The use of DART mass spectrometry for express confirmation of empirical formulas of heterocyclic compounds

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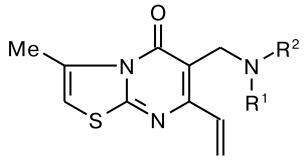
The results of studying the possibility of using DART spectrometry with a time-of-flight mass analyzer to confirm the elemental composition of heterocyclic compounds are presented. The method makes it possible to rapidly determine the molecular weight and to calculate the empirical formula of organic synthesis product.

Key words: DART mass spectrometry, heterocyclic compounds.

A concurrent part of organic synthesis is the monitoring of the reaction course and establishment of the product composition. The simplest and popular method for the monitoring of the reaction course is thin layer chromatography, while more complicated methods, such as NMR spectroscopy and mass spectrometry, are used for structure determination. Elemental composition is usually determined by the combustion of a sample (C, H, N analysis) or using high-resolution mass spectrometry.

There are many analytical approaches based on mass spectrometry.[1] Gas and liquid chromatographic methods combined with mass spectrometry are most popular and traditionally used. These methods are very informative but restricted by the duration of one analysis (on the average, from several minutes to tens of minutes). At the same time, new ionization methods have recently appeared in mass spectrometry, which make it possible to perform superfast analysis of various samples without sample preparation and chromatography. One of these methods is DART (direct analysis in real time) ionization.[2] The source of DART ions allows one to study both solid and liquid objects without sample preparation. A sample is introduced with a glass stick (when analyzing liquids) or tweezers (when analyzing solid objects) into an ion source for several seconds and the mass spectrum is detected. DART mass spectra are rather simple for interpretation, because frequently they contain signals of ions $[M + H]^+$ and almost no signals of fragmentation ions. If a high-resolution mass analyzer is used, this method serves for the calculation of possible empirical formulas of components of studied samples due to the precise determination of ratios of weights to the charge (m/z) of ions $[M + H]^+$ formed from ionized components. Since DART mass spectrometry is a comparatively new method, its potentialities for the determination of the elemental composition of products of organic synthesis are insufficiently studied.[3,4]

In this work, we studied for the first time the DART mass spectra of (*E*)-methyl 3-[(3-methyl-5-oxo-7-vinyl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)methyl]-*N*-methylaminoacrylate (**1**), (*E*)-methyl 3-[(3-methyl-5-oxo-7-vinyl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)methyl]-*N*-isopropylaminoacrylate (**2**), (*E*)-methyl 3-[(3-methyl-5-oxo-7-vinyl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl)methyl]-*N*-(2-phenylethyl)aminoacrylate (**3**), (*E*)-6-(*N*-benzyl-2-methyl-3-oxobut-1-enylamino)methyl-7-vinyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (**4**), (*E*)-dimethyl *N*-[2-(6-methoxymethyl-2-methyl-7-oxo-7*H*-isoxazolo[2,3-*a*]-pyrimidin-5-yl)ethyl]-*N*-(2-phenylethylamino)but-2-enedioate (**5**), and (*E*)-dimethyl 2-[*N*-isopropyl-*N*-(2-methyl-7-oxo-5-vinyl-7*H*-isoxazolo[2,3-*a*]pyrimidin-5-yl)]-methylaminomaleate (**6**).



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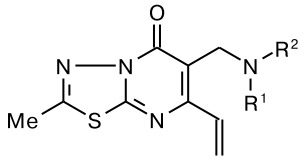

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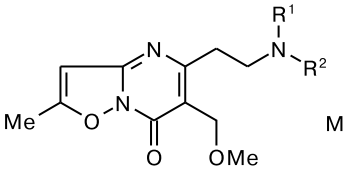

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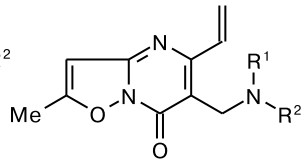

6

Compound	R^1	R^2
1	Me	CH=CHCOOMe
2	Pr^i	CH=CHCOOMe
3	CH_2CH_2Ph	CH=CHCOOMe
4	CH_2Ph	CH=CHC(O)Me
5	CH_2CH_2Ph	C(COOMe)=CHCOOMe
6	Pr^i	C(COOMe)=CHCOOMe

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1963—1964, October, 2010.

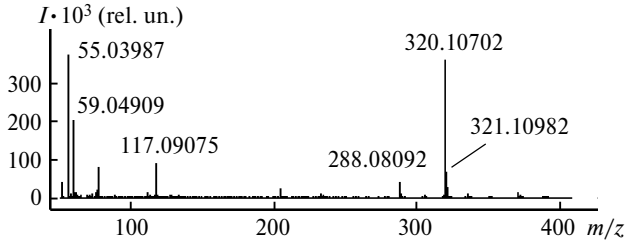

Fig. 1. DART mass spectrum of compound **1**.

Heterocyclic compounds **1—6** were synthesized earlier and their structures were confirmed by a complex of spectral data.[5]

The typical DART mass spectrum for compound **1** as an example is presented in Fig. 1.

For all compounds studied, ions $[M + H]^+$ give the most intense signal in the informative region of the DART mass spectra (see Fig. 1). The intense signal with m/z 55 observed in all spectra belongs to the cluster ion of water $(H_2O)_3H^+$ and the signal with m/z 117 corresponds to the ion $[M - H_2O + H]^+$ of ethoxyethoxyethanol, which is a known contaminant, observed in the DART mass spectra.

High-resolution of a time-of-flight analyzer of the mass spectrometer used makes it possible to additionally confirm the correspondence of the composition of the synthesized substances to the expected one due to the determination of exact values of m/z for ions $[M + H]^+$ followed by the calculation of the possible elemental composition of these ions. For this purpose, the mass spectrum of poly(ethylene glycol) was recorded at the beginning of analysis and then the mass spectrum obtained was used as calibrated one for the high-accuracy compensation of the mass shift. Exact values of m/z of the studied compounds, which were used for the calculation of the possible elemental composition, were computed using the MassCenterMain software (JEOL, Japan). The calculated results for compounds **1—6** are presented in Table 1. They show that DART mass spectrometry allows one to determine empirical formulas of the studied compounds with high reliability.

The possibility to determine molecular weights and calculate empirical formulas of this class of compounds was shown for a series of heterocyclic compounds. The approach used is much faster and simpler than the direct determination of the elemental composition, because it requires no large time expenses and high purity of analyzed substances: if the substance obtained includes by-products of the synthesis or the starting reactants, their elemental compositions can be established by the same method as for the major product. In addition, as it is known from the literature data,[6] DART mass spectrometry can be combined with thin layer chromatography, which can be additionally used for obtaining information about the course of organic synthesis and the composition of the products formed. This approach is restricted by comparatively high cost of the corresponding equipment.

Table 1. DART mass spectra of compounds **1—6***

Compound	$[M + H]^+$ (calculation)	DART, $[M + H]^+$		|δ|
		m/z	Elemental composition	
1	320.1064	320.1072±0.0007	$C_{15}H_{18}N_3O_3S$	0.8
2	348.1377	348.1406±0.0008	$C_{17}H_{22}N_3O_3S$	2.9
3	410.1533	410.157±0.004	$C_{22}H_{25}N_3O_3S$	3.0
4	381.1380	381.1391±0.0009	$C_{20}H_{21}N_4O_2S$	1.1
5	484.2079	484.208±0.003	$C_{25}H_{30}N_3O_7$	0.0
6	390.1660	390.167±0.001	$C_{19}H_{24}N_3O_6$	1.0

* The values of m/z, empirical formulas of ions $[M + H]^+$, and relative measurement errors (|δ|, ppm) were calculated by the data of four DART experiments; $P = 0.95$.

Experimental

Mass spectra were recorded on a JMS-T100LP mass spectrometer (JEOL, Japan) equipped with an FWHM 6000 high-resolution time-of-flight analyzer and a DART ion source (IonSense, USA). Conditions of detection of DART mass spectra: needle voltage, 4000 V; voltages on electrodes 1 and 2, 150 and 250 V, respectively; voltage at the inlet cone of the mass spectrometer, 10 V; temperature, 250 °C; helium flow rate, 2 L min^{-1}. Signals of ions were detected in the real time regime in the m/z range from 50 to 1000, the scanning frequency being 1 spectrum per second.

Analyzed compounds were dissolved in chloroform (99%, Aldrich) and introduced into a DART ion source with a glass stick. The preliminary analysis of poly(ethylene glycol)-600 provides the possibility to compensate the drift of mass numbers in time. The duration of one analysis was at most 5—8 s. The results were computed and exact values of m/z of detected peaks were calculated using the MassCenterMain software (Jeol, Japan).

The authors are grateful to R. A. Abramovich, the Director of the Shared Research and Educational Center of the People´s Friendship University of Russia, for favorable conditions of performing this work.

This work was financially supported by the Council on Grants at the President of the Russian Federation (Grant MK-594.2010.3).

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Received May 19, 2010;
in revised form July 12, 2010