PREPARATION AND CHARACTERIZATION OF MIXED ANHYDRIDES OF *O*-ACYLARYLCARBOHYDROXIMIC ACID

Rajinder P. SHARMA, Kusum SHARMA, Sunita LAKHANPAL, Namita SHARMA
and Bhupendra N. MISRA

Department of Chemistry,
Himachal Pradesh University, Summer Hill, Shimla 171 005, India

Received May 15, 1992
Accepted June 14, 1993

A number of *N*,*O*-diacylhydroxylamines have been prepared by the reaction of potassium salts of hydroxamic acids with a variety of acylating agents which include: benzoyl, *p*-nitrobenzoyl, anisoyl, *p*-chlorobenzoyl and lauroyl chlorides in dioxane under reflux. The structure of the resulting *N*,*O*-diacylhydroxylamines has been determined by spectral analysis. Attempts have been made to prepare mixed anhydrides of several *N*,*O*-diacylhydroxylamines by the acylation reaction in the cold (below 10 °C) using acetyl, benzoyl, *p*-nitrobenzoyl, anisoyl and *p*-toluenesulfonyl chlorides as acylating agents in dioxane using triethylamine as a base. Structures of the resulting mixed anhydrides have been elucidated by spectral methods.

Alkylation of a neutral amide initially leads to the formation of kinetically controlled O-alkyl product which under suitable conditions rearranges to the thermodynamic N-alkyl product. In anology with alkylation, acylation of neutral amides should first form kinetic O-acetyl product and under favourable conditions the thermodynamic N-acyl isomer may be formed. Mixed anhydrides are usually too unstable to be isolated owing to the rapid 1,3-acyl migration during reaction conditions[1 – 3]. Despite their strong tendency to rearrange to imide mixed anhydrides have been isolated from acylation reaction of a number of *N*-acyl-*O*-alkylhydroxylamines[4 – 8]. Very little work on the preparation of mixed anhydride from *N*,*O*-diacylhydroxylamines has been reported presumably due to the fact that *N*,*O*-diacylhydroxylamines are highly sensitive to base induced Lossen rearrangement. Only benzoylation of *N*-benzoyl-*O*-benzoylhydroxylamine has been reported in the literature and both O- and N-benzoylated product has been reported. Aromatic sulfonylation of *N*,*O*-diacylhydroxylamines has not been extensively investigated. Recently Misra et al.[9] have reported the formation of *O*-sulfonylated products from the reaction of *N*,*O*-diacylhydroxylamines and benzenesulfonyl chloride. This finding prompted us to initiate a comprehensive study on the acylation of *N*,*O*-diacylhydroxylamines using a number of acylhalides and sulfonyl halides in order to prepare stable mixed anhydrides which can be utilized as substrates for studying 1,3[O→N]acyl migration. In this preliminary study we report preparation of some known and unknown *N*,*O*-diacylhydroxylamines. Acylation and sulfonylation of several *N*,*O*-diacylhydroxylamines have been studied and the structure of the resulting mixed anhydrides has been established by spectroscopic methods.

EXPERIMENTAL

Melting points are uncorrected. The progress of reactions was monitored by TLC coated with silica gel-G using benzene–ethyl acetate or benzene–petroleum ether as eluants and the spots were developed in a iodine chamber. IR Spectra ($\tilde{\nu}$, cm^{-1}) were recorded in KBr pellets using Perkin–Elmer Infracord Model 337 Spectrophotometer. ^{1}H NMR spectra (δ, ppm) were taken in $CDCl_3$ solutions of FT 100 NMR(Jeol) instrument using TMS as an internal standard. UV-VIS spectra (λ_{max}, nm) were measured in dioxane on UV Spectronic-20 spectrophotometer (Bausch and Lomb). Mass spectra were recorded with MS 9095, using emission current 100 μA at 95 °C in the Laboratory of Mass Spectrometry, Slovak Technical University, Bratislava, The Slovak Republic. Potassium salts of arylcarbohydroxamic acids were prepared by the modified method of Cooley[10].

N-Benzoyl-*O*-lauroylhydroxylamine (*Im*)

Potassium salt of benzohydroxamic acid (3.50 g, 0.02 mol) was suspended in dioxane (50 ml) and to the solution lauroyl chloride (9.73 g, 0.05 mol) was added and the reaction mixture was refluxed in oil bath for 10 min. The solution was cooled to room temperature and then poured in 500 ml of distilled water. Precipitated *N*-benzoyl-*O*-lauroylhydroxylamine was filtered and recrystallized from ethanol in 90% yield, m.p. 109 – 110 °C. For $C_{19}H_{29}O_3N$ (305.4) calculated: 69.60% C, 8.57% H, 4.25% N; found: 69.50% C, 8.60% H, 4.20% N. IR spectrum: 3 300 (NH), 1 770 (COO), 760 (arom.). ^{1}H NMR spectrum: 0.8 – 1.73 m, 23 H ($C_{11}H_{23}$); 2.29 t, 2 H (CH_2CO); 7.36 – 7.89 m, 5 H (arom.).

Other *N*,*O*-diacylhydroxylamines were prepared by the same method as described above and their physical and spectroscopic data are presented in Tables I – III.

TABLE I
Physical data of *N*,*O*-diacylhydroxylamines *I*

Compound	Yield, %	M. p.	λ_{max}, nm
Ia	90	109 – 110	355
Ib	85	165	360
Ic	95	176 – 177	360
Id	95	136 – 137	355
Ie	82	120 – 121	355
If	92	162 – 163	355
Ig	80	157	360
Ih	76	158	355
Ii	90	168	365
Ij	92	132 – 133	355
Ik	72	130	355
Il	90	174 – 175	360

p-Toluenesulfonic *O*-Benzoylbenzohydroximic Anhydride (*IIIa*)

O-Benzoylbenzohydroxamic acid (2.44 g, 0.01 mol) dissolved in dioxane (20 ml) was treated with *p*-toluenesulfonyl chloride (1.87 g, 0.01 mol). To the reaction mixture triethylamine (6.06 g, 0.06 mol) was added and the reaction mixture was stirred for 6 h in an ice bath. After the completion of the reaction (single spot in TLC), the reaction mixture was poured in 250 ml of distilled water and

TABLE II
IR spectral data ($\tilde{\nu}$, cm^{-1}) of the *N*,*O*-diacylhydroxyamines *I*

Compound	NH	OCO	C=N	Aromatic	$C-NO_2$	C–Cl
Ia	3 300	1 750	1 880	760	–	–
Ib	3 420	1 775	1 680	840, 760	1 370	–
Id	3 520	1 770	1 640	750, 840	–	680
Ie	3 280	1 770	1 650	760, 860	–	680
If	3 300	1 740	1 680	760, 850	1 535, 1 370	680
Ig	3 300	1 740	1 660	830	1 370	–
Ih	3 300	1 770	1 650	760	1 530	–
Ii	3 300	1 760	1 650	830, 760	–	–
Ij	3 080	1 765	1 685	760	–	610, 630
Ik	3 300	1 750	1 670	760	1 540	–
Il	3 300	1 750	1 670	760	1 540	–

TABLE III
^1H NMR spectral data of the *N*,*O*-diacylhydroxylamines *I*

Compound	δ, ppm
Ia	7.89 m, 10 H (ArH)
Ib	3.9 s, 3 H (OCH_3); 7.4 – 8.2 m, 8 H (ArH)
Ic	3.9 s, 6 H (OCH_3); 7.0 – 8.1 m, 8 H (ArH)
Id	7.2 – 8.1 m, 9 H (ArH)
Ie	3.81 s, 3 H (OCH_3); 7.03 – 7.42 and 8.24 m, 8 H (ArH)
Ig	7.4 and 8 – 8.4 m, 8 H (ArH)
Ih	3.8 s, 3 H (OCH_3); 7.0 – 8.2 m, 9 H (ArH)
Ii	7.2 – 8.4 m, 9 H (ArH)
Ij	3.8 s, 3 H (OCH_3); 7.0 – 8.2 m, 9 H (ArH)
Ik	3.9 s, 3 H (OCH_3); 7.0 – 8.1 m, 8 H (ArH)
Il	8.24 m, 9 H (ArH)

the product extracted with chloroform (3 × 30 ml). The chloroform solution was washed successively with saturated aqueous solution of sodium bicarbonate (2 × 50 ml), 10% hydrochloric acid (2 × 50 ml) and water (2 × 50 ml). The chloroform solution was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Oily residue was treated with ether–petroleum ether mixture (1 : 1) to give a solid which was recrystallized from ethanol in 60% yield, m.p. 128 °C. For $C_{21}H_{17}NO_5S$ (395.4) calculated: 62.66% C, 3.65% N, 4.44% H; found: 61.80% C, 3.4% N, 4.04% H. IR spectrum: 1 780 (COO), 1 180 (SO_2), 1 600 (C=N), 780 (arom.). ^1H NMR spectrum: 2.33 s, 3 H (CH_3); 7.16 – 8.23 m, 14 H (arom.)

Acylation of a number of *N*,*O*-diacylhydroxylamines using a variety of acyl chlorides in dioxane in the presence of triethylamine was carried out in cold by the same method as described above and resulting mixed anhydrides were isolated in yields varying between 40 – 70%. Physical and spectroscopic data of mixed anhydride are given in Tables IV – VI.

TABLE IV
Physical data of mixed anhydrides *III* prepared from *N*,*O*-diacylhydroxylamines

Compound	Formula M. w.	M. p., °C Yield, %	Calculated/Found				
			% C	% H	% N	% S	% Cl
IIIb	$C_{22}H_{18}N_2O_8S$	92 – 93	56.17	3.82	5.95	6.80	–
	470.4	61	56.4	3.20	5.05	6.50	
IIIc	$C_{24}H_{21}NO_7$	85	66.20	4.82	3.21	–	–
	435.5	64	66.00	4.30	3.01		
IIId	$C_{22}H_{17}NO_5$	157 – 158	70.40	4.53	3.73	–	–
	375.4	60		4.12	3.30		
IIIe	$C_{21}H_{13}N_2O_6Cl$	120 – 121	59.36	3.06		–	8.37
	424.4	62	59.20	3.00			8.20
IIIf	$C_{22}H_{16}NO_6Cl$	120 – 121	64.46	3.90	3.41	–	8.66
	409.9	62	64.30	3.60	3.60		8.20
IIIg	$C_{21}H_{15}NO_4$	94	73.04	4.34	4.05	–	–
	345.0	60	73.00	4.10	4.00		
IIIh	$C_{21}H_{14}NO_4Cl$	60	66.40	3.68	3.68	–	9.35
	379.5	63	66.10	3.30	3.26	–	9.20
IIIi	$C_{17}H_{14}NO$	98	65.38	4.48	4.48	–	–
	312.3	60	65.10	4.20	4.10		
IIIj	$C_{16}H_{11}N_2O_6Cl$	95	52.96	3.03	7.72	–	9.79
	362.8	62	52.60	3.00	7.20		9.50
IIIk	$C_{17}H_{14}N_2O_7$	91	56.98	3.91	7.82	–	–
	358.3	60	56.60	3.50	7.70		

DISCUSSION

N,*O*-Diacylhydroxylamines are very sensitive to Lossen rearrangement and perhaps this is the reason why no attempts have been made to prepare mixed anhydrides of *N*,*O*-diacylhydroxylamines.

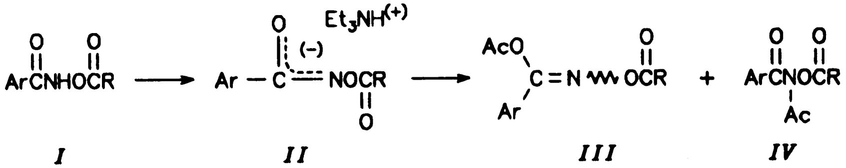
Jones et al.[11] attempted acylation of *N*,*O*-diacylhydroxylamines and reported the formation of both O- and N-acylated products. But rarely these isomers were isolated. In order to investigate acylation and sulfonylation of *N*,*O*-diacylhydroxylamines several *N*,*O*-diacylhydroxylamines have been reacted with appropriate acyl or sulfonyl halides in the presence of base. Acylation of eleven *N*,*O*-diacylhydroxylamines has been carried out at low temperature (below 10 °C) to avoid the formation of Lossen rearrangement products.

TABLE V

IR spectral data ($\tilde{\nu}$, cm^{-1}) of mixed anhydrides prepared from *N*,*O*-diacylhydroxylamines *III*

Compound	COO	CO	C=N	Anhydride	Aromatic	$C-NO_2$	C–Cl	OSO_2
IIIb	1 730	1 710	1 600	1 950 1 860 1 810	850 780 720	1 520	–	1 160
IIIc	1 790	1 630	1 610	1 920	840 760	–	–	–
IIId	1 760	1 635	1 590	1 820 1 910	840 720	–	–	–
IIIe	1 780	1 647	1 604	1 926 1 853	847 750	1 530 1 370	531 685	–
IIIf	1 765	1 691	1 589	1 912	847 756	–	553 671	–
IIIg	1 780	1 730	1 600	1 910	800 780 720	–	–	–
IIIh	1 780	1 720	1 600	1 910	820 720	–	560 620	–
IIIi	1 780	1 680	1 590	–	840 770	–	–	–
IIIj	1 780	1 720	1 604	1 995	850 780 720	1 526 1 340	634	–
IIIk	1 770	1 720	1 610 1 600	1 820	860 720	1 525 1 350	–	–

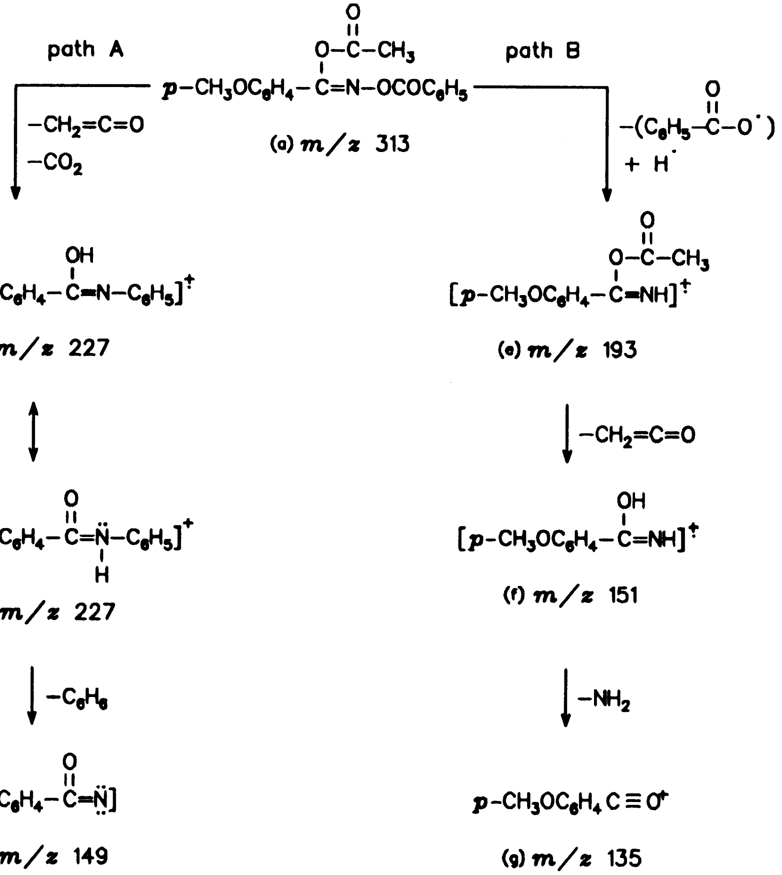
The reaction of *p*-toluenesulfonyl chloride with *N*,*O*-dibenzoylhydroxylamine (*Ia*) in dioxane in the presence of triethylamine afforded a crystalline product which was identified as a *p*-toluenesulfonic *O*-benzoylbenzohydroximic anhydride by spectral analysis. The IR spectrum of the product showed absorption at 1 780 cm^{-1} attributed to the carbonyl ester grouping (OCO), 1 600 cm^{-1} assigned to C=N and at 780 cm^{-1} assigned to the aromatic ring. Another peak in the IR spectrum in the region 1 180 cm^{-1} was assigned to OSO_2 function. The appearance of peak at 1 600 cm^{-1} in the IR spectrum indicated that the product may have the anhydride structure *III* (Scheme 1). ^{1}H NMR spectrum of the product showed an absorption at δ 2.33 due to CH_3 protons and multiplet at δ 7.10 – 8.23 assigned to the aromatic protons.



SCHEME 1

I	*III*	Ar	R	Ac
Ia	*IIIa*	C_6H_5	C_6H_5	*p*-$CH_3C_6H_4SO_2$
Ib	*IIIb*	*p*-$NO_2C_6H_4$	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4SO_2$
Ic	*IIIc*	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4SO_2$
Ia	*IIId*	C_6H_5	C_6H_5	*p*-$CH_3OC_6H_4SO_2$
Id	*IIIe*	C_6H_5	*p*-ClC_6H_4	*p*-$NO_2C_6H_4CO$
Ie	*IIIf*	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	C_6H_5CO
Ia	*IIIg*	C_6H_5	C_6H_5	C_6H_5CO
Id	*IIIh*	C_6H_5	*p*-ClC_6H_4	C_6H_5CO
If	*IIIi*	*p*-$CH_3OC_6H_4$	C_6H_5	CH_3CO
Ig	*IIIj*	*p*-$NO_2C_6H_4$	*p*-ClC_6H_4	CH_3CO
Ib	*IIIk*	*p*-$NO_2C_6H_4$	*p*-$CH_3OC_6H_4$	CH_3CO
Ih	–	*p*-$CH_3OC_6H_4$	*p*-$NO_2C_6H_4$	–
Ii	–	C_6H_5	*p*-$NO_2C_6H_4$	–
Ij	–	C_6H_5	*p*-$CH_3OC_6H_4$	–
Ik	–	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	–
Il	–	*p*-$NO_2C_6H_4$	C_6H_5	–
Im	–	C_6H_5	$C_{11}H_{23}$	–

The fragmentation pattern of acetic *O*-benzoyl-*p*-methoxybenzohydroximic anhydride (*IIIi*, Scheme 1) as typical example is shown in Scheme 2. The molecular ion (a) with *m*/*z* 313 loses a molecule of ketene and one molecule of CO_2 via path A to give the species (b) with *m*/*z* 227 which is resonance stabilized as shown. Fragment (b) then loses a molecule of C_6H_6 to give the species (d) with *m*/*z* 149. Alternatively, the molecular ion may lose a benzoyloxy radical and resulting species may capture a H atom released during fragmentation by path A to give a species (e) with *m*/*z* = 193. This species can lose easily a molecule of ketene to give the species (f) with *m*/*z* 151, which may eliminate an amino radical to form the stable species (g) with *m*/*z* 135.



SCHEME 2

Mass spectral analysis indicates that compound *IIIi* is best represented by the mixed anhydride structure.

Since *N*,*O*-diacylhydroxylamines are highly susceptible to Lossen rearrangement, acylation reaction were carried out at a temperature below 10 °C until no change in TLC behaviour was observed. The formation of the mixed anhydrides is explained by assuming that *N*,*O*-diacylhydroxylamine *I* upon treatment with triethylamine produced an ambident anion *II* and acyl group is preferentially attached to the more electronegative oxygen atom of ambident anion. Misra et al.[9] investigated the reactions of benzenesulfonyl chloride with a number of *N*,*O*-diacylhydroxylamines in the presence of trimethylamine and observed the formation of mixed anhydrides. Oxley et al.[12] studied the reaction of aromatic sulfonyl chloride with a neutral amide and reported the formation of O-sulfonyated products which were quite stable. Misra et al.[8] studied the reaction of *p*-toluenesulfonyl chloride with sodium salt of *N*-benzoyl-*O*-benzylhydroxylamine in benzene and observed in the NMR spectrum of the product two closely spaced peaks at 5.14 and 5.08 for benzyl protons and these were attributed to Z and E isomers of *p*-toluenesulfonyl *N*-benzyloxybenzimino ether. In the present case it is not possible to ascertain which isomer of the mixed anhydride *III* is formed. The mixed anhydride *III* when heated in dioxane at 30 °C did not show any change in TLC or IR spectrum. This tends to indicate that the mixed anhydrides formed are fairly stable and do not isomerise or rearrange to N-acylated products *IV* easily. It is inferred from the analogy of the behaviour of the mixed anhydride[5,7] prepared from *O*-benzylbenzohydroximic acid that the mixed anhydrides *III* obtained from acylation of *N*,*O*-diacylhydroxylamines presumably have Z configuration in which the acyloxy group and lone pair of electrons on the nitrogen are trans to each other. Further studies are in progress in order to ascertain the correct stereochemistry of mixed anhydrides *III*.

TABLE VI
^{1}H NMR spectral data of mixed anhydrides of *O*-acylhydroximic acids *III*

Compound	δ, ppm
IIIb	2.5 s, 3 H (Ar–CH_3); 4.0 s, 3 H (OCH_3); 7.4 – 8.5 m, 12 H (ArH)
IIIc	4.0 s, 3 H (OCH_3); 6.5 – 8.4 m, 12 H (ArH)
IIId	3.88 s, 3 H (OCH_3); 7.3 – 8.5 m, 14 H (ArH)
IIIe	6.27 – 7.00 m, 13 H (ArH)
IIIf	3.84 s, 3 H (OCH_3); 7.26 – 8.2 m, 13 H (ArH)
IIIg	7.16 – 8.0 m, 15 H (ArH)
IIIh	7.3 – 8.2 m, 14 H (ArH)
IIIi	2.5 s, 3 H (OCH_3); 3.75 s, 3 H (OCH_3); 6.7 – 8 m, 9 H (ArH)
IIIk	2.55 s, 3 H (OCH_3); 3.80 s, 3 H (OCH_3); 7.2 – 8.2 m, 8 H (ArH)

The author R.P.S. is grateful to May and Baker, England, for the award of Junior Research Fellowship. We express our gratitude to Prof. L. Lapcik of the University of Bratislava for providing facilities for spectroscopic analysis on some samples.

REFERENCES

1. McCarthy C. G. in: *The Chemistry of the Carbon Nitrogen Double Bond* (S. Patai, Ed.), Chap. 9. Wiley-Interscience, New York 1970.
2. Mumm O., Hesse H., Volquartz H.: Chem. Ber. *48*, 379 (1915)
3. Shubenberg J. W., Archer S.: Org. React. *14*, 31 (1965).
4. Hearn M. T., Ward A. D.: Aust. J. Chem. *22*, 161 (1969).
5. McCarthy D. G., Hegarty A. F.: J. Chem. Soc., Perkin Trans. 2 *1977*, 1080.
6. Challis B. C., Challis J. A., McDermott R.: J. Chem. Soc., Perkin Trans. 2 *1979*, 634.
7. Misra B. N., Sharma N.: Collect. Czech. Chem. Commun. *54*, 2738 (1989).
8. Cooley J. H., Misra B. N., Throckmorton J. R., Bills W. D.: J. Med. Chem. *11*, 196 (1968).
9. Misra B. N., Sharma R. P., Diksha _: Ind. J. Chem., B *25*, 1182 (1986).
10. Cooley J. H., Bills W. D., Throckmorton J. R.: J. Org. Chem. *25*, 1734 (1960).
11. Jones L. W.: J. Am. Chem. Soc. *1*, 20 (1892).
12. Oxley P., Short W. F.: J. Chem. Soc. *1914*, 1948.