Synthesis and stereochemistry of 1,2,4,5-tetraarylimidazolidines

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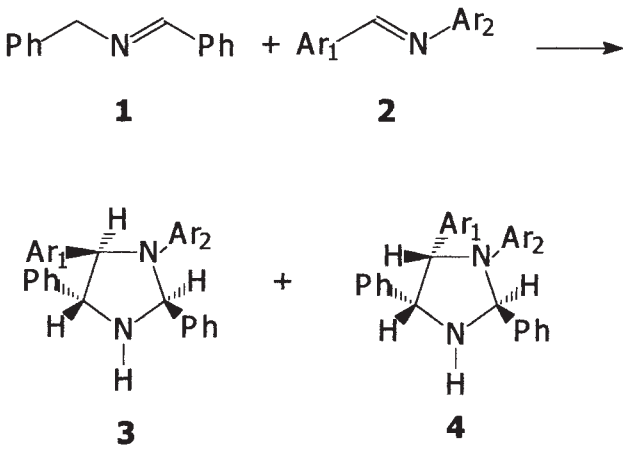
Phase-transfer catalysed reaction of *N*-(benzylidene)benzylamine with arylmethyleneanilines afforded the stereoisomeric 1,2,4,5-tetraarylimidazolidines **3** and **4**; a two-step addition–cyclisation mechanism was suggested on the basis of NMR analysis of the isolated products and the observed epimerisation of the prepared imidazolidines.

Keywords: imidazolidines, imines, two-step cycloaddition, epimerisation, ring-chain tautomerism

The reaction of *N*-(benzylidene)benzylamine with benzylideneaniline is known to result in the formation of two isomeric 1,2,4,5-tetraphenylimidazolidines (**3a** and **4a**) under both anhydrous and aqueous conditions.[2–5] The survey of the literature revealed that the structure of both **3a** and **4a** has not been elucidated. In general, stereochemical studies for polysubstituted imidazolidines are scarce and concerned mainly the stereochemistry of C-4 and C-5 of the imidazolidine ring.[10,14,15] We now present the results of our studies directed to developing methods for the preparation of the isomeric imidazolidines **3** and **4** by phase-transfer catalysed reaction of *N*-(benzylidene)benzylamine **1** and the imines **2** (Scheme 1), and elucidation of their structures.



2,3,4	Ar_1	Ar_2
a	Ph	Ph
b	4-ClC_6H_4	Ph
c	Ph	4-ClC_6H_4
d	4-MeC_6H_4	Ph
e	Ph	4-MeC_6H_4
f	4-$MeOC_6H_4$	Ph
g	Ph	4-$MeOC_6H_4$

Scheme 1

The reaction of **1** with benzylideneaniline (**2a**), resulting in the formation of isomeric imidazolidines with melting points 108°C (**3a**) and 170°C (**4a**) has been investigated under different conditions in order to develop procedures for the preparation of each isomer (Table 1). In all cases formation of both **3a** and **4a** was observed, but further crystallisation of the mixtures yielded pure **3a** or **4a**. Attempts to separate the isomers by column chromatography failed because of their low solubility, and epimerisation and decomposition processes. As can be seen from Table 1, the low melting isomer (**3a**) was formed predominantly when DMSO was used as solvent regardless of the aqueous sodium hydroxide concentration and the presence of TEBA. Using solvents with low polarity, or performing the reaction without any solvent at room temperature yielded diastereoisomeric mixtures in which the higher melting isomer (**4a**) was the main product. No product was isolated when the reaction was carried out at 0°C in the absence of solvent, while at 0°C in CH_3CN 28% of **4a** was obtained. Increasing the temperature to 40°C in CH_3CN led to an increase in chemical yield (71%) but did not improved the stereoselectivity.

Table 1 Yields of **3a** and **4a** obtained under different conditions

Compound	Reaction conditions (Method)	Yield/%[a]
3a	DMSO, 4% NaOH, r.t.,[b] 24 h (**A**)	39 (63)
	DMSO, 50% NaOH, r.t., 24 h (**B**)	55 (73)
	DMSO, 50% NaOH, TEBA, r.t., 24 h (**C**)	62 (73)
4a	50% NaOH, TEBA, r.t., 24 h (**D**)	34 (42)
	50% NaOH, TEBA, 0°C, 24 h (**E**)	–[c]
	50% NaOH, TEBA, 40°C, 1–5 h (**F**)	(71)
	CH_3CN, 50% NaOH, TEBA, 0°C, 24 h, (**G**)	28 (29)
	CH_3CN, 50% NaOH, TEBA, r.t., 24 h (**H**)	(42)
	CH_2Cl_2, 50% NaOH, TEBA, r.t., 24 h (**I**)	16 (50)
	C_6H_6, 50% NaOH, TEBA, r.t., 24 h (**J**)	23 (50)
	C_6H_6, 50% NaOH, Aliquat, r.t., 24 h (**K**)	27 (42)

[a]Yield of pure (TLC, ^1H NMR) diastereoisomer; in brackets are given the yields of mixtures of **3a** and **4a**, obtained after one recrystallisation of the crude product. [b]r.t. = room temperature. [c]No product isolated.

The ^1H and ^{13}C NMR spectra of the stereoisomeric imidazolidines **3a** and **4a** are given in Table 2. There were pronounced differences between the chemical shifts of both proton and carbon signals of the stereoisomers **3a** and **4a**. Quite unexpectedly, when measured in $CDCl_3$, the ^1H and ^{13}C NMR spectra of each **3a** and **4a** revealed the presence of the stereoisomeric imidazolidines **3a–l** and **4a–l** (Fig. 1). Full assignment of ring protons and carbon NMR signals for the four diastereoisomers (Table 2), and the determination of their configuration was achieved on the basis of combined use of inverse heterocorrelation spectra HSQC and NOESY spectra. As can be seen from Table 2, the chemical shifts of the ring protons in the four diastereoisomers are markedly dissimilar, reflecting the different shielding arising from different positions of the phenyl rings. The carbon NMR shifts also differ, the differences arising generally from steric effects. Large nuclear Overhauser enhancements are observed between the ring protons and the

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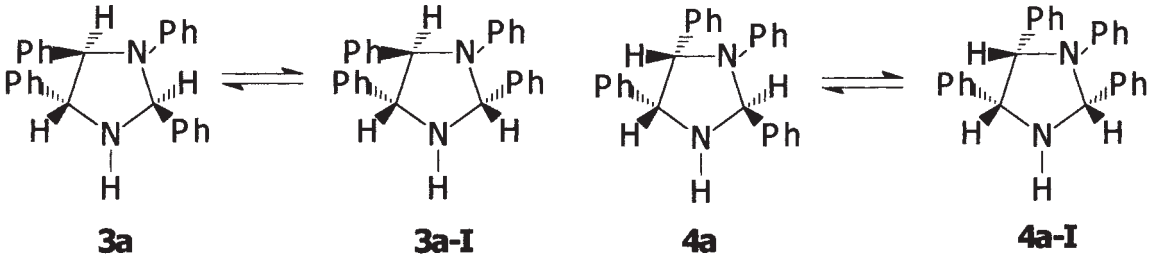


Fig. 1 Structures of the stereoisomers of 1,2,4,5-tetraphenylimidazolidine.

Table 2 ^{1}H and ^{13}C NMR parameters of compounds **3a** and **4a** measured in $CDCl_3$ and CCl_4

Compound	Solvent	H-2	H-5	H-4	$J_{4,5}$	C-2	C-5	C-4
3a	CCl_4	5.65	4.62	4.15	7.0	[a]		
3a	$CDCl_3$	5.76	4.77	4.27	6.7	79.88	73.14	69.55
(**3a-I**)		6.11	5.10	4.36	7.2	79.22	72.49	71.80
4a	CCl_4	5.87	5.02	4.73		[a]		
4a	$CDCl_3$	6.09	5.24	4.95	6.3	76.50	67.14	63.20
(**4a-I**)		5.68	4.97	4.85	7.4	78.55	72.13	66.52

[a]Not measured.

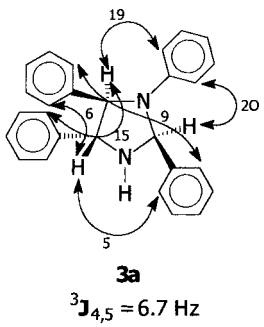
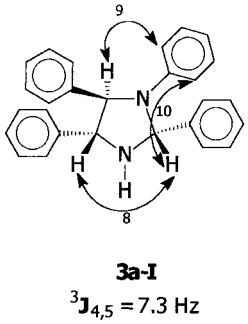
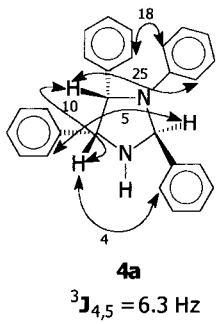


Fig. 2 NOE effects for the isomers of compound **3a**.





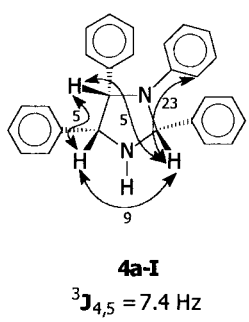


Fig. 3 NOE effects for the isomers of compound **4a**.

ortho protons of the corresponding vicinal phenyl rings, as well as between all *cis*-situated ring protons (Fig. 2 and 3).

It should be noted that, in addition to the signals of the isomers **3a** and **3a–I**, respectively **4a** and **4a–I**, in the NMR spectra measured in $CDCl_3$ the signals of the corresponding open-chain addition products were observed. These facts suggest that the formation of the isomers **3a–I** and **4a–I** occurred by cyclisation of the diastereoisomeric open chain adducts initially formed.

Under analogous conditions for the preparation of both **3a** and **4a** (Table 1), the reactions of *N*-(benzylidene)benzylamine with the Schiff bases **2b–g** gave the corresponding substituted imidazolidines as mixtures of the isomers **3** and **4** (**3:4** ~ 1:1) and, after recrystallisation to diastereoisomeric purity (TLC, ^{1}H NMR), the single isomers **3c**, **3g**, **4b**, **4d**, **4e** and **4f** were obtained. The assignment of structure **3** or **4** to each of the imidazolidines **b–f** was made by comparison of their spectroscopic data with the data obtained for **3a** and **4a**, and NOE measurements. As can be seen from Table 4, the ^{1}H and ^{13}C NMR spectra of compounds **3c** and **3g** are quite similar to those of **3a**, and the spectral data of **4b**, **4d**, and **4f** to **4a**. On the other hand, the observed values of NOE effects are similar to those of **3a** and **4a** (Figs 2 and 3). Furthermore, the ^{1}H NMR spectra of the imidazolidines **b–f**, measured in $CDCl_3$ solution revealed, that the same epimerisation (**3a** → **3a–I** and **4a** → **4a-I**), due most probably to the traces of HCl in $CDCl_3$, was taking place in all cases. Table 5 summarises the spectral data for the stereoisomeric imidazolidines **3**, **3–I**, **4** and **4–I**, as well as the ratios **3**/**3–I** and **4**/**4–I**, measured both immediately, and one week after preparation of the sample. As can be seen from Table 5, the **3**/**3–I** ratio practically did not change, while in most **4**/**4–I** cases the **4–I** isomers drastically increased. On the other hand, in the ^{1}H NMR spectra of all compounds measured in $CDCl_3$, the signals of the open-chain addition products were observed. These signals were also observed in the ^{1}H NMR spectra of the crude **3** and **4**, measured in CCl_4, and therefore, additionally confirmed the suggestion that the formation of the imidazolidines proceeded *via* a two-step Michael addition-cyclization procedure. Unfortunately, attempts to isolate an open-chain product completely failed.

Table 4 ^{1}H and ^{13}C NMR data for the imidazolidines **3** and **4**

Comp.	^{1}H NMR[a]				^{13}C NMR[a]		
	H-2	H-5	H-4	$J_{4,5}$	C-2	C-5	C-4
3a	5.76	4.77	4.27	6.7	79.88	73.14	69.55
3c	5.66	4.70	4.25	6.6	79.91	73.16	69.48
3g	5.64	4.69	4.26	6.7	80.35	73.61	69.53
4a	6.09	5.24	4.95	6.3	76.50	67.14	63.20
4b	6.05	5.18	4.93	6.2	76.49	66.45	62.88
4d	6.07	5.23	4.91	6.2	76.48	66.84	63.18
4e	6.05	5.22	4.93	6.3	76.49	67.18	63.21
4f	6.05	5.19	4.89	6.2	76.37	66.51	63.18

[a]Measured in $CDCl_3$

Table 5 ^{1}H chemical shifts (δ values) of compounds **3** and **4** in $CDCl_3$ solution

Compound	H-2	H-5	H-4	$J_{4,5}$	Me or MeO	Ratio[a] [b]	[c]
3a	5.76	4.77	4.27	6.7	–	95:–[d]:5	95:–[d]:5
3a–l	6.11	5.10	4.36	7.2	–		
3c	5.66	4.70	4.26	6.6	–	95:–[d]:5	94:–[d]:6
3c–l	6.04	5.02	4.31	7.4	–		
3g	5.64	4.69	4.26	6.7	3.63	94:4:2	94:4:2
3g–l	6.06	5.05	4.33	7.3	3.61		
4a	6.09	5.24	4.95	6.3	–	84:7:9	64:22:14
4a–l	5.68	4.97	4.85		–		
4b	6.05	5.18	4.93	6.3	–	95:4:1	45:40:15
4b–l	5.65	4.91	4.82	7.3	–		
4d	6.07	5.23	4.91	6.2	2.20	97:0:3	39:46:15
4d–l	5.67	4.96	4.83	7.3	2.19		
4e	6.05	5.22	4.93	6.3	2.10	99:0:1	37:50:13
4e–l	5.64	4.93	4.82	7.5	2.17		
4f	6.05	5.19	4.89	6.2	3.63	97:0:3	40:46:14
4f–l	5.65	4.93	4.80	7.3	3.68		

[a]Ratio **3/4:3–l/4–l:5/6**. [b]Measured immediately after preparation of the sample. [c]Ratio measured after one week. [d]Trace amounts of the isomer **3–l**, the signal is not integrated.

In conclusion, the reactions reported here are an attractive addition to the existing methodology for the preparation of 1,2,4,5-tetraarylimidazolidines under anhydrous conditions. Although the yields are modest, the method provides a direct entry to these compounds by a simple procedure. The stereochemistry of the prepared compounds is elucidated. A two-step addition-cyclisation mechanism is suggested on the basis of the observed epimerisation of the imidazolidines and NMR analysis of the crude reaction products.

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Techniques used: ^{1}H and ^{13}C NMR, IR, TLC

References: 20

Schemes: 1

Figures: 3

Table 3: Yields of compounds **3** and **4**

Table 6. ^{1}H NMR parameters of compounds **5** and **6**

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