of tertiary amines on the polymer-support. An inherent problem of the synthesis of tertiary amine from secondary amines is an incomplete reaction and/or the formation of a quaternized amine as a by-product. Recently, several useful methods for the syntheses of secondary and tertiary amines from primary alcohols have been reported.[6] On the other hand, none of direct N-alkylation methods is sufficient due to the problems described above.

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As a result of reaction screenings it was found that methylation of secondary amines with methyl iodide on the polymer-support using triphenylphosphine (TPP) and diisopropylazocarboxylate (DIAD) in THF provided the corresponding tertiary amines in good yields (>95%) after cleavage; no quaternizations were observed even with a large excess of methyl iodide.

Efficient direct N-methylations can likely be attributed to the following reasons. The reagent generated under dialkylazocarboxylate and triphenylphosphine deprotonates secondary amine through a transition state **iii** to afford the intermediate **iv** that react with methyl iodide. The generated tertiary amines would form the complexes with an ionic species such as Ph_3PI_2.[7] Complexation of tertiary amines with generated by-product(s) prevents quaternization with an excess of methyl iodide (Scheme 2).

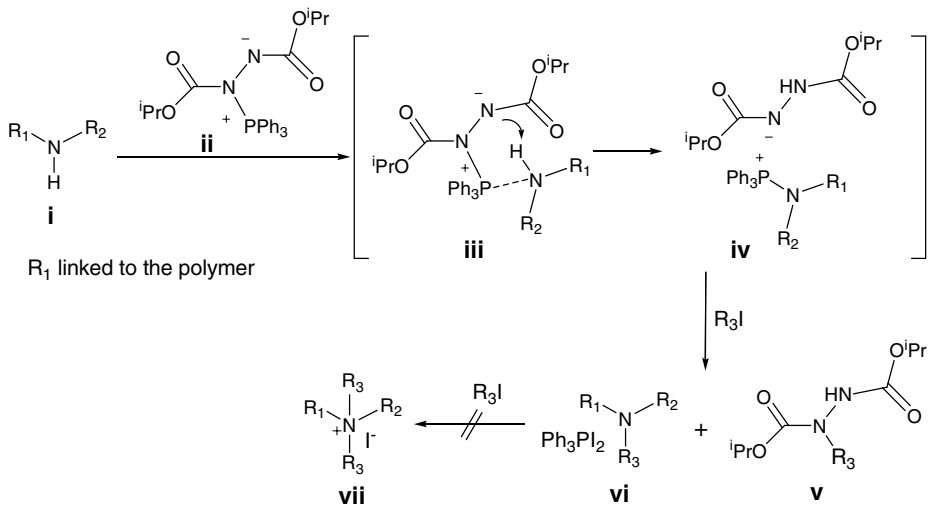
Although a combination of trialkyl or triphenylphosphine and dialkylazocarboxylate (Mitsunobu conditions) have been utilized in the syntheses of esters, phenol ethers, aminations of alcohols, and iodinations of alcohols, Mitsunobu conditions had never been applied to the syntheses of tertiary amines from secondary amines.[8]

To explore the scope and limitations of the tertiary amine synthesis using TPP (or polymer-bound TPP (PS-TPP))/DIAD/alkyl halide, a variety of secondary amines were tested against representative alkyl halides. In order to facilitate the purification of generated tertiary amines, PS-TPP was utilized in the solution reactions. As summarized in Table 1, dialkylamines, dibenzylamines, and phenylmethylamines, **1a**–**1i**, reacted with methyl, ethyl, and butyl iodides to afford the corresponding tertiary amines, **2a**–**2t**, in greater than 90% yields. Although ally bromide and benzyl bromide were applicable to the PS-TPP/DIAD mediated N-alkylation reactions, the corresponding chlorides did not exhibit good enough electrophilicity; the reactions with ally chloride and benzyl chloride gave the desired products in less than 5% conversion. Thus, direct N-alkylations of secondary amines were achieved in excellent yields with alkyl iodides, and allyl and benzyl bromides. Because acid-cleavable *p*-methoxybenzylamine derivatives such as **1f** in Table 1 are excellent substrates for the N-alkylation reactions, we next demonstrated utility of this protocol for the syntheses of low-molecular-weight secondary amine building blocks which are applied to diversifying combinatorial library molecules through path b in Scheme 1.

As summarized in Table 2, secondary amine salts were synthesized by HCl cleavage of the *p*-methoxybenzyl group of **4** and **7**. The tertiary amine resins **7** were synthesized in reliable two steps, reductive amination ($NaBH_4$, $Ti(O^iPr)_4$)[9] and N-alkylation (DIAD, TPP, alkyl halides). N-Alkylation on the polymer-support followed by acid cleavage is very useful protocol for the synthesis of low-molecular-weight secondary amine building blocks; secondary amines can be synthesized without no purification throughout this sequence.

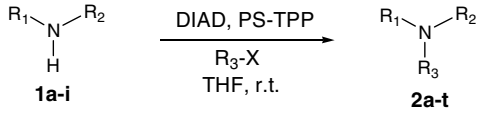
In summary, direct N-alkylation of secondary amines that is amenable to the reactions on the polymer-support are demonstrated. Although the syntheses of tertiary amines described here is not using a new reagent, these protocols, however, are exceedingly useful for the generation of tertiary amine containing library molecules. We are currently applying the described N-alkylation method to deliver small optimized libraries for the development of MenA inhibitors.

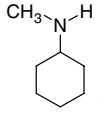
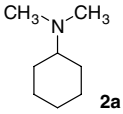
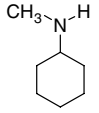
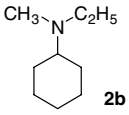
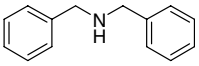
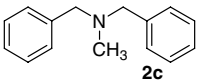
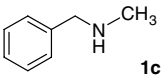
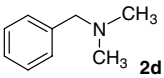
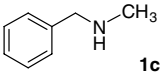
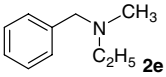
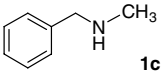
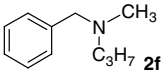
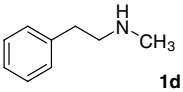
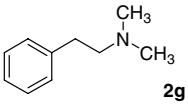
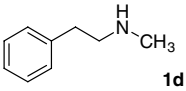
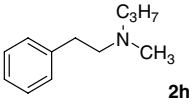
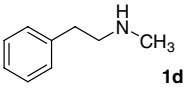
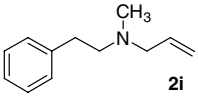
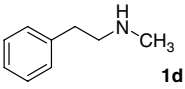
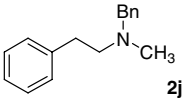
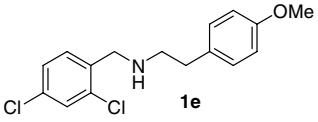
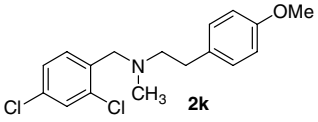
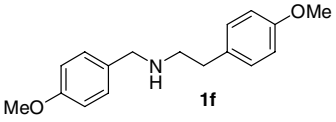
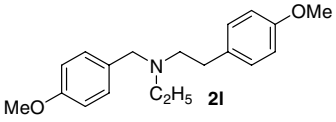
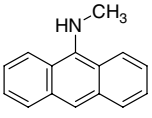
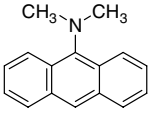
General procedure for the synthesis of tertiary amine in solution phase. To a stirred suspension of the secondary amine (1.0 mmol), PS-TPP (~3.0 mmol/g, 1.5 equiv), and DIAD (1.5 mmol) in THF (5 mL) was added alkyl iodide (3 mmol). The reaction was stirred gently at rt for 12 h and the reaction mixture was filtered, and all volatiles are evaporated in vaccuo. The crude product was purified through a silica gel pad to provide tertiary amine.



Scheme 2. Plausible mechanism of N-alkylation of secondary amine with TPP, DIAD, and alkyl iodides.

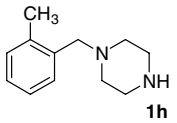
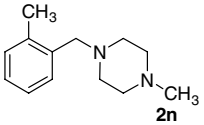
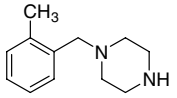
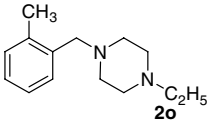
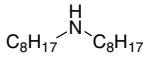
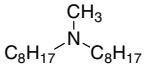
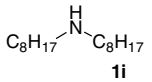
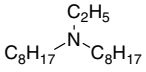
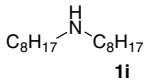
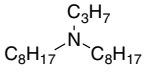
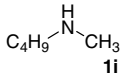
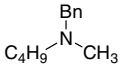
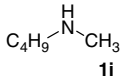
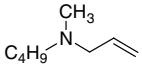
Table 1. N-alkylations of secondary amines[a]



Entry	Secondary amines	R_3–X	Product	Yield (%)
1	 **1a**	MeI	 **2a**	95
2	 **1a**	EtI	 **2b**	90
3	 **1b**	MeI	 **2c**	90
4	 **1c**	MeI	 **2d**	98
5	 **1c**	EtI	 **2e**	95
6	 **1c**	BuI	 **2f**	95
7	 **1d**	MeI	 **2g**	95
8	 **1d**	BuI	 **2h**	91
9	 **1d**		 **2i**	99
10	 **1d**	BnBr	 **2j**	97
11	 **1e**	MeI	 **2k**	96
12	 **1f**	EtI	 **2l**	93
13	 **1g**	MeI	 **2m**	98

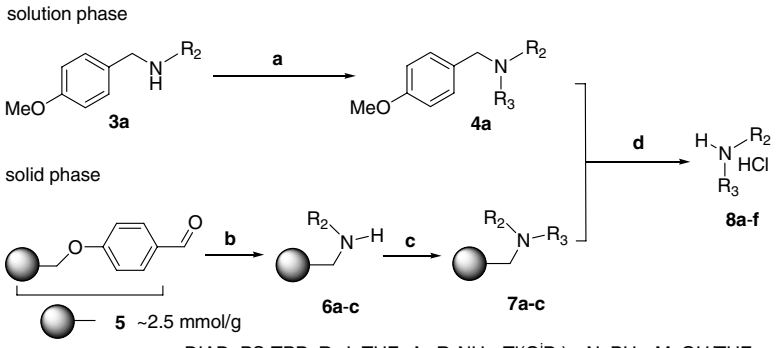
(*continued on next page*)

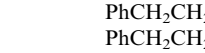
Table 1 (*continued*)

Entry	Secondary amines	R_3–X	Product	Yield (%)
14	 **1h**	MeI	 **2n**	95
15	 **1h**	EtI	 **2o**	90
16	 **1i**	MeI	 **2p**	95
17	 **1i**	EtI	 **2q**	91
18	 **1i**	BuI	 **2r**	91
19	 **1i**	BnBr	 **2s**	98
20	 **1i**		 **2t**	98

[a] All reactions were carried out at 0.1–0.2 M concentrations for 12 h.

Table 2. Syntheses of secondary amines



Entry	Secondary amine	R_2	R_3	Product	Overall yield (%) (from)
1	**3a**	$PhCH_2CH_2$	CH_3	**8a**	85 (**3a**)
2	**3a**	$PhCH_2CH_2$	C_2H_5	**8b**	80 (**3a**)
3	**3a**	$PhCH_2CH_2$	C_3H_7	**8c**	78 (**3a**)
4	**3a**	$PhCH_2CH_2$	Allyl	**8d**	78 (**3a**)
5	**6a**	$PhCH_2CH_2$	CH_3	**8a**	80 (**5**)
6	**6b**		CH_3	**8e**	85 (**5**)
7	**6c**	C_8H_{17}	CH_3	**8f**	88 (**5**)

Experimental procedure for the synthesis of secondary amines **8f** *on the polymer-support*. **6c** was synthesized by using a published procedure. The secondary amine resins **6c** (0.1 mmol) and TPP (3.0 mmol) are placed in a flask and THF (1.5 mL) was added. Into the reaction mixture DIAD (3.0 mmol) and MeI (6 mmol) were added. After 12 h, the polymers were washed with THF–water, CH_2Cl_2–THF, THF, and EtOAc. Into the

tertiary amine resins **7** in CH_2Cl_2 saturated HCl in ether was added. After 2 h, polymers were separated and all volatiles were evaporated in vaccuo to provide **8f** HCl salt. Purity of **8f** was determined by ^1H NMR analysis.

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