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Reaction of 2-alkoxy- and 2-hydroxypropenals with *o*-phenylenediamine: a route to benzimidazoles and quinoxalines

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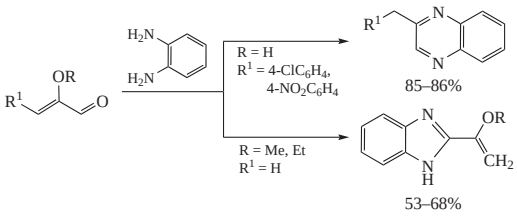
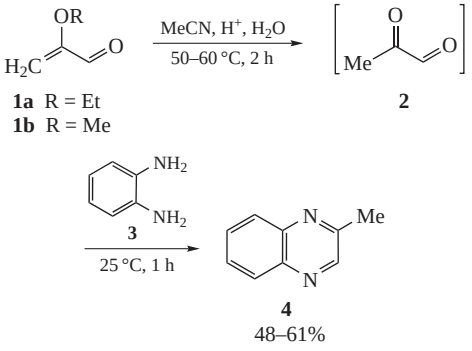
The reaction of *o*-phenylenediamine with 2-alkoxypropenals at room temperature affords 2-(1-alkoxyvinyl)benzimidazoles (53–68%), while 2-hydroxy-3-arylpropenals give 2-(arylmethyl)quinoxalines (85–86%).



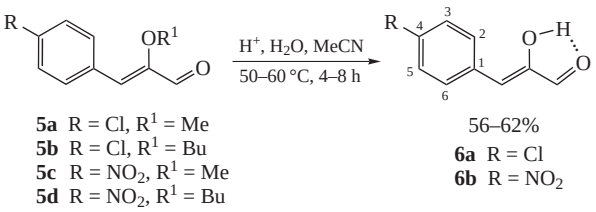
Heterocyclization based on carbonyl compounds including α,β-unsaturated aldehydes is a principal trend in organic synthesis.[1] Benzimidazole[2] and quinoxaline[3] are in a focus of research interest owing to broad spectrum of biological activity of their derivatives. Therefore, the development of straightforward methodology for the synthesis of novel heterocyclic systems represents an urgent challenge. It should be noted that the α-heteroatomic propenals, in which competitive effect of the capto-dative substituents is observed, are rarely employed in the synthesis of heterocycles.

Earlier we have implemented a one-pot synthesis of 2-methylquinoxaline **4** by the cycloaddition of methylglyoxal **2**, *in situ* formed *via* the hydration of 2-alkoxypropenals **1**, to *o*-phenylenediamine **3** (Scheme 1).[4] 2-Alkoxypropenals can be used in weakly acidic medium (25–80 °C, 1–4 h) as convenient equivalent of methylglyoxal for the preparation of heterocyclic compounds.



Scheme 1

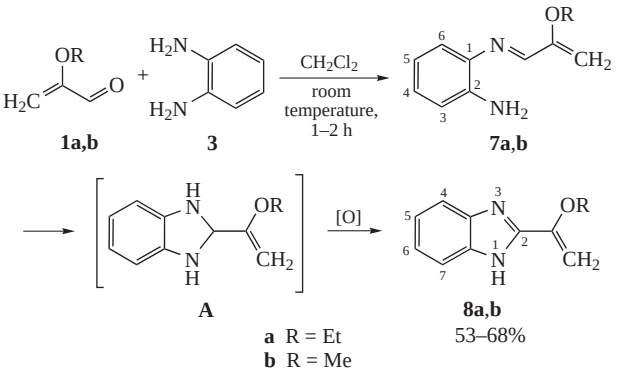
It has been found that the C=C bond of 2-alkoxy-3-(het)-arylpropenals **5** undergoes the hydration according to the Markovnikov rule in a similar fashion (Scheme 2).[5] The products of 2-alkoxy-3-arylpropenals **6a**,**b** hydration appear to be stable in the enol form. The latter is likely due to the formation of quite strong hydrogen bonds as well as to the dative action of the OH group, which is in agreement with electron-withdrawing effect of Cl and NO_2 substituents.



Scheme 2

In continuation of our investigations into the chemistry of α-functionally substituted α,β-unsaturated aldehydes, in the present work we have studied the regiodirectivity of *o*-phenylenediamine **3** addition to 2-alkoxypropenals **1a**,**b** and 2-hydroxy-3-arylpropenals **6a**,**b**.

In fact, the reaction of 2-alkoxypropenals with *o*-phenylenediamine **3** when carried out in dichloromethane without acidic catalyst at room temperature for 1–2 h affords the linear product of condensation at the carbonyl group (^{1}H NMR, Scheme 3). The formed imines **7** upon storage or heating are transformed into the intermediate **A**, which like other imidazolidines[6] is oxidized by air oxygen[7] to more stable benzimidazoles **8**. Thus, compared to earlier synthesis of 2-methylquinoxaline from the same reactants



Scheme 3

in acidic medium,[4] the current procedure allows one to synthesize the stable 2-(1′-alkoxyvinyl)benzimidazoles in good yields.†

To extend the substrate scope of such a procedure, we involved 3-aryl-2-hydroxyacroleins **6a**,**b** in the reaction under similar conditions. Compound **6a** was studied by X-ray diffraction analysis (Figure 1) which proved its enol form of tautomer.‡

The ^{1}H NMR monitoring of the reaction between 3-(4-chlorophenyl)-2-hydroxyacrolein **6a** and *o*-phenylenediamine has revealed that aldehyde **6a** is completely consumed within 3 h, imine **9a** to quinoxaline **10a** ratio being 1 : 1 (Scheme 4). Furthermore, in 24 h only quinoxaline **10a** was detected. Alternative reaction direction leading to benzimidazole is not observed.

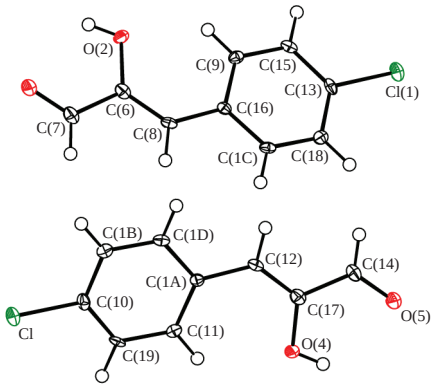
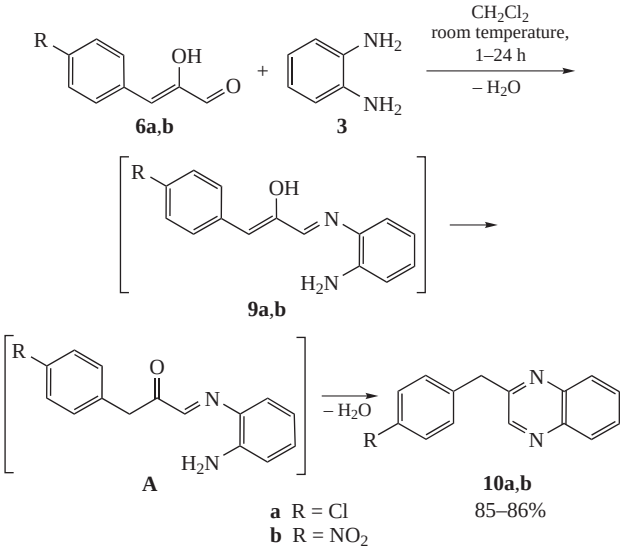


Figure 1 Molecular structure of compound **6a**. Thermal ellipsoids at 50% probability level.

3-(4-Nitrophenyl)-2-hydroxypropenal **6b** reacts with *o*-phenylenediamine faster, even in 1 h only quinoxaline **10b** was displayed. However, imine **9b** can also be detected immediately after mixing the reactants.§



Scheme 4

The structure of quinoxalines **10a**,**b** unambiguously follows from X-ray diffraction analysis of monocrystals (Figure 2)‡ and was confirmed by the data of ^{1}H, ^{13}C, ^{15}N NMR and IR spectroscopy. In a crystal, molecules of compound **10a** are located by layers. The interlayer distance is 3.5 Å that evidences effective π–π-conjugation of the unsaturated fragments in the molecule.

† *2-(1-Ethoxyvinyl)benzimidazole* **8a**. *o*-Phenylenediamine **3** (0.48 g, 4.25 mmol) was added to a solution of compound **1a** (0.45 g, 4.25 mmol) in CH_2Cl_2 (3 ml). In 2 h, intermediate imine **7a** (100%) was detected in the reaction mixture. ^{1}H NMR of **7a** ($CDCl_3$) δ: 1.41 (t, 3H, Me, *J* 7.0 Hz), 3.91 (q, 2H, OCH_2, *J* 7.0 Hz), 4.73 (d, 1H, $=CH_2$, *J* 2.3 Hz), 4.75 (d, 1H, $=CH_2$, *J* 2.3 Hz), 6.67–7.00 (m, 4H, NH_2, H^3, H^4), 6.87 (d, 1H, H^6, *J* 7.8 Hz), 7.00 (t, 1H, H^5, *J* 7.3 Hz), 7.92 (s, 1H, CH=N). The mixture was dried over $MgSO_4$ and then filtered. The solvent was removed. Compound **8a** (0.45 g, 53%) was obtained and recrystallized from CH_2Cl_2, mp 184 °C. ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3H, Me, *J* 7.0 Hz), 4.02 (q, 2H, OCH_2, *J* 7.0 Hz), 4.48 (d, 1H, $=CH_2$, *J* 2.8 Hz), 5.54 (d, 1H, $=CH_2$, *J* 2.8 Hz), 7.21 (m, 2H, H^5, H^6), 7.53 (m, 2H, H^4, H^7). ^{13}C NMR ($CDCl_3$) δ: 14.7 (Me), 63.8 (OCH_2), 87.3 ($=CH_2$), 123.1 (C^4, C^7), 125.3 (C^5, C^6), 135.2 (*C*OCH_2), 148.35 (C^8, C^9), 150.9 (C^2). GC-MS, *m*/*z* (%): 188 $[M]^+$ (66), 173 $[M – Me]^+$ (75), 143 $[M – OEt]^+$ (100), 118 (49) [M – CH_2=C(OEt) – 1]$^+$, 102 (8), 91 (17) $[PhNH]^+$. Found (%): C, 69.89; H, 5.98; N, 15.00. Calc. for $C_{11}H_{12}N_2O$ (%): C, 70.21; H, 6.38; N, 14.89.

2-(1-Methoxyvinyl)benzimidazole **8b** was obtained analogously to **8a** from aldehyde **1b** (0.8 g, 9.3 mmol) and *o*-phenylenediamine **3** (1.0 g, 9.3 mmol) in CH_2Cl_2 (5 ml). ^{1}H NMR of intermediate **7b** (DMSO-d_6) δ: 3.72 (s, 3H, OMe), 4.74 (d, 1H, $=CH_2$, *J* 2.0 Hz), 4.76 (d, 1H, $=CH_2$, *J* 2.0 Hz), 6.65–7.71 (m, 4H, NH_2, H^3, H^4), 6.88 (d, 1H, H^6, *J* 7.7 Hz), 7.03 (t, 1H, H^5, *J* 7.3 Hz), 7.89 (s, 1H, CH=N). The reaction mixture was dried over $MgSO_4$ and then filtered. The solvent was removed. Compound **8b** was isolated by column chromatography on silica gel (elution with hexane–Et_2O, 2 : 1), yield 1.1 g (68%), mp 177 °C. ^{1}H NMR (DMSO-d_6) δ: 3.78 (s, 3H, OMe), 4.53 (d, 1H, $=CH_2$, *J* 2.5 Hz), 5.34 (d, 1H, $=CH_2$, *J* 2.5 Hz), 7.13 (m, 2H, H^5, H^6), 7.50 (m, 2H, H^4, H^7). ^{13}C NMR (DMSO-d_6) δ: 55.2 (OMe), 86.55 ($=CH_2$), 115.1 (C^4, C^7), 122.1 (C^5, C^6), 138.1 (*C*OCH_2), 147.7 (C^8, C^9), 152.0 (C^2). GC-MS, *m*/*z* (%): 174 $[M]^+$ (63), 159 (2) $[M – Me]^+$, 143 (100) $[M – OMe]^+$, 131 (13), 119 (21), 102 (7) $[PhN=C]^+$, 90 (11) $[PhN]^+$. Found (%): C, 68.70; H, 5.68; N, 16.18. Calc. for $C_{10}H_{10}N_2O$ (%): C, 68.94; H, 5.79; N, 16.08.

‡ *Crystallographic data for* **6a**: crystals of 2($C_9H_7ClO_2$) (*M* = 365.19) are monoclinic, space group $P112_1/a$, at 100 K: *a* = 40.217(4), *b* = = 6.8262(8) and *c* = 5.9851(2) Å, β = 90.043(4)°, *Z* = 4, *V* = 1643.1(3) Å^3, d_{calc} = 1.476 g cm^{-3}, μ(MoKα) = 0.41 mm^{-1}, *F*(000) = 752. Total of 24914 reflections were measured and 3119 independent reflections (R_{int} = = 0.0840) were used in a further refinement. The refinement converged to wR_2 = 0.151 and GOF = 1.26 for all independent reflections [R_1 = 0.0650 was calculated against *F* for 2597 observed reflections with $I > 2\sigma(I)$].

Crystallographic data for **10a**: crystals of $C_{15}H_{11}ClN_2$ (*M* = 254.71) are monoclinic, space group $P2_1$, at 100 K: *a* = 10.1720(7), *b* = 4.6105(3) and *c* = 12.8428(9) Å, β = 100.594(3)°, *Z* = 2, *V* = 592.04(7) Å^3, d_{calc} = = 1.429 g cm^{-3}, μ(MoKα) = 0. 30 mm^{-1}, *F*(000) = 264. Total of 16873 reflections were measured and 3495 independent reflections (R_{int} = 0.0590) were used in a further refinement. The refinement converged to wR_2 = = 0.1170 and GOF = 1.090 for all independent reflections [R_1 = 0.0510 was calculated against *F* for 3022 observed reflections with $I > 2\sigma(I)$].

Crystallographic data for **10b**: crystals of $C_{15}H_{11}N_3O_2$ (*M* = 265.27) are monoclinic, space group $P2_1$, at 100 K: *a* = 6.3151(7), *b* = 4.6995(4) and *c* = 20.500(2) Å, β = 91.681(4)°, *Z* = 2, *V* = 608.15(11) Å^3, d_{calc} = = 1.449 g cm^{-3}, μ(MoKα) = 0.10 mm^{-1}, *F*(000) = 276. Total of 21007 reflections were measured and 2386 independent reflections (R_{int} = 0.0632) were used in a further refinement. The refinement converged to wR_2 = = 0.079 and GOF = 1.10 for all independent reflections [R_1 = 0.0329 was calculated against *F* for 2180 observed reflections with $I > 2\sigma(I)$].

The measurements were made on a Bruker D8 VENTURE PHOTON 100 CMOS D diffractometer with MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXTL using a full-matrix least-squares procedure on F^2. The H atoms were determined from a difference Fourier synthesis.

CCDC 1483944–1483946 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

§ *2-(4-Chlorobenzyl)quinoxaline* **10a**. *o*-Phenylenediamine **3** (0.04 g, 0.38 mmol) in CH_2Cl_2 (0.5 ml) was added to a solution of (*Z*)-2-hydroxy-3-(4-chlorophenyl)propenal **6a** (0.07 g, 0.38 mmol) in CH_2Cl_2 (0.5 ml). Molecular sieves 4 Å were added after 10 min. The mixture was stirred at room temperature for 24 h. According to ^{1}H NMR spectrum of the reaction mixture after stirring at room temperature for 3 h, the **10a** : **9a** ratio was 1 : 1. ^{1}H NMR of imine **9a** ($CDCl_3$) δ: 5.76 (s, 1H, CH=C), 6.65–6.76 (m, 4H, NH_2, $H^{3'}$, $H^{4'}$), 7.02 (d, 1H, $H^{6'}$, *J* 8.0 Hz), 7.06 (t, 1H, $H^{5'}$,

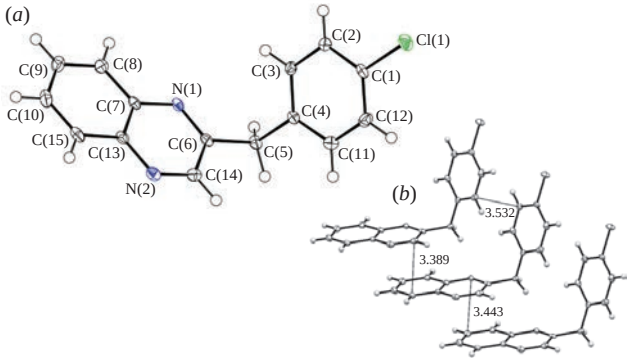


Figure 2 Molecular structure of compound **10a**. Thermal ellipsoids at 50% probability level.

Conjugation is possible between both phenyl and quinoxaline moieties.

A tentative mechanism for **10a**,**b** formation (see Scheme 4) implies initial formation of the Schiff base **9**. Its subsequent tautomerization into keto-form **A** and intramolecular condensation of the keto group with NH_2 fragment furnishes the target quinoxaline cycle **10a**,**b**.

In conclusion, we have developed a straightforward method for the synthesis of 2-(1-alkoxyvinyl)benzimidazoles and 2-(arylmethyl)quinoxalines. The reactivity of 2-heteroatomic 2-alkenals can be controlled by the substituents in their molecules.

The main results were obtained using the equipment of Baikal Analytical Center of Collective Use SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2017.03.020.

References

1 (*a*) N. A. Keiko and N. V. Vchislo, *Asian J. Org. Chem.*, 2016, **5**, 439; (*b*) N. A. Keiko and N. V. Vchislo, *Asian J. Org. Chem.*, 2016, **5**, 1169.

2 (*a*) M. K. Kim, H. Shin, K. Park, H. Kim, J. Park, K. Kim, J. Nam, H. Choo and Y. Chong, *J. Med. Chem.*, 2015, **58**, 7596; (*b*) S. T. Huang, I. J. Hsei and C. Chen, *Bioorg. Med. Chem.*, 2006, **14**, 6106; (*c*) Z. Li, L.-J. Li, T. Sun, L. Liu and Z. Xie, *Dyes Pigm.*, 2016, **128**, 165; (*d*) Y. Shin, J. Suchomel, M. Cardozo, J. Duquette, X. He, K. Henne, Y.-L. Hu, R. C. Kelly, J. McCarter, L. R. McGee, J. C. Medina, D. Metz, T. San Miguel, D. Mohn, T. Tran, C. Vissinga, S. Wong, S. Wannberg, D. A. Whittington, J. Whoriskey, G. Yu, L. Zalameda, X. Zhang and T. D. Cushing, *J. Med. Chem.*, 2016, **59**, 431; (*e*) V. D. Gvozdev, K. N. Shavrin, M. P. Egorov and O. M. Nefedov, *Mendeleev Commun.*, 2016, **26**, 3.

3 (*a*) V. A. Mamedov and A. A. Kalinin, *Russ. Chem. Rev.*, 2014, **83**, 820; (*b*) B. Hu, R. J. Unwalla, I. Goljer, J. W. Jetter, E. M. Quinet, T. J. Berrodin, M. D. Basso, I. B. Feingold, A. G. Nilsson, A. Wilhelmsson, M. J. Evans and J. E. Wrobel, *J. Med. Chem.*, 2010, **53**, 3296; (*c*) R. A. Smits, H. D. Lim, A. Hanzer, O. P. Zuiderveld, E. Guaita, M. Adami, G. Coruzzi, R. Leurs and I. J. P. de Esch, *J. Med. Chem.*, 2008, **51**, 2457; (*d*) D. Benitez, M. Cabrera, P. Hernández, L. Boiani, M. L. Lavaggi, R. Di Maio, G. Yaluff, E. Serna, S. Torres, M. E. Ferreira, N. V. de Bilbao, E. Torres, S. Pérez-Silanes, B. Solano, E. Moreno, I. Aldana, A. L. de Ceráin, H. Cerecetto, M. González and A. Monge, *J. Med. Chem.*, 2011, **54**, 3624.

4 N. A. Keiko, N. V. Vchislo and L. I. Larina, *Russ. J. Org. Chem.*, 2013, **49**, 428 (*Zh. Org. Khim.*, 2013, **49**, 440).

5 N. A. Keiko, N. V. Vchislo, E. A. Verochkina, Yu. A. Chuvashev and L. I. Larina, *Mendeleev Commun.*, 2016, **26**, 431.

6 H. Chikashita, S. Nishida, M. Miyazaki, Y. Morita and K. Itoh, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 737.

7 A. Ben-Alloum, K. Bougrin and M. Soufiaoui, *Tetrahedron Lett.*, 2003, **44**, 5935.

8 S. Lin and L. Yang, *Tetrahedron Lett.*, 2005, **46**, 4315.

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J 7.6 Hz), 7.32 (d, 2 H, H^3, H^5, *J* 8.5 Hz), 7.71 (d, 2 H, H^2, H^6, *J* 8.5 Hz), 8.00 (s, 1H, CH=N). In 24 h, only **10a** was detected. The reaction mixture was filtered. The solvent was removed, and the recrystallization from ethanol gave 0.084 g (86%) of quinoxaline **10a**, mp 76 °C. IR (ν/cm^{-1}): 3035, 2924, 2850, 1557, 1491, 1434, 1093, 1016, 803, 766. ^{1}H NMR ($CDCl_3$) δ: 4.31 (s, 2 H, CH_2), 7.23–7.26 (m, 4 H, ClC_6H_4), 7.70 (dd, 1H, H^6, *J* 6.8, 8.2 Hz), 7.74 (dd, 1H, H^7, *J* 6.8, 8.2 Hz), 8.03 (m, 2 H, H^5, H^8), 8.67 (s, 1H, CH=N). ^{13}C NMR ($CDCl_3$) δ: 42.4 (CH_2), 129.15 ($C^{2'}$, $C^{6'}$), 129.3 (C^5), 129.45 (C^8, C^6), 130.2 (C^7), 130.5 ($C^{3'}$, $C^{5'}$), 133.1 ($C^{4'}$), 136.5 ($C^{1'}$), 141.5 (C^{10}), 142.3 (C^9), 145.75 (C^3), 155.3 (C^2). ^{15}N NMR ($CDCl_3$) δ: –49.2 (CH=N, $^2J_{NH}$ 10.6 Hz), –56.5 (NCH_2). Found (%): C, 70.48; H, 4.31; N, 11.19; Cl, 13.70. Calc. for $C_{15}H_{11}N_2Cl$ (%): C, 70.73; H, 4.35; N, 11.00; Cl, 13.92.

2-(4-Nitrobenzyl)quinoxaline **10b** was obtained analogously to **10a** from aldehyde **6b** (0.1 g, 0.52 mmol) and *o*-phenylenediamine **3** (0.056 g, 0.52 mmol) in CH_2Cl_2 (1 ml). ^{1}H NMR of intermediate imine **9b** (DMSO-d_6) δ: 6.02 (s, 1H, =CH), 7.28–7.38 (m, 2 H, $H^{3'}$, $H^{4'}$), 7.45–7.51 (m, 2 H, $H^{5'}$, $H^{6'}$), 7.94 (d, 2 H, H^2, H^6, *J* 8.9 Hz), 8.11 (d, 2 H, H^3, H^5, *J* 8.9 Hz), 8.33 (s, 1H, HC=N). The recrystallization from ethanol gave 0.116 g (85%) of quinoxaline **10b**, mp 82 °C. IR (ν/cm^{-1}): 3063, 2923, 2853, 1599, 1514, 1345, 1278, 1109, 855, 752. ^{1}H NMR ($CDCl_3$) δ: 4.45 (s, 2 H, CH_2), 7.49 (d, 2 H, $H^{2'}$, $H^{6'}$, *J* 8.45 Hz), 7.72 (dd, 1H, H^6, *J* 6.9, 8.2 Hz), 7.76 (dd, 1H, H^7, *J* 6.9, 8.2 Hz), 8.05 (m, 2 H, H^5, H^8), 8.17 (d, 2 H, $H^{3'}$, $H^{5'}$, *J* 8.45 Hz), 8.71 (s, 1H, CH=N). ^{13}C NMR ($CDCl_3$) δ: 42.45 (CH_2), 124.0 ($C^{3'}$, $C^{5'}$), 129.1, 129.2 (C^6, C^7), 129.7, 130.3 (C^5, C^8), 130.0 ($C^{2'}$, $C^{6'}$), 141.65 (C^2), 142.3 ($C^{1'}$), 145.3 (C^3), 147.2 ($C^{4'}$), 153.8, 153.9 (C^9, C^{10}). ^{15}N NMR ($CDCl_3$) δ: –10.4 (NO_2), –46.6 (CH=N, $^2J_{NH}$ 10.6 Hz), –53.7 (NCH_2). Found (%): C, 67.83; H, 4.26; N, 15.62. Calc. for $C_{15}H_{11}N_3O_2$ (%): C, 67.91; H, 4.18; N, 15.84.