Synthesis of 2-substituted 1-tosyl-3-(1-tosyliminoalkyl)imidazolidines and -hexahydropyrimidines

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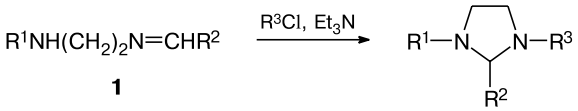
Reactions of *N*-tosylimidoyl chlorides with the Schiff bases of the general formula $TsNH(CH_2)_nN{=}CHR$ (n = 2 or 3; R = Pr^i, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, and 3-$O_2NC_6H_4$) afforded 2-substituted 1-tosyl-3-(1-tosyliminoalkyl)imidazolidines (n = 2) or -hexahydropyrimidines (n = 3).

Key words: *N*-tosylimidoyl chlorides, imidazolidines, hexahydropyrimidines, Schiff bases, heterocyclization, diamines.

Earlier,[1] we have proposed a method for the synthesis of 2-substituted *N*,*N*´-diacylated or -disulfonylated imidazolidines (DI). The method involves base-catalyzed cyclization of the Schiff bases **1** (prepared from *N*-monoacylated/sulfonylated ethylenediamines) in the presence of acylating/sulfonylating agents (Scheme 1).

Scheme 1



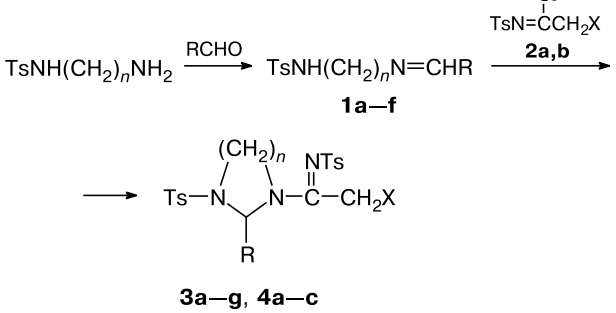
1

R^1, R^3 = AlkCO, ArCO, $AlkSO_2$, $ArSO_2$; R^2 = Alk, Ar

Variation in any of the three components (acyl/sulfonyl substituent in the starting diamine, aldehyde component in imine **1**, and especially acylating/sulfonylating agent) affords a variety of DI. Previously,[1] at the final step of DI synthesis, we have employed carboxylic, sulfonic, and carbamic anhydrides and acid chlorides and chloroformates. Here we used the known[2,3] *N*-tosylimidoyl chlorides **2**. Since compounds **2** may be regarded as analogs of acid chlorides, in which the C=O fragment is replaced by the C=N—Ts fragment, we hoped to use them as cyclization agents. Indeed, imines **1a—d** prepared from *N*-tosylethylenediamine and aldehydes, underwent cyclization in reactions with compounds **2** in MeCN in the presence of Et_3N to give 2-substituted 1-tosyl-3-(1-tosyliminoalkyl)imidazolidines **3a—g** (Scheme 2).

The reaction easily occurred at room temperature, even with imines **1** prepared from *N*-tosylethylenediamine and aldehydes containing electron-withdrawing substituents in the benzene ring (*e.g.*, 3-nitrobenzaldehyde derivative **1d**), which have been reported[1] to form no imidazolidines in reactions with acid chlorides. This process may involve either preliminary synthesis of imines **1** (procedure *A*) or their *in situ* formation (procedure *B*), which is convenient with oily and difficult-to-crystallize compounds **1**.

Scheme 2



3a—g, **4a—c**

1	n	R	**3**	X	R
a	2	Pr^i	**a**	H	Pr^i
b	2	4-$MeOC_6H_4$	**b**	Cl	Pr^i
c	2	4-$Me_2NC_6H_4$	**c**	H	4-$MeOC_6H_4$
d	2	3-$O_2NC_6H_4$	**d**	Cl	4-$MeOC_6H_4$
e	3	Pr^i	**e**	Cl	4-$Me_2NC_6H_4$
f	3	3-$O_2NC_6H_4$	**f**	H	3-$O_2NC_6H_4$
			g	Cl	3-$O_2NC_6H_4$

n = 2 (**3a—g**), 3 (**4a—c**)
2: X = H (**a**), Cl (**b**)
4: X = H, R = Pr^i (**a**); X = Cl, R = Pr^i (**b**); X = H, R = 3-$O_2NC_6H_4$ (**c**)

Imidoyl chlorides **2a,b** also reacted with *N*-tosyltrimethylenediamine derivatives **1e,f**, yielding hexahydropyrimidines **4a—c** (see Scheme 2).

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Table 1. Yields, melting points, and elemental analysis data for 2-substituted imidazolidines **3a—g** and **5a—c** and hexahydropyrimidines **4a—c** and **6**

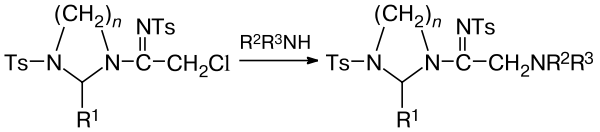
Compound	Yield (%)	M.p. /°C	Found / Calculated (%)					Molecular formula
			C	H	Cl	N	S	
3a	47	150—151	56.72 57.00	6.39 6.30	—	9.19 9.06	13.74 13.83	$C_{22}H_{29}N_3O_4S_2$
3b	65	146—148	53.15 53.05	5.96 5.67	7.03 7.12	8.20 8.44	12.70 12.87	$C_{22}H_{28}ClN_3O_4S_2$
3c	78	155—157	59.30 59.18	5.56 5.54	—	7.90 7.96	12.18 12.15	$C_{26}H_{29}N_3O_5S_2$
3d	30	164—166	55.97 55.56	5.15 5.02	6.14 6.31	7.37 7.48	11.10 11.41	$C_{26}H_{28}ClN_3O_5S_2$
3e	82	188—190	56.05 56.39	5.39 5.43	5.98 6.16	9.88 9.74	11.12 11.15	$C_{27}H_{31}ClN_4O_4S_2$
3f	59	144—145	55.27 55.34	4.78 4.83	—	10.35 10.33	11.77 11.82	$C_{25}H_{26}N_4O_6S_2$
3g	61	164—166	52.06 52.03	4.40 4.37	6.41 6.14	9.96 9.71	10.87 11.11	$C_{25}H_{25}ClN_4O_6S_2$
4a	50	188—190	57.46 57.84	6.54 6.54	—	8.94 8.80	13.22 13.42	$C_{23}H_{31}N_3O_4S_2$
4b	49	184—186	53.71 53.95	6.23 5.90	6.68 6.92	8.06 8.21	12.18 12.52	$C_{23}H_{30}ClN_3O_4S_2$
4c	70	214—216	56.27 56.10	5.01 5.07	—	10.22 10.06	11.27 11.52	$C_{26}H_{28}N_4O_6S_2$
5a	42	116—118	60.88 61.24	6.49 6.38	—	10.17 9.85	10.97 11.27	$C_{29}H_{34}N_4O_4S_2$
5b	60	146—148	56.99 57.43	5.75 5.71	—	10.11 10.30	11.45 11.79	$C_{26}H_{36}N_4O_5S_2$
5c	65	175—177	61.02 60.96	6.60 6.27	—	9.00 9.17	10.17 10.50	$C_{31}H_{38}N_4O_5S_2$
6	69	159—161	57.36 57.63	6.51 6.81	—	9.81 9.96	10.99 11.39	$C_{27}H_{38}N_4O_5S_2$

Attempted analogous reactions with the Schiff bases prepared from *N*-benzoylethylenediamine gave mixtures of unidentified compounds.

The structures of compounds **3a—g** were proved by elemental analysis and ^{1}H NMR spectroscopy. The yields and characteristics of imidazolidines **3a—g** are given in Table 1; their spectroscopic data are presented in Table 2. We believed that a certain structural analogy between imidoyl chlorides **2a,b** and acetyl/chloroacetyl chlorides should lead to the structural similarity of the resulting compounds **3** and cyclic DI amides, respectively. This was confirmed by the ^{1}H NMR spectra of compounds **3** and DI with *N*-acyl substituents.[1] In both cases, the signal for the H(2) proton appears as one or two doublets at δ 5.0—5.5 (R = Pr^i) or as one or two singlets at δ 6.3—6.8 (R = Ar). When moving from imidazolidines to hexahydropyrimidines (*i.e.*, with an extension of the heterocycle by a methylene unit), the signal for the H(2) proton is shifted downfield (δ 5.5—6.5 for **4a,b** and δ 7.6 for **4c**).

Earlier,[1] DI containing *N*-chloroacetyl substituents have been found to react with amines through the replacement of the Cl atom. Since products **3** and DI are similar in structure (and probably in reactivity), we carried out such reactions with compounds **3b,d** and **4b** (Scheme 3) and obtained the corresponding amino de-

Scheme 3



3b,d, **4b** **5a—c**, **6**

Compound	*n*	R^1	NR^2R^3
5a	2	Pr^i	$NHCH_2Ph$
5b	2	Pr^i	Morpholin-4-yl
5c	2	4-$MeOC_6H_4$	Piperidin-1-yl
6	3	Pr^i	Morpholin-4-yl

Table 2. ^{1}H NMR spectra of 2-substituted imidazolidines **3a—g** and **5a—c** and hexahydropyrimidines **4a—c** and **6**

Compound	Solvent	δ (*J*/Hz)			
		Me	CH_2	CH	H arom.
3a	$(CD_3)_2CO$	0.85—1.10 (m, 6 H); 2.00, 2.40, 2.45 (all s, 3 H each)	2.85, 3.15 (both m, 1 H); 3.50—3.80 (m, 2 H); 4.05 (m, 1 H)	2.50 (m, 1 H); 5.30, 5.55 (both d, 1 H, *J* = 9.3)	7.30, 7.40, 7.65, 7.85 (all d, 2 H each, *J* = 8.4)
3b	$(CD_3)_2CO$	0.95 (m, 6 H); 2.40, 2.50 (both s, 3 H each)	3.25 (m, 1 H); 3.75 (m, 2 H); 4.15 (m, 1 H); 4.40, 4.55 (both d, 1 H each, *J* = 6.0)	2.10 (m, 1 H); 5.55 (d, 1 H, *J* = 9.3)	7.25, 7.45, 7.65, 7.85 (all d, 2 H each, *J* = 8.4)
3c	$CDCl_3$	2.12, 2.32 (both s, 3 H); 2.40—2.50 (m, 6 H); 3.80 (s, 3 H)	2.65—4.50 (m, 4 H)	6.42, 6.85 (both s, 1 H)	6.80—7.72 (m, 12 H)
3d	$(CD_3)_2CO$	2.40 (s, 6 H); 3.75 (s, 3 H)	2.75—3.90 (m, 4 H); 4.45, 4.70 (both d, 1 H each, *J* = 12.9)	6.62 (s, 1 H)	6.80, 7.20, 7.55, 7.70 (all d, 2 H each, *J* = 8.4); 7.30 (m, 4 H)
3e	$CDCl_3$	2.40, 2.45, 2.95, 3.00 (all s, 3 H each)	3.20—4.05 (m, 4 H); 4.70, 5.20 (both d, 1 H each, *J* = 12.7)	6.75 (s, 1 H)	6.55—7.80 (m, 12 H)
3f	$(CD_3)_2CO$	2.00, 2.40, 2.45 (all s, 3 H each)	3.20—4.20 (m, 4 H)	6.65, 6.80 (both s, 1 H)	7.20—8.25 (m, 12 H)
3g	$(CD_3)_2CO$	2.40, 2.45 (both s, 3 H each)	3.55—4.20 (m, 4 H); 4.65, 4.75 (both d, 1 H each, *J* = 12.7)	6.60 (s, 1 H)	7.20—8.15 (m, 12 H)
4a	$CDCl_3$	0.80, 0.90 (both d, 3 H, *J* = 6.8); 1.05 (d, 3 H, *J* = 6.8); 2.33, 2.69 (both s, 3 H); 2.42, 2.43 (both s, 3 H each)	1.25—1.40 (m, 2 H); 3.20—3.95 (m, 4 H)	1.70 (m, 1 H); 5.50, 6.45 (both d, 1 H, *J* = 12.5)	7.25—7.35 (m, 4 H); 7.61, 7.78, 7.95 (all d, 4 H, *J* = 8.4)
4b	$(CD_3)_2CO$	0.72, 0.98 (both d, 3 H each, *J* = 6.8); 2.40, 2.45 (both s, 3 H)	1.00—1.35 (m, 2 H); 3.34—3.95 (m, 4 H); 4.70 (s, 2 H)	2.00 (m, 1 H); 6.35 (d, 1 H, *J* = 13.5)	7.32, 7.42, 7.75, 7.95 (all d, 2 H each, *J* = 8.0)
4c	$(CD_3)_2CO$	2.35, 2.73 (both s, 3 H each); 2.45 (s, 6 H)	1.20—1.35 (m, 2 H); 3.05—4.00 (m, 4 H)	7.10, 7.60 (both s, 1 H)	7.21—8.25 (m, 12 H)
5a	$CDCl_3$	0.95 (m, 6 H); 2.45, 2.46 (both s, 3 H each)	3.12—4.10 (m, 8 H)	2.30 (m, 1 H); 5.55 (d, 1 H, *J* = 8.0)	7.12—7.38 (m, 9 H); 7.60, 7.80 (both d, 2 H each, *J* = 10.0)
5b	$(CD_3)_2CO$	0.95 (m, 6 H); 2.45, 2.46 (both s, 3 H each)	2.30 (m, 4 H); 2.70—4.10 (m, 10 H)	2.00 (m, 1 H); 5.60 (d, 1 H, *J* = 7.4)	7.30—7.45 (m, 4 H); 7.68, 7.85 (both d, 2 H each, *J* = 10.0)
5c	$CDCl_3$	2.42, 2.47, 3.83 (all s, 3 H each)	1.34—1.70 (m, 6 H); 2.20—2.55 (m, 4 H); 2.80—4.05 (m, 6 H)	6.70, 7.50 (both s, 1 H)	6.75—7.85 (m, 12 H)
6	$(CD_3)_2CO$	0.78, 0.98 (both d, 3 H each, *J* = 6.8); 2.39, 2.43 (both s, 3 H each)	1.28—1.60 (m, 2 H); 2.25—2.55 (m, 4 H); 3.15—4.20 (m, 10 H)	2.40 (m, 1 H); 6.30 (d, 1 H, *J* = 11.0)	7.20, 7.33, 7.65, 7.90 (all d, 2 H each, *J* = 9.0)

rivatives **5a—c** and **6**. Their structures were proved by elemental analysis and ^{1}H NMR spectroscopy. The yields, characteristics, and spectroscopic data for compounds **5a—c** and **6** are given in Tables 1 and 2.

Thus, with imidoyl chlorides **2** as cyclization agents, we obtained a number of previously unknown 2-substituted 1-tosyl-3-(1-tosyliminoalkyl)imidazolidines and -hexahydropyrimidines.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument. Melting points were determined on a Kofler hot stage. Commercial chemicals were used freshly distilled or recrystallized. The starting imines **1** [1] and imidoyl chlorides **2** [2—4] were prepared according to known procedures. The synthesis of *N*-tosylethylenediamine has been described earlier.[5]

***N*-Tosyltrimethylenediamine.** A solution of tosyl chloride (6.8 g, 3.5 mmol) in benzene (30 mL) was added dropwise for 1 h to stirred trimethylenediamine (7.9 g, 10.7 mmol, 8.9 mL) in benzene (20 mL). The reaction mixture was stirred for 3 h. The precipitate that formed was filtered off, washed with benzene (10 mL) and cold water (10 mL), and recrystallized from water. The yield of *N*-tosyltrimethylenediamine was 4.2 g (52%), m.p. 113—115 °C (*cf.* Ref. 6: m.p. 112—113 °C). The residue that was insoluble in hot water was identified as *N*,*N*´-ditosyltrimethylenediamine (2 g, 16%), m.p. 147—149 °C.

2-Aryl-1-tosyl-3-(1-tosyliminoalkyl)imidazolidines 3c—g and 2-(3-nitrophenyl)-1-tosyl-3-(1-tosyliminoethyl)hexahydropyrimidine (4c) (general procedure *A*). Triethylamine (1 mmol) and imidoyl chloride **2** (1 mmol) were added to a stirred solution or suspension of imine **1b—d,f** (1 mmol) in anhydrous MeCN (5 mL). The reaction mixture was stirred at 20 °C for 3—4 h and then diluted with water. The precipitate that formed was filtered off, washed with water, dried in air, and recrystallized from EtOH.

2-Isopropyl-1-tosyl-3-(1-tosyliminoalkyl)imidazolidines 3a,b and 2-isopropyl-1-tosyl-3-(1-tosyliminoalkyl)hexahydropyrimidines 4a,b (general procedure *B*). Isobutyraldehyde (1 mmol) was added to a solution of *N*-tosylethylenediamine or *N*-tosyltrimethylenediamine (1 mmol) in anhydrous MeCN (5 mL). The reaction mixture was kept at 20 °C for 1 h and Et_3N (1 mmol) and imidoyl chloride **2** (1 mmol) were added. The following steps in this procedure were the same as described above.

Reactions of chloromethyl derivatives 3b,d and 4c with primary and secondary amines (general procedure). An appropriate amine (0.9 mmol) was added to a solution of compound **3b,d** or **4c** (0.44 mmol) in anhydrous MeCN (3 mL). The reaction mixture was kept at 20 °C for 6 h, diluted with water, and left for ~24 h. The precipitate that formed was filtered off, dried in air, and recrystallized from EtOH. This procedure was used to obtain **3-(2-benzylamino-1-tosylimino)ethyl-2-isopropyl-1-tosylimidazolidine (5a)**, **2-isopropyl-3-[2-(morpholin-4-yl)-1-tosylimino]ethyl-1-tosylimidazolidine (5b)**, **2-(4-methoxyphenyl)-3-[2-(piperidin-1-yl)-1-tosylimino]ethyl-1-tosylimidazolidine (5c)**, and **2-isopropyl-3-[2-(morpholin-4-yl)-1-tosylimino]ethyl-1-tosylhexahydropyrimidine (6)**.

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