

Microwave-Assisted Rapid and Selective Synthesis of *cis*- and *trans*-2,4,5-Triarylimidazolines from Aromatic Aldehydes

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Received 4 April 2003

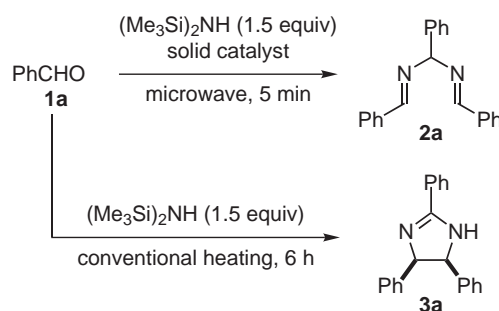
Abstract: Microwave irradiation of a mixture of aromatic aldehydes and hexamethyldisilazane in the presence of a solid catalyst such as alumina afforded methanediamines which were efficiently converted to either *cis*- or *trans*-2,4,5-triarylimidazolines depending on the base used. A one-pot selective synthesis of *cis*- and *trans*-imidazolines from aromatic aldehydes was achieved under microwave irradiation.

Key words: microwave, imidazoline, methanediamine, hexamethyldisilazane, solvent-free

Diarylethylenediamines and their derivatives, which can serve as important chiral ligands¹ and biologically active compounds,² are obtainable from *trans*-2,4,5-triarylimidazolines.³ *trans*-Triarylimidazolines are prepared by isomerization of the corresponding *cis* isomers, which can be obtained from aromatic aldehydes through *N,N'*-bis(arylmethylidene)arylmethanediamines. Prolonged heating is needed to form methanediamines from aromatic aldehydes; for example, it takes over one week to prepare methanediamines with ammonia⁴ and several hours by heating aldehydes with hexamethyldisilazane (HMDS) in the presence of a Lewis acid⁵ or without a Lewis acid under solvent-free conditions.⁶ Recently, a one-pot synthesis of triphenyl- and tris(2-pyridyl)imidazolines has been reported in the reaction of aromatic aldehydes with HMDS and LiBr in DMSO.⁷ Independently, we have found a one-step synthesis of triarylimidazolines on treatment of aromatic aldehydes with HMDS without a solvent.⁸ Studying this synthesis under microwave irradiation,⁹ we found that the reaction was greatly accelerated. We now report a rapid, convenient and selective synthesis of methanediamines as well as *cis*- and *trans*-triarylimidazolines from aromatic aldehydes with HMDS under microwave irradiation.

When a mixture of benzaldehyde **1a** and HMDS was irradiated with microwave, no reaction occurred (Table 1, entry 1). The reaction proceeded to give *N,N'*-bis(phenylmethylidene)phenylmethanediamine **2a** on addition of 5.0-fold excess amount of silica gel¹⁰ to a mixture of **1a** and 1.5 equivalents of HMDS without using a solvent (Scheme 1). The irradiation for 5 minutes afforded **2a** in 79% yield (entry 2). Alumina was found to be more effective

than silica gel, and a high yield of **2a** was achieved on addition of a small amount of alumina (entries 3 and 4).¹¹ Bentonite and montmorillonite K-10 also afforded **2a** but in lower yields (entries 5 and 6).



Scheme 1

Table 1 Reaction of Benzaldehyde **1a** with HMDS under Microwave Irradiation^a

Entry	Solid catalyst	Weight Ratio ^b	Yield of 2a (%)
1	—	0	0
2	silica gel	5.0	79
3	alumina	0.5	94
4	alumina	5.0	89
5	bentonite	5.0	26
6	K-10	5.0	45

^a The mixture was irradiated for 5 min.

^b Weight ratio of the solid catalyst to **1a**.

Thus, the above reaction under microwave irradiation did not afford *cis*-imidazoline **3a** but gave methanediamine **2a**.¹² This is in contrast with the results that *cis*-imidazolines **3** are obtained directly from aldehydes by the conventional heating.⁸ Methanediamines are known to cyclize to imidazolines by the action of a base such as phenyllithium,¹³ *t*-BuOK,¹⁴ or sodium alkoxides.^{3,7} We examined microwave irradiation in the presence of bases. Methanediamine **2a** was isolated by recrystallization of the crude product obtained in the irradiation of aldehyde **1a**, HMDS, and alumina for 5 minutes. Indeed, irradiation of **2a** for 5 minutes with 1.0 equivalent of NaOMe in methanol gave *cis*-imidazoline **3a** in 55% yield (Table 2,

entry 1). The reaction in the presence of 1.0 equivalent of *t*-BuOK in *t*-BuOH gave *cis*-**3a** exclusively in 78% yield after irradiation for 2 minutes (entry 2). The reaction with 0.1 equivalents of *t*-BuOK gave the *trans*-imidazoline *trans*-**3a** predominantly in high yield (entry 3). When the mixture was irradiated for 5 minutes with *t*-BuOK/*t*-BuOH, *trans*-**3a** was obtained exclusively (entry 4).¹⁵ The reaction performed in the presence of DBN without a solvent afforded *cis*-**3a** in high yield (entry 5). DBU also afforded *cis*-**3a** exclusively when the reaction was carried out with 1.0 equivalent of DBU for 2 minutes (entry 8). Several reaction conditions using DBU were examined as shown in Table 2, and *trans*-**3a** was found to be formed exclusively in high yield when the mixture was irradiated in the presence of 10.0 equivalents of DBU for 5 minutes (entry 12).

We next examined a one-pot synthesis of imidazolines **3** from aromatic aldehydes **1**. Since irradiation of a mixture of **1a**, HMDS, alumina, and DBN afforded neither **2a** nor **3a**, we decided to add a base after the formation of methanedianamine **2a**. The results are shown in Table 3. A mixture of **1a**, 1.5 equivalents of HMDS and 50 wt% of

alumina was irradiated for 5 minutes, when methanedianamine **2a** was formed, and then, without isolation, was added 1.0 equivalent of DBN (the equivalency is based on **2a** assumed to be formed in 100% yield). When microwave irradiation was continued for an additional 5 minutes, *cis*-imidazoline *cis*-**3a** was obtained in 85% yield (entry 1).¹⁶ Under these conditions, formation of *trans*-**3a** was not observed although cyclization of **2a** with DBN gave a mixture of *cis*- and *trans*-**3a** (Table 2, entry 6). This is because the reaction starting with **1a** was performed in the presence of alumina even in the cyclization step. Benzaldehydes having various substituents also gave *cis*-imidazolines in high yields. It should be noted that both *p*-anisaldehyde (**1e**) and *p*-dimethylaminobenzaldehyde (**1f**) yielded *cis*-imidazolines *cis*-**3e** and *cis*-**3f** in high yields, respectively (entries 5 and 6), since the conventional thermal reaction of **1e** with HMDS affords *cis*-**3e** only on addition of chlorotrimethylsilane and that of **1f** does not afford **3f** at all even with chlorotrimethylsilane.⁸

We also studied a selective one-pot synthesis of *trans*-imidazoline *trans*-**3** from **1**. Isomerization of *cis*-**3** to *trans*-**3** depends on the base added for the cyclization as well as on the irradiation time as shown in Table 4. As previously shown in Table 3 (entry 1), after irradiation for 5 minutes, further irradiation with 1.0 equivalent of DBN gave *cis*-**3a** exclusively. Prolonged irradiation with DBN also gave only *cis*-**3a** (Table 4, entry 1). Although irradiation with 1.0 equivalent of DBU for 5 minutes gave *cis*-**3a** (entry 2), use of an excess amount of DBU increased the formation of *trans*-**3a**, but it still could not avoid the formation of *cis*-**3a** (entries 3, 4, 5 and 6), these results being in contrast to the exclusive formation of *trans*-**3a** from *cis*-**3a** (Table 2, entry 12). The selective formation of *trans*-**3a** was achieved by irradiation with 3.0 equivalents of *t*-BuOK in *t*-BuOH, although the yields were moderate (entries 8 and 9). From the rather lower yield of **3a** with *t*-BuOK/*t*-BuOH, it was assumed that **2a** was hardly removed from the alumina face in *t*-BuOH. Indeed, *t*-BuOK/DMF improved the yield of *trans*-**3a** (entry 10). Finally, a mixed base, *t*-BuOK/DBU, was found to be the most effective to give *trans*-**3a** (entry 11).¹⁷ Under similar reaction conditions, aldehydes **1b,d,e** gave the corresponding *trans*-imidazolines *trans*-**3b,d,e** selectively in good yields (entries 12–14).

In summary, a rapid, solvent-free, and selective synthesis of *cis*- and *trans*-2,4,5-triarylimidazolines was achieved by microwave irradiation of a mixture of aromatic aldehydes and HMDS in the presence of alumina and subsequently by further irradiation in the addition of a base.


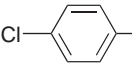
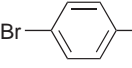
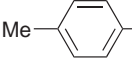
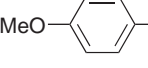
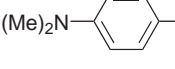


Acknowledgment

This work was partly supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' (No. 14044040) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Table 2 Selective Formation of *cis*-**3a** and *trans*-**3a** from Methanedianamine **2a** with Bases

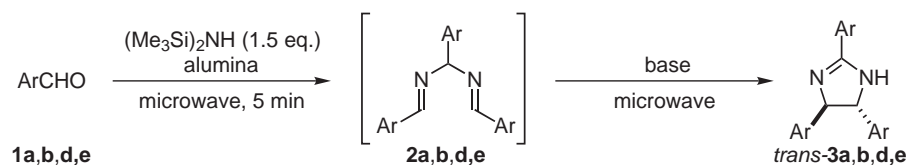
Entry	Base	Equiv	Time (min)	<i>cis:trans</i>	Yield (%)
1	MeONa/MeOH	1.0	5	>98:2	55
2	<i>t</i> -BuOK/ <i>t</i> -BuOH	1.0	2	>98:2	78
3	<i>t</i> -BuOK/ <i>t</i> -BuOH	0.1	5	25:75	86
4	<i>t</i> -BuOK/ <i>t</i> -BuOH	1.0	5	2:>98	96
5	DBN	1.0	2	>98:2	98
6	DBN	1.0	5	50:50	96
7	DBN	1.0	10	39:61	94
8	DBU	1.0	2	>98:2	96
9	DBU	1.0	5	25:75	88
10	DBU	1.0	10	6:94	78
11	DBU	2.0	5	25:75	96
12	DBU	10.0	5	2:>98	83

Table 3 Reactions of Aromatic Aldehydes **1a–h** with DBN under Microwave Irradiation

$\text{ArCHO} \xrightarrow[\text{microwave}]{\text{(Me}_3\text{Si)}_2\text{NH (1.5 equiv) alumina}} \left[\text{Ar} \begin{array}{c} \text{Ar} \\ \text{N} \quad \text{N} \\ \text{Ar} \quad \text{Ar} \end{array} \right] \xrightarrow[\text{microwave}]{\text{base (1.0 equiv)}} \text{Ar} \begin{array}{c} \text{Ar} \\ \text{N} \quad \text{NH} \\ \text{Ar} \quad \text{Ar} \end{array}$							
1a–h		2a–h		3a–h			
Entry	Ar	Aldehyde	Base	Irradiation time		Product	Yield (%)
				step A (min)	step B (min)		
1		1a	DBN	5	5	3a	85
2		1b	DBN	10	3	3b	83
3		1c	DBU	10	1	3c	83
4		1d	DBU	10	5	3d	82
5		1e	DBU	10	10	3e	86
6		1f	DBU	10	10	3f	82
7		1g	DBU	5	5	3g	70
8		1h	DBU	5	5	3h	59

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- (11) Basic, acidic, and neutral alumina showed similar results.
- (12) Irradiation in the presence of silica gel for 10 min gave **3a** in 44% yield together with **2a** and other unidentified products, whereas formation of **3a** was not observed in the irradiation with alumina for 10 min.
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Table 4 One-pot Preparation of *trans*-Triarylimidazolines *trans*-**3** from Aromatic Aldehydes **1**

Entry	Aldehyde	Base	Equiv	Time (min)	Product	<i>cis:trans</i>	Yield (%)
1	1a	DBN	1.0	10	3a	>98:2	87
2	1a	DBU	1.0	5	3a	>98:2	84
3	1a	DBU	1.0	10	3a	80:20	86
4	1a	DBU	5.0	5	3a	70:30	85
5	1a	DBU	5.0	10	3a	37:63	86
6	1a	DBU	20.0	5	3a	33:67	57
7	1a	<i>t</i> -BuOK/ <i>t</i> -BuOH	0.9/4.3	5	3a	>98:2	45
8	1a	<i>t</i> -BuOK/ <i>t</i> -BuOH	3.0/14.4	5	3a	2:>98	57
9	1a	<i>t</i> -BuOK/ <i>t</i> -BuOH	3.0/14.4	10	3a	2:>98	69
10	1a	<i>t</i> -BuOK/DMF	3.0/12.3	5	3a	2:>98	71
11	1a	<i>t</i> -BuOK/DBU	1.0/1.0	5	3a	2:>98	81
12	1b^a	<i>t</i> -BuOK/DBU	1.0/1.0	5	3b	2:>98	68
13	1d^a	<i>t</i> -BuOK/DBU	1.0/1.0	5	3d	2:>98	78
14	1e^a	<i>t</i> -BuOK/DBU	2.0/2.0	10	3e	2:>98	63

^a The mixture was first irradiated for 10 min to form methanediamines.

(15) Irradiation of *cis*-**3a** with 1.0 equiv of *t*-BuOK/*t*-BuOH for 5 min gave *trans*-**3a** quantitatively.

(16) **Typical Procedure for Preparation of *cis*-2,4,5-Triphenylimidazoline (*cis*-**3a**) from **1a**.**

A mixture of benzaldehyde **1a** (209 mg, 1.97 mmol), HMDS (620 μ L, 480 mg, 2.95 mmol), and basic alumina (100 mg, Wako Pure Chemical Industries Ltd., column chromatography grade, 200 mesh, pH 9.0–11.0) was charged in a test tube equipped with a cooler. The mixture was irradiated under argon atmosphere for 5 min in a microwave oven (500 W, 2450 MHz). Then, DBU (100 μ L, 105 mg, 0.69 mmol) was added and the mixture was irradiated for an additional 5 min. After cooling, alumina

was filtered and washed with CH_2Cl_2 . The obtained organic solution was concentrated under vacuum to leave a residue, which was purified by silica gel column chromatography (hexane/EtOAc 9:1) to give 164 mg (85%) of *cis*-**3a**.

(17) **Typical Procedure for Preparation of *trans*-2,4,5-Triphenylimidazoline (*trans*-**3a**) from **1a**.**

A mixture of **1a** (209 mg, 1.97 mmol), HMDS (620 μ L, 480 mg, 2.95 mmol) and, basic alumina (100 mg) was irradiated for 5 min, and then, *t*-BuOK (77 mg, 0.69 mmol) and DBU (100 μ L, 105 mg 0.69 mmol) were added to the mixture which was further irradiated for an additional 5 min. Work-up and purification as described above gave 159 mg (81%) of *trans*-**3a**.