Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2011, **21**, 103–105

Mendeleev Communications

Stereospecific protonation of pyrrole-2-carboxaldehyde *Z*-oximes as a result of through-space cation stabilization with oxime hydroxyl

Boris A. Trofimov,* Andrei V. Ivanov, Igor A. Ushakov,
Andrei V. Afonin, Elena Yu. Schmidt and Al'bina I. Mikhaleva

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 41 9346; e-mail: boris_trofimov@irioch.irk.ru

DOI: 10.1016/j.mencom.2011.03.016

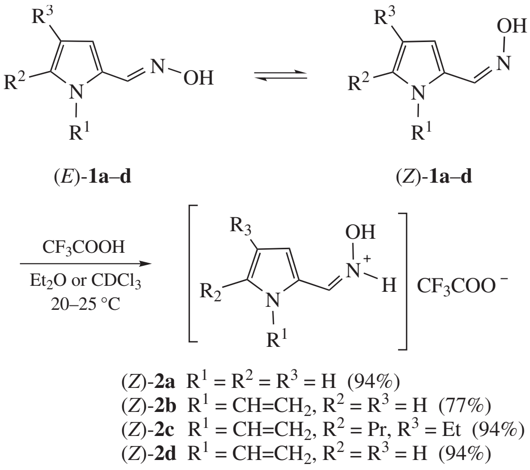
The protonation of the *E*/*Z* mixture of pyrrole-2-carboxaldehyde oxime (CF_3COOH, Et_2O or $CDCl_3$, room temperature) gives *Z*-configured pyrrole-2-carboxaldehyde oxime cations exclusively. The NMR (^1H, ^{13}C and ^{15}N) analysis and quantum chemical calculations [B3LYP/6-311G(d,p)] imply the stereospecific through-space stabilization of these cations by the oxime hydroxyl.

Oximes are of interest as flexible intermediates and powerful auxiliaries in organic synthesis[1] and as biologically active compounds.[1(b)–(d),2] Oximes of the pyrrole series deserve a particular attention since the pyrrole moiety is a key structural unit of chlorophyll, hemoglobin and a great variety of naturally occurring products and pharmaceuticals.[1(e),3] Oxime *E*- and *Z*-isomers demonstrate different reactivity and biological properties,[3,4] although isolation of the individual isomers still remains a challenge.

Recently,[5] during the synthetic study of 1-vinylpyrrole-2-carboxaldehyde oximes we have noticed that such *Z*-configured aldoximes are susceptible to protonation much more rapidly than the *E*-isomers which finally led to the protonated *Z*-isomers only. This phenomenon was a particular case of oxime chemistry related to only pyrrole-2-carboxaldehyde oximes, which implied the pyrrole moiety participation in the stabilization of the *Z*-protonated forms and a special type of configurational-conformational interconversions of the cations. It is noteworthy that the imine basicities of *E*- and *Z*-configurants do not differ considerably.

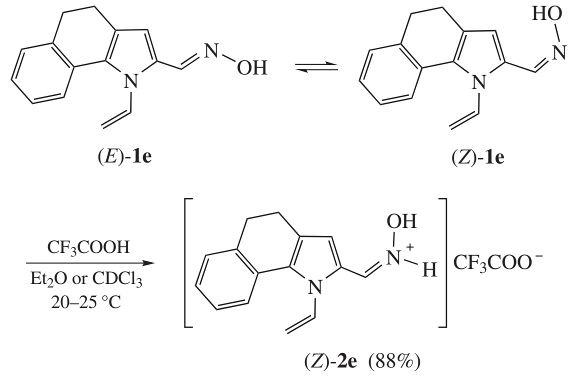
Herein, we have attempted to rationalize what may be the cause of such unusual stereospecificity of the protonation of pyrrole-2-carboxaldehyde oximes isomers.

Pyrrole-2-carboxaldehyde oximes **1a–d** as mixtures of *E*- and *Z*-isomers are protonated with CF_3COOH in Et_2O (room temperature) to afford isolable salts **2a–d** of *Z*-isomers only (Scheme 1). Other strong acids (CF_3SO_3H, HCl) give similar results. Analogously, *E*/*Z* mixture of 1-vinyl-4,5-dihydrobenz[*g*]indole-2-carboxaldehyde oxime **1e** is stereospecifically protonated to furnish salt **2e** (Scheme 2). To the best of our knowledge, for the pyrrole series, these are the first examples of isolation of isomerically pure oxime salts.



(*Z*)-**2a** $R^1 = R^2 = R^3 = H$ (94%)
(*Z*)-**2b** $R^1 = CH{=}CH_2$, $R^2 = R^3 = H$ (77%)
(*Z*)-**2c** $R^1 = CH{=}CH_2$, $R^2 = Pr$, $R^3 = Et$ (94%)
(*Z*)-**2d** $R^1 = CH{=}CH_2$, $R^2 = R^3 = H$ (94%)

Scheme 1



Scheme 2

The unambiguous structural assignment of salts **2a–e** was derived from 2D NOESY and HMBC NMR data.[†] For compounds **2b–e**, the NOE correlations between H-1 and H_X of the vinyl group were observed indicating the *s-trans* mutual disposition of the vinyl group and the C=N bond. In addition, in the 2D ^1H–^{13}C HMBC spectra, the correlations between H-1 and C-3 of the pyrrole moiety took place, the vicinal constant $^3J_{H\text{-}1,C\text{-}3}$ values being about 12.0 Hz. This confirms the *trans*-disposition of these atoms. The *Z*-configuration of salts **2a–e** also follows from the fact that upon gradual addition of an acid to the isomers mixture, the corresponding ^1H NMR signals of the *E*-isomers were disappearing while the signals of the *Z*-isomers were growing in intensity (Figure 1).

Although the oximes protonation was scarcely investigated, it was reported that they were protonated at the nitrogen atom.[2] As ^{15}N chemical shifts of oximes (Table 1) show, the basicity of their *E*- and *Z*-isomers differs by 9–25%, the *Z*-form being slightly more basic. The effect of the substituents in the pyrrole ring on the $\delta_{^{15}N}$ of the imine nitrogen is much higher (the $\delta_{^{15}N}$

[†] NMR spectra were recorded on a Bruker DPX 400 spectrometer (400.13 MHz, ^1H; 101.61 MHz, ^{13}C and 40.55 MHz, ^{15}N) in $CDCl_3$, HMDS was used as an internal standard. The resonance signals in ^1H and ^{13}C NMR spectra were assigned using 2D COSY, NOESY, HSQC and HMBC techniques. The values of characteristic signals for ^{15}N nitrogen atom have been obtained from 2D ^1H–^{15}N HMBC spectra. For the titration experiments, a 2 wt% solutions of oxime in $CDCl_3$, gaseous HCl and 10 wt% solutions of CF_3COOH and CF_3SO_3H in $CDCl_3$ were used.

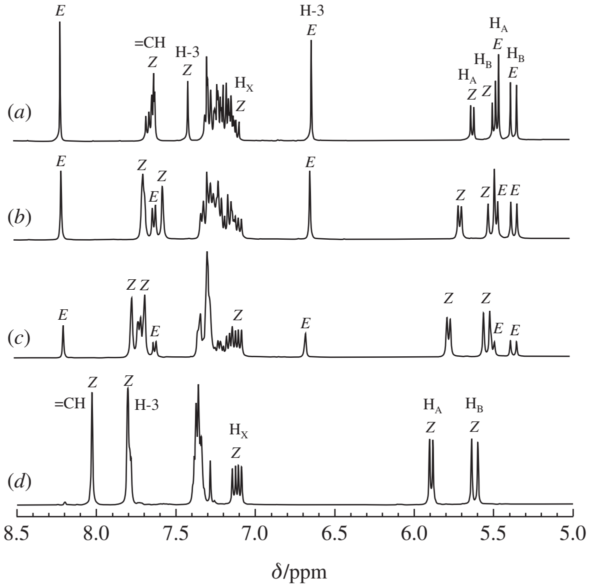
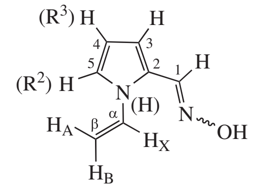


Figure 1 ^{1}H NMR monitoring of oxime **1e** protonation (Scheme 2): (*a*) initial *E*/*Z* mixture of isomers of **1e** (*Z*:*E* = 1:1.7); (*b*) 0.5 equiv. of CF$_3$COOH added (*Z*:*E* = 1:1); (*c*) 0.75 equiv. of CF$_3$COOH added (*Z*:*E* = 1:0.2); (*d*) excess CF$_3$COOH [protonated (*Z*)-**2e** only].

value ranges from –18.6 to –49.4 ppm). Therefore, the difference in basicity of the imine nitrogen of *E*- and *Z*-isomers can not be a reason of the stereospecific protonation of the *Z*-isomers. The attention is drawn by the unexpectedly great low-field shifting of the ^{13}C and ^{1}H signals (Tables 1 and 2) for the 3-position of the pyrrole ring of salts **2a–e** relative to the unprotonated *Z*-isomers (6.8–10.1 ppm for ^{13}C and 0.4–0.8 ppm for ^{1}H). More surprising is the slight low-field shift or, in some cases, even upfield shift of $\delta_{^{13}\mathrm{C}}$ (–2.0 to +1.6 ppm) in the CH=N$^+$ moiety adjacent to the very protonated centre that is accompanied by the low-field shifting of the corresponding hydrogen atom signal (0.4–0.6 ppm).

Such a deep electron density distribution in cations **2a–e** is an evidence of the charge transfer from the pyrrole ring towards the protonated imine moiety. Comparison of the ^{13}C low-field shifts in cations **2a–e** with those in true pyrrolium cations (relative to the unprotonated species)[6] shows that for the former series (6.8–10.1 ppm) it is as much as a half of those for the latter ones (18.8–20.4 ppm). In other words, cations **2a–e** in terms of their electron deficiency are approaching to the real pyrrolium cations. The large positive charge in the 3-position of the pyrrole ring is efficiently stabilized through the space by the lone electron pair of the hydroxy group in the *Z*-configuration (*anti*-conformation) only (Scheme 3).

Table 1 ^{15}N and ^{13}C chemical shifts of *E*- and *Z*-isomers of oximes **1a–e** and salts **2a–e**.



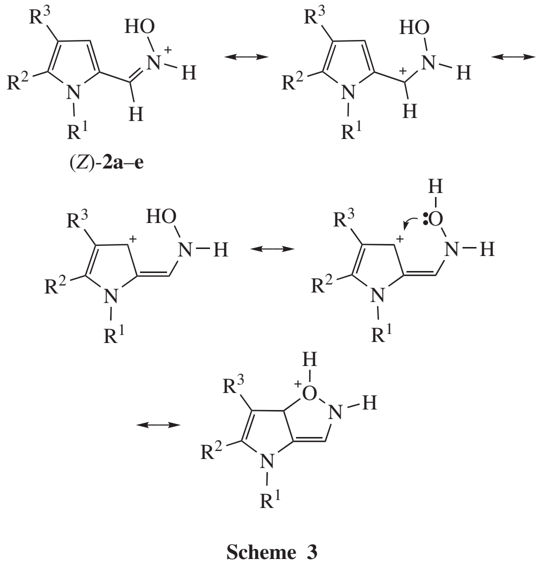
Compound	N–R^1	N=	C-1	C-2	C-3	C-4	C-5	Cα	Cβ
(*E*)-**1a**	–227.8	–41.3	142.6	124.3	113.8	109.8	121.4		
(*Z*)-**1a**	–228.3	–49.4	138.9	124.3	115.3	109.4	121.9		
2a	–225.5	–175.7	139.3	122.5	125.4	111.2	126.2		
(*E*)-**1b**	–210.4	–33.1	142.9	124.8	115.8	110.7	121.7	132.7	100.6
(Z)-**1b**	–210.4	–42.7	135.4	122.5	119.6	111.1	121.2	130.2	104.0
2b	–208.9	–176.3	137.0	120.1	128.4	113.7	128.6	131.3	105.2
(*E*)-**1c**	–211.5	–20.4	142.9	123.3	112.1	124.5	133.3	131.5	111.1
(*Z*)-**1c**	–210.4	–23.6	137.1	121.2	118.5	124.6	132.7	130.6	113.9
2c	–205.3	–177.4	136.2	118.6	126.6	129.9	145.5	128.7	120.1
(*E*)-**1d**	–216.2	–18.6	143.3	126.3	113.2	111.4	137.5	131.9	112.1
(*Z*)-**1d**	–215.7	–20.3	137.5	123.6	119.4	111.2	136.5	131.5	114.2
2d	–209.7	–173.6	135.5	121.5	126.2	113.8	143.5	129.9	117.9
(*E*)-**1e**	–219.4	–19.3	142.7	126.4	110.6	124.6	130.6	132.6	113.7
(*Z*)-**1e**	–218.7	–24.4	137.5	123.5	117.2	124.0	131.4	132.4	115.6
2e	–214.7	–175.6	136.5	120.5	125.1	127.6	140.9	130.6	120.3

Table 2 ^{1}H chemical shifts of *E*- and *Z*-isomers of oximes **1a–e** and salts **2a–e**.

Compound	H-1	H-3	H-4	H-5	H$_A$	H$_B$	H$_X$
(*E*)-**1a**	7.99	6.40	6.22	6.84			
(*Z*)-**1a**	7.29	6.50	6.24	6.95			
2a	7.65	7.08	6.52	7.37			
(*E*)-**1b**	8.10	6.49	6.27	7.15	4.81	5.20	7.55
(*Z*)-**1b**	7.49	7.14	6.37	7.08	4.98	5.29	7.08
2b	8.07	7.92	6.68	7.55	5.42	5.55	7.10
(*E*)-**1c**	8.11	6.51			5.22	5.14	6.91
(*Z*)-**1c**	7.49	7.31			5.36	5.23	6.81
2c	7.85	7.77			5.78	5.44	6.86
(*E*)-**1d**	8.21	6.66	6.29		5.13	4.97	6.98
(*Z*)-**1d**	7.62	7.46	6.39		5.34	5.21	6.80
2d	8.19	7.90	6.67		5.67	5.44	6.81
(*E*)-**1e**	8.17	6.58			5.42	5.33	7.20
(*Z*)-**1e**	7.55	7.36			5.60	5.45	7.10
2e	8.02	7.80			5.89	5.62	7.11

Quantum chemical analysis [B3LYP/6-311G(d,p)][7,‡] confirms that the *Z*-configuration of cation **2b** in *anti*-conformation is indeed by 3.30 kcal mol^{-1} more stable than its *syn*-conformation in which the above stabilization with the hydroxy group cannot be sterically realized (Figure 2). Notably, the *syn*- and *anti*-conformations of the *E*-configuration of the same cation are energetically equal and lie by 2 kcal mol^{-1} above the stabilized *Z*-configuration in *anti*-conformation (1.96 and 2.01 kcal mol^{-1}).

The *Z*-configuration of the unsubstituted pyrrole-2-carboxaldexyde oxime cation **2a** relative to its *E*-configuration is even more stabilized than that of the corresponding 1-vinyl substituted cation **2b** (Figure 3). However, in this case, the most stabilized is the *syn*-conformation which is by 4.60–5.67 kcal mol^{-1} more energetically favorable than the *E*-configuration. This is predictable since the *N*-vinyl group acts as π- and σ-acceptor towards the pyrrole ring.[8] Additionally, in cation **2a**, the pyrrole nitrogen



Scheme 3

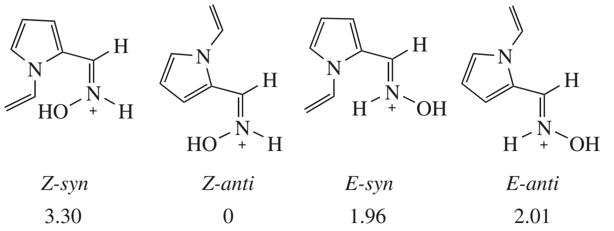


Figure 2 B3LYP/6-311G(d,p) relative energies (kcal mol^{-1}) of configuration of cation **2b** in preferable conformations.

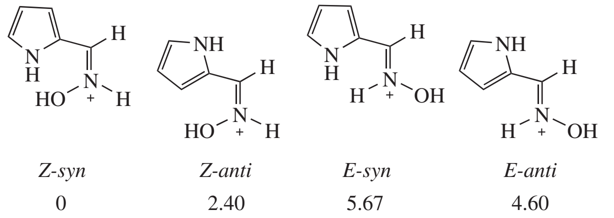
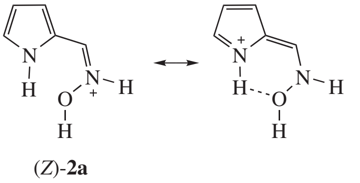


Figure 3 B3LYP/6-311G(d,p) relative energies (kcal mol^{-1}) of configuration of cation **2a** in preferable conformations.

atom is sterically free (no vinyl substituents), therefore, the largest positive charge is expectedly concentrated at the N–H moiety. This is why a stronger stabilization is observed for the *syn*-conformation (Scheme 4). Here, in the *syn*-conformation, the $^{+}$N–H···OH stabilizing interaction (hydrogen bonding) seems more probable (due to the increased acidity of the $^{+}$N–H function). Noteworthy, the *anti*-conformation of this cation is also significantly stabilized (by 2.20 and 3.27 kcal mol^{-1} relative to *anti*- and *syn*-conformations of *E*-configuration, respectively) thus indicating that similar stabilization as in the N-substituted cations (Scheme 3) takes place. The latter is experimentally supported by the large (10.1 ppm) low-field shift of $\delta_{^{13}C}$ for the C-3 atom (Table 1).

The comparison with ordinary (non-pyrrolic oximes) confirms that for acetaldoxime and benzaldoxime, the calculated [B3LYP/6-311G(d,p)] energy preference of the protonated Z-isomers is almost ignorable (0.65 and 0.78 kcal mol^{-1}). Such a small energy difference results in simultaneous existence of the both protonated isomers. As our experiments show, with 10-fold excess CF_3COOH, the *E*/*Z* ratio of benzaldoximes is 1:4. The similar trend of *E*/*Z* isomer ratio was reported for the protonation of acetaldehyde oxime with sulfuric acid though, in contrast to benzaldehyde oxime, the protonated *E*-isomer content prevailed (*E*:*Z* = 11:9).

In conclusion, the stereospecific protonation of pyrrole-2-carboxaldehyde *Z*-oximes has been analyzed by the NMR (^{1}H, ^{13}C, ^{15}N) technique and quantum chemical calculations [B3LYP/6-311G(d,p)] to reveal the through-space stabilization of these cations by the oxime hydroxyl. The essence of the phenomenon is the strong charge transfer from the pyrrole ring towards the protonated oxime function. This stabilization is characteristic of pyrrole-2-carboxaldehyde oximes and does not occur in ordinary aromatic and aliphatic oximes series. The developed stereospecific facile transformation of *E*/*Z* mixture of pyrrole-2-carboxaldehyde oximes to pure salts of *Z*-isomers is the first known method for the synthesis of individual *Z*-isomers of protonated pyrrole-2-carboxaldehyde oximes.



(*Z*)-**2a**

Scheme 4

This work was supported by the Program of the President of the Russian Federation (grant no. NSH-3230.2010.3), the Russian Foundation for Basic Research (grant nos. 08-03-00002a and RFBR-NNSF 10-03-91154) and the National Natural Science Foundation of China (grant nos. 20703049, 20733007, 20573122 and 20873165).

References

1 (*a*) G. H. Barnett, H. J. Anderson and C. E. Loader, *Can. J. Chem.*, 1980, **58**, 409; (*b*) E. Abele and E. Lukevics, *Khim. Geterotsikl. Soedin.*, 2001, 156 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2001, **37**, 141]; (*c*) E. Abele, R. Abele, O. Dzenitis and E. Lukevics, *Khim. Geterotsikl. Soedin.*, 2003, 5 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2003, **39**, 3]; (*d*) E. Abele, R. Abele and E. Lukevics, *Khim. Geterotsikl. Soedin.*, 2003, 963 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2003, **39**, 825]; (*e*) E. Abele, R. Abele and E. Lukevics, *Khim. Geterotsikl. Soedin.*, 2004, 3 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2004, **40**, 1]; (*f*) A. I. Mikhaleva, A. B. Zaitsev and B. A. Trofimov, *Usp Khim.*, 2006, **75**, 884 (*Russ. Chem. Rev.*, 2006, **75**, 797).

2 (*a*) Review of fludioxinyl, March 1995, http://www.pesticides.gov.uk/PSD_PDFs/Evaluations/126_fludioxonil.pdf; (*b*) Chlorfenapyr. http://en.wikipedia.org/wiki/Chlorfenapyr; (*c*) Z. Zhang, A. M. Olland, Y. Zhu, J. Cohen, T. Berrodin, S. Chippari, C. Appavu, S. Li, J. Wilhem, R. Chopra, A. Fensome, P. Zhang, J. Wrobel, R J. Unwalla, C. R. Lyttle and R. C. Winneker, *J. Biol. Chem.*, 2005, **280**, 28468.

3 T. Naito, *Chem. Pharm. Bull.*, 2008, **56**, 1367.

4 (*a*) Y. Li, J. Liu, H. Zhang, X. Yang and Z. Liu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2278; (*b*) Y. Li, H.-Q. Zhang, J. Liu, X.-P. Yang and Z.-J. Liu, *J. Agric. Food Chem.*, 2006, **54**, 3636; (*c*) P.-L. Zhao, C.-L. Liu, W. Huang, Y.-Z. Wang and G.-F. Yang, *J. Agric. Food Chem.*, 2007, **55**, 5697; (*d*) S. Tu, L.-H. Xu, L.-Y. Ye, X. Wang, Y. Sha and Z.-Y. Xiao, *J. Agric. Food Chem.*, 2008, **56**, 5247.

5 A. M. Vasil'tsov, K. Zhang, A. V. Ivanov, I. A. Ushakov, A. V. Afonin, K. B. Petrushenko, S. Li, J. S. Ma, A. I. Mikhaleva and B. A. Trofimov, G. Yang, *Monatsh. Chem.*, 2009, **140**, 1475.
(*a*) M. V. Sigalov, E. Yu. Schmidt and B. A. Trofimov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 1146 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 1060); (*b*) M. V. Sigalov, E. Yu. Schmidt and B. A. Trofimov, *Khim. Geterotsikl. Soedin.*, 1988, 334 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1988, **24**, 272]; (*c*) M. V. Sigalov, E. Yu. Schmidt, A. B. Trofimov and B. A. Trofimov, *J. Org. Chem.*, 1992, **57**, 3934; (*d*) M. V. Sigalov, A. B. Trofimov, E. Yu. Schmidt and B. A. Trofimov, *J. Phys. Org. Chem.*, 1993, **6**, 471; (*e*) M. V. Sigalov, E. Yu. Schmidt, A. I. Mikhaleva, S. E. Korostova, I. M. Lazarev and B. A. Trofimov, *Khim. Geterotsikl. Soedin.*, 1993, 48 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1993, **29**, 40]; (*f*) M. V. Sigalov, A. B. Trofimov, E. Yu. Schmidt and B. A. Trofimov, *Khim. Geterotsikl. Soedin.*, 1993, 825 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1993, **29**, 711].

6 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Nasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malik, A. D. Rabuk, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 2003*, Gaussian, Inc., Pittsburg, 2003.

7 B. A. Trofimov, in *Pyrroles, Part Two: The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles*, ed. R. A. Jones, Wiley, New York, 1992, vol. 48, pp. 131–298.

8 C. E. Holloway and C. P. J. Vuik, *Tetrahedron Lett.*, 1979, **20**, 1017.

Received: 12th October 2010; Com. 10/3610

[‡] The geometries for all structures were calculated at the B3LYP level of theory without symmetry constraints by using the GAUSSIAN 03W program package.[7] The triple splitvalence 6-311G(d,p) basis set of Pople which included *d*-type polarization functions on all nonhydrogen atoms and *p*-type polarization functions on hydrogen atom were adopted in the calculations.