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ARTICLE

Microwave-assisted synthesis of *ortho*-substituent diaryl *N*-(tert-butylsulfinyl) ketimines

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A simple and efficient procedure for the synthesis of *ortho*-substituted diarylketimines has been developed under microwave irradiation, employing the corresponding diarylketones and (*R*)-(+)-tert-butylsulfinamide in the presence of $Ti(O^iPr)_4$. This approach allows for the preparation of most final ketimines (**3a-g**) containing electron-donating groups in good yields in 1 h. For starting materials with strong electron-withdrawing groups, the desired (**3h-m**) products could also be prepared by increasing microwave energy and extension of the reaction time to 2.5 h.

1. Introduction

Enantiomerically pure *N*-(tert-butylsulfinyl)imines have been widely used in asymmetric reactions and the synthesis of chiral primary amines.[1] Recent research suggested that ketimines containing 2-aminophenyl group have also become important intermediates or key structural units in the construction of chiral 1,3-diamines **1**,[2] 1,2-dihydroquinazolinones **DPC-961** (a potent second generation non-nucleoside reverse-transcriptase inhibitor) and **(±)SM-15811** (an effective Ca^{2+}/Na^+ ion exchanger inhibitor with potential utility for the management of ischemic heart disease),[3] chiral auxiliaries and N-heterocyclic carbene ligands **2**,[4] natural products[5] and other pharmacologically active compounds[6] (**Figure 1**). The ketimines containing chiral auxiliaries such as (*R*)-(+)-tert-butylsulfinamide or (*S*)-(-)-tert-butylsulfinamide can lead to chiral primary amines after reduction and hydrolysis. Therefore, the development of efficient methods for the preparation of *N*-(tert-butylsulfinyl) protected 2-aminoaryl ketimines is very important.

Most of the reported synthetic methods for these imines are mainly based on the direct condensation of aldehydes or highly reactive ketones with optically pure (*R*)-(+)-tert-butylsulfinamide in the presence of an activating and dehydrating agent such as copper(II) sulfate,[7] magnesium sulfate/pyridiniump-toluenesulfonate,[6] titanium(IV) alkoxides,[7,8] cesium carbonate,[9] ytterbium(III) triflate,[10] or potassium hydrogensulfate.[11] Although the synthesis of aldimines and ketimines has been reported under microwave irradiation,[8a,8b,12] examples of diaryl sulfinylketimines with steric hindrance such as *ortho*-substitutions are rare.

During the past few years, one of our main research lines has been focused on the use of *N*-(tert-butylsulfinyl)imines in asymmetric synthesis and as chiral auxiliaries.[6,13] Herein we report our studies on developing a fast and efficient procedure for the synthesis of *ortho*-substituent diaryl N-(tert-butylsulfinyl) ketimines.

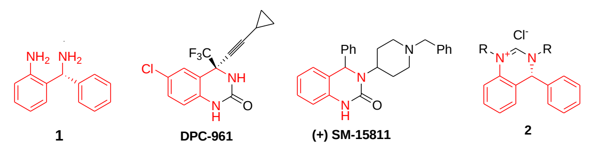

Figure 1. Representative structures containing chiral 1,3-diamine moieties

2. Results and Discussions

At first, we tried to synthesize the desired diaryl sulfinylketimines according to the above mentioned methods.[7-12] After attempts with Lewis acid such as copper(II) sulfate, magnesium sulfate/pyridinium p-toluenesulfonate, titanium(IV) alkoxides, titanium tetrachloride, and ytterbium(III) triflate, we found that stronger Lewis acid $TiCl_4$ was useful for the formation of imines (**Table 1**, **1a-g**).[14] The desired sulfinimides **3a-g** (**Table 1**) were formed at room temperature, but the yields were low. For other diaryl ketones **1h-m** bearing an electron-withdrawing substituent such as a nitro group (**Table 1**), no condensation product was formed even when using $TiCl_4$. This result indicated that more harsh conditions were needed to push the condensation reaction forward. We decided to increase the reaction energy by heating or microwave irradiation. However, when the temperature was raised to 40 ℃ using 2M $TiCl_4$ in toluene, the materials were quickly carbonized and turned black, with no desired product being detected. Therefore, another Lewis acid was chosen to allow for increased reaction energy input such as heating or microwave irradiation. According to the literature,[8a,8b,12] we reasoned that microwave irradiation could be a more effective way to promote the condensation reaction instead of raising the temperature with conventional heating. In order to find a suitable condensation promoter for the microwave-assisted condition, the above mentioned Lewis acids were examined for the synthesis of

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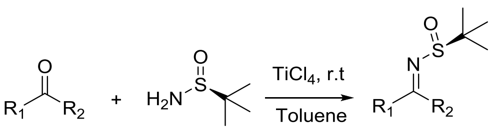
product **3h** at 125 ℃ and 175 W by using a Biotage initiator (Model: Initiator EXP EU 355301). The results revealed that the condensation product could only be obtained with $Ti(O^iPr)_4$. The yield of product **3h** was 20% at 125 ℃ and 175 W. Then, the reaction conditions of synthesizing compound **3h** using $Ti(O^iPr)_4$ were further optimized. The results were shown in **Table 2**. The irradiation energy was critical to the success of the reaction. At 120 ℃ with 160 W input, no product was formed, while at 140 ℃ with 210 W input material decomposition was severe. Reaction carried out at 130 ℃ with 190 W input seemed to have the good balance of starting material conversion and product formation. The optimal condition was achieved with 4 equivalent of $Ti(O^iPr)_4$ and 2.5 h of reaction time.

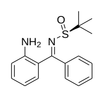
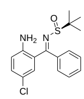
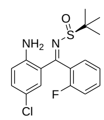
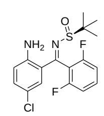
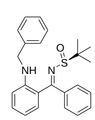
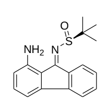
Afterwards, the compounds **3i-m** were synthesized using the optimized condition and the results were summarized in **Table 3** (entries **8-13**). Meanwhile, this procedure was also applied to the synthesis of **3a-g**, and the yields were enhanced from 20–50% (**Table 1** using $TiCl_4$) to 70–89% (**Table 3**). Similar yields were obtained at 10mmol reaction scales.

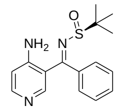
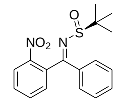
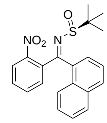
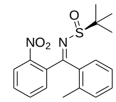
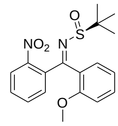
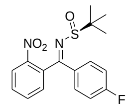
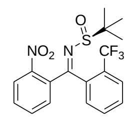
To evaluate whether or not there was any beneficial effect in the use of microwave irradiation, the synthesis of imine **3a** and **3h** was carried out by conventional heating in an oil bath at 130 ℃ in the presence of $Ti(O^iPr)_4$, and no conversion of the starting materials was observed after a reaction time of 3h. Only a trace amount of **3a** was observed after 24 h while **3h** still could not be detected after 24 h. This result indicated that the assistance of microwave is essential to the synthesis of *ortho*-substituted diarylketimines.

As high temperature may cause racemization during the synthesis of sulfinylketimines, we investigated whether or not there was any loss of optical purity in the imines that we had prepared under microwave-assisted conditions. We chose imines **3a**, **3b** and **3h** as test compounds for this study. The corresponding racemic imines were prepared by condensation of the precursor ketones and racemic tert-butylsulfinamide. The optical purities of imines **3a**, **3b** and **3h** were evaluated by HPLC analyses on a chiral column by comparison with the corresponding racemic samples. In all three cases, the enantiomeric excess were >99%. Thus, there was no racemization of the imine products under our reaction conditions.

Table 1. Synthesis of *N*-(tert-butylsulfinyl)ketimines **3a–m** using $TiCl_4$[a] at room temperature

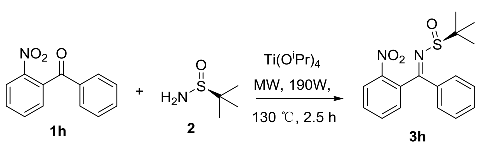


Entry	No.	R1, R2	Structure	Isolated Yields(%)[b]
1	3a	2-$NH_2C_6H_4$, Ph		50
2	3b	*p*-Cl-$NH_2C_6H_3$, Ph		38
3	3c	*p*-Cl-$NH_2C_6H_3$, 2'-FC_6H_4		37
4	3d	*p*-Cl-$NH_2C_6H_3$, 2'-F,6'-FC_6H_3		25
5	3e	2-$NHC_6H_5CH_2C_6H_4$, Ph		31
6	3f	2-$NH_2C_6H_3$, C_6H_4		28

7	3g	2-$NH_2C_5H_3N$, Ph		20
8	3h	2-$NO_2C_6H_4$, Ph		0
9	3i	2-$NO_2C_6H_4$, 1'-naphthyl		0
10	3j	2-$NO_2C_6H_4$, 2'-$CH_3C_6H_4$		0
11	3k	2-$NO_2C_6H_4$, 2'-$CH_3OC_6H_4$		0
12	3l	2-$NO_2C_6H_4$, 4'-FC_6H_4		0
13	3m	2-$NO_2C_6H_4$, 2'-$CF_3C_6H_4$		0

[a]The mixture of **1a-m** (1 mmol), (*R*)-*t*-$BuSONH_2$ (1.1mmol), and 2M $TiCl_4$ (1.5 ml, 3mmol) in toluene were stirred at room temperature for 12h. [b]Yield of isolated product after being subjected to silica gel column chromatography. Compounds **3a–g** were always ≥ 95% pure (400 MHz ^1H NMR).

Table 2: Optimization of reaction conditions for **3h**[a]

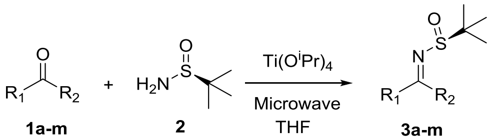


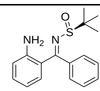
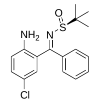
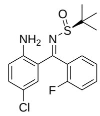
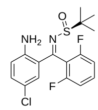
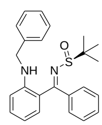
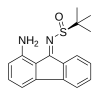
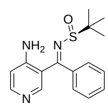
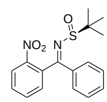
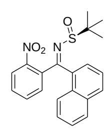
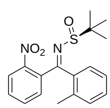
Entry	**1h**/**2**/Ti(O^{i}Pr)$_4$ (eq)	Temp. (℃)/ energy(W)	Reaction time(h)	Conv.	Isolated Yields[b]
1	1/1/2	120/160	1.0	trace	0
2	1/1/3	120/160	1.0	trace	0
3	1/1/4	120/160	1.0	trace	0
4	1/1/2	130/190	1.0	30	21
5	1/1/3	130/190	1.0	32	22
6	1/1/4	130/190	1.0	34	22
7	1/1/4	130/190	1.5	38	26
8	1/1/4	130/190	2.0	50	33
9	1/1/4	130/190	2.5	60	41
10	1/1/4	140/210	0.5	90	trace
11	1/1/4	140/210	1.0	100	trace
12	1/1/4	140/210	1.5	100	trace

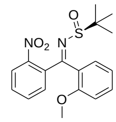
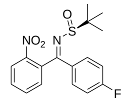
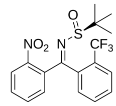
[a]The mixture of **1h** (1 mmol), (*R*)-*t*-$BuSONH_2$ (1.1mmol), Ti(O^{i}Pr)$_4$ (4 mmol) and 1mL THF were stirred under microwave irradiation for 1.0-2.5 h. [b]Yield of isolated product after being subjected to silica gel column chromatography. Compounds **3h** were always ≥ 95% pure

(400 MHz ^{1}H NMR).

Table 3. Microwave-assisted Synthesis of *N*-(tert-butylsulfinyl) ketimines **3a–m**[a]



Entry	No.	R_1, R_2,	Structure	M.W(W)/ Temp.(℃)	Time (h)	Conv.(%)	Yield(%)[b]
1	3a	2-$NH_2C_6H_4$, Ph		160/120	2	>95	89
2	3b	*p*-Cl-$NH_2C_6H_3$, Ph		160/120	2	>95	86
3	3c	*p*-Cl-$NH_2C_6H_3$, 2'-FC_6H_4		160/120	2	>95	85
4	3d	*p*-Cl-$NH_2C_6H_3$, 2'-F,6'-F C_6H_3		160/120	2	>95	73
5	3e	2-$NHC_6H_4CH_2C_6H_4$, Ph		160/120	2	>95	70
6	3f	2-$NH_2C_6H_3$, C_6H_4		160/120	2	>95	84
7	3g	2-$NH_2C_5H_3N$, Ph		160/120	2	>95	83
8	3h	2-$NO_2C_6H_4$, Ph		190/130	2.5	>60	41
9	3i	2-$NO_2C_6H_4$, 1'-naphthyl		190/130	2.5	>60	38
10	3j	2-$NO_2C_6H_4$, 2'-$CH_3C_6H_4$		190/130	2.5	>60	42

11	3k	2-$NO_2C_6H_4$, 2'-$CH_3OC_6H_4$		190/130	2.5	>60	44
12	3l	2-$NO_2C_6H_4$, 4'-FC_6H_4		190/130	2.5	>50	30
13	3m	2-$NO_2C_6H_4$, 2'-$CF_3C_6H_4$		190/130	2.5	>50	19

[a]The mixture of **1a-m** (1 mmol), (*R*)-*t*-BuSONH$_2$ (1 mmol), and Ti(O^{i}Pr)$_4$ (4 mmol) and 1mL THF were stirred under microwave irradiation for 2-2.5 h. [b]Yield of isolated product after being subjected to silica gel column chromatography. Compounds **3a–m** were always ≥ 95% pure (400 MHz^{1}H NMR).

3. Conclusions

In conclusion, we have optimized the condensation of *ortho*-substituted diaryl ketones with (*R*)-(+)-tert-butylsulfinamide in the presence of titanium(IV) isopropoxide under microwave irradiation. This method allows for the preparation of *ortho*-substitue diarylsulfinyl ketimines in moderate to good yield.

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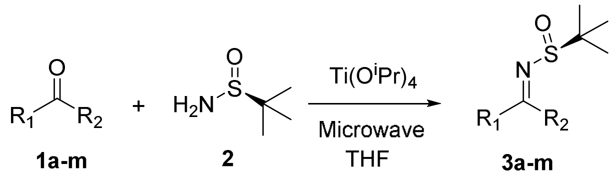
GRAPHICAL ABSTRACT



A simple and efficient procedure for the synthesis of *ortho*-substituted diarylketimines has been developed under microwave irradiation