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Electron transfer-induced oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones

DOI 10.1515/znb-2016-0260
Received December 4, 2016; accepted February 15, 2017

Abstract: A series of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones were oxidized to quinazolin-4(3*H*)-ones using tetrabutylammonium peroxydisulfate. The rate and the outcome of the reaction are dependent on the type and nature of 2-substitution. An electron transfer mechanism is proposed for this study, which is supported by the retention or elimination of 2-substitution during the oxidation process.

Keywords: dihydroquinazolines; oxidation; peroxydisulfates; quinazolines.

1 Introduction

Quinazolin-4-ones are a class of heterocyclic compounds having a fused benzene and pyrimidine rings with the carbonyl group as a part of the heterocyclic ring. 2,3-Dihydroquinazolin-4(1*H*)-ones (DHQZs) and their dehydrogenated derivatives, namely, quinazolin-4(3*H*)-ones (QZs), belong to this family. These compounds exhibit a wide range of pharmaceutical and biological activities such as anticancer [1], antibacterial [2, 3], antimalarial [4], antihypertensive [5], antifungal [6] and anticonvulsant [7]. Thermal oxidation of DHQZs to their corresponding QZs has been reported using $KMnO_4$ [8] and tetrabutylammonium bromide/$CuCl_2$ [9], but the results of many studies concerning the synthesis of these heterocyclic compounds revealed that QZs are prepared as final reaction products during the synthesis of DHQZs. For the latter case, gallium(III) triflate [10], molecular iodine [11], thiamine hydrochloride [12] and bismuth trinitrate [13] have been used for this transformation.

The peroxydisulfate ion is one of the strongest oxidizing agents known in aqueous solution with a redox potential of –2.01 V [14]. The oxidative application of peroxydisulfate ion in organic synthesis has been widely investigated [15]. Tetrabutylammonium peroxydisulfate (TBAPS) belongs to this family and its applications for various organic transformations have been reported [16, 17]. We have earlier used potassium peroxydisulfate ($K_2S_2O_8$, PPS) as an efficient oxidizing agent for the oxidation of a series of 1,4-dihydropyridines [18] and various 2-oxo-1,2,3,4-tetrahyropyrimidines under different reaction conditions in acetonitrile/water solution [19–21]. In further studies, we investigated the oxidation of 2-oxo-1,2,3,4-tetrahyropyrimidine-5-carboxamides using TBAPS under thermal and sono-thermal conditions [22]. The results of these oxidative studies revealed that the oxidation of the heterocyclic compounds considered in these works by PPS occurred by the hydrogen abstraction from the C-4 position of the heterocyclic ring via *in situ* formed hydroxyl radical [19], whereas by using TBAPS an electron transfer-induced mechanism is proposed for the oxidative reaction (Scheme 1) [22].

In continuation to this work, we were interested in using TBAPS for the oxidation of various DHQZs to elucidate the effect of the electronic nature of 2-substitution on the rate of reaction and also possible confirmation of the earlier reported reaction mechanism using a suitable substituent on the C-2 position of the heterocyclic ring.

2 Results and discussion

In order to obtain the optimized oxidation condition, the reaction of **1a** as a model substrate in the presence of various ratios of **1a**:TBAPS in dry acetonitrile was carried out at 70°C until total disappearance of **1a** occurred (as monitored by thin-layer chromatography). The results presented in Table 1 indicate that total conversion of **1a** to **2a** was achieved by taking the ratio of 1:1.5 for **1a**:TBAPS.

In optimized reaction conditions, the oxidation of 2-substituted DHQZs (**1a–k**) by TBAPS in dry acetonitrile under thermal conditions was carried out until total disappearance of DHQZs (Scheme 2). The results are summarized in Table 2.

The characterization of the products **2a–k** and **3** was achieved by the comparison of their IR, ^{1}H NMR and UV data with those of the starting materials **1a–k** as follows:

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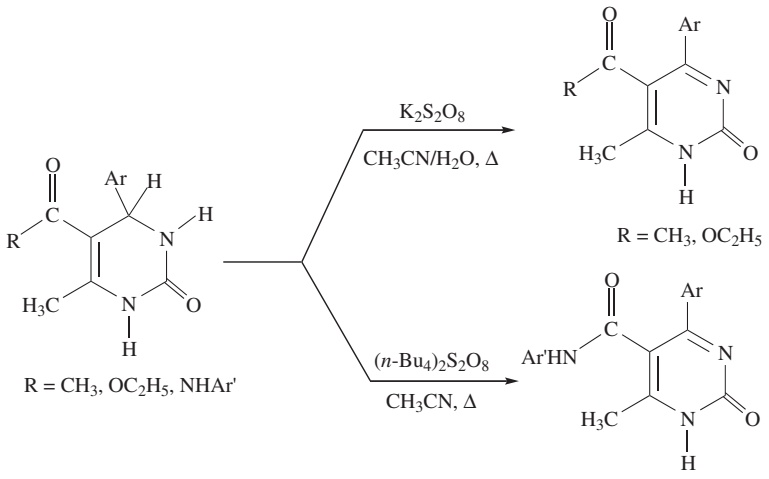


Scheme 1: Thermal oxidation of 2-oxo-1,3,4-tetrahydropyrimidines.

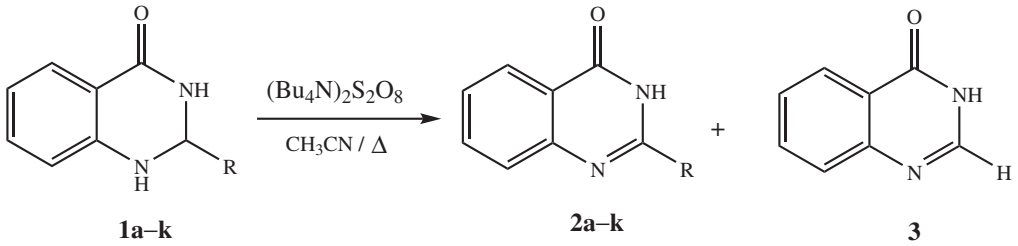
1. A comparison of the IR spectra of the products with those of the starting materials showed a decrease in the intensity of the NH vibration with a small shift to lower frequency. Due to the oxidation of the heterocyclic ring and diminished delocalization of the lone pair on the N-3 atom (cross conjugation), the carbonyl stretching is shifted to higher frequency.
2. A comparison of the ^{1}H NMR spectra of **2a–k** with those of **1a–k** showed the lack of the 1-NH and 2-CH resonances and a simultaneous shift of the 3-NH resonance to a lower field due to aromatization of the heterocyclic ring. But in the case of compound **3**, the lack of the 1-NH resonance and the characteristic peaks of the phenylethyl group are observed upon the oxidative dealkylation process.
3. A comparison of the UV spectra showed a hypsochromic shift in the UV spectra of **2a–k** due to the oxidation of the heterocyclic ring and formation of a semi-aromatic benzo-condensed pyrimidinone ring, which displays in the observed hyperchromic effect (increased absorption intensity) in the aromatic region. In the case of compound **3**, which is formed by the oxidative dealkylation process, the absorption intensity is lower than the corresponding substituted compound **2k**. The UV spectra of the latter observations are presented in Fig. 1.

Table 1: Optimization of the **1a**: TBAPS molar ratio for the oxidation reaction in refluxing dry acetonitrile.

Entry	1a:TBAPS	Time (min)
1	1:1	90[a]
2	1:1.5	30
3	1:1.7	25
4	1:2	15

[a]The reaction is not completed.

The results presented in Table 2 indicate that the type of the substituent located on the C-2 position of the heterocyclic ring, especially the nature of the additional substituent on the phenyl ring, affects the rate and outcome of the reaction. Whereas electron-releasing substituents such as methoxy, dimethylamino or methyl groups facilitate the oxidation process, electron-withdrawing substituents such as nitro group increase the time of reaction. Interesting results are obtained by the location of the



Scheme 2: Oxidation of 2,3-dihydroquinazolin-4(1*H*)-ones by tetrabutylammonium peroxydisulfate.

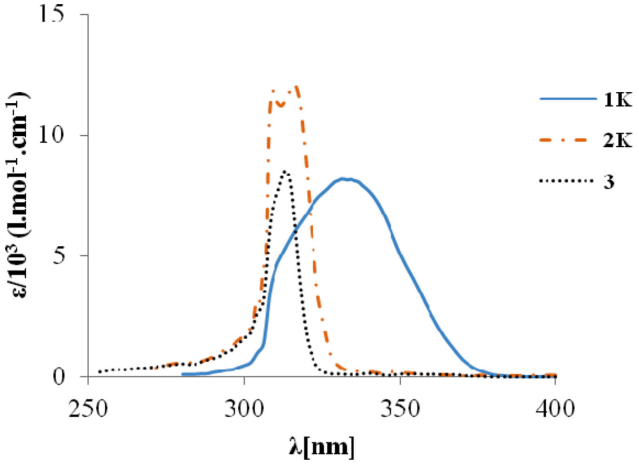


Fig. 1: Comparison of the UV spectra of **1k** with those of the corresponding non-dealkylated and dealkylated oxidation products, **2k** and **3**, respectively in chloroform.

Table 2: Oxidation of DHQZs (**1a–k**) by TBAPS under thermal conditions to QZs (**2a–k**) and **3**.[a]

Comp.	R	Product	R	Time (min)[b]
1a	C_6H_5-	**2a**	C_6H_5-	30
1b	4-$NO_2C_6H_4$-	**2b**	4-$NO_2C_6H_4$-	40
1c	3-$NO_2C_6H_4$-	**2c**	3-$NO_2C_6H_4$-	45
1d	2-$NO_2C_6H_4$-	**2d**	2-$NO_2C_6H_4$-	50
1e	4-$CH_3OC_6H_4$-	**2e**	4-$CH_3OC_6H_4$-	25
1f	3-$CH_3OC_6H_4$-	**2f**	3-$CH_3OC_6H_4$-	20
1g	2-$CH_3OC_6H_4$-	**2g**	2-$CH_3OC_6H_4$-	20
1h	4-ClC_6H_4-	**2h**	4-ClC_6H_4-	40
1i	4-$CH_3C_6H_4$-	**2i**	4-$CH_3C_6H_4$-	25
1j	4-$(CH_3)_2NC_6H_4$-	**2j**	4-$(CH_3)_2NC_6H_4$-	45
1k	$Ph(CH_3)CH$-	**2k**	$Ph(CH_3)CH$-	20
		3	H	

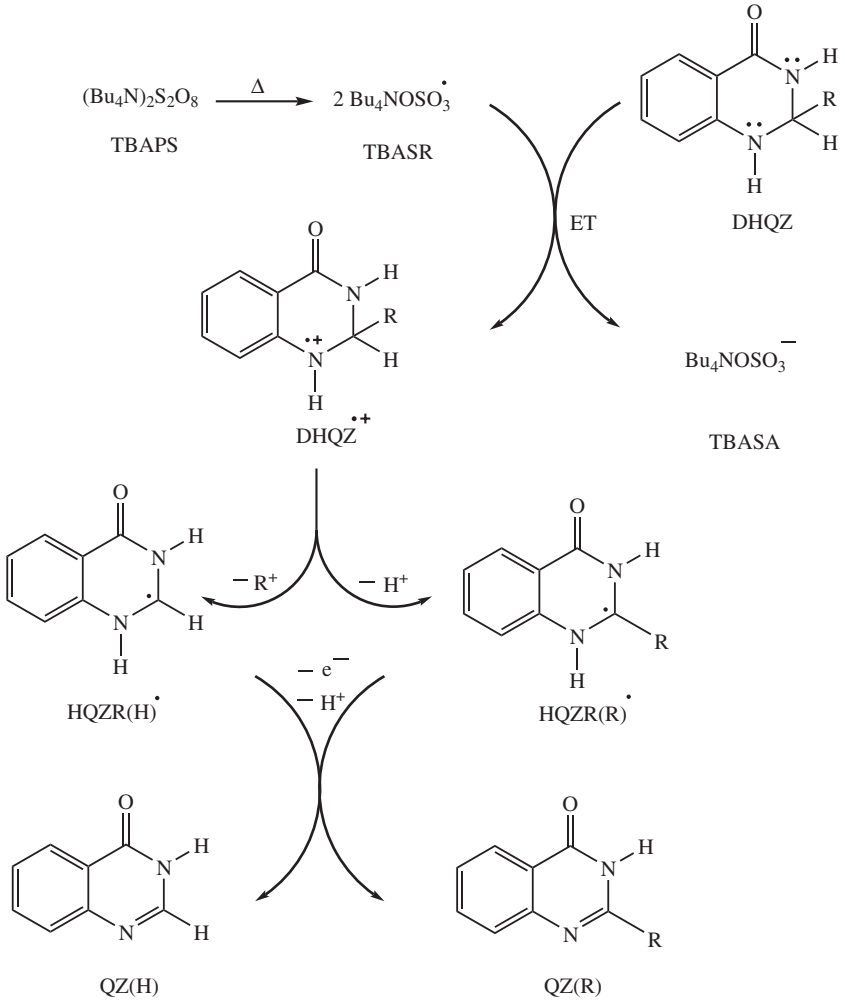
[a]0.115 mmol DHQZs, 0.172 mmol TBAPS in 2.5 mL dry CH_3CN at 70°C.
[b]Times are given after total disappearance of DHQZs.

secondary alkyl group at the C-2 position (**1k**). In this case, non-dealkylated **2k** and dealkylated **3** compounds are observed. These observations are explained as follows.

Recently, we have reported the oxidation of various substituted 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides [22] by TBAPS and also photo-oxidation of DHQZs (the title compounds) in chloroform solution by exposure to the UV light [23]. The results of these studies support the mechanism based on the *electron transfer-induced oxidation* of organic compounds, which starts by the electron transfer from the molecule either in the ground state (thermal oxidation, first study) or in the excited state (photo-oxidation, latter case) to the suitable electron acceptor species present in the reaction vessel. Based on the proposed mechanism in the first study (Scheme 3), the application of heat causes the homolytic cleavage of the weakest O–O bond in the peroxydisulfate ion and formation of tetrabutylammonium sulfate radical (TBASR). Since TBASR is so voluminous to abstract the hydrogen atom from the C-2 position in the heterocyclic ring of DHQZs and starting the oxidative process, an electron transfer process is occurred from a suitable electron-donor position in the molecule to TBASR. Two potential electron-donor positions, N-1 and N-3 atoms, are available for donation of an electron to the TBASR species under formation of 2,3-dihydroquinazolin-4(1*H*)-one radical cation ($DHQZ^{\cdot+}$) and tetrabutylammonium sulfate anion ($Bu_4NOSO_3^-$, TBASA). It seems that the electron pair on the N-1 atom is more readily transferred to the electron-acceptor species rather than the electron pair on the N-3 atom. The reasons of this suggestion and preferred electron donation from N-1 atom are that (i) the electron pair on the N-3 atom is delocalized towards the 4-CO group as a part of the amide group, and (ii) the radical cation formed on the N-1 atom after the first electron removal is stabilized by delocalization of the radical center over the condensed benzene ring. In contrast to this, the radical cation formed on the N-3 atom is destabilized by the attachment of this atom to the 4-CO group. Both these arguments are also supported by the results obtained in our earlier study [23]. The occurrence of the positive charge on the N-1 atom in the $DHQZ(N_1)^{+}$ species forces the molecule to eject a proton, as a competitive way to the back electron transfer process (BET), resulting in the formation of stable benzylic and also donor substituted radical, namely, hydroquinazolinyl radical ($HQZR^{\cdot}$). In the case of **2k**, containing a simultaneous secondary alkyl and benzylic group on the 2-position, exclusion of this group as a stable benzylic cation under the formation of hydroquinazolinyl radical $HQZR(H)^{\cdot}$ is also possible. Further electron removal and proton detachment from both $HQZR(R)^{\cdot}$ and $HQZR(H)^{\cdot}$ species accomplish these processes under the formation of the reaction products (QZs) **2a–k** and **3**. The expulsion of the benzylic and secondary alkyl substituents in the latter proposal is supported by the result obtained on the elimination of the *tert*-butyl group upon oxidative photo-elimination of 2-*tert*-butyl substituted DHQZ [24] and also on the thermal oxidation of 1,4-dihydropyridines [25].

3 Conclusion

Various 2-substituted DHQZs were synthesized and thermal oxidation of these compounds to QZs was studied using TBAPS. An electron transfer mechanism is proposed for this oxidative reaction. The rate and outcome of the reaction are dependent on the nature and type of 2-substitution.



Scheme 3: The mechanism of oxidation of 2-substituted DHQZs using $(Bu_4N)_2S_2O_8$.

4 Experimental section

Melting points were determined on a Stuart Scientific SMP2 apparatus and are not corrected. IR spectra were recorded from KBr disks on a Jasco FT/IR-6300 spectrometer. The ^1H and ^{13}C NMR spectra ([D_6]DMSO) were recorded on Bruker Avance III 400 spectrometers at 400.13 and 100.62 MHz. UV spectra were taken in $CHCl_3$ with a Shimadzu UV-160 spectrometer.

4.1 General procedure for the oxidation of DHQZs by TBAPS

A mixture of 2-substituted DHQZs (**1a–k**, 1 mmol), $(Bu_4N)_2S_2O_8$ (1.5 mmol) in 2.5 mL dry acetonitrile was stirred at 70°C for some specific times (Table 2). After completion of the reaction, the solvent was evaporated and the mixture was extracted with chloroform/water. The organic layer was dried over $MgSO_4$. After evaporation of solvent, the residue was recrystallized from ethanol. The physical and spectroscopic data of the new compounds are reported below.

4.1.1 2-(3-Methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1f)

M.p. 150–153°C, recrystallized from *n*-hexane-ethyl acetate. – IR: $\nu = 3292$, 3192, 1646, 1611, 1490, 1255, 775, 748 cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]DMSO): $\delta = 3.75$ (s, 3 H, OCH_3), 5.72 (s, 1 H, C2-H), 6.67 (m, 1 H, aromatic H), 6.75 (d, $J = 8.4$ Hz, 1 H, aromatic H), 6.91 (dd, $J = 8.4$ Hz, 2 Hz, 1 H, aromatic H), 7.06 (m, 2 H, aromatic H), 7.13 (s, 1 H, N1-H), 7.23–7.32 (m, 2 H, aromatic H), 7.61 (d, $J = 7.2$ Hz, 1 H, aromatic H), 8.31 ppm (s, 1 H, CONH). – ^{13}C NMR (100.62 MHz, [D_6]DMSO): $\delta = 55.05$ (OCH_3), 66.17 (C-2), 112.52, 113.64,

114.34, 114.94, 117.08, 118.89, 127.29, 129.39, 133.27, 143.28, 147.76, 159.17, 163.52 ppm. – UV ($CHCl_3$): $\lambda_{max}(\log \varepsilon) = 332$ nm (3.97).

4.1.2 2-(2-Phenylethyl)-2,3-dihydroquinazolin-4(1*H*)-one (1k)

M.p. 170–173°C, recrystallized from ethanol. – IR: $\nu = 3317$, 3228, 3060, 3031, 1644, 1610, 1508, 1486, 1393, 1153, 757, 700 cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]DMSO): $\delta = 1.26$ (d, $J = 7.2$ Hz, 3 H, CH_3), 3.04 (m, 1 H, C*H), 4.80 (m, 1 H, C2-H), 6.58 (m, 1 H, aromatic H), 6.69 (s, 1 H, N1-H), 6.74 (d, J =8.4 Hz, 1 H, aromatic H), 7.17–7.21 (m, 2 H, aromatic H), 7.24–7.30 (m, 4 H, aromatic H), 7.49 (dd, $J = 7.6$ Hz, 1.2 Hz, 1 H, aromatic H), 7.65 ppm (d, $J = 2.4$ Hz, 1 H, CONH). – ^{13}C NMR (100.62 MHz, [D_6]DMSO): $\delta = 15.83$ (CH_3), 44.51, 68.63 (C-2), 114.08, 114.67, 116.46, 126.38, 127.07, 128.03, 128.46, 133.03, 141.43, 147.49, 163.14 ppm. – UV ($CHCl_3$): $\lambda_{max}(\log \varepsilon) = 354$ nm (sh, 3.61), 334 (3.91).

4.1.3 2-(3-Methoxyphenyl)-quinazolin-4(3*H*)-one (2f)

M.p. 204–206°C, recrystallized from ethanol. – IR: $\nu = 3038$, 2882, 1673, 1608, 1584, 1473, 1222, 1044, 854, 768 cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]DMSO): $\delta = 3.87$ (s, 3 H, OCH_3), 7.14–7.17 (qd, $J = 2.6$ Hz, 0.8 Hz, 1 H, aromatic H), 7.45–7.49 (m, 1 H, aromatic H), 7.52–7.56 (m, 1 H, aromatic H), 7.75–7.77 (m, 1 H, aromatic H), 7.79–7.81 (m, 2 H, aromatic H), 7.83–7.87 (m, 1 H, aromatic H), 8.15–8.17 (dd, $J = 7.6$ Hz, 1.2 Hz, 1 H, aromatic H), 12.56 ppm (s, 1 H, CONH). – ^{13}C NMR (100.62 MHz, [D_6] DMSO): $\delta = 55.36$ (OCH_3), 112.49, 117.59, 120.09, 125.82, 126.62, 127.51, 129.73, 134.61, 159.32 ppm. – UV ($CHCl_3$): $\lambda_{max}(\log \varepsilon) = 315$ nm (4.34).

4.1.4 2-(2-Phenylethyl)-quinazolin-4(3*H*)-one (2k)

M.p. 217–220°C, recrystallized from *n*-hexane-ethyl acetate. – IR: $\nu = 2987$, 2850, 1677, 1610, 1465, 1339, 1246, 878, 769 cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]DMSO): $\delta = 1.61$ (d, $J = 6.8$ Hz, 3 H, CH_3), 4.12 (q, $J = 6.8$ Hz, 1 H, benzylic H), 7.21–7.25 (m, 1 H, aromatic H), 7.28–7.34 (m, 3 H, aromatic H), 7.39–7.41 (m, 1 H, aromatic H), 7.46–7.50 (m, 1 H, aromatic H), 7.68 (d, $J = 8.4$ Hz, 1 H, aromatic H), 7.78–7.82 (m, 1 H, aromatic H), 8.07 (d, $J = 8$ Hz, 1 H, aromatic H), 12.26 ppm (s, 1 H, CONH). – ^{13}C NMR (100.62 MHz, [D_6] DMSO): $\delta = 19.28$, 46.15, 125.66, 125.99, 126.24, 126.86, 127.15, 127.38, 128.24, 128.47, 134.38 ppm. – UV ($CHCl_3$): $\lambda_{max}(\log \varepsilon) = 316$ nm (4.08), 309 (4.07).

4.1.5 Quinazolin-4(3*H*)-one or 4-Hydroxyquinazoline (3)

M.p. 211–215°C, recrystallized from *n*-hexane-ethyl acetate. – IR: $\nu = 3203$, 3130, 2929, 1697, 1659, 1609, 1468, 1325, 1172, 917 cm^{-1}. – ^1H NMR (400.13 MHz, [D_6]DMSO): $\delta = 7.51$–7.55 (m, 1 H, aromatic H), 7.66–7.69 (m, 1 H, aromatic H), 7.80–7.85 (m, 1 H, aromatic H), 8.10–8.14 (m, 2 H, C2-H and aromatic H), 12.25 ppm (s, 1 H, CONH). – ^{13}C NMR (100.62 MHz, [D_6]DMSO): $\delta = 122.58$, 125.79, 126.73, 127.21, 134.31, 145.34, 148.73 ppm. – UV ($CHCl_3$): $\lambda_{max}(\log \varepsilon) = 313$ nm (3.93).

5 Supplementary information

IR, ^1H NMR, ^{13}C NMR and UV spectra of **1f**, **1k**, **2f**, **2k** and **3** are given as supporting information available online (DOI: 10.1515/znb-2016-0260).

Acknowledgments: We are thankful to the Research Council and Office of Graduate Studies of the University of Isfahan for their financial support.

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Supplemental Material: The online version of this article (DOI: 10.1515/znb-2016-0260) offers supplementary material, available to authorized users.

Graphical synopsis

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DOI 10.1515/znb-2016-0260
Z. Naturforsch. 2017; x(x)b: xxx–xxx