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A novel hydride-mediated reductive rearrangement of amide: a facile synthesis of pyrimidyl and triazinyl amines

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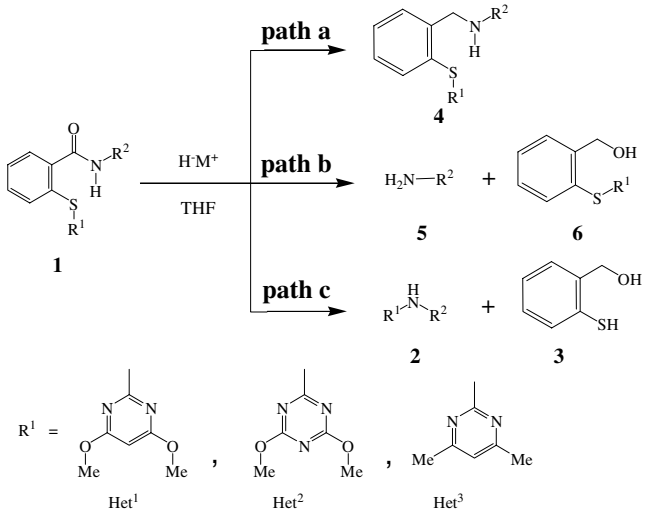
Abstract

$LiAlH_4$ and $NaBH_4$ were found to mediate the conversion of 2-(pyrimidyl-2-ylsulfanyl)-*N*-arylbenzamides and 2-(triazinyl-2-ylsulfanyl)-*N*-arylbenzamides into pyrimidyl and triazinyl amines under notably mild conditions via a novel reductive rearrangement mechanism. These reactions invent a new route to prepare amines, which are a kind of important biologically active compounds and provide the first insight into a novel hydride-promoted reductive rearrangement of amides.

The reduction of amides with metallic hydrides is no doubt a key reaction in organic synthesis.[1–4] It has been suggested that the reduction affords various products via two typical pathways: path a and path b. The attack of the amide carbonyl group by metallic hydride (H^-M^+, i.e., $LiAlH_4$, $NaBH_4$ and so on) occurs through a tetrahedral intermediate, which can proceed either by the breaking of the C–O bond, producing an iminium salt which is further converted to the corresponding amine with the same number of carbon atoms (path a),[1,2] or by the breaking of the C–N bond, leading thus to the amine and the aldehyde which can eventually be reduced to an alcohol (path b).[1,3]

Recently, we used the 2-(pyrimidyl-2-ylsulfanyl)-*N*-arylbenzamides and 2-(triazinyl-2-ylsulfanyl)-*N*-arylbenzamides **1** as probes to investigate whether path a or b would operate in the reduction of heterocyclic amide with lithium aluminum hydride. However, unexpected cleavage products pyrimidyl and triazinyl amines **2** (a kind of important biologically active compounds which have aroused considerable interest and attention in drugs and pesticides[5]) and alcohol **3** were obtained (Scheme 1). Such a strange phenomenon has attracted our considerable interest and



Scheme 1.

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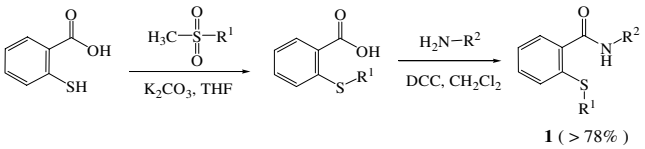
may imply a novel amide reductive pathway. Obviously **2** are not afforded via path a which should arrive to pyrimidyl and triazinyl benzylamine **4** (Scheme 1). Furthermore, a mechanism involving 1,2-fission of amide via path b, followed by an intermolecular nucleophilic substitution of **5** with **6** (Scheme 1) to afford **2** does not occur. This has been confirmed by the crossing experiment. When a solution of **1**, $LiAlH_4$ and *p*-toluidine (molar ratio 1:6:10) was refluxed, only amine **2** was obtained, without isolation of the crossing product amine. Therefore, the reaction may proceed via an intramolecular rearrangement, namely, nucleophilic attack on heterocyclic ring by the amide nitrogen atom occurs without an earlier breakage of the amide C–N. Consequently, such pathway is essentially different from the well-known reductive routes of amide by metallic hydrides. We disclose herein a new methodology to potentially biologically important pyrimidyl and triazinyl amines via a novel reductive rearrangement of amides.

The starting materials for the reductions are 2-(pyrimidyl-2-ylsulfanyl)-*N*-arylbenzamides and 2-(triazinyl-2-ylsulfanyl)-*N*-arylbenzamides **1**, which were easily prepared from the corresponding pyrimidyl and triazinyl benzonic acids and amines in high yields (more than 78%) using a procedure[6] described in Scheme 2.

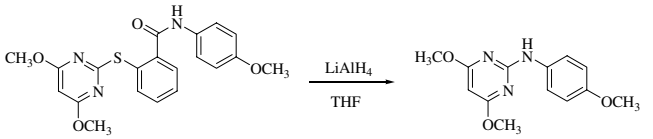
Our initial investigation was based on the reduction of **1a** [$R^1 = 4,6$-dimethoxypyrimidin-2-yl, $R^2 = 4$-$MeOC_6H_4$] with $LiAlH_4$ (Table 1, entries 1–13). The reduction was originally carried out by mixing $LiAlH_4$ and **1a** in THF under room temperature. The reaction mainly yielded **2a** and **3**. Further studies showed that a higher yield of **2a** could be obtained with 6.0 equiv of $LiAlH_4$ in THF under refluxing for 3 h (Table 1, entry 11).[7] Under the same condition, the reduction of substrates with R^2 being other aryl showed that the formation of pyrimidyl amines **2b–h** (Table 2, entries 2–8) is also predominant. Interestingly, the reduction of **1a–d** afforded **2a–d** in 95%, 94%, 85%, and 80% yields, respectively. It seems likely to depend on electronic factors, that is, the electron-donating substituents of the anilines at C4 are favored over the $LiAlH_4$-mediated reductive rearrangement.

Under the same conditions, reactions of **1i–n** [$R^1 = 4,6$-dimethoxy-1,3,5-triazin-2-yl, $R^2 = 4$-$Me_2NC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, phenyl, benzyl] with 6.0 equiv of $LiAlH_4$ gave triazinyl amines **2i–n** in yields from 52% to 67% (Table 2, entries 9–14). Reactions of **1o–q** [$R^1 = 4,6$-dimethylpyrimidin-2-yl, $R^2 = 4$-$MeOC_6H_4$, 4-MeC_6H_4, phenyl] with 6.0 equiv of $LiAlH_4$ gave the desired pyrimidyl amines **2o–q** in excellent yields (Table 2, entries 15–17).



Scheme 2.

Table 1
$LiAlH_4$-mediated reduction of amides **1a** via path c[a]



1a **2a**

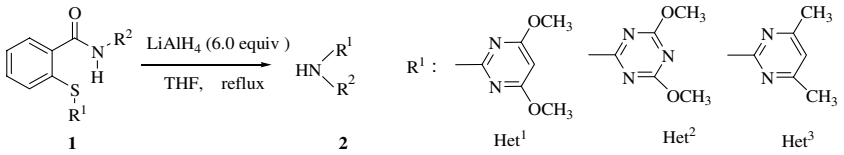
Entry	Ratio of **1a**/$LiAlH_4$	Temp (°C)	Time (h)	Yield of **2a**[b] (%)
1	1/1	rt	10	5
2	1/2	rt	10	8
3	1/3	rt	10	15
4	1/4	rt	6	83
5	1/5	rt	6	85
6	1/6	rt	6	89
7	1/7	rt	6	88
8	1/8	rt	6	89
9	1/9	rt	6	90
10	1/6	40	3.5	92
11	1/6	Reflux	3	95
12	1/5	Reflux	3	91
13	1/4	Reflux	3	88

[a] The reduction of **1a** (1.5 mmol) was carried out in THF (20 mL). A variety of conditions to generate **2a** were investigated including the ratio of amide **1a**/$LiAlH_4$ and temperature.
[b] Isolated yield after column chromatography.

To investigate the scope of hydride, sodium borohydride ($NaBH_4$), a weak reducing agent was then employed. Reductions of amides **1a–c**, **1i**, **1k**, **1l**, and **1o–q** were carried out with 12.0 equiv of $NaBH_4$ in THF under refluxing (Table 3).[7] To our surprise, the reaction absolutely afforded substituted heterocyclic amines **2** in satisfactory yields. The presence of electron-donating substituents of aniline at C4 also appeared to be effective. Interestingly, the reactions of **1i**, **1k**, and **1l** with $NaBH_4$ provided products in higher yields compared with the reactions with $LiAlH_4$ (Table 2, entries 9, 11, 12; Table 3, entries 4–6). These results indicated that $NaBH_4$ was favored over converting 2-(4,6-dimethoxy-1,3,5-triazin-2-ylsulfanyl)-*N*-arylbenzamides into triazinyl amines. As we know, $NaBH_4$ is a mild metallic hydride, which can not reduce secondary amides even at high temperatures without any auxiliary or catalyst.[8]

As summarized in Tables 2 and 3, $LiAlH_4$ and $NaBH_4$ were found to mediate the conversion of a broad variety of **1** containing the different heterocyclic rings R^1 and amide groups R^2 into **2** in moderate to high yields under mild conditions: 1.0 equiv of **1**, 6.0 equiv of $LiAlH_4$ or 12.0 equiv of $NaBH_4$, in THF under reflux for 2–4 h (Table 2, entries 1–17; Table 3, entries 1–9). To the best our knowledge, this is the first example of a new route to pyrimidyl and triazinyl amines via a novel hydride-mediated reductive rearrangement of amide. This class of derivatives is generally prepared via the direct displacement reactions of heterocyclic halides with neutral nitrogen nucleophiles in the presence of bases as catalysts. However, this conventional direct displacement process often result in low isolated yields in the synthesis of pyrimidyl

Table 2
A new methodology to pyrimidyl and triazinyl amines **2** via path c[a]

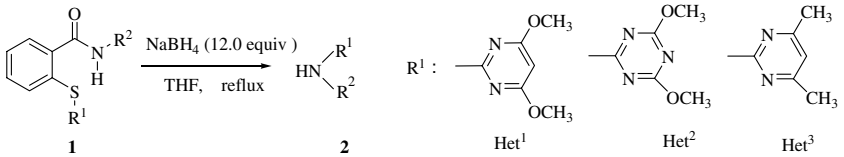


1 **2**

Entry	**1**		Time (h)	Yield of **2**[b] (%)
	R^1	R^2		
1	Het^1	4-$MeOC_6H_4$	3	95 (**2a**)
2	Het^1	4-MeC_6H_4	3	94 (**2b**)
3	Het^1	Ph	3.5	85 (**2c**)
4	Het^1	4-ClC_6H_4	4	80 (**2d**)
5	Het^1	2-MeC_6H_4	4	79 (**2e**)
6	Het^1	3-MeC_6H_4	3.5	84 (**2f**)
7	Het^1	3,4-$Me_2C_6H_3$	3	92 (**2g**)
8	Het^1	1-Naphthyl	4	82 (**2h**)
9	Het^2	4-$Me_2NC_6H_4$	2	67 (**2i**)
10	Het^2	4-$MeOC_6H_4$	2	64 (**2j**)
11	Het^2	4-MeC_6H_4	2	60 (**2k**)
12	Het^2	Ph	2.5	56 (**2l**)
13	Het^2	4-ClC_6H_4	3	52 (**2m**)
14	Het^2	Benzyl	3	52 (**2n**)
15	Het^3	4-$MeOC_6H_4$	2	95 (**2o**)
16	Het^3	4-MeC_6H_4	2	94 (**2p**)
17	Het^3	Ph	2	87 (**2q**)

[a] Conditions: 1.0 equiv **1**, 6.0 equiv $LiAlH_4$, in THF under refluxing.
[b] Isolated yield after column chromatography.

Table 3
The $NaBH_4$-mediated reduction of amides **1** via path c[a]



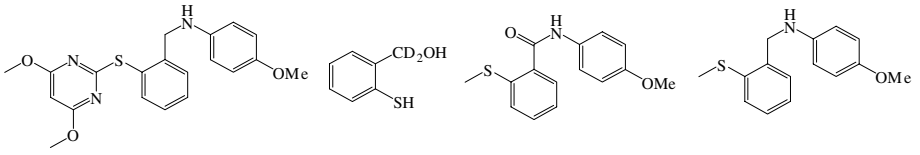
1 **2**

Entry	**1**		Time (h)	Yield of **2**[b] (%)
	R^1	R^2		
1	Het^1	4-$MeOC_6H_4$	3	90 (**2a**)
2	Het^1	4-MeC_6H_4	3	88 (**2b**)
3	Het^1	Ph	3.5	78 (**2c**)
4	Het^2	4-$Me_2NC_6H_4$	2	88 (**2i**)
5	Het^2	4-MeC_6H_4	2	80 (**2k**)
6	Het^2	Ph	2.5	77 (**2l**)
7	Het^3	4-$MeOC_6H_4$	2	90 (**2o**)
8	Het^3	4-MeC_6H_4	2	87 (**2p**)
9	Het^3	Ph	2	82 (**2q**)

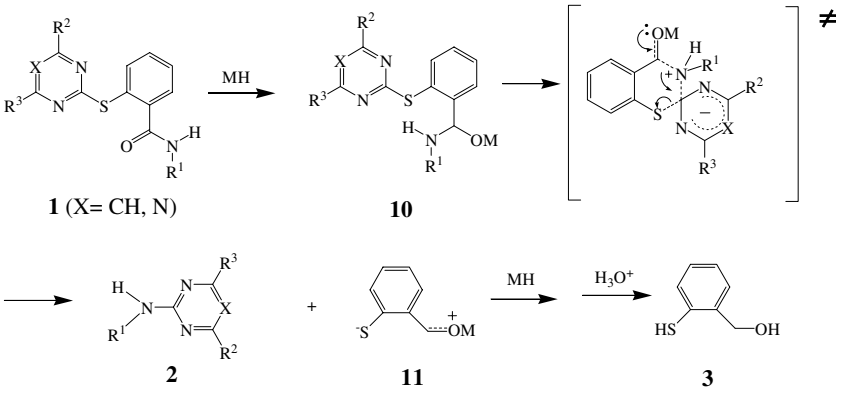
[a] Conditions: 1.0 equiv **1**, 12.0 equiv $NaBH_4$, in THF under refluxing.
[b] Isolated yield after column chromatography.

amines with 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine and amines.[9,10]

At this juncture, it is necessary to make clear what is the essential factor of such a novel reaction. To examine which group of compound **1a** metallic hydride attacked, a deuterium labeling experiment was performed. Under the equal condition the reaction of $LiAlD_4$ with amide **1a** afforded the deuterated product **7** (Scheme 3), along with **2a**. Analysis of product **7** suggests hydride is transferred from $LiAlD_4$ to amide carbonyl carbon. Moreover, amine **4a** (Scheme 3) reacted with $LiAlH_4$, and the reaction did not proceed at all. It is suggested that the reaction does not occur due to the absence of the initial nucleophilic attack of hydride from $LiAlH_4$ to amide carbonyl group. Surely



Scheme 3.



Scheme 4.

such a hydride-transfer step is very critical in the whole process, in other words, the total reaction is triggered and promoted by hydride.

The further mechanistic implication of the reaction was involved in heterocyclic rings. A series of analogues **1** have been proved to be general for the reaction (Tables 2 and 3). However, the reduction of 2-(methylthio)-*N*-phenylbenzamide **8** led to the normal corresponding amine **9** (Scheme 3) without the formation of any rearrangement product. The similar reduction of 2-(arylthio)-*N*-alkylbenzamide with $LiAlH_4$ to the corresponding amines was well documented.[11] Hereby, it can be suggested that the heterocyclic ring at the *ortho*-position of benzamide and the highly electron-deficient nature of the pyrimidyl and triazinyl rings, which renders the nucleophilic substitution reaction plays a pivotal role.

On the basis of the above experimental results, hydride-promoting effect and pyrimidyl and triazinyl ring participation impact are suggested to be the essential factor of such a novel reductive rearrangement reaction. A plausible mechanism for the hydride-mediated formation of pyrimidyl and triazinyl amines reported herein is shown in Scheme 4. Treatment of the starting material amides **1** initially affords a tetrahedral intermediate **10** via transferring a hydride from metallic hydride to carbonyl carbon, followed by an intramolecular nucleophilic attack, an electronic feedback, and a concerted formation and cleavage pathway, leading to the occurrence of 1,5-nitrogen shift and the formation of product amine **2** and intermediate aldehyde **11**, which after reduction and hydrolysis gives alcohol **3**. In the rearrangement process described in Scheme 4, an increase in the electron density of aromatic nitrogen atom would be favorable, due to the result of strengthening the nucleophilic reactivity of the nitrogen atom of amide.

In summary, the experimental investigation has resulted in the first insight into a novel hydride-mediated reductive rearrangement of amide via pyrimidyl and triazinyl participation. Furthermore, our finding provides a new route to prepare the other substituted heterocyclic amines. Further work will systematically address the effect of other heterocyclic ring, bridge atom, amide moiety, and hydride in our laboratory.

Acknowledgments

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Supplementary data

General experimental details and characterization data for compounds **2a**–**q** and **3**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.096.

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7. A variety of conditions to generate **2a** were investigated at first, including the ratio of amide **1a**:$LiAlH_4$ and temperature. It is shown that high yield (95%) of **2a** could be obtained with 6.0 equiv of $LiAlH_4$ in THF under reflux for 3 h. General procedure for the preparation of **2** from the reduction of **1** with $LiAlH_4$ or $NaBH_4$: To a suspension solution of lithium aluminum hydride (9 mmol, 343 mg) or sodium borohydride (18 mmol, 702 mg) in tetrahydrofuran (20 mL) was added dropwise **1** (1.5 mmol) in tetrahydrofuran (15 mL) at room temperature for about 20 min. The mixture was refluxed for 2–4 h. Afterwards, the reaction was then cooled and quenched by the careful addition of ice water (15 mL) and sodium hydroxide (10%, 15 mL) for 1 h. The solid was filtered off under reduced pressure and washed with ethyl acetate (3×20 mL). The organic layer was washed with brine (3×20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under vacuo and the residue was purified by column chromatography on silica gel with petroleum ether–ethyl acetate (10:1) to afford the corresponding products **2** in 52–95% yield.
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10. Corresponding experiments with such conventional direct displacement method adopted were also conducted in the synthesis of amine **2a** with 1 equiv of 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine and 1.2 equiv of 4-methoxybenzenamine in the presence of 1.5 equiv of K_2CO_3 in refluxing THF or DMSO. However, trace of amine **2a** was obtained in THF under reflux for 10 h, and in refluxing DMSO the reaction afforded **2a** only in 20% yield.
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