ACYLATION OF N,N'-BISALKYLIDENETHYLENEDIAMINE IN POLAR MEDIA AS A METHOD FOR THE SYNTHESIS OF 2-R-N,N'-DIACYLIMIDAZOLIDINES

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Azomethines react with acid anhydrides or acid halides to give high yields of N-acylvinylamines [1-3]. According to Breederveld [1], the acid chloride or anhydride initially adds at the C = N bond and then loses HCl or an organic acid by the action of a base

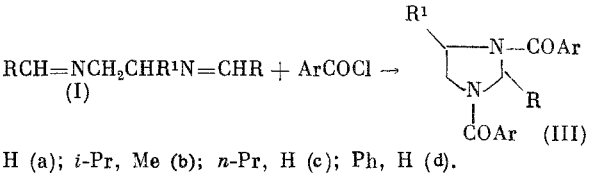
$$RR^1CHCH = NR^2 + R^3COCl \rightarrow RR^1CHCHClNR^2COR^3 \rightarrow \rightarrow RR^1C = CHNR^2COR^3$$

The reaction is carried out in benzene or ether and the acid formed is bound with triethylamine or pyridine.

In a study of bisazomethines obtained from ethylenediamine and aldehydes, we have found that the direction of the reaction of these compounds with acid halides may be changed by varying the polarity of the solvent. Thus, N,N'-diisobutenyl-N,N'-dibenzoylethylenediamine (IIa) is formed in 96% yield upon heating N,N'-diisobutylidenethylenediamine (Ia) with benzoyl chloride and triethylamine in benzene in full accord with previous results [1-3]. However, the same reaction in ethyl acetate gives a mixture of equal amounts of (IIa) and 1,3-dibenzoyl-2-isopropylimidazolidine (IIIa) in overall 80% yield. A mixture of (IIa) and (IIIa) is also obtained in the benzoylation of (Ia) in methylene chloride but in acetonitrile, enamide (IIa) is not formed (as indicated by PMR spectroscopic analysis of the reaction mixture), while the yield of (IIIa) is 72%. Both products were isolated in pure form by chromatography on a silica gel column with elution by 5:1 and 2:1 benzene–ether. However, the relative amounts of these products in any of the reaction mixtures could readily be determined using the PMR spectra of the mixture relative to the methyl and CH-group signals. The methyl groups in enamide (IIa) are nonequivalent and give two singlets at 1.4 and 1.5 ppm, while they appear as a doublet at 1.0 ppm in imidazolidine (IIIa). The δH^2 values for the imidazolidine ring and enamide proton in (IIa) (at 6.4 and 6.1 ppm, respectively) also differ somewhat in $CDCl_3$.

The increase in the yield of the cyclic product of the benzoylation of (IIIa) and the decrease in the yield of enamide (IIa) found upon changing the solvent correlate clearly with the change in the dielectric constant of the medium (Table 1).

The formation of 1,3-diacyl-2-substituted imidazolidines found in this case is also found for other (I) and RCOCl. The acylation of azomethines (I) by aromatic acid chlorides in acetonitrile leads exclusively to imidazolidines (III) without traces of enamides (II)



R, R^1 = *i*-Pr, H (a); *i*-Pr, Me (b); *n*-Pr, H (c); Ph, H (d).

The first step of the reaction is the addition of the acid chloride to the azomethine with the formation of unstable α-halo-N,N'-diacylamines (A). This step is apparently independent of the solvent. However, the nature of the transformations of (A) is entirely a function of the medium effect. In solvent with low polarity, we find dehydrohalogenation with isomerization to the N-acylenamide, while transformations according to the scheme shown on the following page are possible in highly polar solvents. The strong solvent effect on the direction of this reaction is apparently a consequence of the sharp increase in the rate of cyclization

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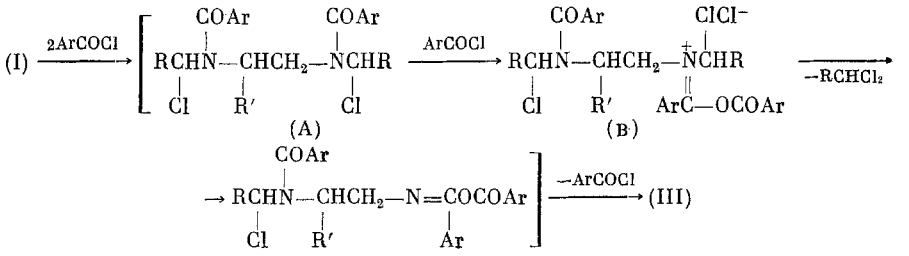


of ionic intermediate (B) in polar media. The competing loss of HCl from chloroamide (A) with the formation of an enamide follows an E_2 elimination mechanism and depends less on the reaction conditions.

The formation of an enamide is impossible in the acylation of N,N'-dibenzylidenethylenediamine (Id) and, thus, the reaction with RCOCl gives the imidazolidine independently of the solvent type.

For comparison with bisalkylideneamines (I), a monoazomethine, namely N-benzylidenemethylamine (IV), was introduced into reaction with PhCOCl in MeCN. The expected N,N'-dibenzoyl-N,N'-dimethylaminalbenzaldehyde $PhCHMe(NCOPh)_2$ (V), which is an acyclic analog of imidazolidines (III) was isolated in about 10% yield from the tarry reaction mixture. The products thus obtained are given in Table 2.

Imidazolidines (III) are a new group of derivatives. There had been previous reports only of 2-H-1,3-diacylimidazolidines [4-8] which were formed in the reduction of imidazole in acetic anhydride [4] or in the reaction of N,N'-diacylethylenediamines with formaldehyde [5-8]. Other aldehydes do not react with diacyldiamines and it was impossible to obtain 2-R-substituted diacylimidazolines by this method [8]. The properties of imidazolidines (III) apparently indicate significant conformational rigidity of these systems. The high-resolution ^{13}C NMR spectra given in Table 3 show signals for C^2, C^4, and C^5 of the imidazolidine ring as well as for R, R^1, and COAr. We should note that the C^4 and C^5 signals in the ^{13}C $\{^1H\}$ NMR spectra are significantly broadened, in contrast to the C^2 signal.

The broadening of the signals for the NCHN and NCH_2 group protons, which is sometimes considerable, is also found in the PMR spectra of (IIIa), (IIIb), (IIId), (IIIe), (IIIg), and (IIIh). This effect may be a consequence of slight inequivalence of the NCH_2CH_2N group protons as a result of quadrupole relaxation of the nitrogen nuclei for NCHN and NCH_2. Indeed, the NCHN signal in the spectrum of (IIIa) taken in acetone-d_6 appears as a doublet, while the NCH_2CH_2N signal appears as AA'BB' multiplet spin system. The methyl protons in the isopropyl group in (IIIc) and (IIIf) are diastereotopic and the PMR spectra contain two doublets (Table 4). Thus, two methyl group signals are seen in the ^{13}C NMR spectrum.

The hypothesis of stereochemical rigidity for (III) is in accord with their unusual thermal behavior. After evaporation of solutions of (III) in various solvents such as $CHCl_3$, ethanol, and benzene, the imidazolidines are obtained as yellowish, chromatographically pure oils which do not crystallize upon trituration with hexane, ether, or ethanol but crystallization is often achieved by freezing of the ethereal solutions with subsequent trituration of the separated oils or solid low-melting amorphous substances with ether. Solids are sometimes obtained in this case with low indefinite melting points (usually at 30-60°C with a 7-10°C melting range). After standing for several days or weeks, the melting point rises spontaneously and the nature of the melting process changes. The melting point becomes sharp for

TABLE 1. Medium Dielectric Constant ε and the Ratio of the Yields of the Products of Azomethine (Ia)

Solvent	ε	(IIa)/(IIIa) mole ratio
C_6H_6	2,28	1:0
$MeCO_2Et$	6,02	1:1
CH_2Cl_2	8,9	1:2
MeCN	36,2	0:1

TABLE 2. 1,3-Diacyl-2-R-imidazolidines (III)

Compound	Ar	R	R¹	Yield, %	Crystallization solv.	Mp (softening) deg C
(IIIa)	Ph	*i*-Pr	H	71,7	EtOH	137–138
(IIIb)	*p*-$NO_2C_6H_4$	*i*-Pr	H	71,0	MeOH–$CHCl_3$, 3 : 1	273
(IIIc)	*p*-$NO_2C_6H_4$	*i*-Pr	Me	63,7	$CHCl_3$	207–210
(IIId)	*p*-$NO_2C_6H_4$	*n*-Pr	H	40,0	$CHCl_3$–$MeCO_2H$, 1 : 1	209–211
(IIIe)	*p*-$NO_2C_6H_4$	Ph	H	37,9	MeOH	204–206
(IIIf)	*p*-$MeOC_6H_4$	*i*-Pr	Me	41,0	EtOH	(124)
(IIIg)	Ph	*n*-Pr	H	33,6	EtOH	(117–119)
(IIIh)	Ph	Ph	H	63,4	EtOH	(60–61)

TABLE 3. ^{13}C NMR Spectra of (III) in $CDCl_3$, δ ppm from TMS ($^1J_{^{13}C,^1H}$, Hz)

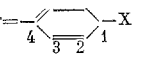
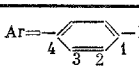
Compound	C^2	C^4	C^5	R	R¹	Ar=  –X
(IIIa)	74,4 (153)	46,9 (143)		18,2, 33,7 (126) (128)	–	C^1 130,4, C^2 127,3, C^3 128,4 (162) (161) (161) C^4 135,9, CO 169,7
(IIIf)	75,6 (155)	53,9 (146)	52,8 (144)	18,3, 18,7 (127) (127) 33,6 (128)	21,1 (128)	**C^1 161,3, C^2 113,5, 113,6** (161) (161) C^3 128,4 129,8, C^4 126,6 (161) (161) 129,2, CO 169,3, 169,8, OMe 55,1, 55,7 (146) (146)
(IIIg)	70,8 (157)	45,6 (142)		13,6, 17,8 (126) (126) 35,9 (126)	–	C^1 130,4, C^2 127,1 (161) (161) C^3 128,5, C^4 135,9, CO 169,1 (163)

TABLE 4. PMR Spectra of (III) in $CDCl_3$, δ ^1H, ppm from TMS (J_{HH}, Hz)

Compound	H^2	H^4 H^5	R	R¹	Ar=  –X
(IIIa)	6,42 br.s	3,82 br.s	1,00 d 2,20 m (7,0)	–	7,50 m
(IIIb)	6,40 br.s	3,84 br.s	1,03 d 2,20 m (6,5)	–	7,78 m, 8,36 m
(IIIc)	6,10 d (8,5)	3,20–4,60 m	0,85, 0,93 (7,0) (7,0) 2,04	1,38 d (6,5)	7,73 m, 8,36 m
(IIId)	6,18 br.t	3,83	0,90–2,30 m	–	7,72 m, 8,33 m
(IIIe)	6,90 br.s	4,00 br.s	7,40 m	–	7,62 m, 8,25 m
(IIIf)	6,23 d (9,0)	3,25–4,75 m	0,80 d 0,90 d (6,5) (6,5) 2,02 m	1,33 d (6,5)	6,92 m, 7,50 m 3,79 s
(IIIg)	6,27 br.s	3,82 s	1,00–2,10 m	–	7,50 m
(IIIh)	7,12 br.s	3,90	7,52 m	–	7,47 m

(IIIa) and all the compounds containing nitro groups, while sharp melting of a portion of the substance is found for (IIIf), (IIIg), and (IIIh) at the temperatures indicated in Table 2 and a mixture consisting of a melt and crystals is formed. The amount of the crystals decreases upon a further increase in the temperature by 50-100°C and an isotropic melt is finally obtained. The "softening" points indicated in Table 2 are stable and invariant over time, as well as upon recrystallization from ethanol. The ^1H and ^{13}C NMR spectra taken in $CDCl_3$ and the IR spectrum in KBr and $CHCl_3$ of the low-melting (30-60°C) and high-melting forms are identical. The low-melting modifications may be obtained from the high-melting forms by sublimation in vacuum. These forms are stable in solution and do not undergo interconversion (careful evaporation of the solutions of both forms in $CHCl_3$ does not alter their melting behavior). Some of the imidazolidines (see Experimental) could not be crystallized after the ordinary workup of the reaction mixtures. In these cases, prior purification was carried out on silica gel columns with benzene–ether eluent with various ratios of the two components.

The separation was followed on Silufol plates in 2:1 benzene–ether (R_f for the imidazolidines was 0.3-0.6 and the spots were developed with iodine vapor). After evaporation of the chromatographically uniform fractions, the oils could be crystallized as described above. Imidazolidines (III) proved inactive against the fungus *Aspergillus niger*.

EXPERIMENTAL

The melting points were found on a Boetius heating stand. The IR spectra were taken on a UR-20 spectrometer and the NMR spectra were taken on Varian DA-60-IL, Tesla BS-497, and Bruker WM-250 spectrometers. The mass spectra were taken on a Varian MAT CH-6 mass spectrometer. The elemental analysis of all the compounds obtained were in accord with the calculated values.

The starting bisazomethines were synthesized by the reaction of ethylenediamine and 1,2-propylenediamine with butyraldehyde, isobutyraldehyde, and benzaldehyde. The low yield of N,N'-di(butylidene)ethylenediamine (1 g) is apparently attributed to the formation of side condensation and polymerization products [9, 10].

N,N'-Di(isobutylidene)ethylenediamine (Ia). A sample of 670 mmoles isobutyraldehyde was added dropwise at 10-20°C to 330 mmoles 70% aqueous ethylenediamine. After 24 h, the upper layer was fractionated in vacuum to yield 62.7% (Ia) with bp 91-92°C (25 mm) [11]. PMR spectrum (δ, ppm, CCl_4, TMS): 1.03 d (12H, Me), 2.29 m (2H, CH), 3.47 s (4H, CH_2), 7.45 d (2H, CH = N), IR spectrum (neat): 1630 cm^{-1} (C=N).

N,N'-Di(isobutylidene)-1,2-propylenediamine (Ib). This product was obtained by analogy to the above procedure in 47% yield with bp 89-91°C (12 mm). PMR spectrum (δ, ppm, CCl_4, TMS): 1.06 d (12H, Me_2CH), 1.19 d (3H, Me), 2.43 m (2H, Me_2CH), 3.25-3.65 m (6H, CH_2CHMe), 7.48 d (2H, CH–N). IR spectrum (neat): 1635 cm^{-1} (C = N).

N,N'-Di(benzylidene)ethylenediamine (Ic) was obtained in 92.7% yield with mp 53°C (from hexane) [12]. PMR spectrum (δ, ppm, $CDCl_3$, TMS): 3.83 s (4H, CH_2CH_2), 7.0-7.66 m (10H, Ph), 8.11 s (2H, CH = N).

N,N'-Di(butylidene)ethylenediamine (Id). A sample of 670 mmoles freshly distilled butyraldehyde was added dropwise at 0°C to 330 moles 70% ethylenediamine. The upper layer was separated after 1 h and the aqueous phase was extracted with chloroform. The combined extracts were dried over $MgSO_4$ and distilled to give 1 g (8.7%) (Id) with bp 75-80°C (10 mm) [13]. This compound is highly unstable and rapidly polymerizes upon standing.

N,N'-Di(isobutenyl)-N,N'-dibenzoylethylenediamine (IIa). A sample of 20 mmoles PhCOCl was added dropwise to a mixture of 10 mmoles (Ia), 22 mmoles Et_3N, and 20 ml benzene and heated at reflux for 1 h. The solution yielded 95.7% (II) with mp 146.5-147°C (from ethanol). Mass spectrum: M^+, m/z 376. PMR spectrum (δ, ppm, $CDCl_3$, TMS): 1.36 s (6H, Me), 1.52 s (6H, Me), 3.90 s (4H, CH_2), 6.12 s(2H, CH), 7.40 m (10H, Ph). IR spectrum (KBr): 1640 cm^{-1} (CON).

1,3-Dibenzoyl-2-isopropylimidazolidine (IIIa). A sample of 20 mmoles PhCOCl was added dropwise to 10 mmoles (Ia), 22 mmoles Et_3N and 20 ml anhydrous acetonitrile, heated at reflux for 2 h, and then evaporated. Benzene extraction of the residue gave 3.94 g of an oil which was crystallized from ethanol. Mass spectrum: M^+, m/z 322. IR spectrum (KBr): 1645 cm^{-1}.

1.3-Di(p-nitrobenzoyl)-2-isopropylimidazolidine (IIIb). A mixture of 50 mmoles (Ia), 100 mmoles p-$O_2NC_6H_4COCl$, and 110 mmoles Et_3N was heated at reflux for 2 h and evaporated. The residue was washed with water. IR spectrum (KBr): 1645 cm^{-1} (amide).

1,3-Di(p-nitrobenzoyl)-4-methyl-2-isopropylimidazolidine (IIIc). This product was obtained analogously from 10 mmoles (Ib), 20 mmoles p-$O_2NC_6H_4COCl$, and 20 mmoles Et_3N. The yield of unpurified (IIIc) was 91.7%, mp 202-206°C. IR spectrum (KBr): 1645 cm^{-1}.

1,3-Di(p-nitrobenzoyl)-2-n-propylimidazolidine (IIId). This product was obtained analogously. IR spectrum (KBr): 1645 cm^{-1} (amide).

1,3-Di(p-nitrobenzoyl)-2-phenylimidazolidine (IIIe). This product was obtained from 8.5 mmoles (Ic), 17 mmoles p-$O_2NC_6H_4COCl$, and 18 mmoles Et_3N in benzene as an orange oil in 76.1% yield. The product was crystallized by treatment with methanol. IR spectrum (KBr): 1648 cm^{-1} (CON).

1,3-Di(p-methoxybenzoyl)-4-methyl-2-isopropylimidazolidine (IIIf). This product was obtained from 8.2 mmoles (Ib), 16.5 mmoles p-$MeOC_6H_4COCl$, and 17.8 mmoles Et_3N. The yield of the dark orange oil was 3.19 g. A sample of 1 g of this oil was placed on a silica gel column (h = 30 cm) and eluted with 10:1, 5:1, and 2:1 benzene—ether. Chromatographically uniform fractions (as monitored on Silufol plates) were combined and evaporated to yield 0.72 g of a light yellow oil, R_f 0.4 (on Silufol, 2:1 benzene—ether). The product was dissolved in 5 ml ether, cooled with dry ice, and the amorphous residue was rapidly filtered, triturated with ether, and refiltered at 20°C to yield 0.42 g (IIIf) as white crystals. Heating to 124°C gives a mixture of a melt and crystals; final melting is achieved at about 170°C. IR spectrum (KBr): 1620 cm^{-1} (CON).

1,3-Dibenzoyl-2-n-propylimidazolidine (IIIg). This product was obtained from 14.9 mmoles (Id), 29.6 mmoles PhCOCl, and 32.4 mmoles Et_3N. The yield of the unpurified product was 2.86 g as an orange oil. A sample of 2.0 g crude (IIIg) was purified chromatographically as described in the synthesis of (IIIf) starting with elution with 5:1 benzene—ether to yield 1.13 g (33.6%) white crystalline (IIIg). Heating to 117-118°C gives a mixture of a melt with crystals; final melting is achieved at about 200°C. IR spectrum (KBr): 1645 cm^{-1} (CON).

1,3-Dibenzoyl-2-phenylimidazolidine (IIIh). This product was obtained from 10 mmoles (Ic), 20 mmoles PhCOCl, and 21 mmoles Et_3N in benzene. The yield was 3.18 g (orange oil). A sample of 1.0 g of the crude product was purified chromatographically as described in the case of (IIIg). The yield of chromatographically pure (IIIh) was 63.4%, R_f 0.5 (on Silufol, 2:1 benzene—ether eluent). The oil was dissolved in ether, cooled with dry ice, and the residue was triturated with ether and refiltered at 20°C to give a crystalline mass. Heating to 60-61°C gives a mixture of a melt with crystals; final melting is achieved at about 100°C. IR spectrum (KBr): 1640 cm^{-1} (CON).

N,N'-Dibenzoyl-N,N'-dimethylaminal of Benzaldehyde (V). A sample of 25.2 mmoles PhCOCl was added dropwise with stirring to 25.2 mmoles freshly distilled (IV) and 29.7 mmoles Et_3N in 20 ml MeCN, heated at reflux for 30 min, and evaporated. Chloroform extraction of the residue yielded (V), which was purified on a silica gel column using benzene and 10:1, 5:1, and 2:1 benzene—ether consecutively as the eluent. The chromatographically uniform fractions were evaporated and the oil was treated with ether. The crystalline precipitate was recrystallized from ethanol to give a 7% yield, mp 180-181°C. PMR spectrum (δ, ppm, $CDCl_3$, TMS): 2.92 s (6H, Me), 6.5-6.8 br.s (1H, CH), 7.0-7.5 (15H, Ph).

CONCLUSIONS

1. The direction of the reaction of bisalkylidene- and bisbenzylidenethylenediamines with acid chlorides depends on the polarity of the solvent used.

2. Acylation of bisalkylidenethylenediamines and bisbenzylidenethylenediamines in highly polar media leads to the formation of 2-alkyl- and 2-aryl-substituted N,N'-diacylimidazolidines.

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