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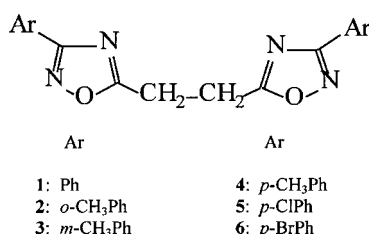
## Letter to the Editor

To the Editor-in-Chief  
Sir,

**Electron ionization mass spectra of bis-1,2,4-oxadiazoles: tandem mass spectrometry and accurate mass measurements**

Many 1,2,4-oxadiazole derivatives possess important biological activities.<sup>1,2</sup> Two of our recent publications cite references of other researchers which describe the pharmacological and other properties of 1,2,4-oxadiazoles.<sup>3,4</sup> Recently, we have prepared new 1,2,4-oxadiazoles and tested their analgesic and antiinflammatory properties with encouraging results.<sup>5,6</sup> For example, phthalimidooxadiazoles have been found to be analgesic, and of one them, viz., *N*-[3-phenyl-1,2,4-oxadiazol-5-yl-methyl]phthalimide, is 37 times more analgesic than aspirin without any significant toxic effect.<sup>5</sup> Even simple oxadiazoles such as 5-

isopropyl-3-aryl-1,2,4-oxadiazoles are antiinflammatory.<sup>6</sup> The 70 eV EI dissociation patterns of 1,2,4-oxadiazoles have been studied extensively by mass spectrometric techniques,<sup>7–12</sup> but for bis-1,2,4-oxadiazoles to our knowledge only one communication has been published<sup>13</sup> reporting low-resolution mass spectra data for compounds **1–6**.

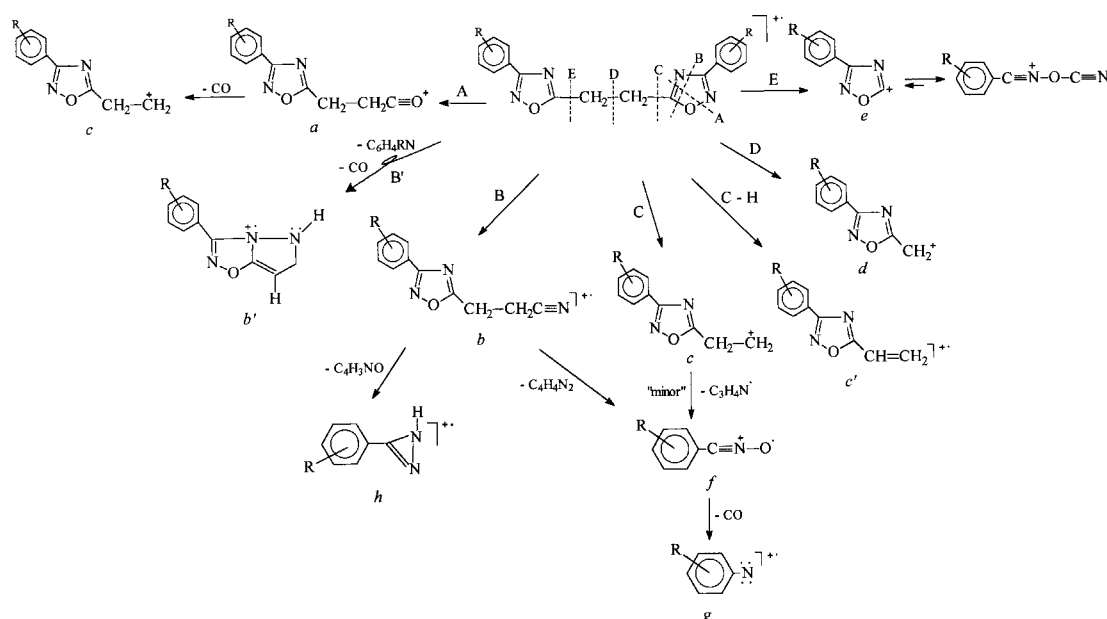


Considering the importance of these heterocyclic compounds, it seemed therefore appropriate to us to perform a more elaborate study so as to more precisely establish the 70 eV EI dissociation patterns of bis-1,2,4-oxadiazoles. This paper reports our accurate mass measurements and 8 keV collision-induced dissociation (CID) tandem mass (MS/MS) spectra collected for the molecular ions and major 70 eV EI fragments of **1–6**, and presents our reinterpretation of the main dissociation patterns of these bis-1,2,4-oxadiazoles.

Scheme 1 depicts the most general dissociation patterns of **1–6** (compounds available from our previous study<sup>13</sup>) as inferred from the data

reported in Tables 1–3. Table 1 lists the low-resolution 70 eV EI mass spectra of **1–6**, Table 2 the accurate mass measurements, and Table 3 the MS/MS spectra of their main 70 eV EI ions. Data were collected using an Autospec EBE instrument (Micro-mass, UK) operating at 10000 resolution (10% valley) for the accurate mass measurements (PFK was used as the internal calibration standard, at an ion-source temperature of 200 °C), and by using 8 keV collision energies with helium for the MS/MS experiments.

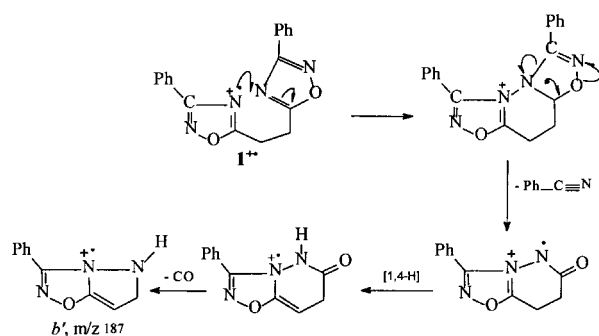
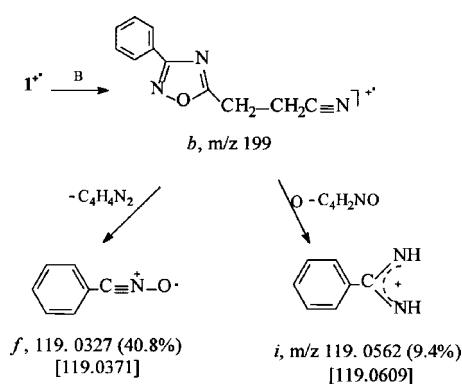
In the 70 eV EI mass spectrum of **1**, its molecular ion of *m/z* 318 is the base peak. MS/MS of **1**<sup>+</sup> produces mainly the fragment ions of *m/z* 201 (*a*), 199 (*b*), 187 (*b'*), 173 (*c*), 172 (*c-H*), 159 (*d*) and 145 (*e*) which result from cleavages of types A, B, B', C, C-H, D and E, respectively (Scheme 1). The composition of *a* of *m/z* 201 is C<sub>11</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup> [calcd. 201.0664, obs. 201.0637]. Ion *b* of *m/z* 199 [calcd. 199.0746, obs. 199.0723] dissociates to form mainly *f* and *i* of *m/z* 119 and *h* of *m/z* 118 [C<sub>7</sub>H<sub>6</sub>N<sub>2</sub><sup>+</sup>:calcd. 118.0501, obs. 118.0486]. Accurate mass measurements show that *m/z* 119 is composed of two isobaric ions, *f* of *m/z* 119.0327 and *i* of *m/z* 119.0562, in a 1:4 ratio. MS/MS spectra indicate that these isobars (*f* and *i*) are formed from both *b* (Scheme 2) and *c* (Scheme 1), and that *f* dissociates mainly to *g* of *m/z* 91. It has already been estab-



**Scheme 1.**

**Table 1.** Main ions and their relative abundances (in parentheses) observed in the 70 eV EI low-resolution mass spectra for compounds 1–6

Compound	
1	319 (20.7), 318 (100), 201 (2.5), 199 (5.3), 187 (2.6), 173 (22.5), 172 (11.6), 145 (4.4), 119 (40.8), 119 (9.4), 118 (11.8), 91 (11.6)
2	347 (20.5), 346 (2.2), 215 (3.4), 214 (1.8), 187 (14.0), 159 (100), 133 (28.7), 132 (35.9), 131 (21.0), 116 (21.5), 104 (9.1), 103 (2.8), 91 (91.6), 89 (6.6), 77 (10.0), 65 (4.7), 55 (25.5)
3	347 (20.9), 346 (100), 303 (9.1), 215 (2.7), 187 (26.3), 173 (4.5), 159 (4.4), 133 (50.8), 132 (29.8), 116 (7.6), 104 (3.7), 91 (14.0), 77 (5.4), 65 (2.2), 55 (38.8)
4	347 (24), 346 (100), 215 (3.5), 187 (23.5), 173 (4.2), 159 (7.5), 133 (51.7), 132 (40.3), 131 (6.0), 116 (6.3), 104 (6.0), 103 (2.2), 91 (13.4), 89 (3.7), 77 (7.2), 65 (5.6), 55 (39.3)
5	390 (11.8), 389 (12.5), 388 (66.8), 387 (20), 386 (100), 235 (6.0), 233 (10.8), 207(31), 206 (18.2), 179 (17.5), 153 (61.9), 152 (23.8), 125 (11.6)
6	477 (21.3), 476 (100), 475 (11.2), 474 (53.9), 279 (10.3), 277 (8.9), 251 (13.5), 250 (13.5), 223 (5.7), 197 (50.2), 196 (19.9), 169 (4.0)



lished that *f*, ionized benzonitrile oxide, loses CO to give  $C_6H_5N^+$  of  $m/z$  91.<sup>14</sup>

Ion *b'* of  $m/z$  187 ( $C_{10}H_9N_3O^+$ , calcd. 187.0745, obs. 187.0723) is observed as a minor 70 eV EI fragment of  $1^+$  (Table 1) but it appears as an important fragment in the MS/MS spectrum (Table 3). Ion *b'* is likely formed via an interesting dissociation channel that probably involves two oxadiazole moieties followed by consecutive

losses of neutral benzonitrile and carbon monoxide (Scheme 3).

Methyl substitution on the phenyl ring facilitates dissociation, and hence  $2^+$  of  $m/z$  346 (42%) is a major ion but no longer the base peak in the 70 eV EI spectrum of **2** (Table 1). The dissociation behavior of  $2^+$  also differs considerably from that of  $1^+$  owing to an *ortho* effect of the methyl substituent that induces interesting dissociation channels (Scheme 4). For instance, an

intramolecular [1,5-H] shift from the *ortho* methyl group to N-2 produces the rearranged molecular ion *j*, which then suffers E-type cleavage to give ion *e'* of  $m/z$  159 [ $C_9H_7N_2O^+$ : calcd. 159.0599, obs. 159.0558], the base peak in the EI mass spectrum of **2**. Ion *e'* loses, in turn,  $OCN^+$  to give *k* of  $m/z$  117, which loses a hydrogen atom to give *l* of  $m/z$  116 (Scheme 4). Ion  $2^+$  also undergoes A-type cleavage to give the acylium ion *a* of  $m/z$  215, which dissociates in turn by  $C_4H_2O_2$  loss to give *m* of  $m/z$  133. Similarly, *a* eliminates  $C_4H_3O_2$  to give *n* of  $m/z$  132, which dissociates in turn to *o* of  $m/z$  105 and *p* of  $m/z$  104. Loss of a hydrogen radical from *o* may also form *p* of  $m/z$  104.

The *m*-tolyl isomer **3** shows fewer fragment ions compared to its *o*-tolyl isomer **2**, and  $3^+$  of  $m/z$  346 is the base peak in its 70 eV EI mass spectrum (Table 1). MS/MS of  $m/z$  346 forms *r* of  $m/z$  303 [ $C_{19}H_{17}N_3O^+$ : calcd. 303.1372, obs. 303.1410] as the most abundant fragment ion (Scheme 5) and five other ions, viz., those of  $m/z$  215, 214, 187, 186, and 159. To form *r*,  $3^+$  is assumed to undergo a 1,2-shift of the *m*-tolyl group, which migrates from C-3 to N-4 to give the distonic ion *q* (Scheme 5). The heterocyclic ring of *q* then opens between C<sub>3</sub>-N<sub>4</sub> to give *q'*, which undergoes a [1,5-H] shift to furnish *q''*, which finally loses a neutral HCNO molecule to provide *r* of  $m/z$  303. Surprisingly, the isomeric *r* of  $m/z$  303 was not detected in the EI mass spectrum of the *o*- and *p*-tolyl isomers **2** and **4**, respectively; hence, this dissociation channel appears to occur exclusively for the *m*-tolyl isomer **3**.

Although the isomeric *r* of  $m/z$  303 was not detected in the EI mass spectrum of the *p*-tolyl isomer **4**, several dissociation channels are, however, common to compounds **3** and **4** (Scheme 6). For example, both **3** and **4** undergo E-type cleavage to produce *e* of  $m/z$  159. Ion *e* tautomerizes to *e'*- and loses  $NCO^+$  to afford ionized *meta*- or *para*-tolyl nitrile *k* of  $m/z$  117, which, after H $\cdot$  loss, likely forms the cyanotropylium ion *s* of  $m/z$  116. Another dissociation pattern common to **3** and **4** is of B-type, and *b* dissociates to *f* of  $m/z$  133 with the  $C_8H_7NO^+$  composition. No  $m/z$  133

**Table 2.** Molecular and fragment ions, their observed and calculated [in brackets] masses and relative abundances (%), observed in the 70 eV high-resolution EI mass spectra for compounds 1–6

Compound	R	M+	<i>a</i>	<i>b</i>	<i>c</i>	<i>c'</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>	<i>h</i>
1	H	318.11169	201.0637	199.0723	173.0687	172.0602	159.0527	145.0361	119.0327	91.0371	118.0486
		[318.11168] (100%)	[201.0662] (2.5%)	[199.0744] (5.3%)	[173.0713] (22.5%)	[172.0635] (11.6%)	[159.0557] (5.2%)	[145.0401] (4.5%)	[119.0370] (40.8%)	[91.0421] (11.6%)	[118.0530] (11.8%)
2	<i>o</i> -CH <sub>3</sub>	346.1430	215.0872	None	187.0909	186.0819	None	159.0599	None	105.0586	132.0711
		[346.1426] (42%)	[215.0818] (3.4%)		187.0869 (14.0%)	[186.0791] (1.7%)		[159.0557] (100%)		[105.0577] (2.0%)	[132.0686] (35.9%)
3	<i>m</i> -CH <sub>3</sub>	346.1429	215.0840	None	187.0904	None	173.0740	159.0585	133.0617	None	132.0655
		[346.1426] (100%)	[215.0818] (2.7%)		[187.0869] (26.3%)		[173.0713] (4.5%)	[159.0557] (4.3%)	[133.0526] (50.8%)		[132.0686] (24.8%)
4	<i>p</i> -CH <sub>3</sub>	346.1429	215.0828	213.0907	187.0877	186.0798	173.0715	159.0619	133.0586	None	132.0588
		[346.1426] (100%)	[215.0818] (3.5%)	[213.0900] (8.6%)	[187.0869] (23.5%)	[186.0791] (10.1%)	[173.0713] (4.2%)	[159.0557] (7.5%)	[133.0526] (51.7%)		[132.0586] (40.3%)
5	<i>p</i> -Cl	386.0338	235.0207	233.0261	207.0226	206.0152	193.0121	179.0012	152.9900	124.9913	152.0028
		[386.0335] (100%)	[235.0275] (6.0%)	[233.0355] (10.8)	[207.0324] (30.9%)	[206.0246] (18.4%)	[193.0168] (4.0%)	[179.0012] (5%)	[152.9981] (61.9%)	[125.0032] (11.6%)	[152.0141] (23.8%)
6	<i>p</i> -Br	473.9321	278.9814	276.9835	250.9799	249.9725	None	222.9593	196.9493	–	195.9630
		[473.9324] (53.9%)	[278.9767] (10.3%)	[276.9849] (8.9%)	[250.9818] (13.5%)	[249.9740] (13.5%)		[222.9506] (5.7%)	[196.9475] (50.2%)	[168.9526] (4.0%)	[195.9635] (19.9%)

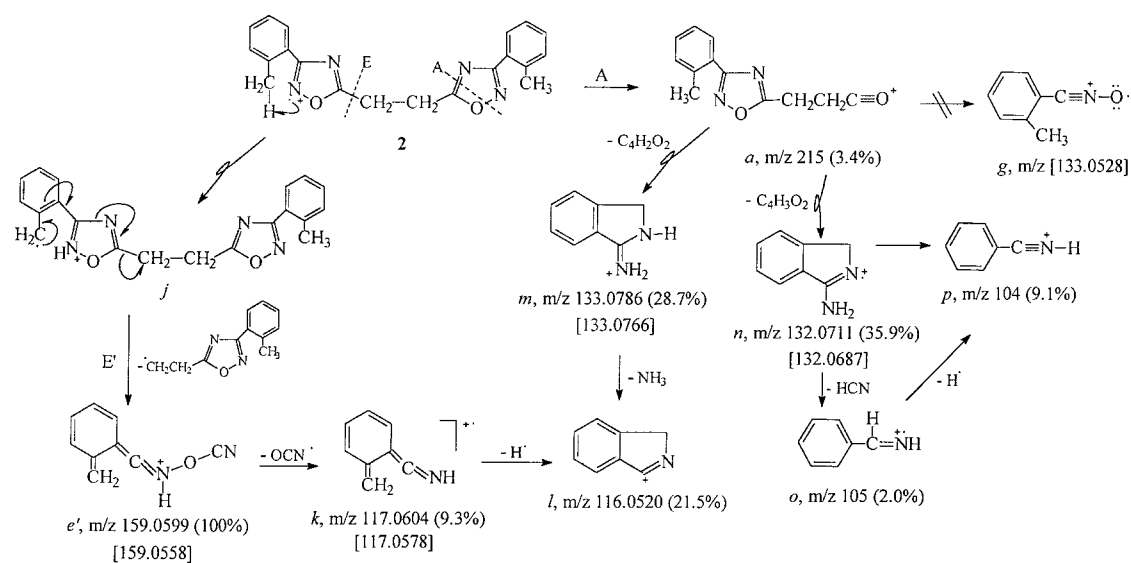
ions with C<sub>8</sub>H<sub>9</sub>N<sub>2</sub><sup>+</sup> composition are formed from either **3** or **4**. MS/MS of *m/z* 133 from **4** (Table 3) confirms dissociation of *f* to *m/z* 105 and 104 (Scheme 6). No B'-type cleavage was observed for either **3** or **4**.

The molecular ion of **5** is the base peak in its 70 eV EI mass spectrum (*m/z* 386, Table 1). As expected for a molecule containing two chlorine atoms, the main isotopomeric ions of *m/z* 386, 388 and 390 are formed in the

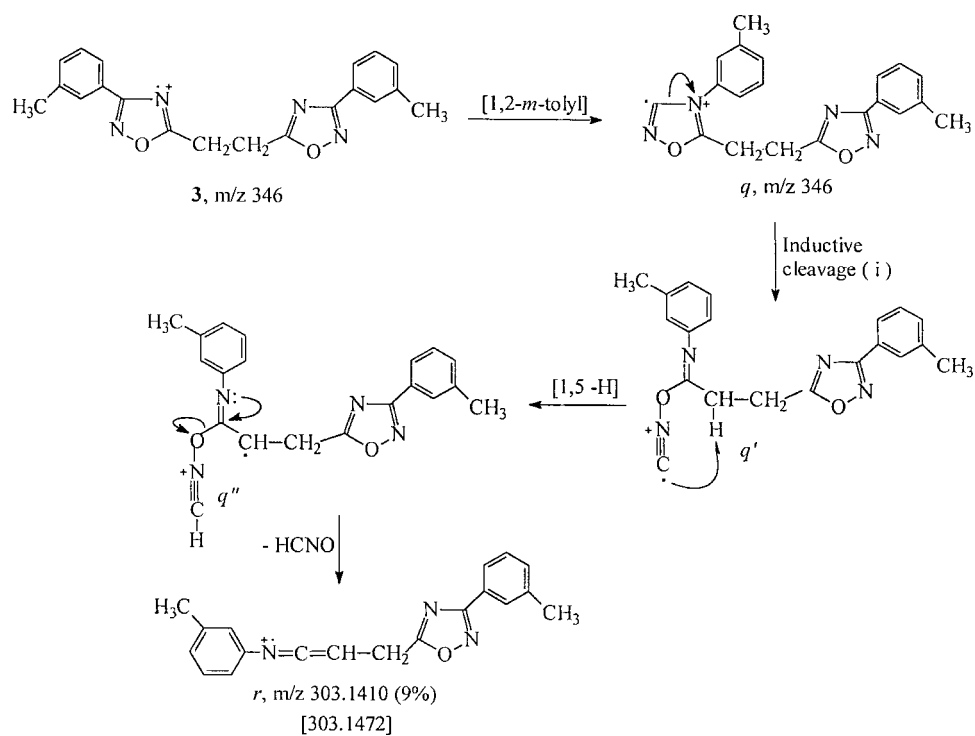
relative ratio of 9:6:1. MS/MS of **5**<sup>+</sup> of *m/z* 386 (Table 3) confirms its dissociation to *m/z* 317, 235, 207, 206, 179, 153 and 152, *m/z* 207 being far the most abundant fragment ion. The ion of *m/z* 235 [C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>Cl<sup>+</sup>: calc. 235.0275,

**Table 3.** Major fragment ions observed in the 8 keV CID MS/MS spectra of selected ions for compounds 1–6

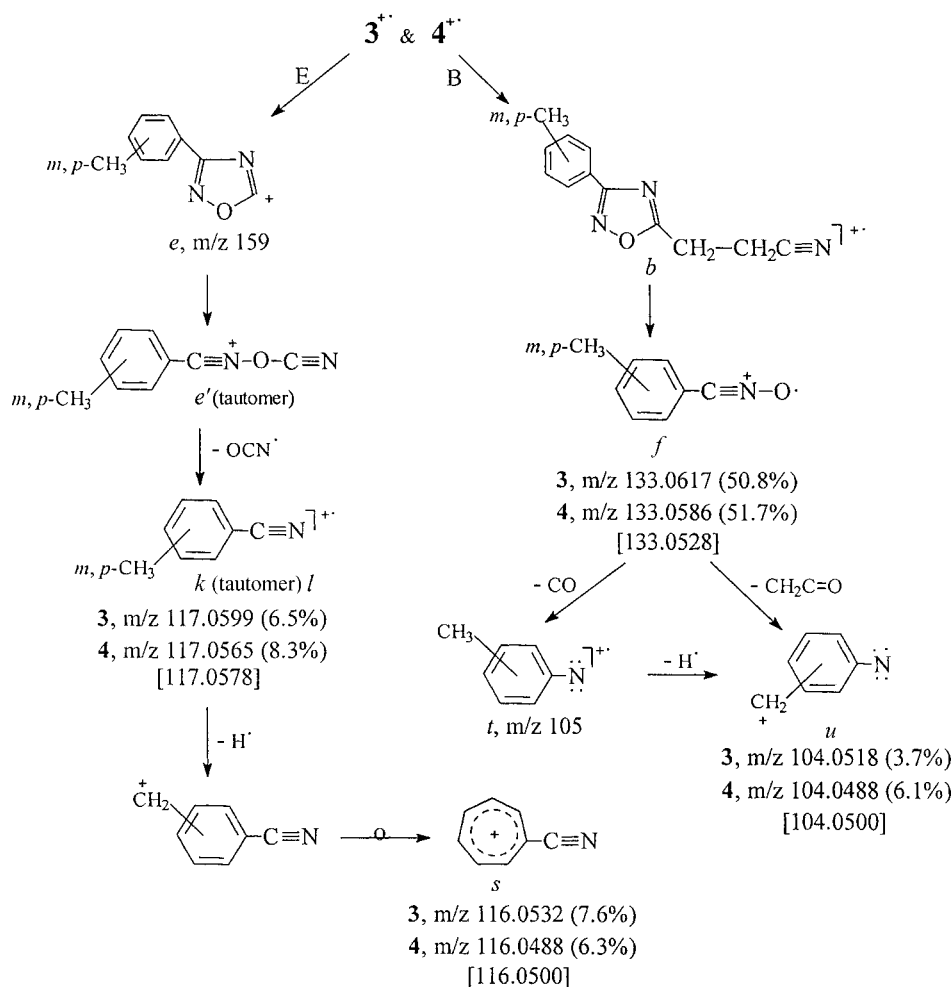
Compound	Parent ion ( <i>m/z</i> )	Daughter ions (relative abundance, %)
1	318	201 (18.0), 199 (7.0), 187 (16.0), 173 (100.0), 172 (35.5), 159 (4.0), 145 (25.7).
	199	173 (6.0), 172 (9.5), 171 (7.0), 119 (100.0), 118 (47.0).
	173	172 (100.0), 119 (8.5).
	119	91 (100.0), 89 (7.0), 88 (13.0).
2	346	214 (34.0), 189 (22.0), 188 (22.0), 159 (100.0).
	215	187 (100.0), 186 (11.0), 133 (20.0), 116 (9.5).
	187	186 (100.0), 133 (35.1).
	159	158 (42.0), 131 (12.0), 130 (14.0), 117 (44), 116 (100.0).
	132	131 (100.0), 105 (28.0), 104 (44.0), 89 (5.0).
	116	89 (100.0), 88 (9.0).
3	346	303 (100.0), 215 (23.0), 214 (12.0), 187 (43.0), 186 (17.0), 159 (20.5).
	303	274 (18.5), 247 (100.0), 232 (11.5), 187 (26.5), 143 (21.5).
	215	187 (100.0), 186 (22.0), 133 (16.5).
	187	170 (21.0), 159 (36.0), 158 (25.0), 144 (35.0), 133 (100.0), 118 (14.5).
	116	89 (100.0).
4	346	277 (17.5), 248 (8.5), 215 (52.0), 187 (100.0), 159 (52.0), 145 (8.0).
	213	186 (22.5), 133 (100.0), 132 (47.0).
	187	186 (100.0), 133 (7.0).
	159	158 (100.0), 131 (8.5), 91 (18.0).
	133	132 (100.0), 104 (24.5), 91 (29.0), 89 (8.0).
	117	116 (65.0), 90 (100.0), 89 (43.5).
5	386	317 (8.0), 235 (16.0), 207 (100.0), 206 (32.0), 179 (26.0), 153 (31.5), 152 (29.0)
	231	207 (26.5), 153 (100.0), 152 (47.0), 141 (11.5), 137 (23.5), 125 (13.0), 111 (19.0).
	207	153 (5.5).
	169	164 (16.0), 153 (14.5), 151 (45.0), 144 (31.5), 118 (18.0), 99 (19.0), 97 (100.0).
	153	152 (100.0), 125 (10.0).
6	474	405 (12.0), 279 (16.0), 277 (9.5), 265 (13.5), 253 (43.5), 252 (33.5), 251 (100.0), 250 (43.0), 223 (44.0), 197 (62.0), 196 (51.0), 169 (3.0).
	279	250 (9.0), 199 (37.0), 197 (24.0).
	250	197 (48.0)
	223	208 (68.0), 195 (100.0), 183 (31.0), 155 (58.0).
	197	169 (100.0), 155 (21.0), 117 (25.0).



Scheme 4.



Scheme 5.



Scheme 6.

obs. 235.0207] is of type *a* (see Scheme 1). The most abundant fragment ion of  $m/z\ 207$  [ $\text{C}_{10}\text{H}_8\text{N}_2\text{OCl}^+$ : calc.207.0324, obs. 207.0226] is of type *c*. MS/MS of  $m/z\ 207$  shows that it dissociates to  $m/z\ 153$  to a limited extent. The fragment of  $m/z\ 206$  is of type *f*; that of  $m/z\ 179$  is likely of type *g*; that of  $m/z\ 153$  is likely ionized *p*-chlorobenzonitrile oxide ( $\text{C}_7\text{H}_4\text{NOCl}^+$ : calc.152.9982, obs. 152.9900]; and that of  $m/z\ 152$  has the composition  $\text{C}_7\text{H}_5\text{N}_2\text{Cl}^+$  (calc. 151.9789, obs. 152.0028) and corresponds to fragment *h*. In summary, compound **5** (and also **6**) has similar behavior to that of **1**.

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