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Aust. J. Chem.
http://dx.doi.org/10.1071/CH16101

Full Paper

Capto-Dative Stabilization by Thermal Oxidation of 2-Oxo-1,2,3,4-tetrahydropyrimidines*

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Various 4,6-diaryl substituted 2-oxo-1,2,3,4-tetrahydropyrimidines (THPMs) were oxidized to 2-oxo-1,2-dihydropyrimidines (DHPMs) by potassium peroxydisulfate (PPS) in aqueous acetonitrile solution under thermal conditions. Based on the proposed oxidation reaction mechanism by way of a radical, a *capto-dative* stabilized radical intermediate, among two possible formed double benzylic/allylic radical centres, governs the type of product formed. Whereas the electron-donating nature of the additional methoxy-substituent enhances the rate of oxidation, its attachment to the radical intermediate decreases the radical stability, simultaneously causing the shift of the radical centre to the *capto-dative* stabilized benzylic radical centre. The data of the density functional theory computational studies concerning the bond lengths to the radical centres and Mulliken population analysis support the results of the experimental work.

Manuscript received: 21 February 2016.
Manuscript accepted: 22 February 2016.
Published online: 23 March 2016.

Introduction

2-Oxo-1,2,3,4-tertahydropyrimidines (THPMs) or dihydropyrimidinones, also known as Biginelli compounds,[1] and the corresponding oxidized derivatives, namely 2-oxo-1,2-dihydropyrimidines (DHPMs) or 2-pyrimidinones, display various biological and pharmacological activities.[2–6] 5-Unsubstituted THPMs, known as Biginelli-like compounds, and the corresponding dehydro-compounds also exhibit pharmacological activities.[7,8] In contrast to various methods for the synthesis of 5-substituted THPMs,[9] there are few reports on the synthesis of 5-unsubstituted THPMs. These compounds are normally synthesized via a one-pot cyclo-condensation of an aldehyde, an enolizable carbonyl compound, and urea or thiourea in the presence of a suitable catalyst,[10] or they are obtained by condensation of urea or thiourea with chalcones.[11]

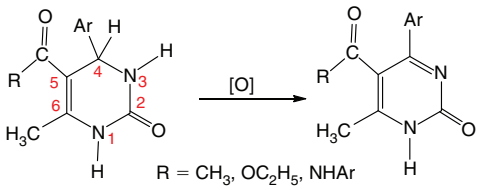
The readily available peroxydisulfate ion ($S_2O_8^{2-}$) alone or in the presence of a metal ion co-catalyst is an excellent and versatile oxidizing agent of a variety of organic and inorganic compounds.[12–15] Thermal or photochemical O–O bond cleavage of this ion leads to the formation of two sulfate radical ions, which are able to abstract hydrogen or to accept an electron from a hydrogen-donating molecule or electron-donating species, respectively, present in the medium.[16–18]

In the course of our studies concerning the chemistry of THPMs, we have investigated the steric and electronic effects of the substituent at the 4- (various aryl groups) and 5-positions (5-acetyl, 5-carboethoxy, and 5-carboxamide groups) of the heterocyclic ring on the rate of thermal oxidation,[19–21] photooxidation,[22–24] and voltammetric studies (Scheme 1).[25,26] The results of these studies indicate that the electronic nature of the 4-substituent has more effect on the rate of oxidative processes compared with those of the 5-substituent.

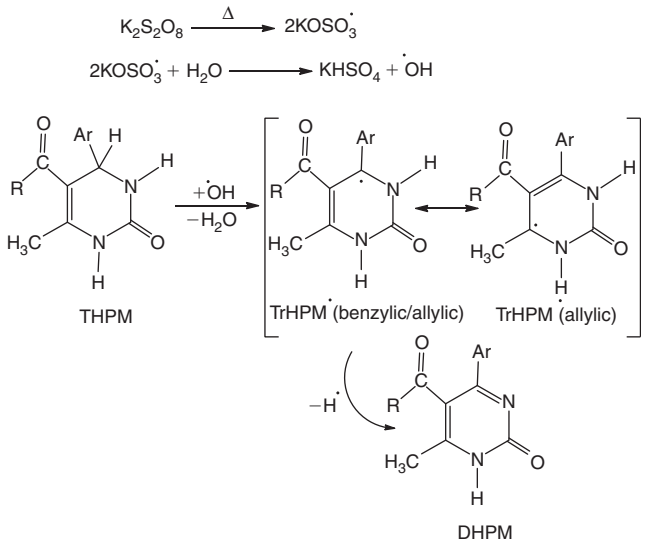
Based on the proposed mechanism for the thermal oxidation of 5-carboethoxy- and 5-acetyl-THPMs by potassium peroxydisulfate (PPS) in aqueous acetonitrile solution,[19,20] the hydrogen attached to the C_4-atom of the heterocyclic ring is removed in the rate determining step by an in situ formed hydroxyl radical. This hydrogen removal process results in the formation of benzylic- and allylic-radical intermediates, namely, the trihydropyrimidinyl radical (TrHPM$^{\bullet}$). Owing to the greater stability of the benzylic radical intermediate, further removal of a second hydrogen atom from the 3-NH position results in the formation of DHPMs (Scheme 2). Introducing the hydroxyl radical as an active species in the oxidation reactions by PPS is also supported by the oxidation of folic acid[15] or hydroxymethylation of quinoxalines in methanol,[16] known as the Minisci reaction.

In continuation to these works, we extended our investigations on 5-unsubstituted THPMs, in which two different aryl groups are located at the 4- and 6-positions of the heterocyclic ring. It is expected that in the new system involving these 4,6-diaryl-THPMs, due to the absence of any substitution at the 5-position: i) the steric hindrance caused by the substituent in 5-substituted THPMs is omitted and ii) the presence of the aryl

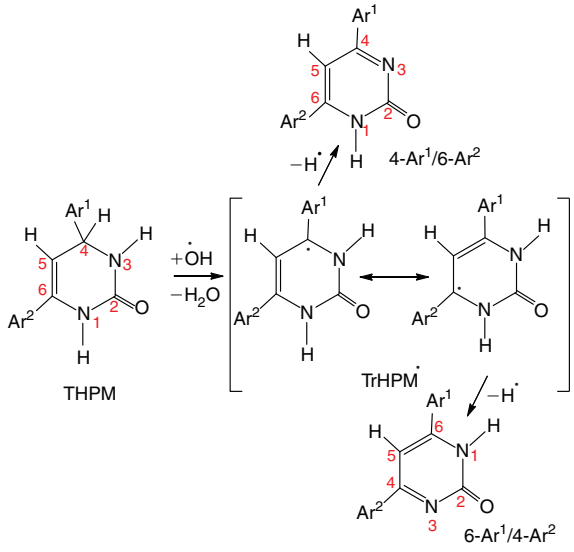
*Dedicated to Professor Dr Dietrich Döpp, University of Duisburg-Essen, Germany, on the occasion of his 80th birthday.



Scheme 1. 2-Oxo-1,2,3,4-tetrahydropyrimidines.



Scheme 2. Benzylic/allylic and allylic radical intermediates involved in the oxidative process.



Scheme 3. Involvement of two different benzylic/allylic radical intermediates in the oxidative process.

group instead of a CH_3 group on the 6-position should influence the electron density of the heterocyclic ring, depending on the electronic nature of the additional substitutent on the aryl rings. Therefore, the oxidation of the new compounds by PPS should pass through two different benzylic/allylic radical intermediates, which may result in the formation of two different DHPMs, namely 4-Ar^1/6-Ar^2 and/or 6-Ar^1/4-Ar^2 (Scheme 3).

Results and Discussion

Under optimized reaction conditions a mixture of 0.23 mmol of **1a**–**g** and 0.23 mmol $K_2S_2O_8$ (mol ratio 1 : 1) in 6 mL of CH_3CN/H_2O (5/1) was reacted in a preheated oil bath at 80°C. The progress of the reaction was followed by TLC until total disappearance of **1a**–**g** (Scheme 4). The results are presented in Table 1.

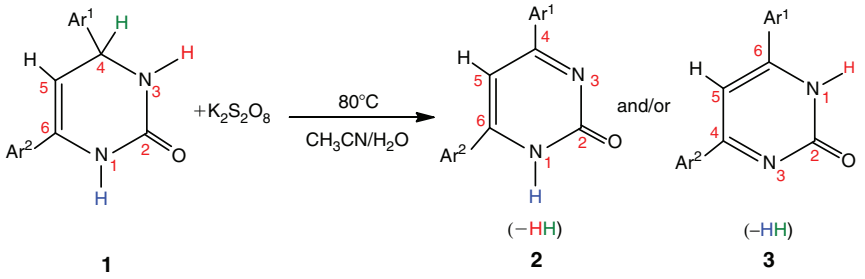
The results presented in Table 1 indicate that by oxidation of the parent molecule **1a** and removal of two hydrogens, the compound **2a** (4-Ph/6-Ph, the same as **3a**) is formed. While for the oxidation of **1b**–**g** with a methoxy group at the *ortho-, meta-*, or *para*-positions of the 4- or 6-aryl rings, independent of the location of the substituted aryl ring, either at the 4- or at the 6-position of the heterocyclic ring, a sole product with the methoxy-substituted aryl ring attached to the C-atom of the heterocyclic ring neighbouring the NH moiety is formed. This was confirmed by the observation of the same IR, ^{1}H NMR, ^{13}C NMR, and UV spectra of the products **3b**, **3c**, and **3d** formed by the oxidation of **1b** or **1e**, **1c** or **1f**, and **1d** or **1g**, respectively (the spectra are presented in the Supplementary Material). The characterization of the products **2a** and **3b**–**d** was achieved by comparison of their IR, ^{1}H NMR, ^{13}C NMR, and UV data with those of the starting materials **1a**–**g** as follows:

1. A comparison of the IR spectra 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 formation of a semi-aromatic heterocyclic ring, the carbonyl stretching is shifted to higher frequency.
2. A comparison of the ^{1}H NMR spectra with those of the starting materials **1a**–**g** showed the lack of the resonances of 4-CH and one of the NH protons and simultaneous shift of another NH resonance to lower field due to oxidation of the heterocyclic ring.
3. A comparison of the ^{13}C NMR spectra showed an increase of peaks in the aromatic region.
4. A comparison of the UV spectra (Table 2) showed a bathochromic shift in the UV spectra of the products due to oxidation of the heterocyclic ring and formation of the amino conjugated dienone system.

Mechanistic Studies

Since monitoring by TLC is not a confident way to explain the electronic effect of the substituent at the 4- or 6-positions of the heterocyclic ring on the rate of reaction, especially in the case of reactions having short reaction times (the present study), the reactions of **1b** and **1e** with a *p*-methoxyphenyl substituent at the 4- and 6-position of the heterocyclic ring, respectively, were followed by UV spectroscopy. The slopes in the extinction versus time diagrams (ET diagrams)[27] at 380 nm for these compounds (Fig. 1) derived from their UV reaction spectra indicate that compound **1b** has a comparatively higher reaction rate constant (7.2×10^{-3} mol L^{-1} s^{-1}) than **1e** (6.0×10^{-3} mol L^{-1} s^{-1}). These data are supported by the observed experimental reaction times of 15 and 20 min for the total disappearance of **1b** and **1e**, respectively.

The observed electronic effect in the shortening of the reaction time for total disappearance of **1b** compared with that of **1e** by PPS in the present study can be explained by considering the reaction mechanism presented in Schemes 2 and 3. Based on the proposed mechanism, hydrogen removal from the 4-position of the heterocyclic ring in the rate determining step results in the



Scheme 4. Oxidation of 4,6-diaryl-2-oxo-1,2,3,4-tetrahydropyrimidines.

Table 1. Oxidation of 4,6-diaryl-THPMs (1a–g) by PPS under thermal conditions to 2-oxo-1,2-dihydropyrimidines (DHPMs)[A]

THPM	Ar^1	Ar^2	DHPM	Ar^1	Ar^2	Time[B] [min]	Yield[C] [%]
1a	C_6H_5	C_6H_5	**2a**	C_6H_5	C_6H_5	40	78
1b	4-$CH_3OC_6H_4$	C_6H_5	**3b**	4-$CH_3OC_6H_4$	C_6H_5	15	82
1c	3-$CH_3OC_6H_4$	C_6H_5	**3c**	3-$CH_3OC_6H_4$	C_6H_5	15	77
1d	2-$CH_3OC_6H_4$	C_6H_5	**3d**	2-$CH_3OC_6H_4$	C_6H_5	26	87
1e	C_6H_5	4-$CH_3OC_6H_4$	**3b**	4-$CH_3OC_6H_4$	C_6H_5	20	81
1f	C_6H_5	3-$CH_3OC_6H_4$	**3c**	3-$CH_3OC_6H_4$	C_6H_5	15	62
1g	C_6H_5	2-$CH_3OC_6H_4$	**3d**	2-$CH_3OC_6H_4$	C_6H_5	21	88

[A]0.23 mmol THPMs, 0.23 mmol PPS in 6 mL CH_3CN/H_2O at 80°C.
[B]Times are given after total disappearance of THPMs.
[C]Isolated yield after recrystallization.

Table 2. Comparison of the UV-absorption (λ_{max}, nm) of 1a–g with those of the products in chloroform solution

THPM	λ_{max} (log ε)	DHPM	λ_{max} (log ε)
1a	350 (sh, 2.56), 278.8 (3.77), 246 (3.90)	**2a**	360 (sh, 3.78), 346.2 (3.92), 280.2 (4.00), 263.4 (3.95), 253.4 (3.97)
1b	355 (sh, 2.53), 279.4 (3.80), 243.6 (3.79)	**3b**	360 (4.07), 346.2 (4.15), 290 (sh, 3.97), 248.2 (4.05)
1c	300 (sh, 3.27), 283.2 (3.58), 245 (3.81)	**3c**	375 (sh, 3.81), 356.5 (4.05), 330 (4.03), 298 (4.04), 257 (4.04)
1d	300 (sh, 3.29), 275 (3.76), 245 (3.24)	**3d**	380 (sh, 3.88), 361.5 (4.06), 336 (4.00), 300 (sh, 3.89), 257 (3.99)
1e	355 (sh, 2.78), 280.6 (3.74), 245.4 (3.80)	**3b**[A]	360 (4.04), 346.2 (4.18), 290 (sh, 3.97), 249.6 (4.04)
1f	335 (sh, 2.04), 277.2 (3.71), 250 (3.22)	**3c**[B]	375 (sh, 3.78), 354.5 (4.03), 330.5 (4.01), 297.5 (3.99), 257.5 (4.00)
1g	300 (sh, 3.55), 281.4 (3.66), 250 (3.48)	**3d**[C]	380 (sh, 3.92), 363 (4.09), 335 (4.00), 300 (sh, 3.91), 257 (4.00)

[A]The product is obtained by oxidation of **1e**.
[B]The product is obtained by oxidation of **1f**.
[C]The product is obtained by oxidation of **1g**.

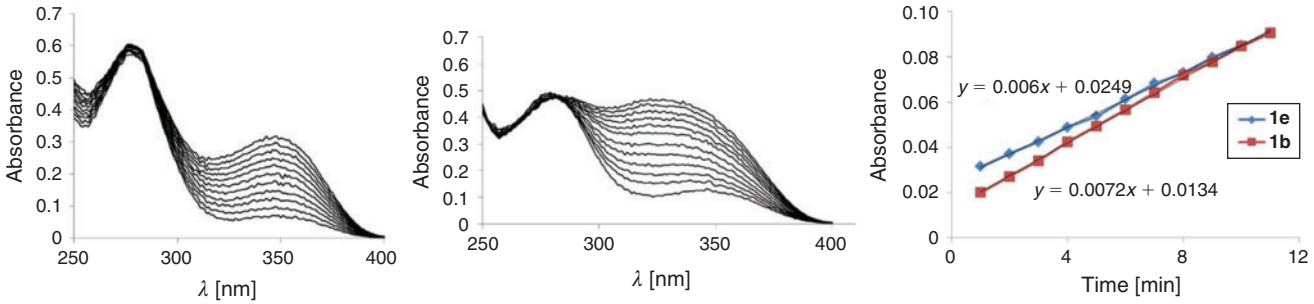
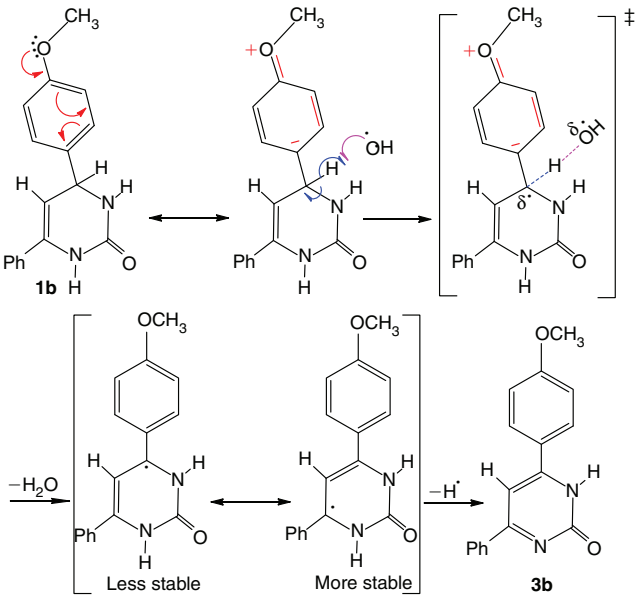


Fig. 1. Reaction spectra of thermal oxidation of **1b** (left) and **1e** (middle) by PPS in acetonitrile/water and the corresponding extinction time (ET) diagrams; Time interval 10 min.

formation of a double benzylic/allylic TrHPM$^{\bullet}$ intermediate. Further removal of the second hydrogen from this intermediate causes the formation of the DHPM molecules, namely, 4-Ar^1/6-Ar^2 and/or 6-Ar^1/4-Ar^2. The methoxy group at the *ortho*/*para*- or *meta*-position of the 4-aryl ring behaves as a σ-donor or σ-acceptor group due to the attachment of the 4-aryl ring with the sp^3 C-atom of the heterocyclic ring, respectively. While due to the conjugation of the 6-aryl ring with the C_6=C_5 double bond,



Scheme 5. Contribution of the oxygen lone pair to facilitate the 4-H removal by hydroxyl radical.

this group at the mentioned positions of the 6-aryl ring behaves as a π-donor or π-acceptor, respectively, if the 6-aryl ring can be orientated co-planar to the C_6=C_5 double bond of the heterocyclic ring. The balance of the negative inductive effects and the positive electron-pushing resonance effects of the methoxy group at the *para*-position of the phenyl ring at the C_4-position of the heterocyclic ring (compound **1b**), makes this substituent an electron-donating species. This causes an electron population on the aromatic carbon atom attached to the C_4-atom of the heterocyclic ring (Scheme 5). Therefore, as expected, the homolytic hydrogen removal from 4-CH by a hydroxyl radical in the rate determining step will be facilitated compared with that in compound **1a** containing the normal phenyl ring at this position. This is illustrated in Scheme 5.

Cyclic voltammetric measurements of compounds considered in the present study elucidate the steric and electronic effects of the methoxy substituent on the oxidation peak potentials (Table 3). A comparison of the measured oxidation peak potentials shows clearly that the location of the methoxy group at the right position (*para*-position, compound **1b**), which does not sterically hinder the conjugation of its lone pairs with the phenyl ring, facilitates the electron detachment process. In contrast to this observation, due to the steric hindrance of the lone pairs of this group at the 2-position (*ortho*-position, compound **1d**) to conjugate, the group's electron donation effect on the lowering of the oxidation peak potential is retarded. In this case only an upward orientation of the methyl group allows the lone pairs of the oxygen atom to conjugate with the phenyl ring. These data also explain why all methoxy-substituted THPMs (**1b**–**g**) are oxidized faster than the parent compound **1a**, which supports the obtained oxidation times in the experimental work.

The surprising results obtained in the present study are that the same products **3b**, **3c**, and **3d** are observed upon oxidation of **1b** or **1e**, **1c** or **1f**, and **1d** or **1g**, respectively. This can be explained by the influence of the electronic effect of the additional substituent on the electron-donating ability of the substituted aromatic ring and on the stability of the radical intermediate involved in this oxidative reaction. According to frontier molecular orbital (FMO) theory, the presence of an electron-donating substituent on the olefinic C=C double bond causes an increase of both HOMO and LUMO levels, while the connection of the C=C double bond with the electron-withdrawing groups decreases these levels.[28]

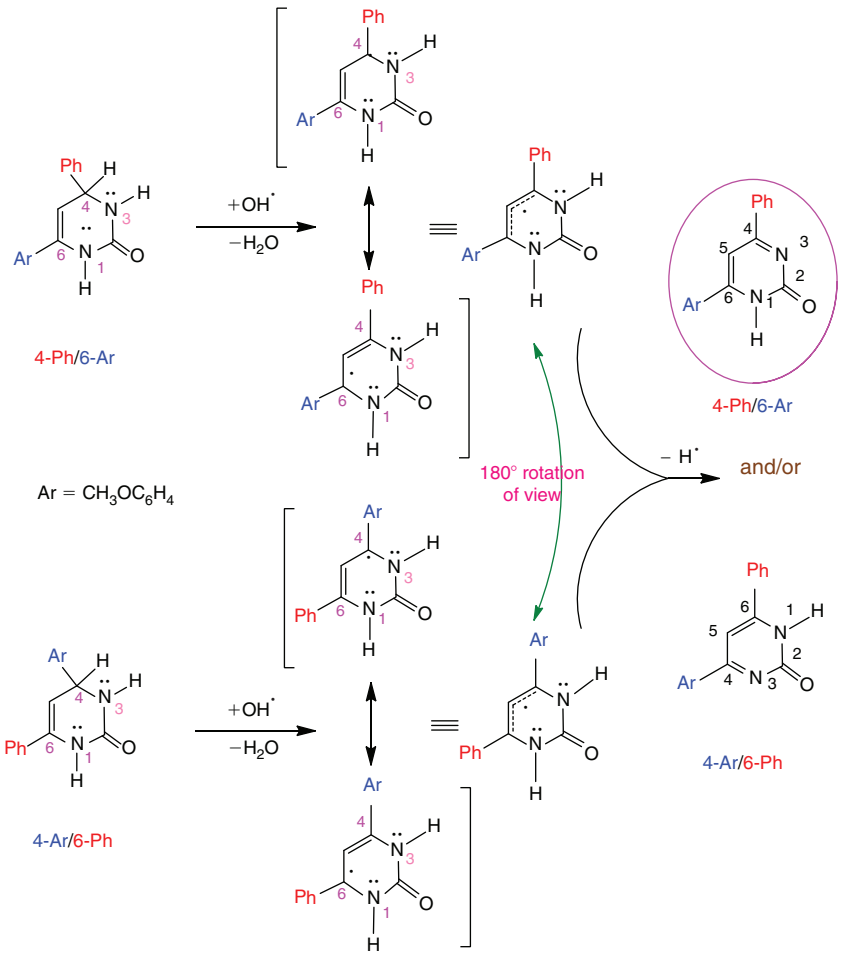
Table 3. The oxidation peak potential (E_p), versus ferrocene redox potential (0.583 V), obtained from cyclic voltammograms in acetonitrile for THPMs (1a–g)

Compound	E_p [V]
1a	1.274
1b	1.154
1c	1.204
1d	1.248
1e	1.165
1f	1.245
1g	1.181

Keeping these effects in mind, the stability of a radical centre is dependent on its possible interactions with the attached α-substituents. These interactions may be delocalization of the single electron over the attached conjugating π-system, hyperconjugation with the attached alkyl substituent, or interaction with the attached electron-withdrawing or electron-donating substituents.[29] Such interactions with α-substituents, which result in the stability of the radical centres, are rationalized in term of one-electron molecular orbital (OEMO) theory.[29]

The concept of *capto-dative* radical stabilization, in which the synergetic effect of the electron-donor (*dative*) and the electron-acceptor (*capto*) substituent on the same radical centre leads to an enhanced stabilization compared with that expected from the sum of the stabilization energies of the separate substituents, has been proposed by Viehe and co-workers.[30] The origin of this extra stabilization is easily explained using a perturbational molecular orbital (PMO) approach.[31] Simultaneous interaction of the singly occupied molecular orbital (SOMO) of the radical centre with the π-acceptor or π-donor results in the enhanced stability of this single electron.[32,33]

Based on the proposed mechanism, the hydrogen in the 4-position is removed by the in situ formed hydroxyl radical in the rate determining step under formation of the TrHPM$^{\bullet}$ intermediate. There are two types of substituted THPMs considered in the present study. In the first type (compounds **1b**, **1c**, and **1d**), the methoxy-substituted aryl ring is attached to the C_4-atom of the heterocyclic ring, whereas in the second type (compounds **1e**, **1f**, and **1g**), the substituted aryl ring is attached to the C_6-atom. Upon delocalization of the single electron in the two different TrHPM$^{\bullet}$ intermediates, the two double benzylic/allylic radicals are converted into each other (Scheme 6). Further removal of the second hydrogen atom from one of the N_1- or N_3-positions in these intermediates results in the formation of the final DHPM product, namely, 4-Ph/6-Ar or 4-Ar/6-Ph. The important decision factor in the second hydrogen removal is reasonably the stability of one of these radical intermediates as a more stable and preferred candidate involved in the second hydrogen removal process. In both these radical intermediates, the radical centre is attached to the nitrogen atom in the heterocyclic ring. Based on the mentioned OEMO theory,[29] the radical centre can be stabilized by interaction with the nitrogen lone pair, as an electron-donating substituent. The important point on increasing the stability of the radical centre is additional interaction either with the methoxy-substituted aryl ring, again as an electron-releasing substituent, or interaction



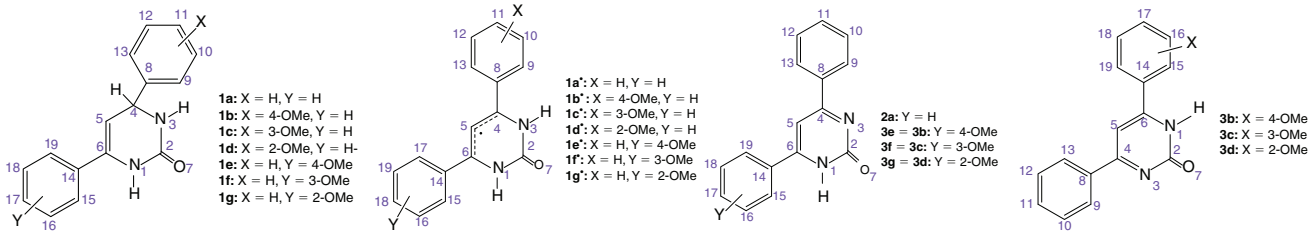
Scheme 6. Hydrogen abstraction by the hydroxyl radical leading to the possible formation of two different products.

with the phenyl ring, as an electron-withdrawing substituent. The concept of the *capto-dative* effect explains that the radical centre attached to the phenyl ring, as a *capto-dative* stabilized radical centre, is more stable than the other radical attached to the methoxy-substituted aryl ring.[32,33] This means that simultaneous interactions of the radical centre with the nitrogen lone pair (electron donor, *dative*) and the phenyl ring (electron acceptor, *capto*) support the suggestion that the *capto-dative* stabilized radical centre is the preferred radical intermediate involved in the second hydrogen removal, therefore, the formation of 4-Ph/6-Ar DHPMs is expected.

Computational Studies

Density functional theory (DFT) at the B3LYP/6–31++G(d,p) level using the *Gaussian98* package[34] was applied to study structural, electronic, and bonding characteristics of THPMs, the TrHPM$^{\bullet}$ intermediate, and the corresponding DHPM products considered in the present study. The numerical results of the DFT study concerning the selected bond lengths and the dihedral angles related to the orientation of the aryl rings towards the heterocyclic ring are extracted from the optimized structures and are listed in Table 4. A comparison of the bond lengths in the TrHPM$^{\bullet}$ intermediate, especially the bond length of the C-radical centre with the substituted and unsubstituted aryl ring, indicates that due to effective delocalization of the single electron towards the phenyl ring, the bond length is shorter than the bond length with the substituted aryl ring. The radical centre in **1a**$^{\bullet}$ is a double benzylic/allylic radical either on the C_4- or C_6-atoms and is delocalized with the phenyl rings at the 4- or 6-positions of the heterocyclic ring, therefore, the C_4–C_8 and the C_6–C_{14} bond lengths are 1.4574 Å. This is illustrated in Fig. 2. Since the radical centre obtained by the hydrogen removal from the remaining THPMs (**1b**–**g**) is more delocalized with the phenyl ring than with the substituted aryl ring, the C–C_{phenyl} bond length is shorter than C–C_{aryl} bond length. In a true allylic radical and in the absence of any additional stabilization or delocalization of the single electron, which is considered as a symmetrical allylic radical due to the delocalization of the single electron over three allylic carbon atoms, the electron density on both ends of the radical is equal to 0.5 in the Ψ_2 molecular orbital and both of the C_1–C_2 and C_2–C_3 bonds have the same partial double-bond character (Scheme 7). Such a situation is observed in the case of **1a**$^{\bullet}$, which is bonded to the phenyl ring at both ends of the delocalized radical, as a symmetrical double benzylic and allylic radical centre in the present study. In **1a**$^{\bullet}$, both C_6–C_5 and C_5–C_4 bonds have equal distances of 1.3932 Å and the Mulliken spin densities on the C_4- and C_6-atoms are 0.3946. This situation has been changed by attachment of the carbon atoms of the conjugated radical centre to the phenyl and methoxy-substituted phenyl rings (aryl ring). In this case an asymmetrical double benzylic radical intermediate is formed, which is supported by the observed different

Table 4. Bond lengths (Å) and dihedral angles (°) of 4,6-diaryl-THPMs, trihydropyrimidyl radical (TrHPM•) and DHPMs obtained by using the B3LYP/6–31++G(d,p) calculations



Comp.	N_1–C_2	C_2–N_3	N_3–C_4	C_4–C_5	C_5–C_6	N_1–C_6	C_2–O_7	C_4–C_8	C_6–C_{14}	β_1^A	β_2^B	γ_1^C	γ_2^D
1a	1.3889	1.3680	1.4680	1.5093	1.3462	1.4026	1.2290	1.5312	1.4837	−52.1	71.2	−37.5	140.2
1a•	1.3823	1.3823	1.4051	1.3932	1.3932	1.4051	1.2248	1.4574	1.4574	21. 2	157.4	−21.1	157.4
2a	1.4183	1.3747	1.3207	1.4306	1.3768	1.3629	1.2245	1.4932	1.4862	0.0	180.0	0.0	180.0
1b	1.3876	1.3714	1.4726	1.5125	1.3469	1.4017	1.2289	1.5246	1.4835	−54.35	67.5	37.7	−140.8
1b•	1.3813	1.3831	1.4064	1.3908	1.3964	1.4073	1.2254	1.4574	1.4544	−21.3	155.7	18.9	−158.0
3b	1.4191	1.3762	1.3219	1.4301	1.3760	1.3627	1.2247	1.4907	1.4758	16.1	−162.7	−35.2	143.5
1c	1.3878	1.3685	1.4687	1.5094	1.3461	1.4024	1.2295	1.5327	1.4835	−51.3	72.4	−37.5	140.5
1c•	1.3816	1.3827	1.4054	1.3923	1.3937	1.4058	1.2252	1.4582	1.4569	−22.8	155.4	−20.7	157.8
3c	1.4189	1.3766	1.3214	1.4314	1.3738	1.3623	1.2244	1.4908	1.4806	−15.4	164.2	38.2	141.1
1d	1.3952	1.3656	1.4737	1.5049	1.3469	1.4029	1.2291	1.5357	1.4839	68.5	−167.3	38.1	−139.8
1d•	1.3856	1.3770	1.4042	1.3975	1.3911	1.4042	1.2264	1.4614	1.4580	23.5	−159.3	21.4	−156.6
3d	1.4161	1.3773	1.3213	1.4286	1.3781	1.3600	1.2255	1.4918	1.4835	17.5	−161.9	33.9	−147.9
1e	1.3874	1.3693	1.4698	1.5090	1.3467	1.4026	1.2294	1.5322	1.4814	−56.4	67.4	−37.8	140.5
1e•	1.3828	1.3813	1.4069	1.3964	1.3901	1.4059	1.2253	1.4545	1.4585	−19.7	158.7	−23.5	155.2
3e = 3b	1.4191	1.3762	1.3219	1.4299	1.3758	1.3628	1.2247	1.4911	1.4767	−16.6	163.1	−35.7	143.6
1f	1.3867	1.3716	1.4711	1.5115	1.3464	1.4012	1.2288	1.5273	1.4842	−53.9	67.9	38.6	−139.7
1f•	1.3822	1.3828	1.4060	1.3941	1.3923	1.4054	1.2250	1.4567	1.4587	−20.2	156.8	21.6	−155.3
3f = 3c	1.4189	1.3764	1.3215	1.4318	1.3741	1.3622	1.2245	1.4904	1.4804	−14.4	164.7	38.2	−140.4
1g	1.3896	1.3703	1.4685	1.5116	1.3476	1.4037	1.2295	1.5266	1.4867	−54.0	67.6	44.6	−138.4
1g•	1.3769	1.3843	1.4029	1.3900	1.3999	1.4039	1.2266	1.4589	1.4602	−21.7	155.5	19.8	−161.4
3g = 3d	1.4159	1.3771	1.3213	1.4289	1.3783	1.3601	1.2256	1.4917	1.4831	−15.6	163.5	33.9	−147.4

[A] N_3–C_4–C_8–C_9 dihedral angle; [B] C_4–C_5–C_8–C_9 dihedral angle; [C] N_1–C_6–C_{14}–C_{15} dihedral angle; [D] C_5–C_6–C_{14}–C_{15} dihedral angle.

Mulliken spin densities on the C_4- and C_6-atoms and the different double bond characters of the C_6–C_5 and C_5–C_4 bonds shown in Fig. 2. The greater Mulliken spin density of 0.4040 on the C_6-atom in **1b•** compared with 0.3973 on the C_4-atom of this radical and also the greater Mulliken spin density of 0.3946 on the C_4-atom in **1e•** compared with 0.3922 on the C_6-atom of this radical and different partial double-bond character of the C_6–C_5 and C_5–C_4 bonds support our argument that due to the electron-withdrawing character of the phenyl ring, the benzylic radical centre with the phenyl ring as a part of the *capto-dative* stabilized radical centre is more stabilized, therefore, the elimination of the hydrogen atom from the neighbouring NH moiety to this radical centre leads to the formation of 4-Ph/6-Ar DHPMs (Scheme 6).

The sum of the Mulliken spin densities on both benzylic radical parts, namely, on the C_4, C_9, C_{11}, and C_{13} atoms (Part I), and on the C_6, C_{15}, C_{17}, and C_{19} atoms (part II) in radicals **1a•**, **1b•**, and **1e•** are 0.7607 and 0.7607, 0.7080 and 0.8073, and 0.7879 and 0.6969, respectively. A comparison of these data indicates that in the case of the symmetrical benzylic radical **1a•**, the sum of the spin densities on both parts is equal to 0.7607, whereas for unsymmetrical benzylic radicals **1b•** and **1e•** the single electron is more delocalized over the phenyl ring than over the *p*-methoxyphenyl ring, which displays a greater sum of the spin density on the benzylic radical attached to the phenyl group than the benzylic radical attached to the *p*-methoxyphenyl group. These results support the argument that the behaviour of the phenyl group as an electron-withdrawing member of the *capto-dative* radical involved preferable removal of the second hydrogen.

The structure of **3d** obtained by the oxidation of **1d** was confirmed by X-ray diffraction analysis. This crystal structure presented in Fig. 3 indicates that the 2-methoxyphenyl substituent is located on the 6-position of the heterocyclic ring next to the NH moiety.

Conclusion

Thermal oxidation of some methoxy-substituted 4,6-diaryl-THPMs was achieved using PPS in aqueous acetonitrile solution. The results indicate that a *capto-dative* stabilized radical intermediate among two possibly formed double benzylic/allylic radical centres governs the type of product formed. The data of the DFT computational studies concerning the bond lengths to the radical centres and Mulliken population analysis support the results of the experimental work.

Experimental

The 4,6-diaryl-substituted THPMs considered for this study were synthesized according to the reported procedure.[35] Melting points were determined on a Stuart Scientific SMP2 apparatus and were not corrected. IR spectra were recorded

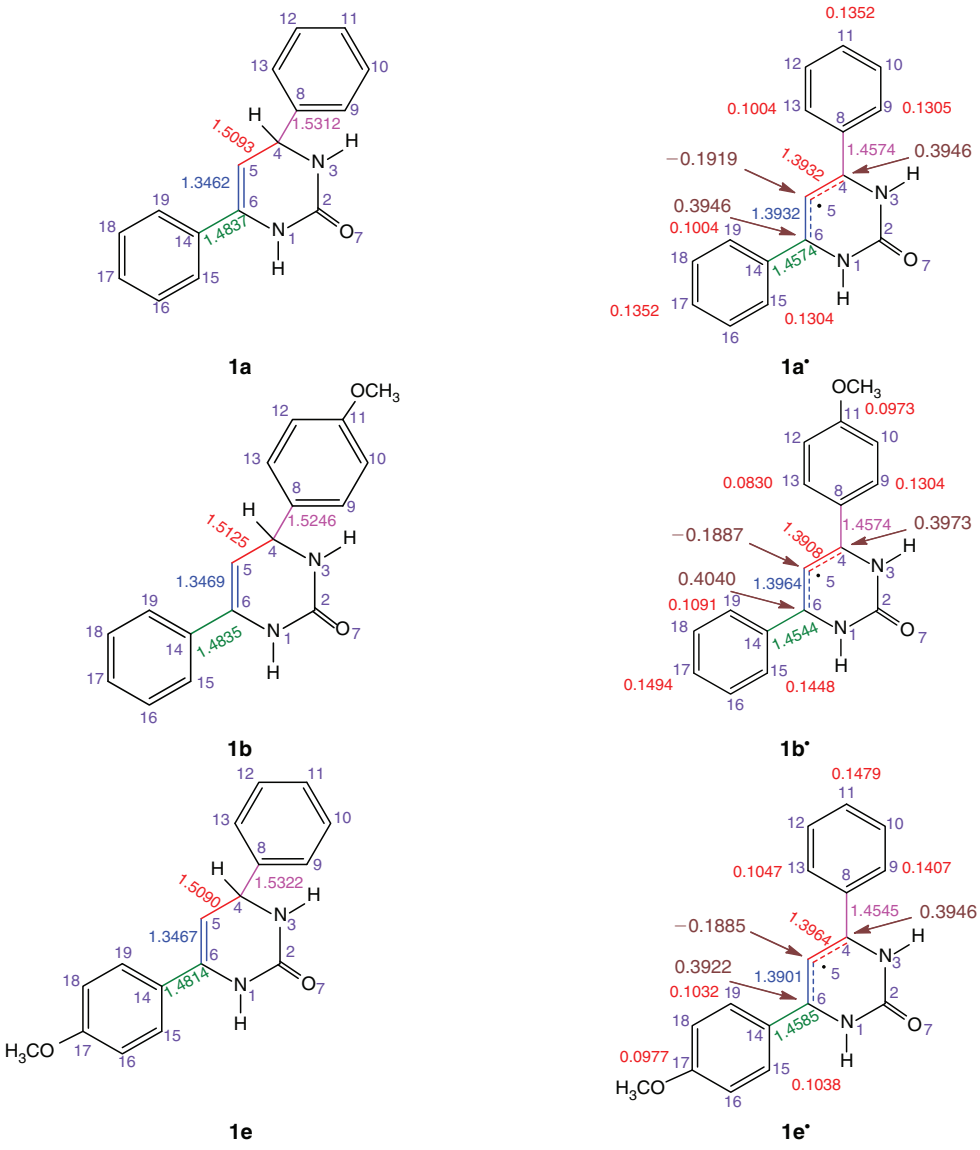
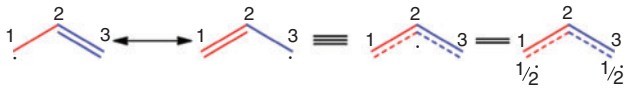


Fig. 2. Comparison of the bond lengths and the Mulliken spin densities in the symmetric (**1a**•) and asymmetric (**1b**• and **1e**•) double benzylic/allylic radical intermediates.



Scheme 7. Single electron delocalization in a symmetrical allylic radical.

using KBr pellets on a Jasco FT/IR-6300 spectrometer. The ^{1}H and ^{13}C NMR spectra (DMSO-d_6) were recorded on a Bruker Avance III 400 spectrometer at 400 and 100 MHz. The ^{1}H NMR spectra are reported as follows: chemical shifts, [multiplicity, number of protons, coupling constants J (Hz), and assignment]. UV spectra (in $CHCl_3$) were measured with a Shimadzu UV-160 spectrometer.

Cyclic Voltammetry (CV) Measurements

Solutions with concentrations of 1 mM of THPMs and 50 mM of tetrabutylammonium perchlorate in acetonitrile were prepared. The CV measurements were performed using a SAMA 500 Potentio/Galvanostat. All electrochemical experiments were carried out in a conventional three electrode system at room temperature. A silver electrode, a large area Pt plate (99.99 %), and a glass carbon electrode (GCE) were used as reference, counter, and working electrodes, respectively.

Oxidation of 4,6-Diaryl-THPMs by PPS

A mixture of 0.23 mmol **1a–g** and 0.23 mmol $K_2S_2O_8$ (mol ratio 1 : 1) in 6 mL CH_3CN/H_2O (5/1) was reacted in a preheated oil bath at 80°C for the time given in Table 1. The progress of the reaction was followed by TLC until total disappearance of **1a–g**. The solvent was evaporated under reduced pressure, water was added, and the mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized from *n*-hexane/ethyl acetate or washed with *n*-hexane.

*4,6-Diphenyl-2-oxo-1,2-dihydropyrimidine (**2a**)*

Mp 236–237°C, recrystallized from *n*-hexane/ethyl acetate. ν_{max} (KBr)/cm^{-1} 3285, 3006, 2895, 2741, 1625, 1577, 1490, 1456, 1420, 1336, 993, 763, 684. δ_H (400 MHz, DMSO-d_6) 7.54–7.60

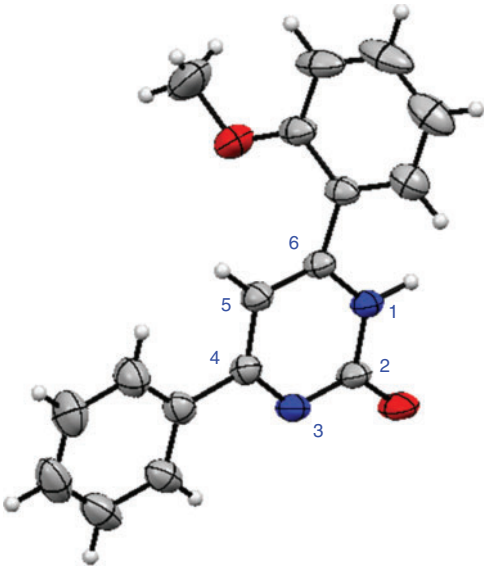


Fig. 3. The structure of compound **3d** showing the presence of the substituted aryl ring next to the NH moiety.

(m, 7H, Ar-H and 5-H), 8.16–8.18 (m, 4H), 12.07 (s, 1H, N_1-H). δ_C (100 MHz, DMSO-d_6) 100.40, 127.55, 128.79, 131.45, 134.68, 159.93. λ_{max} ($CHCl_3$)/nm (log ε) 360 (sh, 3.78), 346.2 (3.92), 280.2 (4.00), 263.4 (3.95), 253.4 (3.97).

*6-(4-Methoxyphenyl)-4-phenyl-2-oxo-1,2-dihydropyrimidine (**3b**)*

M. p. 254–256°C, recrystallized from *n*-hexane/ethyl acetate. λ_{max} (KBr)/cm^{-1} 3271, 3099, 2999, 2903, 2833, 1611, 1577, 1513, 1458, 1424, 1395, 1338, 1261, 1172, 1028, 991, 822 cm^{-1}. δ_H (400 MHz, DMSO-d_6) 3.86 (s, 3H, OCH_3), 7.10 (d, *J* 8.8, 2H, Ar-H), 7.49 (s, 1H, 5-H), 7.53–7.61 (m, 3H, Ar-H), 8.14–8.18 (m, 4H, Ar-H), 11.94 (s, 1H, N_1-H). δ_C (100 MHz, DMSO-d_6) 55.44, 99.08, 114.18, 127.50, 128.76, 129.36, 131.35, 162.07. λ_{max} ($CHCl_3$)/nm (log ε) 360 (4.07), 346.2 (4.15), 290 (sh, 3.97), 248.2 (4.05).

*6-(3-Methoxyphenyl)-4-phenyl-2-oxo-1,2-dihydropyrimidine (**3c**)*

Mp 221–222°C, recrystallized from *n*-hexane/ethyl acetate. λ_{max} (KBr)/cm^{-1} 3285, 3092, 3000, 2900, 2826, 1628, 1592, 1539, 1498, 1460, 1384, 1346, 1266, 1182, 1042, 915, 843, 773. δ_H (400 MHz, DMSO-d_6) 3.87 (s, 3H, OCH_3), 7.15–7.17 (m, 1H, Ar-H), 7.48 (t, *J* 8.0, 1H, Ar-H), 7.56–7.60 (m, 6H, Ar-H), 8.18 (br s, 2H, Ar-H), 12.09 (s, 1H, N_1-H). δ_C (100 MHz, DMSO-d_6) 55.34, 112.34, 117.52, 119.92, 127.60, 128.80, 129.93, 131.50, 159.55. λ_{max} ($CHCl_3$)/nm (log ε) 375 (sh, 3.81), 356.5 (4.05), 330 (4.03), 298 (4.04), 257 (4.04).

*6-(2-Methoxyphenyl)-4-phenyl-2-oxo-1,2-dihydropyrimidine (**3d**)*

Mp 239–240°C, washed with *n*-hexane. λ_{max} (KBr)/cm^{-1} 3194, 3116, 3072, 3000, 2888, 1636, 1598, 1581, 1532, 1461, 1394, 1287, 1248, 1182, 1017, 762. δ_H (400 MHz, DMSO-d_6) 3.86 (s, 3H, OCH_3), 7.11 (t, *J* 7.6, 1H, Ar-H), 7.21 (d, *J* 8.4, 2H, Ar-H), 7.53–7.59 (m, 5H, Ar-H), 8.11 (br s, 2H, Ar-H), 11.94 (s, 1H, N_1-H). δ_C (100 MHz, DMSO-d_6) 55.75, 102.0, 111.95, 120.55, 127.52, 128.81, 130.27, 131.49, 132.39, 156.99. λ_{max} ($CHCl_3$)/nm (log ε) 380 (sh, 3.88), 361.5 (4.06), 336 (4.00), 300 (sh, 3.89), 257 (3.99).

*6-(4-Methoxyphenyl)-4-phenyl-2-oxo-1,2-dihydropyrimidine (**3e** = **3b**)*

Mp 256–258°C, recrystallized from *n*-hexane/ethyl acetate. δ_H (400 MHz, DMSO-d_6) 3.86 (s, 3H, OCH_3), 7.10 (d, *J* 8.8, 2H, Ar-H), 7.49 (s, 1H, 5-H), 7.53–7.61 (m, 3H, Ar-H), 8.14–8.18 (m, 4H, Ar-H), 11.94 (s, 1H, N_1-H). δ_C (100 MHz, DMSO-d_6) 55.44, 99.13, 114.18, 127.50, 128.76, 129.36, 131.35, 162.07. λ_{max} ($CHCl_3$)/nm (log ε) 360 (4.04), 346.2 (4.18), 290 (sh, 3.97), 249.6 (4.04).

*6-(3-Methoxyphenyl)-4-phenyl-2-oxo-1,2-dihydropyrimidine (**3f** = **3c**)*

Mp 220–221°C, recrystallized from *n*-hexane/ethyl acetate. δ_H (400 MHz, DMSO-d_6) 3.87 (s, 3H, OCH_3), 7.15–7.17 (m, 1H, Ar-H), 7.48 (t, *J* 8.0, 1H, Ar-H), 7.56–7.60 (m, 6H, Ar-H), 8.18 (br s, 2H, Ar-H), 12.09 (s, 1H, N_1-H). δ_C (100 MHz, DMSO-d_6) 55.34, 101.36, 112.34, 117.51, 119.92, 127.60, 128.79, 1129.93, 131.49, 159.64. λ_{max} ($CHCl_3$)/nm (log ε) 375 (sh, 3.78), 354.5 (4.03), 330.5 (4.01), 297.5 (3.99), 257.5 (4.00).

*6-(2-Methoxyphenyl)-4-phenyl-2-oxo-1,2-dihydropyrimidine (**3g** = **3d**)*

Mp 240–241°C, washed with *n*-hexane. δ_H (400 MHz, DMSO-d_6) 3.87 (s, 3H, OCH_3), 7.11 (t, *J* 7.6, 1H, Ar-H), 7.21 (d, *J* 8.4, 2H, Ar-H), 7.53–7.59 (m, 5H, Ar-H), 8.11 (br s, 2H, Ar-H), 11.94 (s, 1H, N_1-H). δ_C (100 MHz, DMSO-d_6) 55.75, 102.01, 111.95, 120.55, 127.52, 128.81, 130.27, 131.49, 132.39, 156.98. λ_{max} ($CHCl_3$)/nm (log ε) 380 (sh, 3.92), 363 (4.09), 335 (4.00), 300 (sh, 3.91), 257 (4.00).

Crystallographic Data

CCDC 1434836 contains the supplementary crystallographic data for compound **3d**. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax: (+44) 1223-336-033, or email: deposit@ccdc.cam.ac.uk.

Supplementary Material

FT-IR, ^{1}H NMR, and ^{13}C NMR spectra of the oxidation products are available on the Journal's website.

Acknowledgements

The authors are thankful to the Research Council and Office of Graduate Studies of the University of Isfahan for their financial support.

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