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Mass Spectrometry of Heterocyclic Compounds: Benzo[*b*]pyrazolo[3,4-b]-1,6-naphthyridines

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The mass spectra of a number of benzo[*b*]pyrazolo[3,4-b]-1,6-naphthyridines are presented. The fragmentation involves elimination of CO molecule followed by other fragments, such as halogen (Cl, Br) or halogen acids (HCl, HBr) and HCN, *etc*.

Keywords: Fragmentations, Pyrazoles, Pyrazolo-[3,4-b]-pyridines, Naphthyridines.

INTRODUCTION

Naphthyridine have received considerable attention over the past years because of their wide range of biological activities including antitumor [1-3], antiinflammatory [4-6], and antifungal [6] activities. Pyridopyrimidine is one of the most important "privileged medicinal scaffolds", which are molecular frameworks used for the development of pharmaceutical agents for diverse applications. A large variety of pyridopyrimidine derivatives have been used as antitumor [7], antibaceterial [8], anti-inflammatory [9], antifungal [10] and antileishmaniasis [11] agents. Therefore, the synthesis of these molecules has attracted considerable attention. Gangjee and co-workers have described the construction of pyrimidonaphthyridine skeleton *via* multistep reaction [3]. However, the continued development of diversity synthesis of compounds library, including pyrimidonaphthyridine, benzonaphthyridine, pyrazolonaphthyridine and azabenzo[b]fluorene frameworks, is still strongly desired, because of their profound chemical and biological significance. We had previously described the synthesis of a number of benzo[*b*]pyrazolo[3,4-b]-1,6-naphthyridines (**1-9**) and would, now, like to report their fragmentation behaviour during their mass spectrometric studies.

EXPERIMENTAL

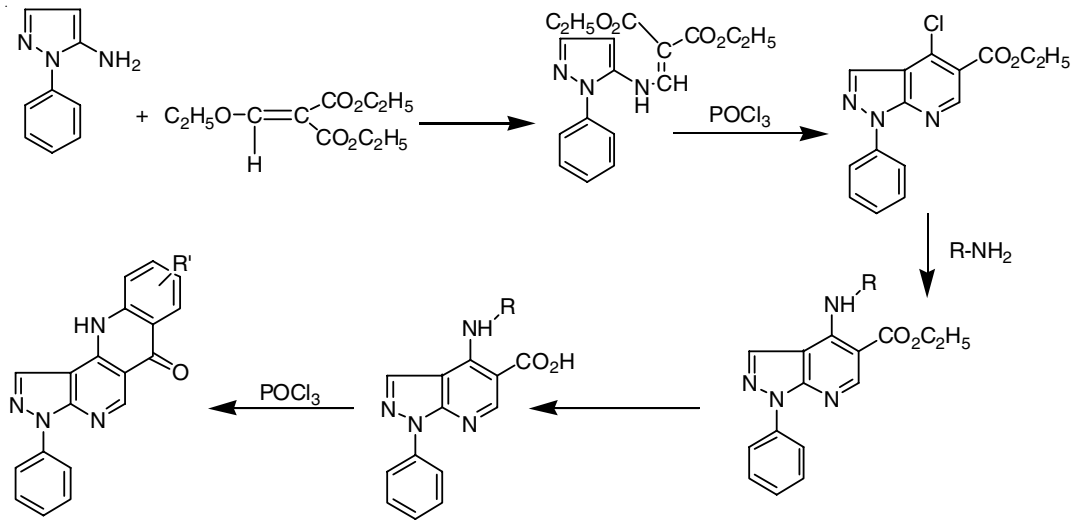
Mass spectra (low resolution) were recorded on a Finnegan MAT-112 instrument at HEJ Institute of Chemistry, Karachi, Pakistan.

Synthesis of benzo[*b*]pyrazolo[3,4-*b*]-1,6-naphthyridines (1-9): These were prepared according to the method already reported in our earlier communication [12]. 5-Amino-1-phenylpyrazole by successive condensation with diethyl ethoxymalonate in ethanol followed by the thermal cyclization (Gould-Jacobs reaction) provided ethyl 4-oxo-1-phenylpyrazolo-[3,4-b]pyridine-5-carboxylate. A chlorodesoxygenation with $POCl_3$ gives the corresponding 4-chloro derivative which in turn reacts with various anilines to give the 4-anilino intermediate. This intermediate on tandem hydrolysis and cyclization provides the desired products (**1-9**) (**Scheme-I**).

RESULTS AND DISCUSSION

Mass spectrometric literature, including their fragmentation for various representative heterocyclic ring systems, was earlier reported by Porter and Baldas [13]. The present series of compounds under study combine a two basic systems-pyridine and the naphthyridines and showed interesting behaviour in their mass spectrometric fragmentation.

Mass spectral data of benzo[*b*]pyrazolo[3,4-b]-1,6-naphthyridines (**1-9**) as collected in Table-1 provides main common fragments for the various compounds in the series. All the mass spectra displayed molecular ion peaks as also the base peak, the most intense in the spectrum. The fragmentation as can be seen from various schemes, seems to follow a pattern of the loss of expected fragment CO (*m/z* 28) followed by others, such as halogen (Cl, Br) or halogen acid (HCl, HBr) and some proton loss is also observed in some cases. Successive loss of HCN (*m/z* 27) molecules also completes the scheme with the stable C_6H_5 fragment invariably present as a terminal moiety, which can further break down in the well known pattern [13].



Scheme-I

TABLE-1
MASS SPECTRAL DATA OF BENZO[*b*]PYRAZOLO[3,4-b]-1,6-NAPHTHYRIDINES (**1-9**)

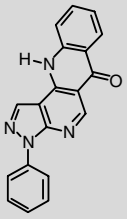
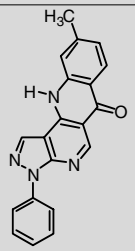
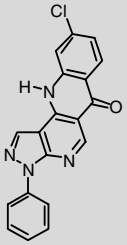
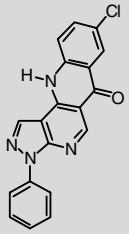
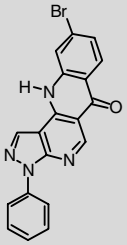
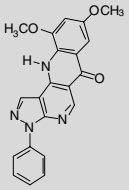
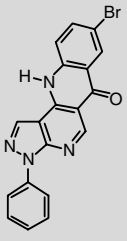
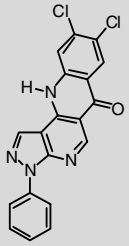
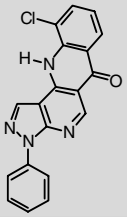
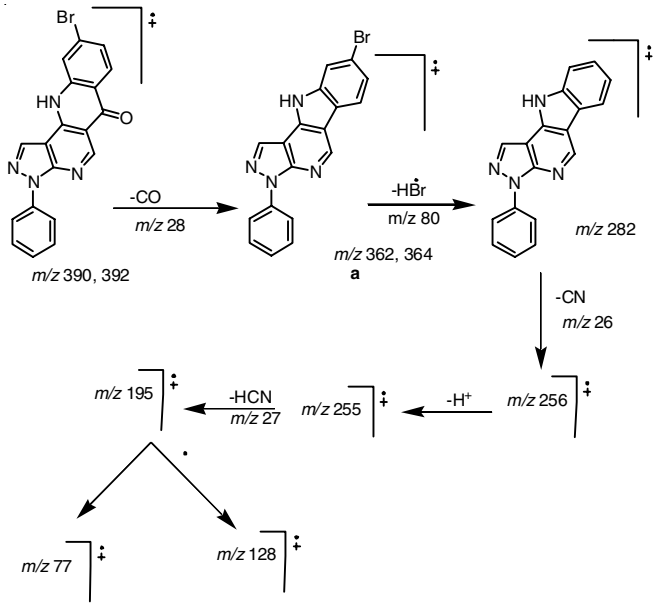
Compd. No.	Structure	Mass spectra *m/z* (relative intensity)	Compd. No.	Structure	Mass spectra *m/z* (relative intensity)
1		313 (22), 312 (100), 311 (39), 284 (20), 156 (9), 77 (18), 51 (7)	**6**		327 (23), 326 (100), 325 (31), 299 (12), 298 (6), 270 (3), 194 (3), 163 (5), 77 (8)
2		349 (6), 348 (33), 347 (31), 346 (100), 345 (31), 321 (6), 319 (17), 254 (3), 173 (5), 77 (23)	**7**		349 (7), 348 (33), 347 (33), 346 (100), 345 (32), 321 (4), 319 (19), 173 (9), 142 (7), 85 (12), 83 (18), 77 (49), 57 (5), 51 (25)
3		393 (21), 392 (98), 391 (48), 390 (100), 364 (11), 362 (13), 346 (6), 312 (6), 311 (8), 310 (5), 282 (10), 281 (6), 256 (8), 255 (7), 254 (6), 196 (5), 195 (5), 155 (5), 152 (5), 141 (5), 128 (6), 77 (48), 76 (5), 75 (8), 63 (5), 52 (21)	**8**		393 (6), 392 (35), 391 (43), 390 (100), 389 (64), 372 (14), 362 (15), 361 (45), 360 (19), 359 (29), 331 (6), 319 (5), 318 (9), 317 (8), 316 (5), 303 (5), 195 (9), 174 (5), 173 (8), 158 (5), 153 (5), 77 (39), 51 (11)
4		393 (22), 392 (100), 391 (46), 390 (100), 389 (26), 365 (14), 363 (14), 311 (8), 310 (5), 282 (10), 281 (6), 256 (8), 255 (7), 254 (6), 196 (5), 195 (5), 152 (7), 141 (50), 128 (9), 127 (5), 101 (5), 84 (7), 78 (5), 77 (53), 76 (6), 75 (9), 69 (7), 63 (6), 58 (6), 55 (9), 51 (23)	**9**		384(13), 383 (19), 382 (66), 381 (41), 380 (100), 379 (33), 355 (10), 353 (16), 191 (5), 190 (9), 77 (33), 51 (11)
5		349 (7), 348 (33), 347 (31), 346 (100), 345 (32), 321 (7), 319 (19), 254 (3), 173 (7), 141 93), 77 (18), 51 (5)			

TABLE-2
VARIOUS COMMON FRAGMENTS FOR COMPOUNDS **1-9**

Compd. No.	M	M-H$^+$	M-CO	M-HCN	M-2HCN	Others
1	312	311	284	–	–	–
2	348, 346	347, 345	–	321, 319	–	–
3	392, 390	391, 389	365, 363	–	–	M-Br
4	392, 390	391, 389	365, 363	–	–	M-Br
5	348, 346	347, 345	321, 319	–	–	–
6	326	325	298	299	–	–
7	348, 346	347, 345	321, 319	–	–	–
8	372	–	–	–	318	–
9	380	379	353	353	–	–

Although the most common fragments are collected in the Table-2. However, a detailed fragmentation scheme is shown in the following **Scheme-II**.



Scheme-II

Fragmentation pattern for compound 3: The fragmentation pattern of **3** is presented in **Scheme-I**. It gives M$^+$ peak at *m/z* 392 and 390, which by the loss of a CO (*m/z* 28) gives peak at *m/z* 364 and 362 which further loses HBr molecule followed by the loss of CN (*m/z* 26) and gives a peak at *m/z* 256. It further loses proton and HCN molecule brings to shorter fragments till a fragment corresponding to a phenyl C_6H_5 (*m/z* 77) is given off.

Conclusion

In this communication, we have presented a possible mass fragmentation pattern of a number of benzo[*b*]pyrazolo[3,4-b]-1,6-naphthyridines. The fragmentation involves elimination of CO molecule followed by other fragments, such as halogen (Cl, Br) or halogen acids (HCl, HBr) and HCN, *etc*.

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