Characteristic fragmentation behavior of 5-[1-aryl-1H-pyrrol-2-yl]-1H-tetrazole by electrospray ionization tandem mass spectrometry☆

Wei Liu*, Yanling Guo, Cong Han, Xiaonan Huang

College of Sciences, *Tianjin University of Science and Technology*, *Tianjin* 300457, *China*

Received January 26, 2008

Abstract

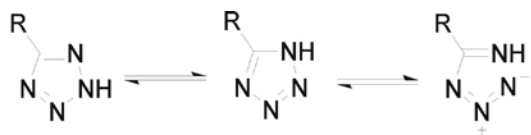
Eight 5-substituted 1H-tetrazole derivatives synthesized from 1-arylpyrrole-2-carbonitrile were investigated by electrospray ionization multi-stage mass spectrometry (ESI-MS^n) to establish a general structural elucidation of 5-substituted 1H-tetrazole derivatives. Their fragmentation pathways are proposed on the basis of the MS^n studies. There are very different characteristic fragment ions in the positive and negative ion MS/MS spectra. The tetrazole group of title compounds underwent elimination of HN_3 in the positive ion mass spectrometry and N_2 in the negative ion mass spectrometry, respectively. [Life Science Journal. 2008; 5(2): 25 – 29] (ISSN: 1097 – 8135).

Keywords: tetrazole; electrospray ionization; fragmentation pathway

1 Introduction

Tetrazoles are an increasing popular functionality[1] with wide-ranging applications. They have roles in coordination chemistry as a ligand, in medicinal chemistry as a metabolically stable surrogate for a carboxylic acid group[2], and in various materials science applications, including specialty explosives[3]. Structural elucidation of tetrazoles involved is helpful in understanding how and why they own these functions. For tetrazole and its 5-substituted derivatives, tautomeric and ring-chain isomerisms are known (Scheme 1)[4]. To date, reports on mass spectrometric investigations of 5-substituted tetrazoles are scarce[5–9]. In those case, loss of N_2 upon electron impact is observed mainly and loss of N_3· is only of minor importance.

Electrospray ionization tandem mass spectrometry (ESI-MS^n) is a very powerful tool for structural determination and the facility to trap electrosprayed ions and examine their gas-phase chemistry is likely to prove of great benefit in advanced analytical applications[10]. To our best knowledge, however, no ESI-MS investigation on the fragmentation patterns of tetrazoles, either themselves or their derivatives, has been reported until now. In the present work, we report the MS behavior of 5-[1-aryl-1H-pyrrol-2-yl]-1H-tetrazole which are potential active compounds in pharmaceutical and medicinal chemistry[11]. The structures of the title compounds are shown in Scheme 2.



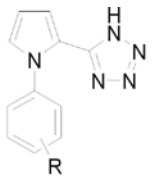
Scheme 1. Tautomeric and ring-chain isomerisms of tetrazole.

2 Materials and Methods

5-[1-aryl-1H-pyrrol-2-yl]-1H-tetrazole were prepared by methods described in the literature[12]. The ESI mass spectra of compounds 1 – 8 were acquired using a Bruker ESQUIRELC^{TM} ESI ion trap spectrometer equipped with

☆Supported by the Science Fund of Tianjin University of Science and Technology for financial support (No. 20060428).

*Corresponding author. Tel: 86-22-6060-0812; Email: liuwei2006@tust.edu.cn



1. R= H, **2**. R= *o*-CH_3, **3**, R= *m*-CH_3, **4**. R= *p*-CH_3
5. R= *p*-OCH_3, **6**. R= *o*-Cl, **7**. R= *p*-Cl, **8**. R= *p*-F

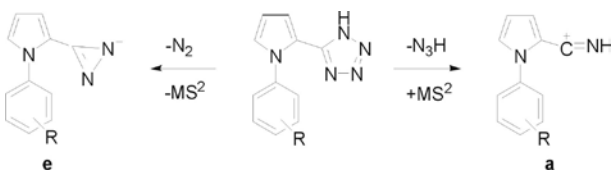
Scheme 2. Structures of the title compounds 1 – 8.

a gas nebulizer probe, capable of analyzing ions up to m/z 6000. The experiments were operated in the positive mode as follows: nitrogen was used as a drying gas at a flow rate of 4 L/min; nebulizer pressure 7 psi; capillary voltage 4 kV; heated capillary temperature 300 °C. The samples dissolved in methanol were ionized by ESI and continuously infused into the ESI chamber at a flow rate of 1.4 ml/min by a Cole-Parmer 74900 syringe pump (Cole-Parmer Instrument Co.). The scan range of the ions is m/z 50 – 800 and a cut-off mass of 50 was used during ion accumulation. The ions of the mass-to-charge ratio (m/z) of interest were isolated and fragmented by collision with helium to obtain MS^n spectra. The fragmentation amplitude values were 0.5 – 1.0 V and the fragmentation time was 40 ms.

3 Results and Discussion

The fragmentation pathways of title compounds are shown in Scheme 3 and the major fragment ions of 1 – 8 are listed in Table 1 and labeled as a – f (For the structures of a – f, see Schemes 3 – 6). Compounds 1 – 8 displayed similar fragmentation patterns. The mass spectrum and tandem mass spectra of compound 8 were selected as representatives and are shown in Figures 1 and 2. All of the fragment ions produced from compound 8 could be rationalized by the fragmentation paths indicated in Schemes 4 – 5, which have been confirmed by ESI-MS^n spectra.

There are very different characteristic fragment ions in the positive and negative ion MS/MS spectra, as shown above. The tetrazole group of title compounds underwen-telimination of HN_3 in the positive and N_2 in the negative ion mass spectrometry, respectively. Similar fragmentations were also observed for tetrazole derivatives under thermolysis conditions previously. Thermal decomposition of tetrazole derivatives have been reviewed by Lesn-



Scheme 3. Characteristic fragmentation pathways of protonated and deprotonated title compounds.

Table 1. Tandem mass spectra of compounds 1 – 8.

Compounds	Precursor ions	Fragment ions
1 (FW = 211)	212 [M+H$^+$]	212(27), 169(100)[a]
	169(36)[a]	142(100)[b], 115(36)[c]
	142(45)[b]	115(100)[c]
	210[M-H$^+$]	210(6), 182(100)[e]
	182(17)[e]	154(100)[f]
2 (FW = 225)	226[M+H$^+$]	226(4), 183(100)[a]
	183(14)[a]	167(13)[d], 156(100)[b],
	156(17)[b]	128.6(8)[c]
	224[M-H$^+$]	129(100)[c]
	196(6)[e]	224(14), 196(100)[e],
		154(42)
		168(12)[f], 153(100)
3 (FW = 225)	226[M+H$^+$]	226(6), 183(100)[a]
	183(11)[a]	167(12)[d], 156(100)[b],
	156(29)[b]	129(6)[c]
	224[M-H$^+$]	129(100)[c]
	196(7)[e]	224(4), 196(100)[e]
		168(100)[f]
4 (FW = 225)	226[M+H$^+$]	226(33), 183(94)[a],
	183(100)[a]	118(100)
	224[M-H$^+$]	167(39)[d], 156(39)[b]
	196(72)[e]	224(26), 196(100)[e]
		168(100)[f]
5 (FW = 241)	242[M+H$^+$]	242(18), 199(100)[a]
	199(30)[a]	184(100), 171(8)[b]
	171(100)[b]	144(14)[c]
	240[M-H$^+$]	240(7), 212(100)[e],
	212(9)[e]	197(65), 184(24)[f],
		169(100)
6 (FW = 245)	246[M+H$^+$]	246(32), 203(100)[a]
	203(44)[a]	176(7)[b], 168(100)[d]
	176(100)[b]	149(34)[c]
	244[M-H$^+$]	244(100), 216(84)[e],
	216(100)[e]	188(19)[f]
		188(31)[f]
7 (FW = 245)	246[M+H$^+$]	246(20), 203(100)[a]
	203(14)[a]	176(6)[b], 168(100)[d]
	176(100)[b]	149(22)[c]
	244[M-H$^+$]	244(11), 216(100)[e]
	216(68)[e]	188(100)[f]
8 (FW = 229)	230[M+H$^+$]	230(10), 187(100)[a]
	187(22)[a]	167(30)[d], 160(100)[b],
	160(80)[b]	140(23)
	228[M-H$^+$]	133(100)[c]
	200(6)[e]	228(7), 200(100)[e]
		172(100)[f]

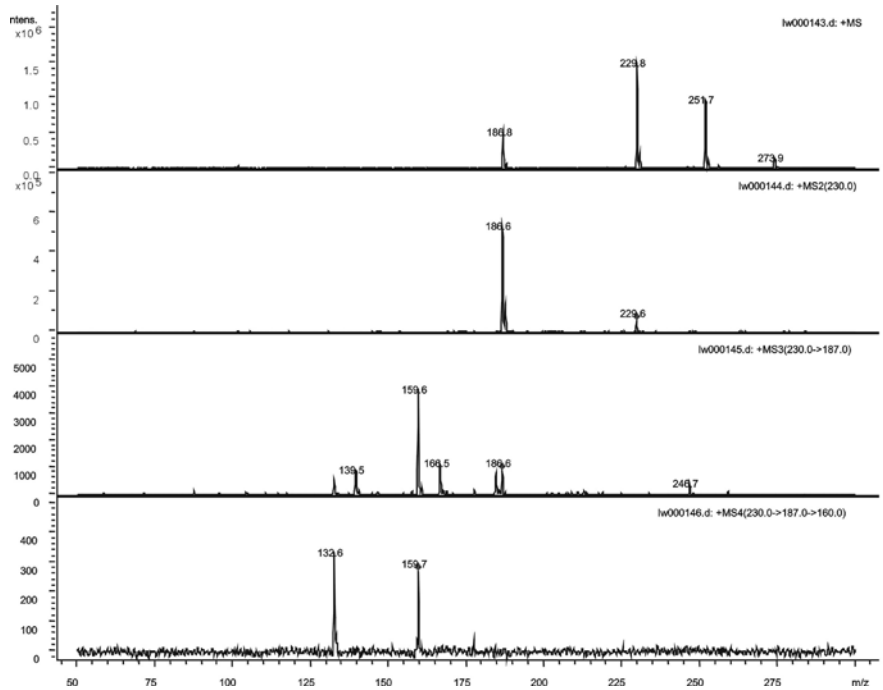


Figure 1. Positive-ion ESI-MS^n of $[M+H]^+$ of compound 8.

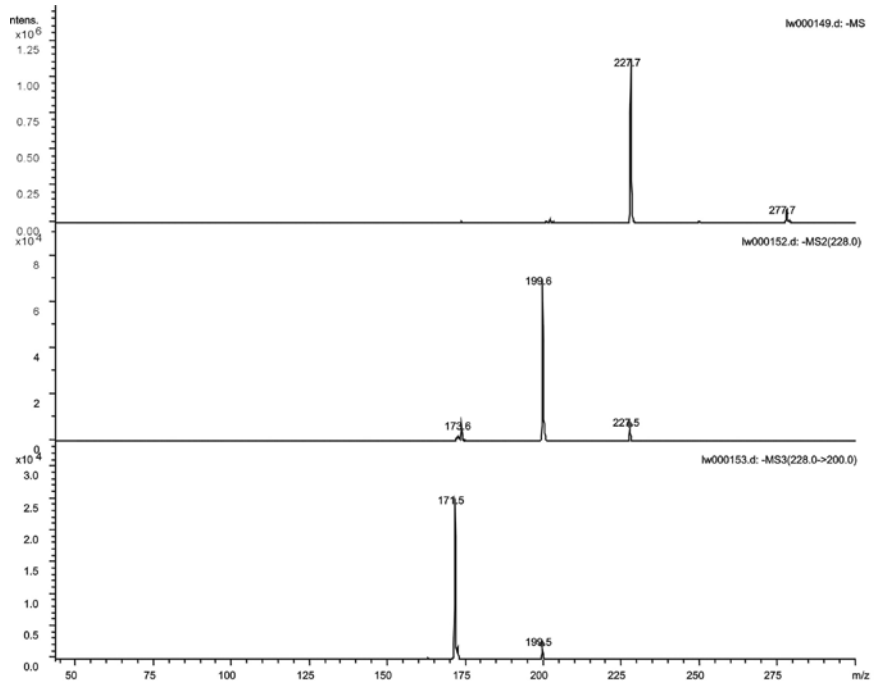
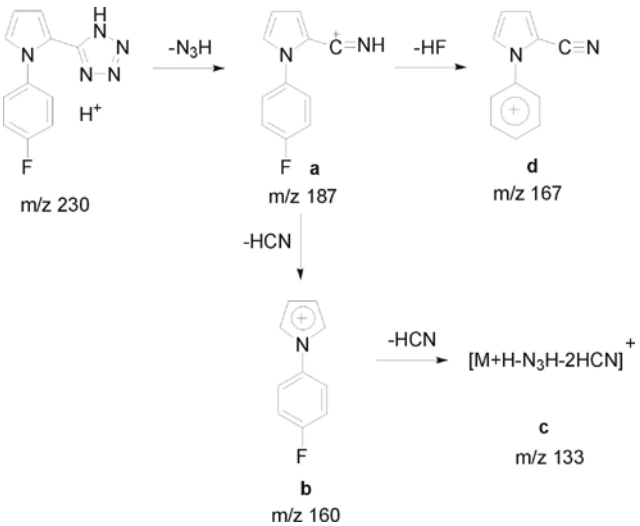


Figure 2. Negative-ion ESI-MS^n of $[M-H]^-$ of compound 8.

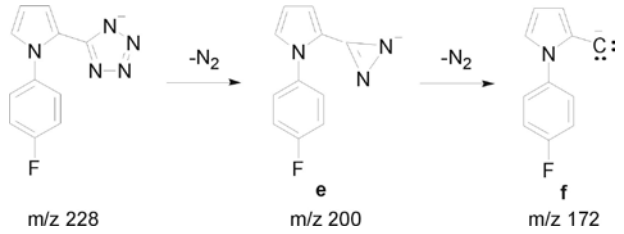
ikovich *et al*[13]. It was shown that there are two radically different pathways of the tetrazole ring fragmentation connected with the formation of a molecule of nitrogen or hydrogen azide.

In the positive ion MS/MS spectra, the protonated molecular $[M+H]^+$ loses HN_3 uniquely to afford the fragment ions a. In order to further confirm the fragmentation pattern, the ESI-MS^n spectrum of the ions a was record-

ed. There are two main fragmentation pathways. At first, the precursor ions a undergo a hydrogen transfer to give the ions b by loss of one molecule of HCN, which could further under a rearrangement to yield the ions c by loss of the other molecule of HCN. The other way is loss RH from phenyl ring to yield the ions d. Compared with the positive ion mass spectra, in the negative ion MS/MS spectra, deprotonated molecular $[M-H]^-$ loses a molecule of N_2 to yield ions e, which could further generate ions f by loss of the other N_2 molecule in ESI-MS^3 spectra.

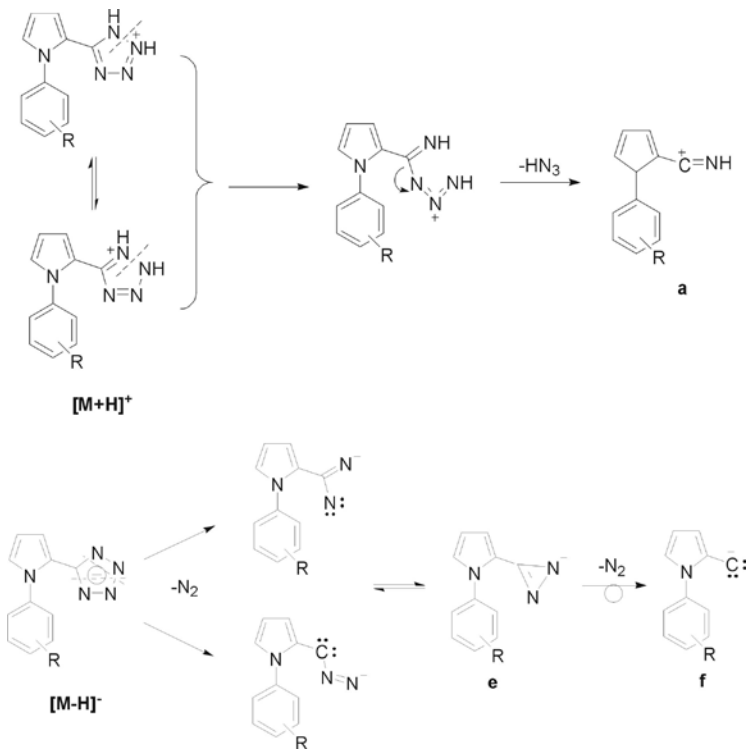


Scheme 4. Proposed fragmentation pathways of prorogated compound 8.



Scheme 5. Proposed fragmentation pathways of deprotonated compound 8.

The proposed fragmentation mechanisms, as suggested by observations from tandem mass spectra, of the title compounds are shown in Schemes 6. The C-substituted tetrazole structure can be considered as a hybrid between two tautomeric forms (Scheme 1), of which the 1H-tetrazole isomers are more stable in condensed phase while the 2H-tetrazoles are reported to be the energetically preferred tautomer in gas phase[14]. Sometimes the above equilibrium transformations make it impossible to propose an unambiguous scheme for the fragmentation mechanisms of the tetrazole rings. In the present work, either



Scheme 6. Mechanism proposed for detailed fragmentation pathways of title compounds.

protonated 1H-tetrazoles or 2H-tetrazole is likely to cause the ring-opening via cleavage of the bond N1-N2. This is then followed by the release of a HN_3 molecule through the C-N4 bond breaking. In the negative ion MS/MS spectra, on elimination of the nitrogen molecule from deprotonated tetrazoles, highly reactive intermediate ions (carbene-like ion or nitrene-like ion) are observed, which could probably form substituted isodiaziridine anions e. The precursor ion e could further undergo rearrangement to lose the second nitrogen molecule to yield carbene-like ion f. During the pyrolysis studies of 5-substituted tetrazoles in the gas phase, carbene and nitrene are also observed, whose stabilization leads to many reaction products[15]. In comparison, no ion-molecule reactions with carbene and nitrene ions are observed in the ESI process.

4 Conclusions

Positive and negative ion electrospray ionization mass spectra of eight 5-substituted 1H-tetrazole derivatives were studied and their fragmentation pathways were rationalized and supported by tandem mass spectrometry. The characteristic losses of HN_3 and N_2 molecules were observed in positive and negative ion MS/MS spectra, respectively. This finding could be valuable for the structural analysis and characterization of 5-sub stituted 1H-tetrazoles. These observations may also have some potential applications in the interpretation of thermal decomposition behavior of tetrazole rings.

References

1. Butler RN. In Comprehensive Heterocyclic Chemistry. Pergamon: Oxford, U. K., 1996; Vol. 4.
2. Singh H, Chawla AS, Kapoor VK, *et al*. Medicinal chemistry of tetrazoles. Prog Med Chem 1980; 17: 151 – 83.
3. Chavez DE, Hiskey MA, Gilardi RD, *et al*. 3,3'-azobis(6-amino-1,2,4,5-tetrazine): A novel high-nitrogen energetic material. Angewandte Chemie-International Edition 2000; 39(10): 1791.
4. Benson FR. Tetrazoles, Tetrazines and Purines and Related Ring Systems. In: Elderfield RC (ed). Heterocyclic Compounds. Wiley, New York, 1967; 8: 1 – 104.
5. Forkey DM, Carpenter WM. Mass spectrometry of methyltetrazoles. Org Mass Spectrom 1969; 3: 433 – 45.
6. Brady LE. Electron impact-induced fragmentation of 5-aminotetrazole. J Heterocycl Chem 1970; 7: 1223 – 5.
7. Tou JC. Competitive and consecutive eliminations of N_2 and CO (or C_2H_4) from some heterocyclics under electron impact. J Heterocycl Chem 1974; 11: 707 – 11.
8. Razynska A, Tempczyk A, Malinski E, *et al*. Application of mass spectrometry to the study of prototropic equilibriums in 5-substituted tetrazoles in the gas phase:experimental evidence and theoretical considerations. J Chem Soc, Perkin Trans 2 1983; 3: 379 – 83.
9. Seldes AM, D'Accorso N, Souto MF, *et al*. Gas-phase conversion of tetrazoles to oxadiazoles: isolation and characterization of the N-acylated intermediate. J Mass Spectrom 2001; 36: 1069 – 73.
10. Dass C. Recent developments and applications of high-performance chromatography electrospray ionization mass spectrometry. Current Organic Chemistry 1999; 3(2): 193 – 209.
11. Bovy PR, Reitz DB, Collins JT, *et al*. Nonpeptide angiotensin II antagonists: N-phenyl-1H-pyrrole derivatives are angiotensin II receptor antagonists. J Med Chem 1993; 36: 101 – 10.
12. Liu W, Ma Y, Yin YW, *et al*. Synthesis of 5-[1-Aryl-pyrrol-2-yl]-1H-tetrazole. Chem J Chinese Universities 2006; 27: 1472 – 5.
13. Lesnikovich AI, Levchik SV, Balabanovich AI, *et al*. The thermal decomposition of tetrazoles. Thermochim Acta 1992; 200: 427 – 41.
14. Wong MW, Toung RL, Wentrup C. Tautomeric equilibrium and hydrogen shifts of tetrazole in the gas phase and in solution. J Am Chem Soc 1993; 115: 2465 – 72.
15. Gleiter R, Rettig W, Wentrup C. Ring expansion in aromatic nitrenes and carbenes. Helv Chim Acta 1974; 57: 2111 – 24.