N,N'-Diacylated imidazolidines and hexahydropyrimidines

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A method for the preparation of *N*-monoacyl imidazolidines and hexahydropyrimidines (as hydrochlorides) by interaction of monoacylated derivatives of ethylenediamine and trimethylenediamine with chloromethyl methyl ether was developed. Also a method for the preparation of *N,N'*-diacylimidazolidines and hexahydropyrimidines either by acylation of their monoacyl derivatives or by reaction of the corresponding *N,N'*-diacyl alkylenediamine derivatives with dimethoxymethane, diacetoxymethane, 1,3,5-trioxane or chloromethyl methyl ether was designed.

Key words: *N*-mono- and *N,N'*-diacylated imidazolidines, *N*-mono- and *N,N'*-diacylated hexahydropyrimidines, *N,N'*-diacylated alkylenediamines, acylation, methylation, cyclization.

N,N'-Diacylated imidazolidines (**1**) and hexahydropyrimidines (**2**) exhibit bactericide and fungicide activities.[1,2] For this reason, the development of expedient methods for the synthesis of these compounds is of importance.

Compounds **1** and **2** can be prepared by condensation of ethylenediamine (EDA) or trimethylenediamine (TMDA) with formaldehyde followed by acylation.[3] This route allows one to synthesize only compounds **1** and **2** unsubstituted at position 2, and with the same acyl substituents at the nitrogen atoms. Some 2-substituted **1** and **2** (also with the same acyl groups) can be obtained by reactions of acyl chlorides with Schiff's bases of EDA or TMDA.[4–6] Finally, the possibility of cyclization of some *N,N'*-diacyl derivatives of EDA and TMDA into compounds **1** and **2** by reaction with formaldehyde in the presence of acid catalysts has been demonstrated.[1,7] Several unsymmetrical derivatives **1** and **2** have been obtained by this method. However, attempts to apply this reaction to other aldehydes have failed.

In this work we investigated the possibility of synthesizing compounds **1** and **2** by reactions of *N,N'*-diacyl and *N*-monoacyl EDA and TMDA derivatives with alkenylating reagents (formaldehyde, acetaldehyde, and benzaldehyde dimethylacetals, 1,3,5-trioxane, diacetoxymethane, di(acetoxymethyl) ether and chloromethyl methyl ether (CME)) in various solvents using $Et_2O \cdot BF_3$ as an acid catalyst.

The unsymmetrically substituted diacyl alkylenediamines (ADA) required for the study were prepared by reactions of monoacyl ADA with acyl, sulfo-, and carbamoyl chlorides in the presence of Et_3N.

$$R^1NH(CH_2)_n NH_2 + R^2X \xrightarrow{Et_3N} R^1NH(CH_2)_n NHR^2$$

R^1, R^2 = AlkCO, ArCO, R_2NCO, $AlkSO_2$, $ArSO_2$
n = 2, 3.

The structures of the products were confirmed by ^1H NMR and IR spectra. Yields and characteristics of *N,N'*-diacylated ADA are presented in Table 1.

The efficiency of the cyclization of the ADA studied is determined by the nature of the starting reagents and the reaction conditions. The basic results are presented in Table 2. Dimethoxymethane, diacetoxymethane, 1,3,5-trioxane, di(acetoxymethyl) ether, and chloromethyl methyl ether were used as methylenating agents to give similar yields of cyclization products.

$$R^1NH(CH_2)_nNHR^2 + XCH_2Y \xrightarrow[AcOH]{BF_3 \cdot Et_2O} R^1\text{-}N\text{-}(CH_2)_n\text{-}NR^2$$

1, 2

R^1, R^2 = AlkCO, ArCO, $AlkSO_2$, $ArSO_2$.
XCH_2Y = $MeOCH_2OMe$, $(CH_2O)_3$, $AcOCH_2OAc$, $AcOCH_2OCH_2OAc$, $ClCH_2OAc$.
n = 2 (**1**), 3 (**2**).

The yields of the reactions carried out in AcOH at 80—100 °C are 40—95 % and decrease significantly in other solvents, *e.g.*, ethyl acetate or dioxane. The nature of the acyl substituents significantly affects the cyclization

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Table 1. Yields and characteristics of alkylenediamines $R^1NH(CH_2)_nNHR^2$

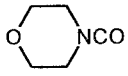
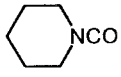
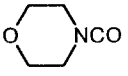
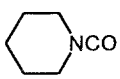
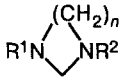
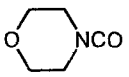
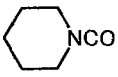
R^1	R^2	*n*	Yield (%)	M.p., °C	IR spectrum (ν/cm^{-1})	Solvent	^{1}H NMR spectrum(δ, ppm)				References
							CH_3	CH_2	aromatic nucleus	NH	
Bz	Bz	2	70	250							8
p-MeC_6H_4CO	*p*-MeC_6H_4CO	2	68	233—236		DMSO-d_6	2.35 s	3.44 s	7.3 d, 7.9 d	8.5 s	9
p-MeC_6H_4CO	Bz	2	62	190—193		DMSO-d_6	2.35 s	3.45 s	7.2—7.9 m	8.55 s	
Bz	$PhSO_2$	2	66	102—105	3290 (NH), 1650 (CO), 1330, 1160 (SO_2)	$CDCl_3$	—	3.15 t, 3.55 t	7.1—7.9 m	6.2 s	
p-MeC_6H_4CO	$PhSO_2$	2	68	115		DMSO-d_6	2.4 s	2.8 t, 3.4 t	7.3—7.8 m		
Bz	Ts	2	74	135—137	3280 (NH), 1640 (CO), 1330, 1160 (SO_2)	CD_3OD	2.3 s	3.0 t, 3.3 t	7.2—7.8 m		10
p-MeC_6H_4CO	Ts	2	62	117—120		$CDCl_3$	2.3 s	3.1 t, 3.5 t	7.15—7.7 m	6.1 s	
p-MeC_6H_4CO	*o*-NO_2—Ts	2	57	129—132	3410 (NH), 1630 (CO), 1530 (NO_2), 1340, 1170 (SO_2)	DMSO-d_6	2.3 s	2.9 t, 3.3 t	7.2—8.3 m		
Bz	Ms	2	49	119—121		DMSO-d_6	2.85 s	3.1—3.5 m	7.3—7.9 m	7.1 s, 8.45 s	
Bz	EtCO	2	50	157—160		DMSO-d_6	1.0 t	2.05 q, 3.1—3.5 m	7.5—7.9 m	8.5 s	11
Bz		2	65	187—189		$CDCl_3$	—	3.3—3.55 m	7.5—7.8 m	6.6 s, 8.5c	
Bz		2	65	184—186		$CDCl_3$	—	1.4 s, 3.0 s, 3.3 t, 3.4 t	7.45—7.8 m	6.6 s, 8.5 s	
$PhSO_2$	$PhSO_2$	2	64	168—170							12
Ts	Ts	2	70	164—165							12
Ts	$PhSO_2$	2	67	141—144		DMSO-d_6	2.4 s	2.9 t, 3.3 t	7.2—7.7 m		
Ts	*p*-$NO_2C_6H_4SO_2$	2	73	207—209	3280 (NH), 1550 (NO_2), 1330, 1160 (SO_2)						
p-$NO_2C_6H_4SO_2$	*p*-$NO_2C_6H_4SO_2$	2	70	277—279							12
o-NO_2-*p*-Ts	*o*-NO_2—Ts	2	68	189—191		DMSO-d_6	2.3 s	2.9 s	7.3—8.3 m		
Ts	Ms	2	52	119—122		$CDCl_3$	2.35 s, 2.85 s	3.2—3.5 m	7.3—7.9 m	7.0 s	
Ts		2	76	128—129	3380 (NH), 1640 (CO), 1320, 1160 (SO_2)	$CDCl_3$	2.4 s	3.0—3.4 m	7.3 d, 7.7 d	5.6 s, 6.7 s	
Ts		2	76	136—139	3420 (NH), 16040 (CO) 1330, 1160 (SO_2)	$CDCl_3$	2.2 s	1.3, 2.8, 3.4	7.1 d, 7.55 d	5.5 s, 6.0 s	
Bz	Bz	3	82	145—147							13
Bz	Ts	3	85	112—115							13

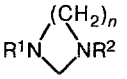
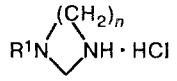
Table 2. Yields and characteristics of methylenediamines (**1**, **2**) obtained by methylenation of *N,N'*-diacylalkylenediamines

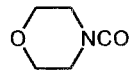
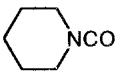
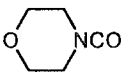
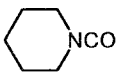
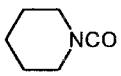


1, **2**

R^1	R^2	*n*	Methylenating reagent	Time h	*T*/°C	Yield (%)	M.p., °C	^{1}H NMR spectrum ($CDCl_3$, δ, ppm) CH_3	CH_2—CH_2	CH_2	aromatic nucleus	References
Bz	Bz	2	$(MeO)_2CH_2$	3	80	70	138—141	—	3.85 s	5.15 s	7.45 s	3
			$(AcO)_2CH_2$	3	80	67						
			$(CH_2O)_3$	3	80	64						
			$ClCH_2$—O—Me	3	80	40						
p-MeC_6H_4CO	Bz	2	$(MeO)_2CH_2$	3	80	74	72—76	2.4 s	3.85 m	5.15 s	7.25—7.55 m	
p-MeC_6H_4CO	*p*-MeC_6H_4CO	2	$(MeO)_2CH_2$	3	80	68	139—142	2.4 s	3.85 m	5.15 s	7.20 d, 7.45 d	
Bz	$PhSO_2$	2	$(MeO)_2CH_2$	1	80	69	106—109	—	3.4—3.7 m	4.9 s	7.4—7.9 m	
Bz	Ts	2	$(MeO)_2CH_2$	2	80	65	120—123	2.35 s	3.1—3.6 s	4.75 s	7.45—7.65 m	
p-MeC_6H_4CO	$PhSO_2$	2	$(MeO)_2CH_2$	1	100	50	100—101	2.4 s	3.5 m	4.35 s	7.25-8.0 m	
p-MeC_6H_4CO	Ts	2	$(MeO)_2CH_2$	2	80	54	140—143	2.35 s, 2.45 s	3.4-3.6 m	4.85 s	7.2—7.65 m	
p-MeC_6H_4CO	*o*-NO_2—Ts	2	$(MeO)_2CH_2$	4	100	32	111—114	2.4 s, 2.75 s	3.65 m	4.9 s	7.2—8.3 m	
Bz	Ms	2	$(MeO)_2CH_2$	2	80	49	77—80	2.95 s	3.7—3.85 m	4.95 s	7.4—7.6 m	
Bz	EtCO	2*	$(MeO)_2CH_2$	2	115	32	78—81	1.2 t	3.7—4.0 m	2.3 q, 5.0 d	7.5 m	
Bz		2	$(MeO)_2CH_2$	4	115	0						
$PhSO_2$	$PhSO_2$	2	$(MeO)_2CH_2$	0.5	80	84	153—154	—	3.1 s	4.4 s	7.2—7.4 m	14
			$(AcOCH_2)_2O$	0.5	115	80						
			$ClCH_2$—O—Me	1	80	81						
			$ClCH_2$—O—Me	24	20	10						
Ts	Ts	2	$(MeO)_2CH_2$	1	80	78	160					14
Ts	$PhSO_2$	2**	$(AcO)_2CH_2$	1	80	95	148—149	2.4 s	3.2 s	4.6 s	7.2—7.9 m	
Ts	*p*-$NO_2C_6H_4SO_2$	2	$(AcO)_2CH_2$	3	115	24	170—173	2.4 s***	3.3 m	4.6 s	7.3—8.4	
Ts		2	$(AcO)_2CH_2$	4	115	0						
o-NO_2-Ts	*o*-NO_2-Ts	2	$(MeO)_2CH_2$	3	115	32	189—192	—***	3.3 s	4.55 d	7.6 d, 7.9 d, 8.25 s	
			$ClCH_2OMe$	3	115	38						
p-$NO_2C_6H_4SO_2$	*p*-$NO_2C_6H_4SO_2$	2	$(MeO)_2CH_2$	10	115	0						
Bz	Bz	3	$(MeO)_2CH_2$	3	80	42	92—93	—	—	1.35 m, 5.14 s, 3.8 t	7.35 s	3
Bz	Ts	3	$(MeO)_2CH_2$	3	80	41	126—128	2.4 s	—	1.75 m, 3.35—3.7 m	7.25—7.65	

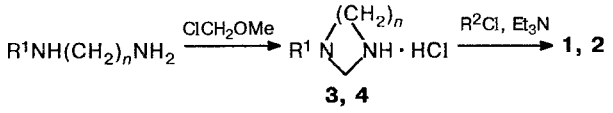
*Found (%): C, 67.28; H, 6.61; N, 12.26. $C_{13}H_{16}N_2O_2$. Calculated (%): C, 67.22; H, 6.94; N, 12.08.
**Found (%): C, 52.28, H, 5.32; S, 17.24. $C_{17}H_{18}N_2O_4S_2$. Calculated (%): C, 52.43; H, 4.96; S, 17.40. ***In DMSO-d_6.

Table 3. Yields, m.p., and ^{1}H NMR spectral data of methylenediamines  (**1**, **2**) obtained by acylation of 

R^1	R^2	*n*	Yield* (%)	M.p./°C	^{1}H NMR spectrum ($CDCl_3$, δ, ppm)			
					CH_3	CH_2—CH_2	CH_2	aromatic nucleus
Bz	Ts	2	25	119—122				
Bz	*o*-NO_2—Ts	2	22	124—125	2.7 s	3.6 s	4.9 s	
Bz		2	25	115—118	—	3.7 m	3.45 t, 3.7 t, 4.95 s	7.5 m
Bz		2	26	104—107	—	3.7 s	1.6, 3.3, 4.9	7.45
Ts		2**	27	139—141	2.45 s	3.3 t, 4.5 t	3.2 t, 3.65 t, 4.65 s	7.25 d, 7.7 d
Ts		2	24	Oil	2.4 s	3.45 m	1.5 s, 3.05 s, 4.6 s	7.25 d, 7.65 d
Ts	*o*-NO_2—Ts	3	21	183—185	2.45 s, 2.7 s	—	1.4 m, 3.15 t, 3.4 t, 5.7 s	7.3—8.4 m
Ts		3	21	99—100	2.45	—	1.6 m, 3.4 m, 3.7 t, 4.5 s	7.3 d, 7.7 d

*Overall yields of two stages.
** Found (%): C, 53.23; H, 6.43; N, 11.92; S, 9.54. $C_{15}H_{21}N_3O_4S$. Calculated (%): C, 53.07; H, 6.25; N, 12.38; S, 9.45.

process. Sulfonyl derivatives cyclize particularly smoothly. However, even in this case, cyclization is hampered by the introduction of electron-withdrawing nitro groups. In the presence of nitro groups in the *para*-positions of both benzenesulfonyl substituents cyclization fails completely. Attempts to cyclize of alkylenediamides in which one of the acyl groups was a morpholino- or piperidinocarbonyl group were also unsuccessful. This fact stimulated us to develop a more general method for the synthesis of compounds **1** and **2** by cyclization of *N*-monoacyl EDA or TMDA into *N*-monoacyl imidazolidine salts (**3**) or hexahydropyrimidine salts (**4**) followed by their acylation, respectively.



R^1 = ArCO, $ArSO_2$; R^2 = ArCO, $ArSO_2$, R_2NCO; **1**, **3**: *n* = 2; **2**, **4**: *n* = 3.

We showed that it is possible to use CME as a cyclizing reagent in the first step. The reaction of CME, *e.g.*, with *N*-*p*-tosylethylenediamine, affords the hydrochloride (**3a**, R^1 = *p*-Ts). Compound **3a** is highly hygroscopic and it is therefore not possible to isolate **3a** in an individual state. The action of bases results in decomposition of **3a**. Treatment of **3a** with picric acid (to prepare non-hygroscopic picrate) gives mixtures of salts. The structure of **3a** was confirmed by the presence of the NCH_2N signal in the ^{1}H NMR spectrum (δ ~4.5 ppm) and by the transformation of **3a** to *N*-benzoyl-*N'*-*p*-tosylimidazolidine by treatment with BzCl in the presence of Et_3N. *N*-Tosyltrimetylenediamine and *N*-benzoylethylenediamine react with CME in a similar way. Hydrochlorides **3** and **4** were transformed into compounds **1** and **2**, respectively, by treatment with acyl, sulfo-, and carbamoyl chlorides (Table 3).

Experimental

The ^{1}H NMR spectra were recorded with a Jeol FX-90Q (89.55 MHz) instrument, and the IR-spectra were recorded

with an UR-20 spectrometer in KBr pellets. Diacetoxymethane and di(acetoxymethyl) ether were obtained using a reported procedure,[15] and the monoacyl ADA were obtained using procedures from Refs. 9, 11.

Preparation of symmetrical *N,N'*-diacyl ADA. A solution of acyl chloride (10 mmol) in benzene was added with stirring to a solution of ADA (10 mmol) in benzene. The solution was stirred at 20 °C for 1 h, and the precipitate was filtered off, washed with water, and dried.

Preparation of unsymmetrical *N,N'*-diacyl ADA. Et_3N (10 mmol) and acyl chloride (10 mmol) were added to a solution of *N*-monoacyl ADA (10 mmol) in dioxane with stirring. The mixture was kept at 20 °C for 1—2 h, and the precipitate was filtered off, washed with water to remove $Et_3N \cdot HCl$, and dried. The filtrate was evaporated, and the residue crystallized when triturated with ether. The precipitates were combined.

Preparation of *N,N'*-diacyl imidazolidines 1 and hexahydropyrimidines 2. a. A mixture of *N,N'*-diacyl ADA (1 mmol), methylenating reagent (2 mmol) and $Et_2O \cdot BF_3$ (1 mmol) in glacial AcOH (10 mL) was heated at 80—120 °C for 0.5—3.0 h. The volatile reagents were distilled off, the residue was extracted with $CHCl_3$, the extract was washed with a $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was removed, and the residue was treated with a small amount of ether. If the product was not crystallized, it was isolated by preparative TLC on silica gel (using benzene : acetone, 9 : 1 as an eluent).

b. Excess CME was added to *N*-monoacyl ADA (2 mmol) and the mixture was kept for 2—3 h until the starting material completely dissolved. The excess CME was removed *in vacuo*, the residue was dissolved in dioxane, and then acyl chloride (2 mmol) and Et_3N (4 mmol) were added. The mixture was kept at 20 °C for 1—2 h and filtered off. The filtrate was evaporated and compounds **1** and **2** were isolated from the residue by preparative TCL.

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