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Microwave-Accelerated Methodology for the Direct Reductive Amination of Aldehydes

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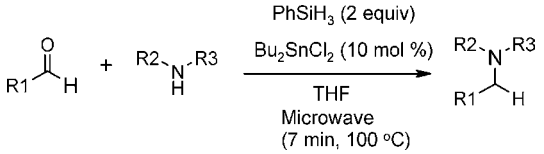
ABSTRACT



An improved procedure for the direct reductive amination of aldehydes was developed which uses dibutyltin dichloride as catalyst in the presence of phenylsilane as reductant. Rapid reaction is promoted by the use of microwave conditions with anilines, secondary and primary amines being suitable reactants.

The synthesis of secondary and tertiary amines by the reductive amination of aldehydes and ketones is usually a relatively fast and efficient reaction providing synthetically useful organic intermediates and pharmaceutically relevant compounds. A variety of methods are available for the direct reductive amination of aldehydes and ketones, the most popular using $NaBH_3CN$ or $NaBH(OAc)_3$. These reactions offer the advantages of simplicity, wide availability of substrates, mild reaction conditions, and tolerance to other functional groups. Among the most recent developments in this area is the use of a mild dibutyltin dichloride (Bu_2SnCl_2)-catalyzed procedure utilizing the selective reducing agent, phenylsilane ($PhSiH_3$), in a nonprotic solvent.[1] A further development has been described using triethylsilane for catalytic reductive alkylation of aldehydes with secondary amines using an iridium compound.[2] Both methods utilize neutral reaction conditions and mild reducing agents that tolerate the presence of other functional groups not compatible with other methods. In addition, the use of organic soluble reductants such as organosilanes removes the need for prechromatography steps during product isolation. Such manipulations are usually required when removing excess or spent organic insoluble metal salts introduced as reductants or promoters, e.g., $NaCNBH_3$.

Although these catalytic metal systems maintain the benefits and improve the methodology, there are still some limitations in substrate compatibility. Secondary alkylamines gave moderate yields while primary alkylamines gave the corresponding imines and phenylsilane decomposition. In addition, there would appear to be correlation between reaction time and reactivity (nucleophilicity) of the amine species. To extend the scope of the mild Bu_2SnCl_2 procedure, we investigated the possible use of microwave-assisted heating during both imine formation and subsequent reduction. It has been demonstrated that other metal-catalyzed reactions benefit strongly from microwave heating, exhibiting accelerated reaction cycles.[3] Moreover, microwave-assisted formation of imines and their reduction using either $NaBH_3CN$, $NaBH_4$, or $NaBH(OAc)_3$ have been previously accomplished by others.[4−7]

The effect of microwave heating on the reported protocol for direct reductive amination was tested using Bu_2SnCl_2

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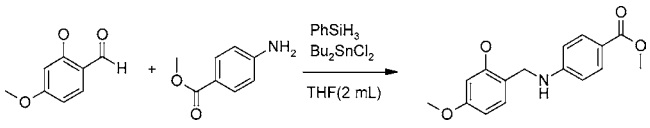
(0.02 equiv) as catalyst. It was hoped that these initial results would show a reduction in reaction times from hours to minutes. This would allow a high-throughput synthesis of a set of desired secondary amines to be realized that could be further manipulated to yield molecules of interest to ongoing research programs. The weakly nucleophilic methyl 4-aminobenzoate and 2-hydroxy-4-methoxybenzaldehyde were selected for this initial investigation. Reductive amination was promoted by $PhSiH_3$.

Table 1 shows the variation in catalyst and reductant tested

Table 1. Direct Reductive Amination with Microwave Heating[a]



entry	Bu_2SnCl_2 (mol %)	$PhSiH_3$ (equiv)	conversion[b] (%)
1	2	1.1	58[c]
2	5	1.1	64[c]
3	5	2	60[c]
4	10	0	100[d]
5	10	2	71[e]
6	0	2	nr

[a] 100 °C (150 W) for 7 min (including 2 min ramp time). [b] Conversion measured by HPLC. [c] Aldehyde, amine, and imine observed. [d] Only imine was observed. [e] Isolated yield of analytically pure product.

to find optimum conditions for the microwave-promoted reaction. The initial conditions (entry 1) did not fully convert the starting materials to either imine intermediate or product amine; therefore, both catalyst and reductant were increased. Full conversion to imine within the microwave heating time could be achieved with 10 mol % of Bu_2SnCl_2, and increasing the reductant to 2 equiv consumed all imine formed. This revised protocol gave 71% overall yield of isolated (via column chromatography), analytically pure compound (entry 5). In the absence of catalyst, no reaction occurred (entry 6). With a set of microwave conditions now in hand, their generality was examined using a variety of anilines and aldehydes (Table 2).[8]

The microwave reaction conditions appear to allow the use of a variety of starting materials confirming the benefit of microwave heating. All of the imines were reduced readily yielding the expected secondary amines, except entry 10. The high conversion rates and good yields indicated that both imine formation and imine reduction rates were considerably enhanced by microwave heating. As reported earlier, no reduction occurred in the absence of catalyst.

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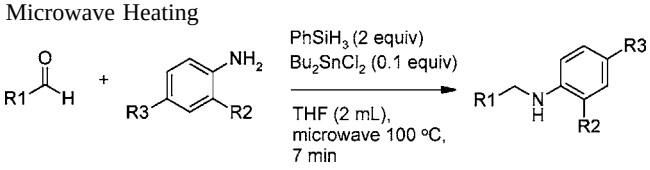
(8) **General Experimental Procedure.** Aldehyde (1 mmol) and aniline (1 mmol) were added to a solution of dibutyltin dichloride (10 mol %) in 2 mL of THF at room temperature. Phenylsilane (2 mmol) was added, and the vial was capped and heated in the microwave reactor at 100 °C for 7 min (2 min ramp time followed by 5 min at 100 °C). The reaction mixture was evaporated and purified on silica eluting with ethyl acetate/hexane.

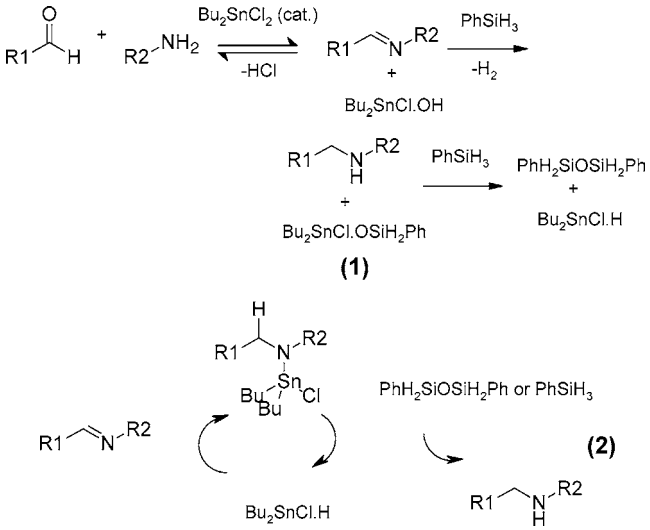
Table 2. Direct Reductive Amination of Aldehydes with Microwave Heating



entry	R1	R2	R3	yield[a] (%)
1	PhCH=CH	H	H	80[b]
2	4-$(CH_3O)C_6H_4$	H	H	73
3	$(CH_3)_2CH$	H	H	65
4	PhCH=CH	$CH_3OC{=}O$	Cl	55
5	4-$(CH_3O)C_6H_4$	$CH_3OC{=}O$	Cl	71
6	$(CH_3)_2CH$	$CH_3OC{=}O$	Cl	60
7	PhCH=CH	H	$CH_3OC{=}O$	80
8	4-$(CH_3O)C_6H_4$	H	$CH_3OC{=}O$	54
9	$(CH_3)_2CH$	H	$CH_3OC{=}O$	93
10	2-(OH)-4-$(CH_3O)C_6H_3$	$CH_3OC{=}O$	Cl	nr[c]

[a] Isolated yield of chromatographed product. [b] 6% of tertiary aniline was formed, which was separated from the expected product by silica chromatography. [c] Imine was formed but not reduced.

The microwave conditions thus far have reproduced earlier work[1] but dramatically shortened the reaction time from hours to minutes. Interestingly, the earlier work in this area indicated that primary and secondary alkylamines decomposed $PhSiH_3$ with vigorous gas evolution and second that 1 mol of water was required for $PhSiH_3/Bu_2SnCl_2$ to reduce a preformed imine. We therefore considered a potential mechanism that accounted for these observations:



The mechanism implies that Bu_2SnCl_2 catalyzes the formation of imine and forms the organotin compound dibutylchlorotin hydroxide, $Bu_2SnClOH$. This in turn reacts with $PhSiH_3$ to give siloxystannane $Bu_2ClSnOSiH_2Ph$ and release of H_2 (**1**).[9] The siloxystannane thus formed could react further to yield siloxanes and dibutyltin chlorohydride (Bu_2SnClH). The reactivity of tin hydrides toward amines has been extensively studied.[10] Among these, dibutyltin dihydride (Bu_2SnH_2) has been shown to be stable to amines

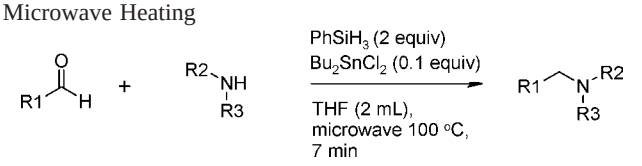
but also unreactive toward imines,[11] whereas Bu_2SnClH has been shown to reduce imines readily.[12] Indeed, organotin hydride species generated in situ from organotin oxides[13] and polysiloxanes have been identified as being responsible for tin-catalyzed reactions even in the presence of stoichiometric amounts of siloxanes and would support Bu_2SnClH as a possible in situ generated catalytic reductant. Regeneration of Bu_2SnClH would thus occur from the intermediate tin amide complex during the catalytic cycle by the action of $PhSiH_3$ or siloxane (**2**).[14] The proposed mechanism does lend itself to testing; the first step in the pathway indicates that the active tin intermediate is $Bu_2SnClOH$; this material can be prepared readily by simple hydrolysis of Bu_2SnCl_2.[15]

To test the possibility of $Bu_2SnClOH$ being an initial active tin species, *N*-benzylidinaniline was reacted with phenylsilane under various conditions.[16] When the reduction was conducted in the presence 10 mol % of freshly prepared $Bu_2SnClOH$, the imine was fully converted to the expected secondary amine, indicating that at least the first steps in the proposed mechanism could be viable.[17]

Considering the mechanism, this reveals the possibility that primary and secondary alkylamines could be considered as potential substrates provided imine formation could be forced to near completion. Our earlier orienting experiments on the reductive alkylation of anilines (Table 1, entry 4) indicated that 10 mol % of Bu_2SnCl_2 gave near-quantitative imine formation. Pleasingly, a test reaction between 2-phenylethylamine and isobutyraldehyde, using the optimized microwave conditions, resulted in the expected *N*-isobutylphenethylamine (entry 6). This was obtained as a single product in 70% yield after simple extraction.

A series of primary and secondary amines were then alkylated with a range of aryl and alkyl aldehydes using the above conditions (Table 3). All reaction products were obtained as expected in moderate to good yields and isolated by extraction or cation exchange methods as analytically pure samples. Even the sterically demanding imine formed from 2-hydroxy-4-methoxybenzaldehyde and L-valine methyl ester was readily reduced and obtained in 41% isolated yield.

Table 3. Direct Reductive Amination of Aldehydes with Microwave Heating



entry	R1	R2	R3	yield[a] (%)
1	2-(OH)-4-(CH_3O)C_6H_3	$PhCH_2CH_2$	H	61
2	2-(OH)-4-(CH_3O)C_6H_3	morpholine		81
3	2-(OH)-4-(CH_3O)C_6H_3	cyclohexyl	H	67
4	2-(OH)-4-(CH_3O)C_6H_3	L-$(CH_3)_2CHCH(NH_2)COOCH_3$	H	41
5	$(CH_3)_2CH$	cyclohexyl	H	63
6	$(CH_3)_2CH$	$PhCH_2CH_2$	H	70
7	$(CH_3)_2CH$	4-(morpholinyl-4-CH_2)-$C_6H_4CH_2$	H	74
8	4-(CH_3O)C_6H_4	morpholine		74
9	4-(CH_3O)C_6H_4	$PhCH_2CH_2$	H	85
10	2-(CH_3O)C_6H_4	*N*-Boc-piperazine		69[b]

[a] Isolated yield of analytically pure product. [b] The yield was increased from 23% when reaction was performed at 50 °C instead of 100 °C.

It was noted that during addition of phenylsilane to the reaction mixture as expected a slight gas evolution occurred. However, the initial pressure levels measured inside the microwave vessel during reaction were similar to those obtained during reductive alkylation of anilines.

The series of successful transformations demonstrate that the rate of imine formation is greatly accelerated evidenced by the lack of tertiary amine formation.[18] However, whether Bu_2SnCl_2 improves the rate of formation of carbinol amine or the succeeding dehydration step or both is not clear at the moment.[19]

In summary, a highly efficient microwave-accelerated protocol for direct catalytic reductive amination has been developed. The microwave-accelerated protocol expands the scope of the reaction beyond those previously reported, and the simple extractive ion-exchange isolation steps allow a fast-throughput synthesis of secondary and tertiary amines.

Supporting Information Available: Spectroscopic and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Gibbons, A. J.; Sawyer, A. K.; Ross, A. *J. Org. Chem.* **1961**, *26*, 2304. It was also reported that dibutylchlorotin hydroxide readily loses water to form bis(dibutylchlorotin) oxide.

(16) A solution of imine (1 mmol) and $PhSiH_3$ (2 mmol) in THF was reacted in the presence of 10 mol % of $Bu_2SnClOH$ or 10 mol % HCl (4 M in dioxane) or both to rule out possible catalytic involvement of HCl. The reactions were monitored by ^1H NMR following the disappearance of imine proton signal at δ 8.49 ppm and appearance of CH_2 signal at δ 4.34 ppm. When $Bu_2SnClOH$ was dried under reduced pressure for longer time, the catalytic activity was lost. For the imine reduction experiments, freshly prepared tin hydroxide was used; the characteristic IR frequency for O−H stretching at 3421 cm^{-1} was absent after drying.

(17) Another possible explanation for why 1 mol of water is needed could be that it hydrolyses the tin amide intermediate releasing $Bu_2SnClOH$ from which Bu_2SnClH is regenerated according to the proposed mechanism (Scheme 1).

(18) In control experiments, reacting 4-methoxybenzaldehyde (1.5 mmol) and cyclohexylamine (1.5 mmol) in the presence of (a) 2 mol % Bu_2SnCl_2 and 1.1 equiv of $PhSiH_3$ (7 min, 100 °C, 150 W) or (b) preforming imine in the presence of Bu_2SnCl_2 (7 min, 100 °C, 150 W) followed by reduction with $PhSiH_3$ (7 min, 100 °C, 150 W) resulted in a significant amount of tertiary amine (40% and 11%, respectively). Optimized conditions gave the secondary amine as a single product in 67% isolated yield (Table 3 entry 3).

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