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Mass Spectrometer as a Probe in the Synthesis of 2-Substituted Benzimidazoles.

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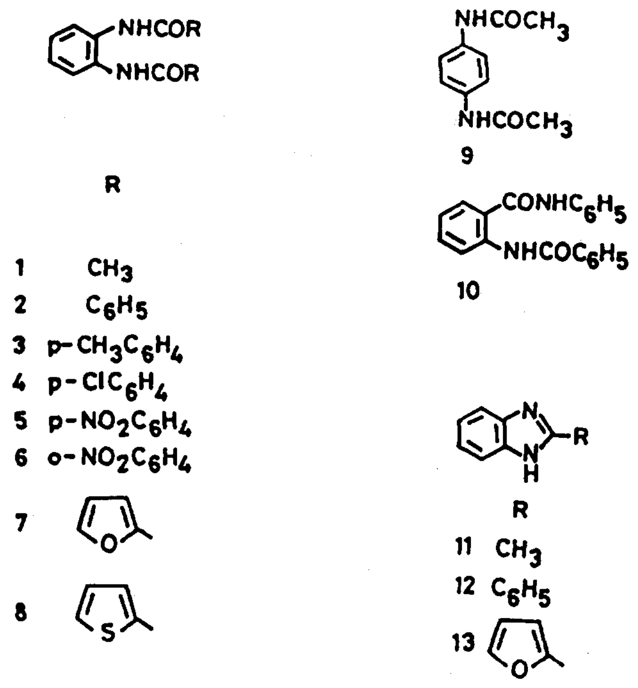
Abstract: The pyrolysis of N,N'-diacyl-1,2-benzenediamines leads to the formation of 2-substituted benzimidazoles. This new synthetic approach towards the synthesis of 2-substituted benzimidazoles is developed based on the electron impact studies of N,N'-diacyl-1,2-benzenediamines under 70 eV conditions, in which important fragment ions corresponding to 2-substituted benzimidazoles are observed. The mechanisms and ion-structures, proposed in the mass spectral study, are supported by high-resolution, B/E and B^2/E linked-scan spectra and Collision Activated Decomposition (CAD)-B/E linked-scan spectra.

INTRODUCTION

The past decade had witnessed the utility of the mass spectrometer as a reaction vessel with the aid of FT-ICR techniques.[1] A few condensed phase reactions such as Claisen rearrangement,[2] Beckmann rearrangement[3] e.t.c., have also been observed in gas phase. Mass spectrometric synthesis of ketals,[4] acetates[5] and esters[6] are reported under CI conditions. The structures of the product ions are identified with the help of CAD-MIKE spectra. Synthesis of quinazolone alkaloids and benzoxazinones by retro mass spectral analysis is achieved.[7] However, there is no report of a gas phase reaction performed to excellence in the laboratory on observing the mass spectral decomposition processes.

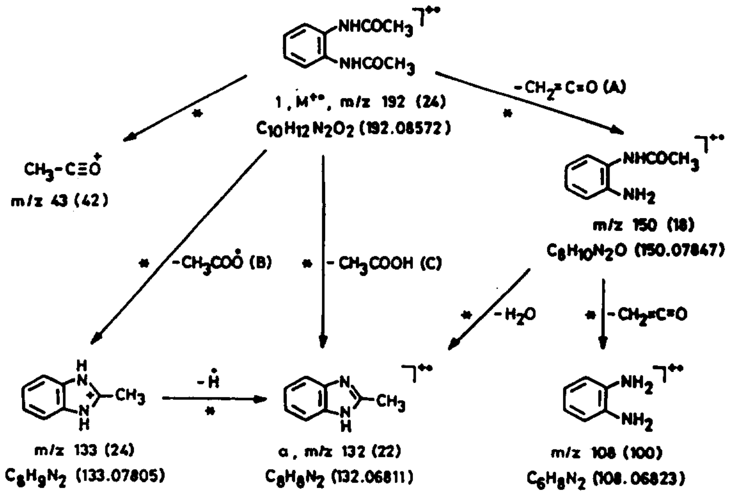
Mass spectral behaviour of substituted anilides has been fairly well documented.[8] Hydrogen migration has been noticed in the electron impact study of substituted pivalanilides.[9] Ejection of neutral species is a favoured fragmentation observed in some ortho substituted anilides.[10,11] The electron impact study of various N,N'-diacyl-1,2-benzenediamines (scheme 1) has been undertaken in this work in order to examine the occurrence of ortho interaction in the molecular ions leading to the ejection of neutral species which can give indication towards their thermal behaviour.



Scheme 1

RESULTS AND DISCUSSION

The base peak in the mass spectrum of N,N'-diacetyl-1,2-benzenediamine (**compound 1**) is observed at m/z 108, which corresponds to a stepwise loss of two ketene moieties from the $M^{+\cdot}$ as revealed by the linked-scan studies of the respective ions (Table 2 and 3). The most interesting fragment ion noticed in the mass spectrum of **1**, is the ion a at m/z 132 (scheme 2,Table 1,Fig 2). The accurate mass of the ion *a* is found to be 132.06811 which corresponds to an elemental composition of $C_8H_8N_2$. This fact reveals that *a* is formed by the expulsion of CH_3COOH from the $M^{+\cdot}$ of 1. Ion *a* is formed by three pathways as adduced from the B/E and B^2/E linked-scan spectra (Table 2 and 3). The 2-methylbenzimidazole structure assigned to *a* is confirmed with the help of CAD-B/E linked scan spectra of *a* and that of the $M^{+\cdot}$ of 2- methylbenzimidazole, taken as reference compound, which are found to be identical with the characteristic fragmentations (Fig 1).



Scheme 2

Table 1.Partial Mass Spectra of Compounds 1-10*.

Compound	M⁺˙	[M-RCOO]⁺	[M-RCOOH]⁺˙	[R-CO]⁺	Other ions.
1	192 (24)	133 (24)	132 (22)	43 (42)	150 108 (18)(100)
2	316 (12)	195 (12)	194 (54)	105 (100)	77 (62)
3	344 (34)	209 (38)	208 (92)	119 (100)	-
4	386 (12)	229 (21)	228 (46)	139 (100)	111 (38)
5	406 (10)	240 (19)	239 (100)	150 (6)	193 (26)
6	406 (16)	240 (-)	239 (8)	150 (100)	256 (37)
7	296 (28)	185 (40)	184 (44)	95 (100)	-
8	328 (25)	201 (22)	200 (42)	111 (100)	83 (29)
9	192 (100)	-	-	43 (50)	150 108 (52) (90)
10	316 (14)	-	-	105 (58)	224 93 (84) (100)

* The figures in parenthesis indicate the intensity of the ion.

Table 2. B/E Linked-Scan Spectral Data.

Compound	Parent ion m/z	m/z value of the daughter ions with abundances in parenthesis
1	$M^{+\cdot}$;192	150 (14) 133 (9) 132 (100) 92 (90)
	150	149 (100) 132 (16) 80 (7)
	133	132 (100) 80 (8)
	132	131 (100) 117 (15) 107 (18) 80 (20)
2	$M^{+\cdot}$;316	298 (4) 195 (11) 194 (51) 105 (100)
	195	194 (100) 168 (36)
	194	193 (100) 167 (25) 165 (14) 152 (22)
7	$M^{+\cdot}$;296	229 (100) 185 (5) 184 (88) 95 (25)
	185	184 (100) 158 (26)
	184	183 (100) 157 (50) 116 (55) 93 (22)

Table 3. B^2/E Linked-Scan Spectral Data.

Compound	Daughter ion m/z	m/z value of parent ions with abundances in parenthesis
1	150	192 (100)
	133	192 (85) 150 (100)
	132	192 (100) 150 (22) 133 (26)
	108	150 (100)
2	195	316 (100)
	194	316 (100) 195 (9)
	105	316 (100)
7	185	296 (100)
	184	296 (100) 185 (42)
	95	296 (100)

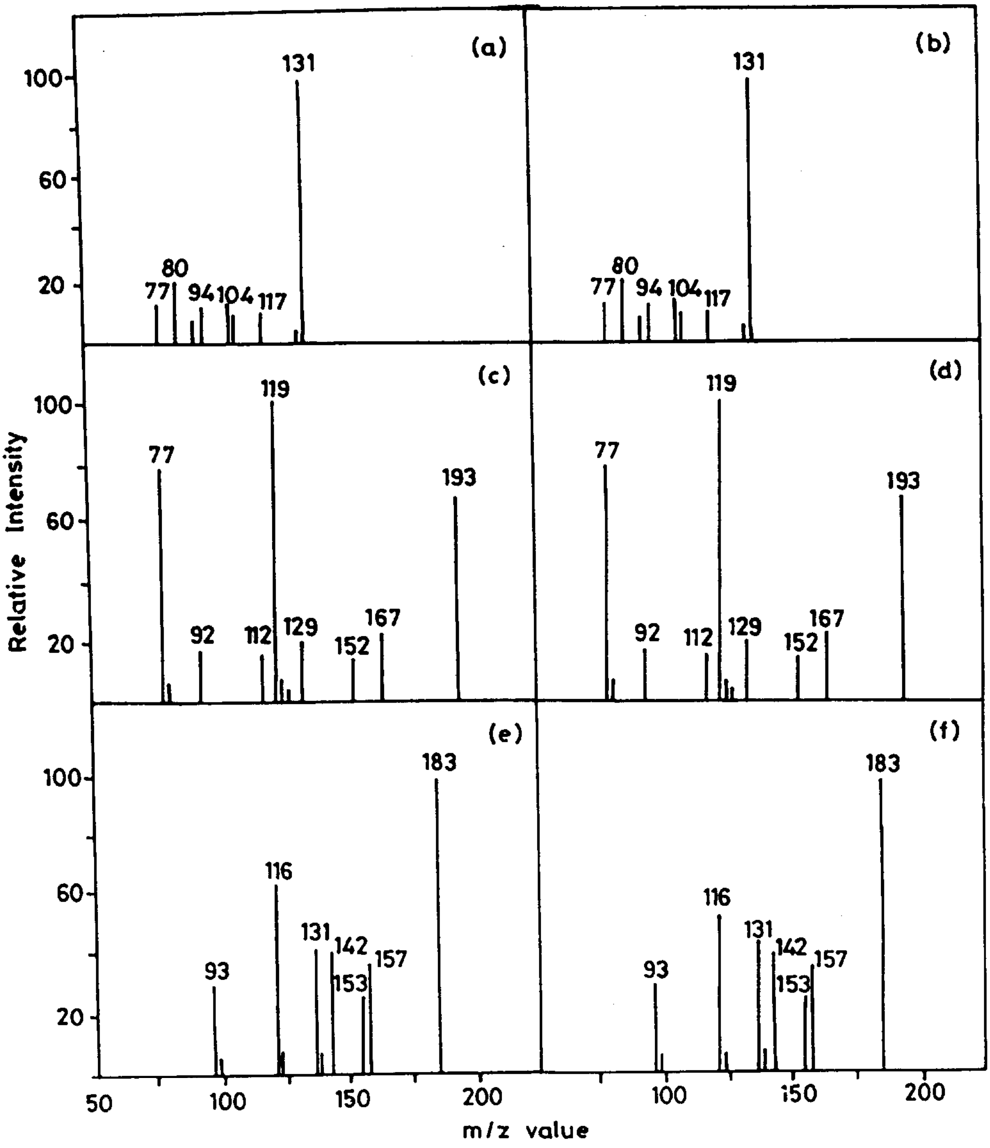


Fig. 1 CAD-B/E linked-scan spectra of ions at (a) m/z 132 from $M^{+\bullet}$ of 1 (b) m/z 132, $M^{+\bullet}$, of 11 (c) m/z 194 from $M^{+\bullet}$ of 2 (d) m/z 194, $M^{+\bullet}$, of 12 (e) m/z 184 from $M^{+\bullet}$ of 7 (f) m/z 132, $M^{+\bullet}$, of 13.

In the literature, the thermolysis of a few ortho substituted anilides has been shown to exhibit similar behaviour as observed in their EI spectra. An interesting study on this perspective is the mass spectral retrosynthesis of o-phthalamic acids,[12] in which both EI and thermally induced H_2O

loss is noticed. The regiochemistry of thermal deamination has been predicted from the distribution of fragment ions in the electron impact study of N,N'-substituted diamides of phthalic acid.[13] Cyclisation of N-acetyl-N'-benzoyl-o-phenylenediamine with substituents in the 4 and 5 positions of the phenylene moiety in a melt yielding a mixture of 2-methylbenzimidazole and 2-phenylbenzimidazole has been reported by Piotrovski etal[14] in 1975.

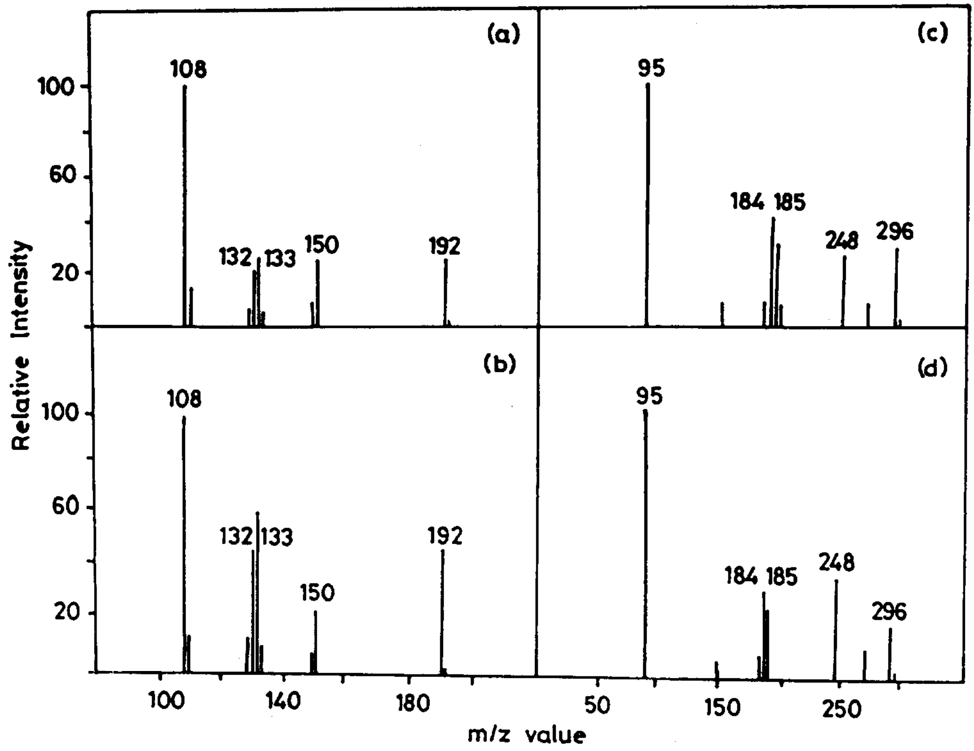
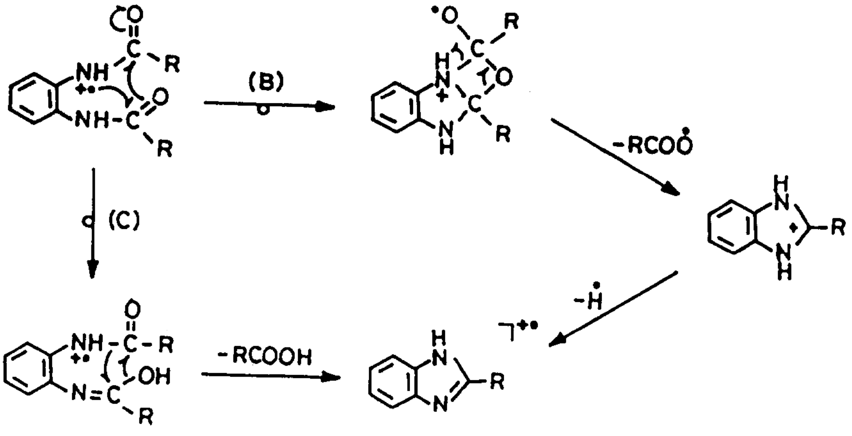


Fig. 2 EI spectra of compound (a) 1 at the source temperature of 150°C (b) 1 at the source temperature of 20°C (c) 7 at the source temperature of 150°C (d) 7 at the source temperature of 20°C.

The fragment ions corresponding to 2-substituted benzimidazoles are also observed in all the other N,N'-diacyl-1,2-benzenediamines **(compounds 2-8)** studied (Table 1). The significant difference in these compounds, in comparison with **1**, is the formation of the cyclic ion through two pathways (B) and (C) only (scheme 3). This is due to the absence of the β -hydrogen with respect to the -NH- group in the anilide moiety, making the pathway (A) in scheme 1 impossible in these compounds. 2-Substituted benzimidazole radical cation structures are proposed for the [M-COOH] ions noticed in these compounds. The CAD-B/E linked-scan spectra of the ions at m/z 194 and m/z 184 from the molecular ions of **2** and **7** are found to be identical with those of the molecular ions of 2-phenylbenzimidazole and 2-(2-furyl)benzimidazole respectively (Fig 1), confirming the 2-substituted benzimidazole structures proposed for the [M-COOH] ions in these compounds.



Scheme 3

The fact, that the cyclised ion corresponding to 2-substituted benzimidazole is formed through the ortho interaction, is confirmed by the absence of [M-COOH] ion in compound **9**,(Table 1) where the two N-acyl groups are para to each other. Furthermore, the required regiochemistry for the formation of [M-COOH] ion is proved to be ortho N,N'-diacyl groups by the absence of such an ion in compound **10** (Table 1) wherein the amide functions are reversed. The transfer of the OH radical in the enol form of one of the anilide groups to the carbonyl carbon of the other followed by cyclisation in the molecular ions of these compounds (scheme 3) resulting in the ejection of RCOOH is proposed for the direct formation of 2-substituted benzimidazole radical cations.

With this knowledge of the ortho substituted anilides to undergo thermal cyclisations and the EI behaviour of N,N-diacyl-1,2-benzenediamines (Compounds **1-8**) affording 2-substituted benzimidazole radical cations in good abundances, the pyrolytic study of these compounds are undertaken. Interestingly, the simple pyrolysis of all the bis-anilides yielded the corresponding 2-substituted benzimidazoles in good yields (Table 5).This pyrolytic method can be considered to be superior when compared with the literature methods[15] in the synthesis of benzimidazoles in having short reaction times, easy workup procedure and not requiring hazardous reagents.[15] The optimum temperatures and times to obtain maximum yields are shown in Table 5.

The mass spectra of the compounds **1** and **7** are studied under cold conditions (ion-source temparature 20°C) to examine whether the formation of 2-substituted benzimidazoles is by an initial thermal decomposition of the substrate in the ion-source prior to fragmentation. Since no significant change is observed in the intensities of the $M^{+\cdot}$ and the cyclised ions in the mass spectra of compounds **1 and 7** taken under normal source temperature conditions (150°C) and cold conditions (Fig 2), it can be adduced that 2-substituted benzimidazole cation radicals are formed as a result of electron impact induced fragmentations. This argument is further supported by the fact that the formation of the 2-substituted benzimidazole cation radicals from the corresponding molecular ions are indicated by the metastable decompositions in the first field free region.

CONCLUSIONS

It can be concluded from this study that the careful probing of mass spectral fragmentations can lead to the synthetic clues in mimicking the gas phase reaction in the laboratory. The formation of 2-substituted benzimidazoles from N,N'-diacyl-1,2-benzenediamines by thermolysis occurs by an unusual elimination of the corresponding carboxylic acid. The mechanism, involved in the elimination of RCOOH from the N,N'-diacyl-1,2-benzenediamines leading to the formation of 2-substituted benzimidazole in the pyrolytic method which is difficult to visualise, becomes evident from the electron impact study.

EXPERIMENTAL

General considerations: The melting points were determined on a Toshniwal capillary melting point apparatus and are uncorrected. The infrared spectra were recorded using Shimadzu IR-470 infrared spectrophotometer using KBr. The ^{1}H-NMR spectra were recorded with Hitachi R-600-60MHz nmr instrument. Mass spectra were taken on a Finnigan MAT 8230 mass spectrometer through direct probe insertion at 25°C. Accurate mass measurements were carried out at a resolution of 8000 (10% valley) at an ionisation energy of 70 eV and accelerating voltage of 3 kV and perfluorokerosene was used as the reference. The CAD-B/E linked-scan spectra,

Table 4. Synthesis and Charectarisation Data[a] of N,N'-Diacyl-1,2-benzenediamines

Compound	Yield (%)	Mp (lit)[b] (°C)	IR (KBr) cm^{-1}		HRMS for $M^{+\cdot}$	
			C=O	N-H	Calculated	Observed
1	98	184 (186)	1668	3248	192.08988	192.08572
2	92	300 (302)	1652	3258	316.12118	316.11854
3	85	228 (228)	1648	3264	344.15248	344.15093
4	86	232 (234)	1651	3266	386.04324	386.04654
5	85	265 (265)	1658	3282	406.09134	406.09563
6	80	266 (267)	1660	3276	406.09134	406.09354
7	84	212 (212)	1646	3246	296.07971	296.07998
8	95	266 (266)	1644	3232	328.03403	328.03756

a) ^{1}H-NMR spectra could not be recorded as the bis-anilides were insoluble in usual NMR solvents.

b) See references 16,19-21

Table 5. Synthesis and Characterisation Data[a] of 2-Substituted Benzimidazoles

R	T (°C)	Time (min)	Yield (%)	Mp (lit)[b]	IR (KBr) cm^{-1} C=N	IR (KBr) cm^{-1} N-H	Mass spectral data m/z (relative intensity)
CH_3	200	30	96	175 (175)	1602	3396	$M^{+\cdot}$ 132 (100) 131 (74) 104 (10)
C_6H_5	320	60	92	296 (296)	1600	3420	$M^{+\cdot}$ 194 (100) 193 (48) 167 (8)
p-$CH_3C_6H_4$	300	60	78	265 (266)	1596	3426	$M^{+\cdot}$ 208 (100) 207 (25) 193 (7)
p-ClC_6H_4	300	60	92	292 (293)	1592	3424	$M^{+\cdot}$ 228 (100) 193 (22) 111 (12)
p-$NO_2C_6H_4$	300	60	80	327 (327)	1594	3440	$M^{+\cdot}$ 239 (100) 193 (64)
o-$NO_2C_6H_4$	300	60	79	264 (265)	1590	3442	$M^{+\cdot}$ 239 (100) 193 (26)
2-furyl	250	60	85	286 (287)	1590	3426	$M^{+\cdot}$ 184 (100) 183 (36) 157 (12)
2-thienyl	250	60	88	254 (254)	1589	3428	$M^{+\cdot}$ 200 (100) 199 (54) 173 (20)

a) All the 2-substituted benzimidazoles synthesised were characterized through ^1H-NMR spectra using DMSO-d_6 as the solvent.

b) See references 15a-f, 16

in the first field free region were investigated using helium as the collision gas with a Finnigan MAT 8230 mass spectrometer at an ionisation energy of 70 eV and an accelerating voltage of 3kV.

Preparation of N,N'-diacyl-1,2-benzenediamines : The compounds **1** and **9** were prepared according to the literature procedure[16] and compound **10** was obtained by adopting the procedure reported by Ashare.[17] The bis-anilides **2-8** were prepared by reacting the acid chlorides obtained[18] with 1,2-benzenediamines.[19] All the N,N'-diacyl-1,2-benzenediamines synthesised were purified by recrystallisation using 85% ethanol. The yields and spectral data are tabulated in Table 4.

Pyrolysis of N,N'-diacyl-1,2-benzenediamines : In a typical procedure the N,N'-diacyl-1,2-benzenediamine (1mmol) was taken in 50ml round-bottomed flask fitted with an air condenser and heated on a sand bath according to the conditions specified in Table 5. The resulting solid was extracted in dichloromethane (2 x 50ml). The extract was washed thoroughly with saturated $NaHCO_3$ solution (100 ml). The solvent was evaporated through rotaryevaporator and the crude products were obtained. Recrystallisation was effected in H_2O for the compound where R = CH_3, and in absolute ethanol for the other substituted benzimidazoles. All the 2-substituted benzimidazoles were characterised thoroughly by their melting points and spectral data (Table 5).

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