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ORIGINAL PAPER

An improved and one-pot procedure to the synthesis of symmetric amines by domino reactions of 5-methyl-1,3,4-thiadiazole-2-amine, a new nitrogen atom donor, and alkyl halides

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Abstract A new one-pot method has been introduced in this work for the synthesis of symmetrical primary, secondary, and tertiary alkyl amines from alkyl halides and 5-methyl-1,3,4-thiadiazole-2-amine as a nitrogen-transfer reagent. In this method, all three types of amines have been successfully prepared after changing the ratio of substrates and base control. In addition to the introduction of a new nitrogen-transfer reagent, other important features of this work include normal atmospheric conditions and excellent yields under mild reaction conditions.

Graphical abstract
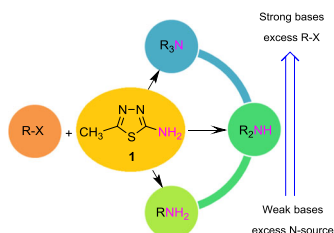
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Introduction

Amines found in a wide range of natural products, bioactive molecules, and industrial materials [1]. They are important building blocks in organic synthesis and the chemical industry. For example, they are used in the synthesis of pharmaceuticals and agrochemicals, and also as building blocks for polymers and dyes [2, 3]. Owing to the numerous applications of amines, their synthesis has perhaps received more attention than the preparation of many other functional groups in organic chemistry [4]. Accordingly, the development of methods for the selective synthesis of amines is an obvious problem in organic chemistry [5].

The most classic method for amine synthesis is Hoffmann alkylation, that is, reaction of ammonia with alkyl halides producing a mixture of primary, secondary, and tertiary amines and ammonium salts [6]. Other methods of formation of amines include catalyzed amination of alcohols [7, 8], and reduction of amides [9, 10] or carboxylic acids [11] in the presence of ammonia. However, there are practical difficulties associated with the use of ammonia, including its storage, handling, and transportation [10, 12]. In addition, this reaction usually results in an over-alkylation that often gives rise to mixtures of primary, secondary, and tertiary amines [1, 13, 14].

There are many interesting approaches for the synthesis of secondary and tertiary amines. These methods traditionally include *N*-alkylation of amines with alkyl halides (or with dialkyl sulfates or sulfonates) [15–17], reductive amination of carbonyl [18, 19] and nitrile compounds [20], or hydroamination of unsaturated hydrocarbons [21, 22]. Unfortunately, the disadvantages of these methods include the use of expensive catalysts and starting materials, low selectivity, concomitant formation of large amounts of wasteful salts, and harsh workup procedures [17].

Moreover, difficulty in working with ammonia has led organic chemists to use nitrogen-transfer reagents to overcome these disadvantages. Compared to the impressive progress being made in the *N*-alkylation of organic amines, reports dealing with the direct synthesis of amines using nitrogen-transfer reagents are scarcely available. Nitrogen-containing compounds have been evaluated for their ability to transfer nitrogen. Nitrogen-transfer reactions aim for a direct synthesis of primary, secondary, and tertiary amines. Some of the nitrogen-transfer reagents electrophile or nucleophile include: urea [23], *N,N*-dialkyl-O-aryl sulfonylhydroxylamines [24, 25], azide [26, 27], aziridines [28], and *O*-alkyloximes [29].

After a successful presentation of sulfur-transfer reagents in our previous works [30–33], herein, we wish to report an economical and environmental friendly method for synthesis of symmetrical alkyl amines from alkyl halides and 5-methyl-1,3,4-thiadiazole-2-amine (**1**) as a new nitrogen-transfer reagent. In this process, N-source **1** is a basic, solid reagent that can be easily prepared and handled. In addition, for the first time, in the presence of this reagent, all three types of highly selective amines were successfully prepared (Scheme 1).

Scheme 1
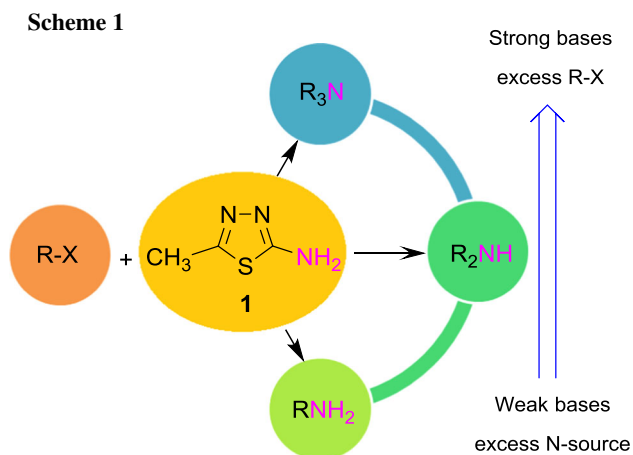
Results and discussion

The reaction of benzyl chloride with 5-methyl-1,3,4-thiadiazole-2-amine (**1**) in the presence of a base and in a mixture EtOH/H$_2$O at room temperature was studied under

Table 1 Optimization of the reaction conditions
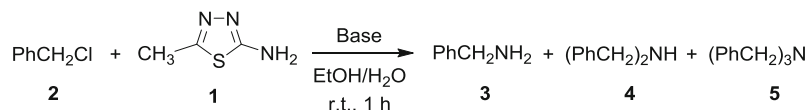
Entry	PhCH$_2$Cl/mmol	N-source **1**/mmol	Base /mmol	Yield/%[a] 3:4:5
1	1	1	–	NO
2	1	1	KOH (2)	trace:trace:56
3	1	1	KOH (3)	21:10:67
4	1	0.5	KOH (3)	11:trace:86
5	**1**	**0.3**	**KOH (3)**	**nd:nd:98**
6	1	0.3	NaOH (3)	nd:nd:96
7	1	0.3	*t*-BuOK (3)	10:nd:88
8	1	1	K$_2$CO$_3$ (3)	20:72:trace
9	**1**	**0.5**	**K$_2$CO$_3$ (3)**	**trace:92:trace**
10	1	0.3	K$_2$CO$_3$ (3)	trace:68:15
11	1	0.5	K$_3$PO$_4$ (3)	trace:88:trace
12	1	1	Et$_3$N (3)	75:15:trace
13	1	0.5	Et$_3$N (3)	66:18:12
14	**1**	**1.5**	**Et$_3$N (3)**	**94:trace:trace**
15	1	1.5	Pyridine (3)	87:trace:trace
16	1	1.5	Pyrrole (3)	92:trace:trace

Reaction conditions: benzyl chloride, 5-methyl-1,3,4-thiadiazole-2-amine (**1**), base at 25 °C and 2 cm^3 EtOH/H$_2$O (10:1) under normal atmospheric conditions

Bold values indicate optimization of the reaction conditions in terms of N-source amounts and base at room temperature

[a] Isolated yield by column chromatography

normal atmospheric conditions to optimize the reaction conditions. According to the results shown in Table 1, it was observed that there was no reaction in the absence of a base (Table 1, entry 1). In addition, the amount of 3 mmol from KOH showed a superior effect on the reaction conversion and reaction in less than 3 mmol from KOH was incomplete (Table 1, entries 2, 3). The selectivity of the N-alkylation is influenced by both the stoichiometric amounts of the starting materials and type of the base. We found that by increasing the stoichiometric amounts of benzyl chloride in the presence of a strong base, the reaction moved forward to production of tertiary amine (Table 1, entries 4, 5). KOH, NaOH, and t-BuOK displayed similar behavior in similar conditions stoichiometry (Table 1, entries 5–7). As expected, in stoichiometric amounts of 1:0.5 from benzyl chloride: 5-methyl-1,3,4-thiadiazole-2-amine and in the presence of an average base, the main product was a dibenzyl amine (Table 1, entries 8, 9).

It is interesting that average bases such as K_2CO_3 and K_3PO_4 take a mid-path. The main resultant product is secondary alkyl amine (Table 1, entries 9–11). When a weak base was added, the reaction will be majority converted into primary alkyl amine (Table 1, entries 12, 13). We found that by increasing the stoichiometric amounts of N-source 1 in the presence of a weak base, the reaction progressed to the production of benzyl amine. (Table 1, entries 14–16).

After the optimized reaction conditions were established, a large number of alkyl halides were examined to explore the scope of this reaction. Accordingly, the number of alkyl amine was synthesized in the presence of alkyl halides (1 mmol) using 1.5 mmol of 5-methyl-1,3,4-thiadiazole-2-amine (1) at 25 °C under normal atmospheric conditions and Et_3N as base. As shown in Table 2, primary, secondary, and tertiary alkyl halides worked well with this procedure to efficiently yield the corresponding alkyl amines as only product in good-to-excellent yields (Table 2, entries 1–10).

In addition, this protocol efficiently generated symmetric secondary amines. A range of this material were obtained with alkyl halides (1 mmol) using 0.5 mmol of 5-methyl-1,3,4-thiadiazole-2-amine (1) at 25 °C under normal atmospheric conditions using K_2CO_3 as base (Table 3). As shown in Table 3, primary, secondary, and tertiary alkyl halides worked well with this procedure to efficiently yield the corresponding alkyl amines in good-to-excellent yields (Table 3, entries 1–10). In addition, it was observed that secondary and tertiary alkyl halides generate less than 10% primary amines (Table 3, entries 9–10).

The reaction efficiency for the synthesis of tertiary amines was examined in the presence of alkyl halides (1 mmol) using 0.3 mmol of 5-methyl-1,3,4-thiadiazole-2-amine (1) at 25 °C under normal atmospheric conditions and KOH as base. Various types of primary alkyl halides

Table 2 Synthesis of primary amines from alkyl halides
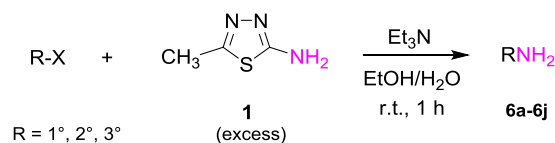
Entry	R-X	R-NH₂	Yield/%[a]	M.p.	References
1	PhCH₂Cl	6a	94	Oil	[34]
2	PhCH₂Br	6b	96	Oil	[34]
3	Ph(CH₂)₂Br	6c	93	Oil	[35]
4	Ph(CH₂)₃Br	6d	91	Oil	[35]
5	CH₃(CH₂)₃Br	6e	89	Oil	[34]
6	CH₃(CH₂)₆Br	6f	85	Oil	[34]
7	CH₃(CH₂)₇Br	6g	82	Oil	[34]
8	(CH₂)₅CHBr	6h	82	Oil	[34]
9	CH₃CH₂CHBrCH₃	6i	84	Oil	[34]
10	(CH₃)₃CBr	6j	81	Oil	[34]

Reaction conditions: alkyl halide (1 mmol), N-source 1 (1.5 mmol), Et_3N (3 mmol) 25 °C and 2 cm³ EtOH/H₂O (10:1) under normal atmospheric for 1 h

[a] Isolated yield

Table 3 Synthesis of symmetric secondary amines from alkyl halides
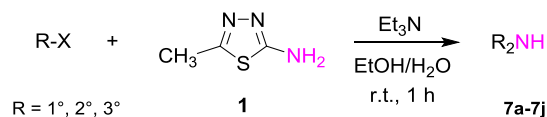
Entry	R-X	R$_2$NH	Yield/%[a]	M.p.	References
1	PhCH$_2$Cl	**7a**	92	Oil	[36, 37]
2	PhCH$_2$Br	**7b**	90	Oil	[36, 37]
3	Ph(CH$_2$)$_2$Br	**7c**	88	Oil	[36, 37]
4	Ph(CH$_2$)$_3$Br	**7d**	85	Oil	[36]
5	CH$_3$(CH$_2$)$_3$Br	**7e**	82	Oil	[37]
6	CH$_3$(CH$_2$)$_6$Br	**7f**	84	Oil	[37]
7	CH$_3$(CH$_2$)$_7$Br	**7g**	81	Oil	[37, 41]
8	(CH$_2$)$_5$CHBr	**7h**	70[b]	Oil	[37]
9	CH$_3$CH$_2$CHBrCH$_3$	**7i**	78[b]	Oil	[37]
10	(CH$_3$)$_3$CBr	**7j**	75[b]	Oil	[37]

Reaction conditions: alkyl halide (1 mmol), N-source **1** (0.5 mmol), K$_2$CO$_3$ (3 mmol) at 25 °C and 2 cm^3 EtOH/H$_2$O (10:1) under normal atmospheric for 1 h

[a] Isolated yield

[b] Products mixed with less than 10% of primary amine

Table 4 Synthesis of symmetric tertiary amines from alkyl halides
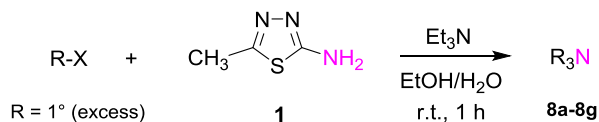
Entry	R-X	R$_3$N	Yield/%[a]	M.p. (lit. m.p.)/°C	References
1	PhCH$_2$Cl	**8a**	98	91–94 (91–93)	[38, 40]
2	PhCH$_2$Br	**8b**	95	91–94 (91–93)	[38, 40]
3	Ph(CH$_2$)$_2$Br	**8c**	88	31 (28–30)	[39]
4	Ph(CH$_2$)$_3$Br	**8d**	92	Oil	[39]
5	CH$_3$(CH$_2$)$_3$Br	**8e**	85	Oil	[40]
6	CH$_3$(CH$_2$)$_6$Br	**8f**	90	Oil	[38]
7	CH$_3$(CH$_2$)$_7$Br	**8g**	91	Oil	[40, 41]

Reaction conditions: alkyl halide (1 mmol), N-source **1** (0.3 mmol), KOH (3 mmol) at 25 °C and 2 cm^3 EtOH/H$_2$O (10:1) under normal atmospheric for 1 h

[a] Isolated yield

reacted very well with N-source **1** (Table 4, entries 1–7). It was observed that secondary and tertiary alkylhalides generated tertiary amines in very small amounts. This could be because of steric hindrance. Thus, at the end, a mixture of elimination products, primary, and secondary amines were produced.

Two possible mechanisms have been proposed for this reaction. On using a strong base such as KOH, the reaction mechanism progressed to Scheme 2. When ammonia was generated in situ, trialkylamine was produced in the presence of excess R-X (Scheme 2) [21, 22]. When a weak base such as Et_3N was used, N-source **1** seemed to act as a better nucleophile. Given that N-source **1** in excess, all of alkyl halide was converted to **9**. Finally, in the presence of the Et_3N, primary amines were generated (Scheme 3).

Although we cannot clearly determine the reaction pathway for the synthesis of secondary amines from alkyl halides and N-source **1**, it seems reaction can progress through both reaction pathways.

Scheme 2

Scheme 3
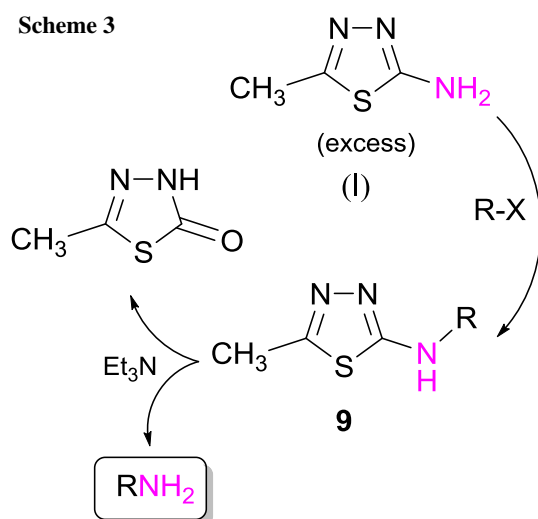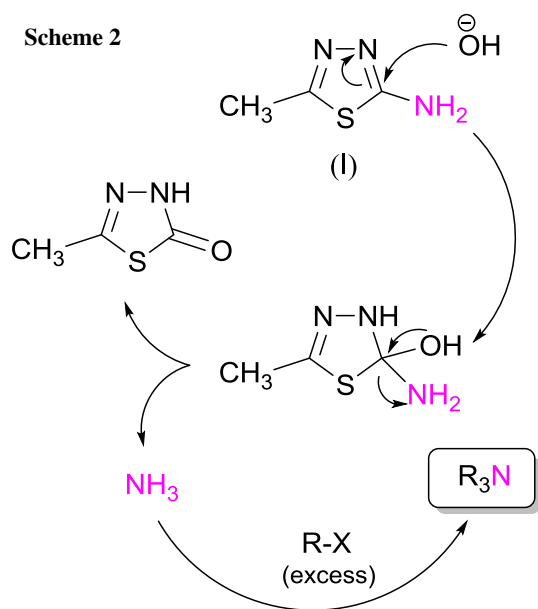
Conclusions

In summary, a novel, effective, and one-pot procedure was developed for the direct synthesis of primary, secondary, and tertiary alkyl amine from various alkyl halides and 5-methyl-1,3,4-thiadiazole-2-amine (**1**) in mild conditions. The important feature of this method is the introduction of a new nitrogen-transfer reagent. The reagent was a stable and nontoxic solid, which could be used to prepare all three types of amines. This protocol has several advantages: normal atmospheric conditions, catalyst-free systems, easily available and low-cost reagents, using green solvent instead of the usually used organic solvents, simple work up without further purification, and accomplishment reaction at room temperature.

Experimental section

All reagents and starting materials were obtained commercial from Sigma–Aldrich and Merck. Melting points were determined on an Electrothermal 9100 apparatus. Fourier transform infrared (FT-IR) spectra were obtained on a Bruker VERTEX 70 instrument, with samples being dispersed on potassium bromide pellets. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solution. The progress of the reaction was monitored by TLC using silica-gel SILG/UV 254 plates.

Typical experimental procedure for primary amines synthesis

A mixture of alkyl halide (1.0 mmol) and 5-methyl-1,3,4-thiadiazole-2-amine (**1**) (1.5 mmol) were added to a flask containing 3 mmol Et_3N and 2 cm^3 $EtOH/H_2O$ (10:1). The reaction continued at room temperature under atmospheric conditions 1 h. The reaction progress was controlled by thin-layer chromatography. Then, crude reaction mixture was purified by column chromatography (petroleum ether/ethyl acetate 1:4) to give the primary amines in good yields.

Typical experimental procedure for secondary amines synthesis

A mixture of alkyl halide (1.0 mmol) and 5-methyl-1,3,4-thiadiazole-2-amine (**1**) (0.5 mmol) were added to a flask containing 3 mmol K_2CO_3 and 2 cm^3 $EtOH/H_2O$ (10:1). The reaction continued at room temperature under atmospheric conditions until 1 h. The reaction progress was

controlled by thin-layer chromatography. The solvent was evaporated under vacuum. Then, crude reaction mixture was purified by column chromatography (petroleum ether/ ethyl acetate 1:1) to give the secondary amines in good yields.

Typical experimental procedure for tertiary amines synthesis

A mixture of alkyl halide (1.0 mmol) and 5-methyl-1,3,4-thiadiazole-2-amine (**1**) (0.3 mmol) were added to a flask containing 3 mmol KOH and 2 cm^3 EtOH/H_2O (10:1). The reaction continued at room temperature under atmospheric conditions until 1 h. The reaction progress was controlled by thin-layer chromatography. The solvent was evaporated under vacuum. Then, crude reaction mixture was purified by column chromatography (petroleum ether/ethyl acetate 8:1) to give the tertiary amines in good yields.

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