ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
https://www.icf.ro/rrch/

Rev. Roum. Chim.,
2024, *69*(1–2), 57–61
DOI: 10.33224/rrch.2024.69.1-2.07

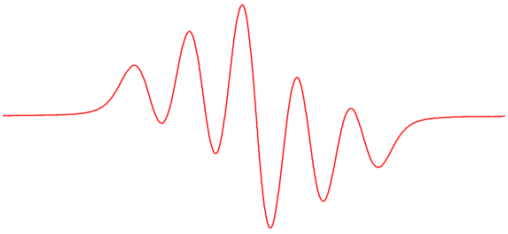
SYNTHESIS OF NOVEL *p*-AMINOPHENYL DERIVATES OF DPPH FREE RADICAL

Adela F. DOBRE,[a] Augustin M. MADALAN,[a] Victorita TECUCEANU,[b] Anamaria HANGANU[a,b] and Petre IONITA[*,a]

[a] University of Bucharest, Faculty of Chemistry, Panduri 90, Bucharest, Roumania
[b] Institute of Organic and Supramolecular Chemistry, Spl. Independentei 202b, Bucharest, Roumania

Received August 5, 2023

2,2-Diphenyl-1-picrylhydrazyl (DPPH) is an intensely coloured organic stable free radical with paramagnetic and redox properties. In this work we present three new derivatives of DPPH, in which an amino substituent was designed for one of the *p*-phenyl position. The synthetic details and the structural characterizations of the compounds are shown.



INTRODUCTION

Hydrazyl free radicals are a well-known class of open-shell molecules that possess very appealing and applicative properties, like redox behavior, intense colour that changes in acid-base or redox reactions, high hydrophobicity, and, of course, due to the unpaired electron, paramagnetism.[1,2]

The most encountered stable free radical of hydrazyl type is 2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl, best known as DPPH. Although nowadays most of the literature data is about its use as the main reagent in the total antioxidant capacity assay,[3-5] also it can be found data about the synthesis of other (novel) DPPH-derivatives with multifunctional properties (besides the ones counted before), like cations complexing, fluorescence, spin-scavengers, nitric oxides sensors, and so on.[6] Starting from DPPH, a new class of diazenium betaines with interesting and peculiar properties was revealed in recent years.[7-9]

Most of the DPPH derivatives are obtained either by direct reaction of DPPH with a reactive specie (free radical) that usually led to a *p*-phenyl adduct, following a radical + radical coupling reaction, or by a step-by-step procedure, in which the final molecule is constructed. Pursuing our interest in novel DPPH derivatives, in this work are presented three novel compounds, herein denoted **A-C** (Fig. 1).

EXPERIMENTAL

All chemicals, solvents and materials were purchased from Merck, Sigma-Aldrich or Chimopar, and used as received. Compounds **1** and **2** were synthesized as previously published

[*] Corresponding authors: p_ionita@yahoo.co.uk

and all physical data were identical with those from literature. Picryl chloride was obtained in a similar manner.[10] UV-Vis measurements were performed on an UVD-3500 double-beam spectrophotometer. Solutions of compounds **A-C** in ethanol were diluted as appropriate and the spectra recorded between 300–800 nm, using 1 cm pathlength quartz cells (usual concentration 10^{-4} M). ^{1}H- and ^{13}C-NMR spectra were recorded in deuterated chloroform ($CDCl_3$) at room temperature, using a Bruker Advance spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The residual solvent peaks were taken as the internal reference and the chemical shifts δ are reported as ppm values. MS spectra were recorded on a Varian 310 – MS LC/MS/MS triple quadrupole mass spectrometer fitted with an electrospray ionization interface (ESI). ESR spectra were recorded on a Jes FA100 Jeol apparatus.

X-ray crystallographic analysis. X-ray diffraction measurements for the compound **2** were performed on a Rigaku XtaLAB Synergy-S diffractometer operating with Mo-Kα (λ = 0.71073 Å) micro-focus sealed X-ray tube. The structure was solved by direct methods and refined by full-matrix least squares techniques based on F^2. The non-H atoms were refined with anisotropic displacement parameters. Calculations were performed using SHELX-2018 crystallographic software package. A summary of the crystallographic data and the structure refinement for compound **2** are given in Table 1. CCDC reference number: 2280341.

Table 1

Crystallographic data, details of data collection and structure refinement parameters for compound **2**

Compound	**2**
Chemical formula	$C_{16}H_{14}N_2O_2$
M (g mol^{-1})	266.29
Temperature, (K)	293(2)
Wavelength, (Å)	0.71073
Crystal system	*Monoclinic*
Space group	*P2$_1$/c*
a (Å)	11.9802(7)
b (Å)	7.0345(4)
c (Å)	16.4179(10)
α (º)	90
β (º)	94.803(5)
γ (º)	90
V (Å^3)	1378.76(14)
Z	4
D_c (g cm^{-3})	1.283
μ (mm^{-1})	0.086
F(000)	560
Goodness-of-fit on F^2	1.042
Final R_1, wR_2 [I>2σ(I)]	0.0389, 0.1008
R_1, wR_2 (all data)	0.0524, 0.1096

General synthesis procedure. To 10 mmol of compound **1** (2.26 g) or **2** (2.62 g) was added 150 mL methanol and the stirred solution was cooled in an ice-bath, followed by addition of 2 mL concentrated hydrochloric acid (35 %) and 1.2 g of sodium nitrite dissolved in 10 mL of cold water. After 30 min., ice-cold water was added until the nitroso-derivative precipitated, allowed to stand in fridge for 2 hours, then filtered off and used directly for the reduction step. Reduction step was performed as well in methanol (100 mL), adding 10 g Zn dust and 15 mL glacial acetic acid (the acid was added over a period of 2 h). After another 30 min. of stirring, the mixture was filtered and the filtrate washed several times with methanol. To the methanolic solution was added 350 mL of water and the mixture was extracted with DCM (3 x 100 mL). The organic phase was separated, dried over anhydrous sulphate and the solvent removed. The residue was dissolved in 50 mL of methanol and 1 g of picryl chloride and 2.5 g of solid sodium hydrogen carbonate was added, and the mixture refluxed for 1 h, followed by filtration, washing the filtrate with DCM, and the organic solution removed by a rotavap. The residue was chromatographed on a silica gel column using DCM as eluent. Pure compounds were obtained in 5-10% yields.

*Compound **A**, N-[4-(N-(2,4,6-trinitroanilino)anilino)phenyl] acetamide*, $C_{20}H_{16}N_6O_7$ M.W. 452. ^{1}H-NMR (500 MHz, $CDCl_3$, δ ppm, J Hz): 10.11 (s, 1H, NH), 9.15 (s, 1H, H_{Ar}), 8.45 (s, 1H, H_{Ar}), 8.04 (s, 1H, NH), 7.46 (d, 2H, H_{Ar}, 8.7 Hz), 7.29 (t, 2H, H_{Ar}, 7.7 Hz), 7.14 (t, 1H, H_{Ar}, 7.4 Hz), 7.06-7.02 (m, 4H, H_{Ar}), 2.12 (s, 3H, CH_3) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$, δ ppm): 168.9, 145.9, 141.9, 139.8, 136.3, 135.9, 133.5, 129.4, 126.2, 125.5, 125.0, 121.6, 121.1, 119.8, 24.2 ppm. -ESI-MS 491 (M-H$^+$). R_f=0.09 (silicagel/DCM). Yields ~ 200 mg.

*Compound **B**, 1-[4-(N-(2,4,6-trinitroanilino)anilino)phenyl] pyrrolidine-2,5-dione*, $C_{22}H_{16}N_6O_8$ M.W. 492. ^{1}H-NMR (500 MHz, $CDCl_3$, δ ppm, J Hz): 10.23 (s, 1H, NH), 9.15 (s, 1H, H_{Ar}), 8.45 (s, 1H, H_{Ar}), 7.34 (t, 1H, H_{Ar}, 7.6 Hz), 7.28-7.21 (m, 3H, H_{Ar}), 7.15-7.06 (m, 5H, H_{Ar}), 2.83 (s, 4H, CH_2) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$, δ ppm): 176.6, 145.8, 141.7, 139.7, 136.5, 133.7, 129.7, 129.3, 127.4, 127.1, 126.6, 122.1, 121.7, 119.5, 118.9, 28.3 ppm. -ESI-MS 491 (M-H$^+$). R_f=0.22 (silicagel/DCM). Yields ~ 150 mg.

*Compound **C**, methyl-4-oxo-4-[4-(N-(2,4,6-trinitroanilino) anilino)anilino]butanoate*, $C_{23}H_{20}N_6O_9$ M.W. 524. ^{1}H-NMR (500 MHz, $CDCl_3$, δ ppm, J Hz): 10.12 (s, 1H, NH), 9.11 (s, 1H, H_{Ar}), 8.43 (s, 1H, H_{Ar}), 8.17 (s, 1H, NH), 7.42 (d, 2H, H_{Ar}, 8.8 Hz), 7.26 (t, 2H, H_{Ar}, 8.0 Hz), 7.12 (m, 1H, H_{Ar}), 7.03-7.00 (m, 4H, H_{Ar}), 3.64 (s, 3H, CH_3), 2.83 (t, 2H, CH_2, 6.5 Hz), 2.59 (t, 2H, CH_2, 6.6 Hz) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$, δ ppm): 173.6, 170.0, 145.9, 141.9, 141.6, 139.7, 136.2, 135.9, 133.4, 129.7, 129.3, 127.1, 125.2, 121.6, 120.8, 119.5, 51.9, 31.6, 28.9 ppm. -ESI-MS 523 (M-H$^+$). R_f = 0.11 (silicagel/DCM). Yields ~ 250 mg.

RESULTS AND DISCUSSION

4-Aminodiphenylamine was chosen as starting material. Protection of the amino group was performed by acetylation, using acetic anhydride, or by using succinic anhydride; in this way, either 4-acetamido-diphenylamine (**1**) or 4-succinimido-diphenyamine (**2**) was obtained in very good yields (Fig. 1).[11] The next steps were nitrosation (with sodium nitrite in acidic media), reduction (either with Zn and acetic acid or with hydrazine and Pd/C), and coupling with picryl chloride (1-chloro-2,4,6-trinitrobenzene), finally yielding compounds **A-C** (Fig. 1).

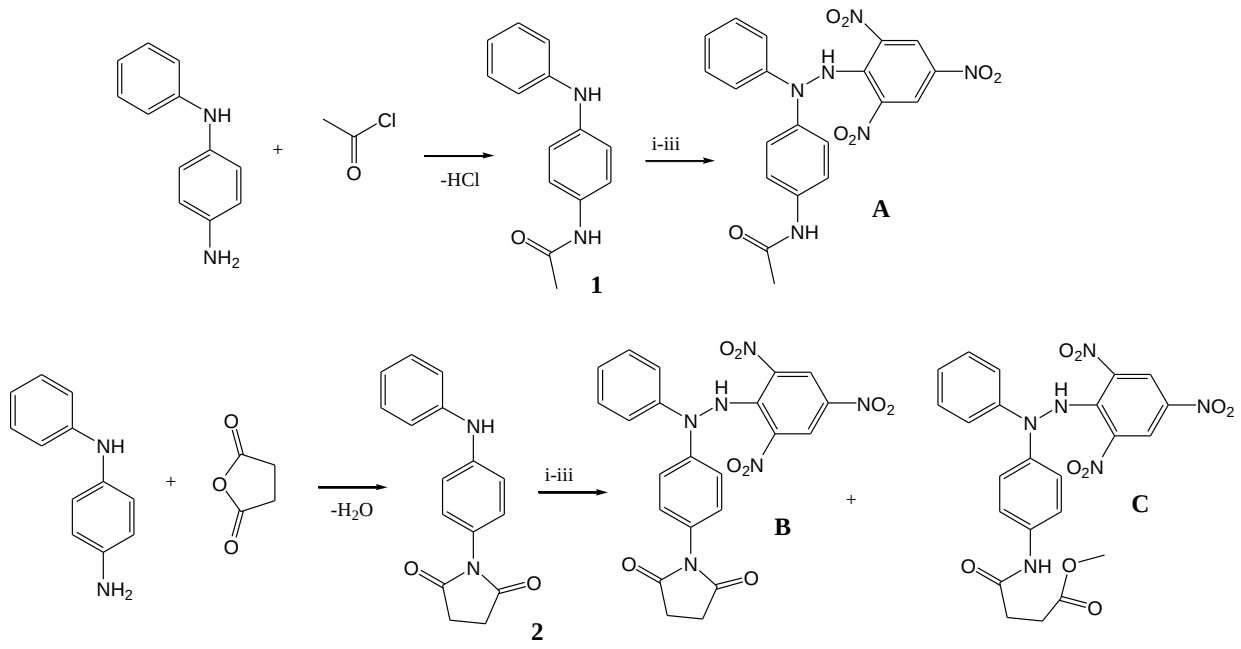


Fig. 1 – Synthesis of compounds **A-C** (i)- sodium nitrite/H^+; (ii)- Zn/H^+; (iii)- picryl chloride).

In the case of 4-succinimido-diphenyamine **2**, the slow evaporation of the solvent led to crystallization of the compound, and the crystals thus obtained were suitable for single crystal X-ray diffractometry. Therefore, the solid-state structure of compound **2** was determined by X-ray diffraction on single crystal and details are presented next. The compound **2** crystallizes in the monoclinic $P2_1/c$ space group with one molecule in the asymmetric unit (Fig. 2). For the secondary amine fragment, the dihedral angle between the mean planes of the two benzene rings bound to the N2 nitrogen atom is 45.4°. The N2-C8 and N2-C11 bond lengths are: 1.3960(19), respectively 1.3819(19) Å. The central benzene ring makes with succinimide fragment a dihedral angle of 52.5° (calculated also between the mean planes through the atoms forming the rings). Selected bond lengths for the succinimide fragment are: C1-O1 = 1.203(2), C4-O2 = 1.2041(18), C1-N1 = 1.388(2), C4-N1 = 1.3952(18) and C5-N1 = 1.4353(18) Å.

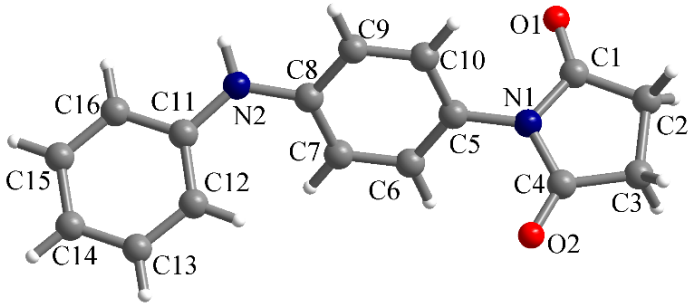


Fig. 2 – View of the asymmetric unit in the crystal structure of compound **2**.

The secondary amino group is involved in hydrogen interaction with one oxygen atom from a succinimide fragment belonging to a neighboring molecule. The hydrogen interactions generate supramolecular chains running along the crystallographic *c* axis (Fig. 3a). The distance for the hydrogen interaction is: (N2)H2N··· O2' = =2.153 Å. The corresponding angle is: N2-H2N··· O2' = 160.3° (symmetry code: ' = *x*, 1.5–*y*, 0.5+*z*). The central benzene rings from neighboring chains establish CH···π interactions (2.87–3.05 Å – Fig. 3b) expanding the supramolecular array to a 2D system in the crystallographic *bc* plane.

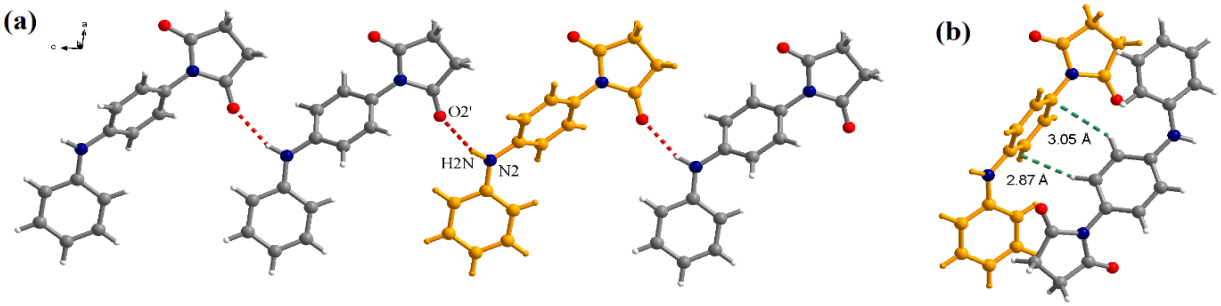


Fig. 3 – View of a packing diagram showing the supramolecular chain formed by hydrogen interactions (a) and details of the CH···□ interactions (b).

Nitrosation of the compounds **1** and **2** worked well, and the nitroso-derivatives were employed directly in the next steps without purification (TLC controls showed almost pure derivatives). However, the reduction of the nitroso-derivatives to the corresponding hydrazines occurs with simultaneous formation of many by-products, lowering the final yields. Anyway, the hydrazines already formed were reacted fast with picryl chloride to afford the desired compounds **A** and **B** (compound **C** was obtained as a by-product, probably formed *via* methanolysis of the compounds **B**). Because compounds **A-C** are colored in yellow-red they can be easily spotted on TLC plates and thus their isolation is quite easy.

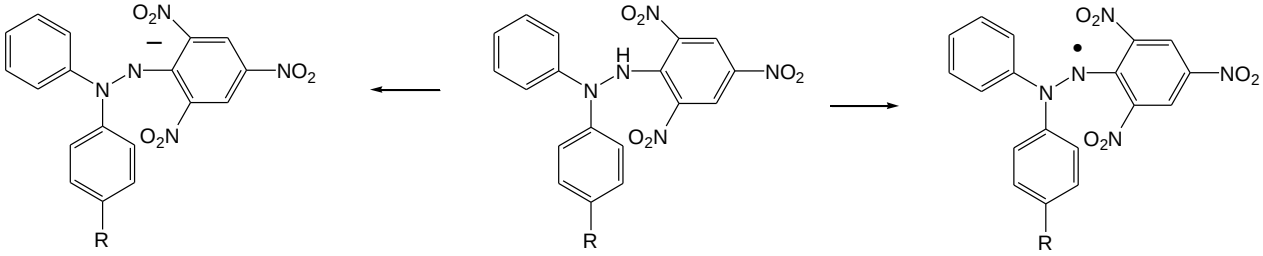


Fig. 4 – Acid-base and redox processes of compounds **A-C.**

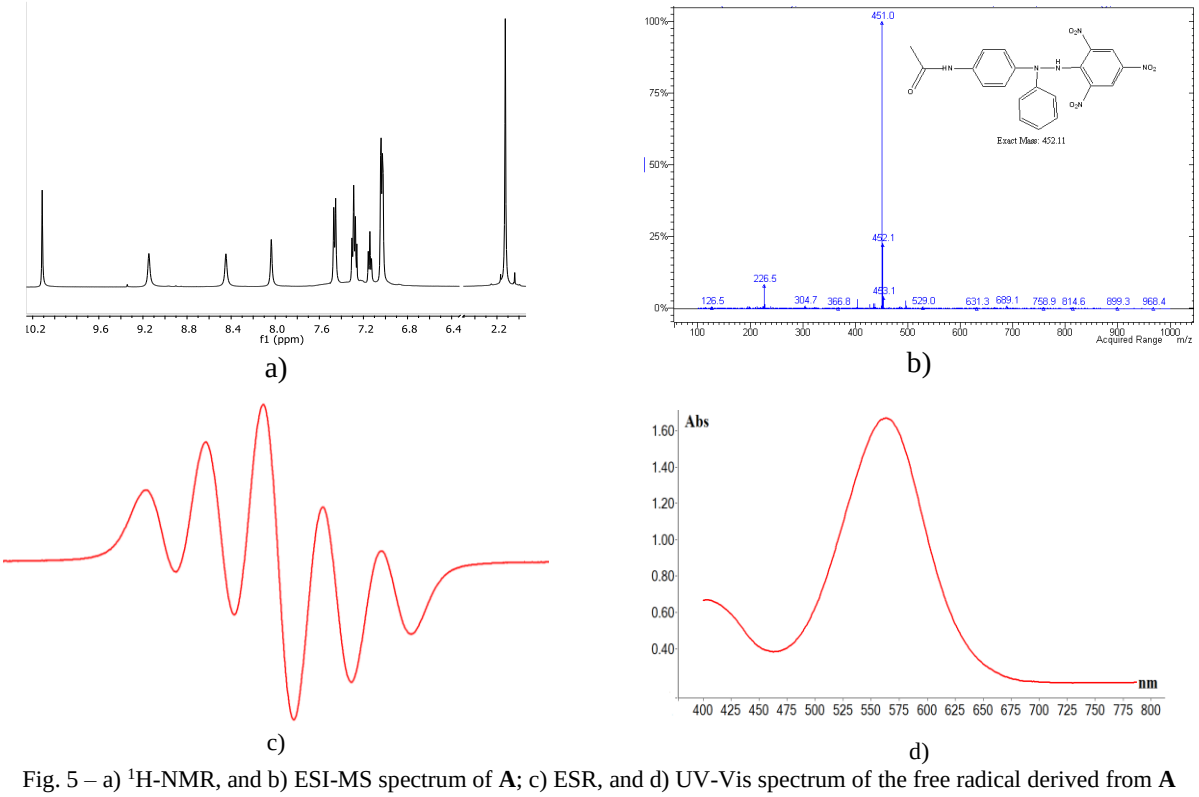


Fig. 5 – a) ^{1}H-NMR, and b) ESI-MS spectrum of **A**; c) ESR, and d) UV-Vis spectrum of the free radical derived from **A**

The structure of compounds **A-C** was elucidated by ^{1}H- and ^{13}C-NMR, ESI-MS, UV-Vis and ESR (after oxidation to the corresponding radicals, see Fig. 4 and Fig. 5a–d). Thus, in the hydrazines **A-C** the proton from the hydrazine N*H* group is observed in ^{1}H-NMR around 10.1 ppm, while the proton from the *p*-N*H*-phenyl is noticed at about 8.1 ppm; the two hydrogens from the picryl ring are non-equivalent and appear at about 9.2 and 8.5 ppm, respectively. ESI-MS data are also consistent with the structures (see Experimental and Fig. 5b).

As any other similar hydrazines, compounds **A-C** gave by oxidation the corresponding persistent radicals (Fig. 4), with an ESR spectrum (Fig. 5c) very similar of DPPH, consisting in five lines, with the intensity ratio of 1:2:3:2:1. The coupling constants were $a_{N1} = a_{N2} = 9$ Gauss, practically identical with those of DPPH. As mentioned before, compounds **A-C** are yellow-red solids, soluble in organic solvents, showing in ethanol an absorption wavelength at 330, 331, and 330 nm and a molar absorption coefficient (log ε) of about 4.20 in all cases; by addition of a base, the colour turns to brown, due to the formation of the corresponding anions, with a maximum absorption wavelength at 432, 431, and 431 nm (log ε being 4.08 in all cases); as well, oxidation of the parent compounds **A-C** to the corresponding persistent hydrazyl free radicals is associated with a strong colour shift to violet, the thus obtained free radicals having a maximum absorption wavelength at 551, 520, and 522 nm (log ε was 4.15 for all cases); this colour-changing behavior is well known for the DPPH-derivatives.[2]

CONCLUSIONS

Three new derivatives of the well-known DPPH stable free radical were obtained, although in modest yields (due to many by-products obtained in the reduction step of the *N*-nitroso-derivatives to the corresponding hydrazines). These were characterized by different techniques, such as UV-Vis, NMR, MS, etc. Similar with DPPH, compounds **A-C** showed acid-base and redox properties, that are accompanied by colour changes. These derivatives might be used further for novel hydrazyl derivatives, including diazenium-betaines.

Acknowledgements. Partial funding from CSUD-UB is acknowledged.

REFERENCES

1. A. R. Forrester, J. M. Hay and R. H. Thomson, "Organic chemistry of stable free radicals", Academic Press, London, 1968.
2. P. Ionita, *Int. J. Molec. Struct*., **2021**, *22*, art. no. 1545.
3. M. C. Foti, *J. Agric. Food Chem*., **2015**, *63*, 8765–8776.
4. K. H. Musa, A. Abdullah, B. Kuswandi and M. A. Hidayat, *Food Chem*., **2013**, *141*, 4102–4106.
5. Z. Akara, *J. Enzyme Inhib. Med. Chem*., **2017**, *32*, 640–647.
6. P. Ionita, *Lett. Org. Chem*., **2008,** *5*, 42–46.
7. T. Constantinescu, M. T. Caproiu, N. Zarna, A. Caragheorgheopol, H. Caldararu, G. Stanciuc, M. Radu, V. Badescu and A. T. Balaban, *New J. Chem*., **1997**, *21*, 575–579.
8. I. C. Covaci, T. Constantinescu, M. T. Caproiu, H. Caldararu, P. Ionita and A. T. Balaban, *Pol. J. Chem.*, **2001**, *75*, 1427–1440.
9. A. T. Balaban, T. Constantinescu, M. T. Caproiu, M. Giorgi and T. S. Balaban, *Z. Naturforsch. B*, **2017**, *72*, 89–94.
10. P. Ionita, M. T. Caproiu and A. T. Balaban, *Rev. Roum. Chim*., **2000**, *45*, 935–941.
11. A. Bujor, A. Hanganu, V. Tecuceanu, A. M. Madalan, M. Tudose, L. Marutescu, M. Popa, C. M. Chifiriuc, I. Zarafu and P. Ionita, *Antioxidants*, **2023**, *12*, art. no. 713.