Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2014) 38: 56 – 62

doi:10.3906/kim-1303-46

NH-acidities and Hammett correlation of 3-*para* substituted phenyl-1,2,4-oxadiazol-5(4*H*)-ones and 1,2 $\lambda^4$3,5-oxathiadiazole 2-oxides in nonaqueous media

Nedime DÜRÜST, Yaşar DÜRÜST*, Emine Özge GÖZLÜKAYA
Department of Chemistry, Abant İzzet Baysal University, Bolu, Turkey

Received: 16.03.2013 • **Accepted:** 09.09.2013 • **Published Online:** 16.12.2013 • **Printed:** 20.01.2014

Abstract: NH acidities of some 3-(*p*-substitutedphenyl)-1,2,4-oxadiazol-5(4*H*)-ones and 4-(*p*-substitutedphenyl)-1,2 $\lambda^4$3,5-oxathiadiazole 2-oxides were determined in methanol by means of potentiometric titration with sodium methoxide. pK_a values of the title compounds calculated from the potentiometric data were interpreted on the basis of structural effects caused by *para*-substituted groups on the phenyl ring by plotting pK_a values versus Hammett σ_p^+ constants, which gave excellent linear correlations.

Key words: Potentiometry, oxadiazol-5(4*H*)-one, oxathiadiazol 2-oxide, linear Hammett correlation

1. Introduction

1,2,4-Oxadiazol-5(4*H*)-ones and 1,2$\lambda^4$3,5-oxathiadiazole 2-oxides are typical acidic heterocycles that are classically used by medicinal chemists as carboxylic acid bioisosters.[1] In particular, heterocyclic scaffold 1,2,4-oxadiazol-5(4*H*)-ones are found in AT1 antagonists, COX inhibitors, PLA2 inhibitors, and modulators of GluR,[2–5] and they serve as precursors and protecting groups for amidines, which are utilized as an important class with biological functionality and as antihypertensive drugs.[6–10] Moreover, 3*H*-1,2$\lambda^4$3,5-oxathiadiazole 2-oxides have been reported to be used to control hyperglycemia associated with type 2 (noninsulin dependent) diabetes mellitus, and they were clinically found to have advantages over 4 divergent classes of drugs that are in use.[11]

Potentiometric titration in nonaqueous media is a standard method for the determination of the basicity and acidity of various heterocyclic compounds, particularly in pharmaceutical analyses since many organic compounds of pharmaceutical importance do not dissolve in water thoroughly. Furthermore, due to the amphotericity of water, only a very limited range of acid and base strengths can be determined in this solvent and in trying to compare the protonation and deprotonation tendencies of such heterocycles in alternant solvents.[12–15]

In continuation of our studies on the acid-base equilibria of amidoximes and related heterocyclic compounds,[16–18] we report herein acidity measurements and Hammett correlations of a series of 3-(*para*-substituted phenyl-1,2,4-oxadiazol-5(4*H*)-ones and 4-(*para*-substituted phenyl)-3*H*-1,2λ^4,3,5-oxathiadiazole 2-oxides (Scheme 1) in methanol as nonaqueous medium.

*Correspondence: yasardurust@ibu.edu.tr

2. Experimental

1,2,4-Oxadiazol-5(4*H*)-ones (**2a**–**l**) and 1,2λ^4,3,5-oxathiadiazol-2-oxides (**3a**–**l**) were prepared according to the procedures described previously.[19−24]

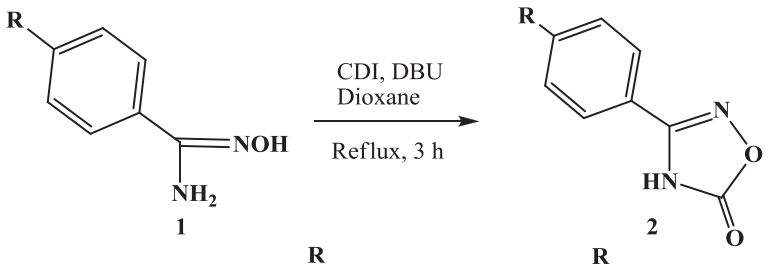
2.1. Potentiometric titrations

Titrations were performed in a 50-mL glass vessel designed for this work and equipped with a combined pH electrode (Ingold), argon inlet and outlet tubes, a magnetic stirrer, and an inlet for titrant (sodium methoxide) addition. A microburette with 0.01-mL graduations was used to add titrant. A Thermo Scientific Orion 4 Star pH/ISE meter equipped with a modified electrode (saturated KCl solution in anhydrous methanol instead of aqueous KCl solution) was used to read out the cell EMF.

The concentrations of the oxadiazolones and oxathiadiazole 2-oxides were maintained as 10^{-3} M in dry methanol. Potentiometric measurements were conducted with constant stirring of 30 mL of sample solution (magnetic stir-bar) at 25.0 ± 0.1 °C. Titration curves were constructed by plotting the potential change (from the initial baseline value) versus the concentration of the titrant solution added. In order to calculate the end points the Kolthoff method was utilized. The half neutralization potentials (HNP) were then determined by using fine sigmoidal curves. In calculations of the pK_a values, mV value of a standard buffer solution and HNP values from the sigmoidal curves of the samples were used, and 59 mV was taken as corresponding to 1 pH unit.

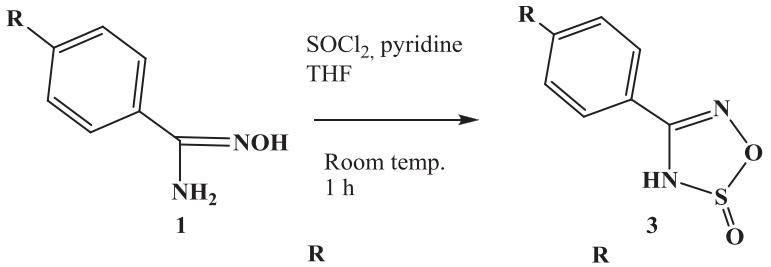
3. Results and discussion

3-Aryl-substituted 1,2,4-oxadiazol-5(*4H*)-ones **2a**–**l** were synthesized following the literature procedure[25,26] by reacting monoamidoximes with 1,1'-carbonyldiimidazole (CDI) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 3-aryl substituted 1,2λ^4,3,5-oxathiadiazole 2-oxides **3a**–**l** were prepared similarly to the procedure[27] described by the condensation of mono amidoximes **1a**–**l** with thionyl chloride along with pyridine (Schemes 1 and 2).



	R		R
2a	H	**2g**	MeO
2b	Me	**2h**	MeS
2c	F	**2i**	CF_3
2d	Cl	**2j**	CN
2e	Br	**2k**	NO_2
2f	I	**2l**	NMe_2

Scheme 1. Synthesis of 3-*p*-substituted phenyl-1,2,4-oxadiazol-5(4*H*)-ones **(2a–l)**.



	R		R
3a	H	**3g**	MeO
3b	Me	**3h**	MeS
3c	F	**3i**	CF_3
3d	Cl	**3j**	CN
3e	Br	**3k**	NO_2
3f	I	**3l**	NMe_2

Scheme 2. Synthesis of 3-*p*-substituted phenyl-3*H*-1,2λ^4,3,5-oxathiadiazole 2-oxides **(3a–l)**.

pK$_a$ values of aromatic heterocyclic compounds bearing oxygen and nitrogen in the same ring, namely oxadiazolones and oxathiadiazole 2-oxides, were determined potentiometrically in nonaqueous medium, anhydrous methanol, by using sodium methoxide as titrant. Overall results are compiled in Table 1, indicating the σ_p^+ constants for each substituent encountered, and typical titration curves for each series of the compounds are shown in Figures 1 and 2.

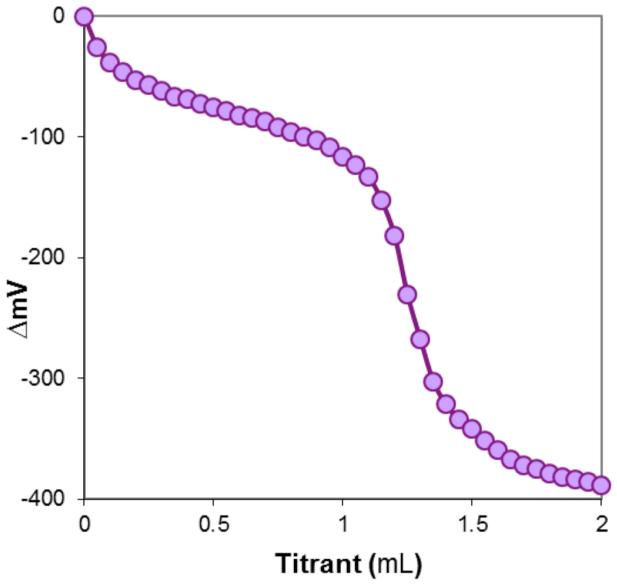


Figure 1. Representative titration curve of mL titrant vs. ΔmV of 4-*p*-nitrophenyl-1,2,4-oxadiazol-5(4*H*)-one **(2k)**.

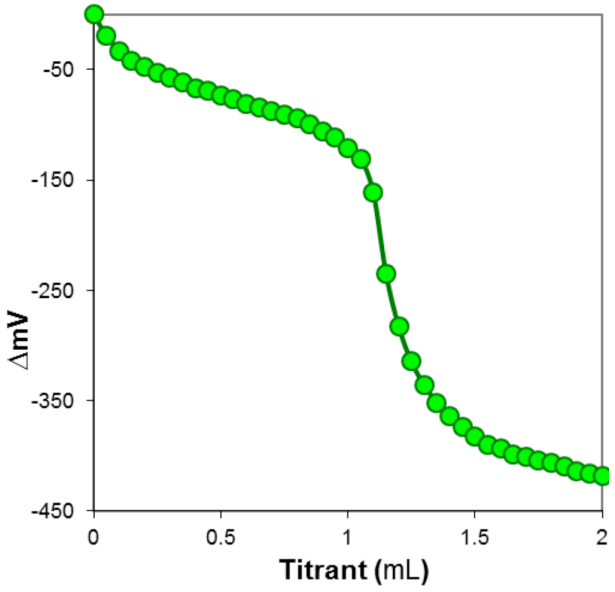
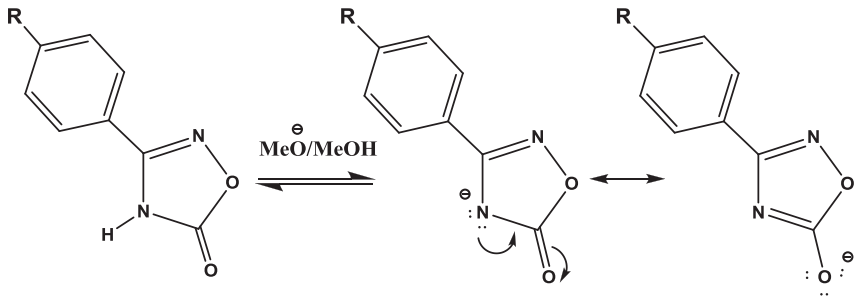


Figure 2. Representative titration curve of mL titrant vs. ΔmV of 3-*p*-nitro 3*H*-1,2 λ^4,3,4,5-oxathiadiazole 2-oxide **(3k)**.

Table 1. Experimental pK_a values of oxadiazolones (**2a–l**) and oxathiadiazole 2-oxides (**3a–l**) in methanol.

Entry	R	pK_a (oxadiazolone)	σ_p^+	Entry	R	pK_a (oxathiadiazole 2-oxide)
2a	H	6.35 ± 0.02	0.00	**3a**	H	6.12 ± 0.01
2b	CH_3	6.80 ± 0.04	–0.31	**3b**	CH_3	6.40 ± 0.04
2c	4-F	6.50 ± 0.01	–0.07	**3c**	4-F	6.17 ± 0.05
2d	4-Cl	6.30 ± 0.02	0.11	**3d**	4-Cl	6.05 ± 0.07
2e	4-Br	6.18 ± 0.05	0.15	**3e**	4-Br	5.76 ± 0.01
2f	4-I	6.28 ± 0.03	0.14	**3f**	4-I	5.90 ± 0.03
2g	4-CH_3O	7.24 ± 0.06	–0.78	**3g**	4-CH_3O	7.00 ± 0.08
2h	4-CH_3S	7.10 ± 0.06	–0.60	**3h**	4-CH_3S	6.80 ± 0.02
2i	4-CF_3	5.69 ± 0.13	0.61	**3i**	4-CF_3	5.45 ± 0.06
2j	4-CN	5.60 ± 0.01	0.66	**3j**	4-CN	5.36 ± 0.07
2k	4-NO_2	5.44 ± 0.10	0.79	**3k**	4-NO_2	5.07 ± 0.12
2l	4-$N(CH_3)_2$	8.30 ± 0.16	–1.70	**3l**	4-$N(CH_3)_2$	8.04 ± 0.15

Deprotonation of the oxadiazolones **2a–l** by methoxide will take place on the sp^3-hybridized 4-amino nitrogen. The resulting heterocyclic anion, oxadiazol-5-olate, is now stabilized due to the delocalization of negative charge through exocyclic oxygen, thus producing an aromatic oxadiazole structure (Scheme 3).

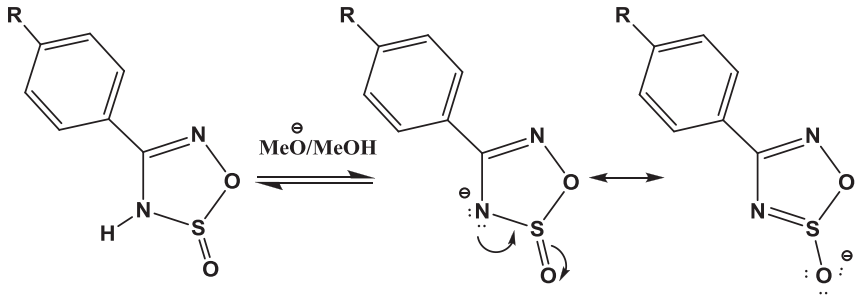


Scheme 3. Deprotonation of 1,2,4-oxadiazol-5(4*H*)-ones and resonance structures of the anion.

Electron-withdrawing and electron-releasing substituents (R groups) existing on the *para* position of the phenyl ring in the case of oxadiazolones will have a remarkable impact on the acidities of these heterocycles. In this regard, electron-donating substituents like dimethylamino, methoxy, and thiomethoxy cause an increase in pK_a values as much as 8.30, 7.24, and 7.10, respectively, while electron-withdrawing ones, such as NO_2, CN, and CF_3, give rise to much lower pK_a values of 5.44, 5.60, and 5.69, respectively, which are in accord with the decreasing values of Hammett sigma *para* constants.

In a similar manner, we can illustrate the deprotonation of oxathiadiazole 2-oxides, which further gives 4-aryl-1,2λ^4,3,5-oxathiadiazol-2-olate with aromatic stability (Scheme 4).

Again we can observe the higher acidities of the oxathiadiazole 2-oxides compared to oxadiazolones in the case of electron-withdrawing substituents and this tendency can be attributed to the higher polarization of S=O bond than C=O bond, causing easier deprotonation of NH hydrogens of oxathiadiazole 2-oxides.



Scheme 4. Deprotonation of 1,2λ^4,3,5-oxathiadiazole 2-oxides and resonance structures of the anion.

pK_a values obtained for the title compounds were correlated with Hammett σ_p^+ constants,[28] which have also been used for *para* substituents interacting with the aromatic ring through resonance delocalization of the lone pairs.[29,30] In Figure 3, it can be clearly perceived that electron-releasing groups (ERGs), i.e. dimethylamino, methoxy, and thiomethoxy, which have lower Hammett σ_p^+ values with higher pK_a values, appeared on one end of the line (right lower end), and electron-withdrawing (EWG) substituents, i.e. NO_2, CN and CF_3, which have higher Hammett σ_p^+ constants with lower pK_a values, appeared on the other end of the graph (left upper end). In general, the acidities measured experimentally in nonaqueous solvents such as methanol, dimethyl sulfoxide, dimethoxyethane, and acetonitrile are expected to be lower than those obtained in water due to the higher stabilization of the ionic species in water.[31–35]

A similar observation was made for oxathiadiazol-2-oxides (Figure 4).

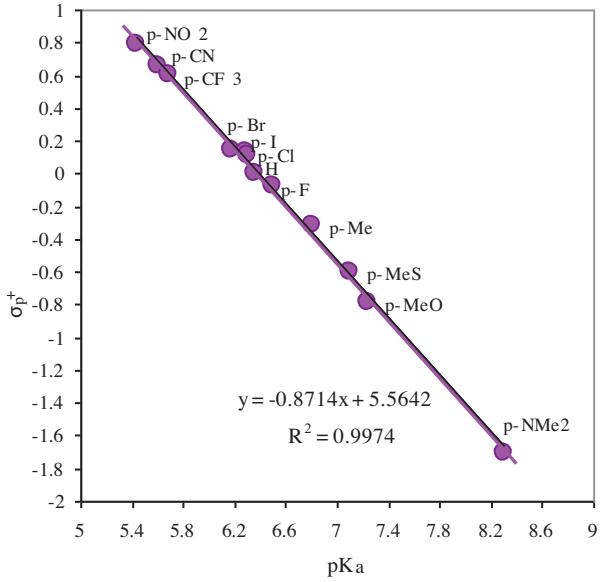


Figure 3. Hammett plot indicating linear correlation between electronic parameter of the substituents on the oxadiazol-5(4*H*)-ones (**2a–l**) and pK_a values obtained in anhydrous methanol.

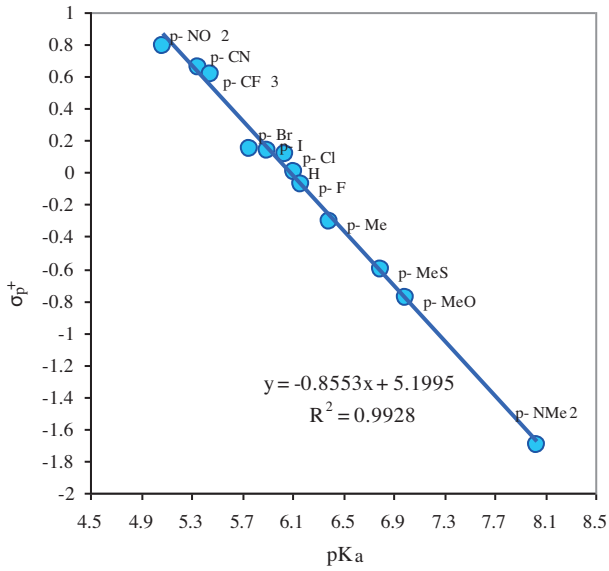


Figure 4. Hammett plot indicating linear correlation between electronic parameter of the substituents on the oxathiadiazol-2-oxides (**3a–l**) and pK_a values obtained in anhydrous methanol.

These results are in good accordance with the expected behavior of these groups predicated on the proticity of amino hydrogen of oxadiazolones. In this regard, when there are electron-releasing groups present

on the phenyl ring there will be an increase in electron density, which may result in resonance delocalization of the lone pairs on the N, O, and S atoms ($N(CH_3)_2$, CH_3O, CH_3S) through the aromatic ring, thus reducing their acidity to a remarkable extent. In the presence of electron-withdrawing groups (NO_2, CN, CF_3) on the phenyl ring, a reverse effect on pK_a values is observed due to the substantial decrease in the electron density of the amino nitrogen atom of the oxadiazolones mesomerically, thus causing an increase in the proticity of amino hydrogens.

4. Conclusions

In this work, we clearly demonstrated the acidity measurements (pK_a) of a series of oxadiazolones and 1,2,4,5-oxathiadiazol-2-oxides potentiometrically in anhydrous methanol. In addition, excellent linear correlations between pK_a values and Hammett σ_p^+ constants were established and the results were interpreted by taking account of the electronic–mesomeric nature of the existing groups on the phenyl ring at the 3-position of the title oxygen, nitrogen containing 5-membered heterocycles.

Acknowledgment

We are grateful to Abant İzzet Baysal University Directorate of Research Project Commission for its financial support (BAP Grant No: 2011.03.03.442).

References

1. Wermuth, C. G. In *The Practice of Medicinal Chemistry*; 2nd ed.; Wermuth, C. G., Ed., Academic Press: London, UK, 2003.
2. Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228–5235.
3. Boschelli, D. H.; Connor, D. T. U.S. Patent 5,114,958, May 19, 1992.
4. Dong, C. Z.; Ahamada-Himidi, A.; Plocki, S.; Aoun, D.; Touaibia, M.; Meddad-Bel Habich, N.; Huet, J.; Redeuilh, C.; Ombetta, J. E.; Godfrold, J. J.; et al. *Bioorg. Med. Chem.* **2005**, *13*, 1989–2007.
5. Valgeirsson, J.; Nielsen, E.; Peters, D.; Mathiesen, C.; Kristensen, A. S.; Madsen, U. *J. Med. Chem.* **2004**, *47*, 6948–6957.
6. Schroeder, A.; Kotthaus, J.; Schade, D.; Clement, B.; Rehse, K. *Archiv Pharm.* **2010**, *343*, 9–16.
7. Clement, B.; Reeh, C.; Hungeling, H. Ger. Offen. **2009**, DE 102008007381 A1 20090813.
8. Bolton, R. E.; Coote, S. J.; Finch, H.; Lowdon, A.; Pegg, N.; Vinader, M. V. *Tetrahedron Lett.* **1995**, *36*, 4471–4474.
9. Nardi, A.; Demnitz, J.; Grunnet, M.; Christophersen, P.; Jones, D. S.; Nielsen, E. O.; Stroebaek, D.; Madsen, L. S. PCT Int. Appl. **2008** WO 2008135591 A1 20081113.
10. Kohara,Y.; Imamiya, E.; Kubo, K.; Wada, T.; Inada, Y.; Naka, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1903–1908.
11. Ellingboe, J. W.; Alessi, T. R.; Dolak, T. M.; Nguyen, T. T.; Tomer, J. D.; Guzzo, F. S.; Bagli, J. F.; McCaleb, M. L. *J. Med. Chem.* **1992**, *35*, 1176–1183.
12. Fritz, J. S. *Acid-Base Titrations in Non-Aqueous Solvents*; Allyn and Bacon: Boston, USA, 1973.
13. Dewick, P. M. *Essentials of Organic Chemistry: For Students of Pharmacy, Medicinal Chemistry and Biological Chemistry*; John Wiley & Sons: Chichester, West Sussex, UK, 2006.
14. Rochester, C. H. *Acidity Functions, in Organic Chemistry*, Ed. Blomquist, A. T. Academic Press, London, UK, 1970.
15. Gündüz, T.; Kılıç, E.; Atakol, O.; Köseoğlu, F. *Analyst* **1989**, *114*, 475–477.
16. Akay, A.; Dürüst, N.; Dürüst, Y.; Kılıç, E. *Anal. Chim. Acta* **1999**, *392*, 343–346.

17. Dürüst, N.; Akay, A.; Dürüst, Y.; Kılıç, E. *Anal. Sci.* **2000**, *16*, 825–827.
18. Dürüst, Y.; Dürüst, N.; Akcan, M. *J. Chem. Eng. Data* **2007**, *52*, 718–720.
19. Dürüst, Y. *Phosphorus Sulfur Silicon* **2009**, *184*, 2923–2935.
20. Dürüst, Y.; Akcan, M.; Martiskainen, O.; Siirola, E.; Pihlaja, K. *Polyhedron* **2008**, *27*, 999–1007.
21. Dürüst, Y.; Yıldırım, M.; Aycan, A. *J. Chem. Res.* **2008**, *4*, 235–239.
22. Nicolaides, D. N.; Varella, E. A. In: *The Chemistry of Acid Derivatives* Vol. 2. Suppl. B., Patai, S. Ed., Wiley: New York, NY, USA, 1992.
23. Eloy, F.; Lenaers, R. *Chem. Rev.* **1962**, *62*, 155–183.
24. Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Pufko, D. E.; Porco, J. A. Jr. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 209–212.
25. Kitamura, S.; Fukushi, H.; Miyawaki, T.; Kawamura, M.; Konishi, N.; Terashita, Z. I.; Naka, T. *J. Med. Chem.* **2001**, *44*, 2438–2450.
26. Dias, A. M.; Cabral, I. M.; Vila-Chã, A. S.; Cunha, D. P.; Senhorães, N.; Nobre, S. M.; Sousa, C. E.; Proença, M. F. *Synlett* **2010**, 2792–2796.
27. Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. J. *Med. Chem.* **1996**, *39*, 5228–5235.
28. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *2*, 165–195.
29. Fernández, I.; Frenking, G. *J. Org. Chem.* **2006**, *71*, 2251–2256.
30. Yoshida, T.; Hirozumi, K.; Harada, M.; Hitaoka, S.; Chuman, H. *J. Org. Chem.* **2011**, *76*, 4564–4570.
31. Sarmini, K.; Kenndler, E. *J. Biochem. Biophys. Methods* **1999**, *38*, 123–137.
32. Kütt, A.; Leito, I.; Kaljurand, I.; Soovali, L.; Vlasov, V. M.; Yagupolskii, L. M.; Koppel, I. A. *J. Org. Chem.* **2006**, *71*, 2829–2838.
33. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
34. Bordwell, F. G; Liu, W. Z. *J. Phys. Org. Chem.* **1998**, *11*, 397-406.
35. Zhao, Y. Y.; Bordwell, F. G.; Cheng, J. P.; Wang, D. F. *J. Am. Chem. Soc.* **1997**, *119*, 9125–9129.