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The reaction of 1,5,6-trimethylbenzimidazole with 1,3-diphenylprop-2-yn-1-one and water: en route to β-amino enones and benzodiazocinones

Kseniya V. Belyaeva, Ludmila V. Andriyankova, Lina P. Nikitina, Andrei V. Afonin, Igor A. Ushakov, Anastasiya G. Mal'kina and Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 395 241 9346; e-mail: boris_trofimov@irioch.irk.ru

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Refluxing the mixture of 1,5,6-trimethylbenzimidazole, 1,3-diphenylprop-2-yn-1-one and water in MeCN for 70 h affords (*Z*)-3-[2-(*N*-formyl-*N*-methylamino)-4,5-dimethylphenylamino]-1,3-diphenylprop-2-en-1-one (75%) and 1,8,9-trimethyl-3,5-diphenyl-1,6-benzodiazocin-2(1*H*)-one (13%).

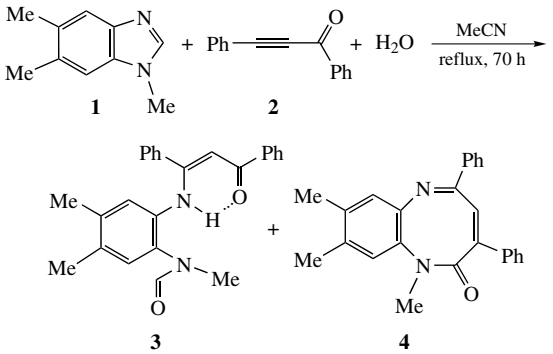
Vinyl carbanions accompanied by inner ammonium cations, the zwitterionic adducts of imidazoles to electron-deficient acetylenes, invoke a growing interest as convenient intermediates for functionalization of the imidazole ring.[1] In the presence of water, 1-substituted imidazoles undergo the ring opening to stereoselectively produce functionalized (*Z*,*Z*)-diazadienes.[2] In the case of benzimidazoles, this reaction may lead to *N*-aryl-substituted β-amino enones.

In 1979, the reaction of 1-substituted benzimidazoles with 4-phenylbut-3-yn-2-one (boiling in toluene for 3–8 days) was studied.[3] However, instead of the expected β-amino enones, benzodiazocinones, the products of the benzimidazole ring expansion were isolated in 7–9% yields, whereas the formation of any open-ring compounds was not mentioned.[3] Later, the structure of these benzodiazocinones was confirmed by X-ray analysis.[4] Since then no information about this reaction appeared in the literature.

Meanwhile, *N*-aryl-substituted β-amino enones and fused diazocinones represent rare families of densely functionalized compounds often possessing a specific biological activity. For example, 5-hydroxymethyl-2-isopropyl-1-methyl-1,4,5,6-tetrahydro-1,4-benzodiazocin-3(2*H*)-one (BL-V8) is a selective modulator for protein kinase C.[5] Diazocinones fused with the pyridine ring are the HIV integrase inhibitors.[6] For the synthesis of fused diazocinones, a variety of methods were developed, including three-component reactions,[7(a)] intramolecular condensation,[7(b)–(f)] N-arylation[7(g)] or Friedel–Crafts,[7(h)] however, most of them were multi-step.

Therefore, we have revisited the reaction of substituted benzimidazoles with acylacetylenes and water. Here we report a preliminary result on the reaction between 1,5,6-trimethylbenzimidazole **1**, 1,3-diphenylprop-2-yn-1-one **2** and water.

Unlike previous publication,[3] the major product of this reaction proved to be the expected (see above) *N*-aryl-substituted β-amino enone **3** (75% yield). The corresponding benzodiazocinone **4**



Scheme 1

was isolated in 13% yield (Scheme 1).† The reaction is stereoselective with respect to product **3**: exclusively *Z*-isomer is formed. This configuration follows from the known *trans*-nucleophilic addition to acetylenes[8] and is additionally stabilized by the strong intramolecular H-bonding (see Scheme 1).

The reaction proceeds in boiling MeCN requiring 70 h for its completion. The reactants molar ratio **1**:**2**:water was 1:1:1. The

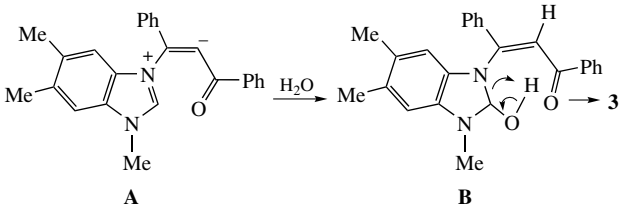
† ^{1}H and ^{13}C NMR and 2D spectra were recorded on an AV-400 Bruker BioSpin spectrometer with HMDS as an internal standard. IR spectra were recorded on a Bruker Vertex-70 instrument. 1,5,6-Trimethylbenzimidazole[10] **1** and benzoylphenylacetylene[11] **2** were prepared by published procedures. Column and thin-layer chromatography was carried out on neutral Al_2O_3 with chloroform–benzene–ethanol (20:4:1) mixture as an eluent.

*(Z)-3-[2-(*N*-Formyl-*N*-methylamino-4,5-dimethylphenylamino)]-1,3-diphenylprop-2-en-1-one* **3**. 1,5,6-Trimethylbenzimidazole **1** (0.160 g, 1 mmol) in MeCN (3.5 ml) was added to a mixture of acetylene **2** (0.206 g, 1 mmol) and H_2O (0.018 g, 1 mmol) in MeCN (1.5 ml). The mixture was stirred at 82 °C for 70 h. The solvent was removed, column chromatography afforded amino enone **3** (0.288 g, 75%) as a yellow powder, mp 142–143 °C (hexane–benzene, 1:1), *syn*/*anti* rotamers, 90:10. IR (microlayer, ν/cm^{-1}): 1681 (C=O), 1603 (C=C). *Syn*-**3**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.70 (s, 1H, N^{8}H), 7.94 (m, 2H, *o*-H, COPh), 7.57 (s, 1H, N^{1}CHO), 7.45–7.30 (m, 5H, C^{9}Ph; 3H, *m*-H, *p*-H, COPh), 6.76 (s, 1H, H^3), 6.68 (s, 1H, H^6), 6.13 (s, 1H, H^{10}), 3.05 (s, 3H, N^{1}Me), 2.15 (s, 3H, C^{5}Me), 2.09 (s, 3H, C^{4}Me). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 190.0 (*C*OPh), 162.9 (N^{1}CHO), 161.9 (C^9), 139.7 (*i*-C, CO*Ph*), 137.0 (C^5), 135.4 (C^4), 134.9 (C^7), 133.5 (*i*-C, C^9*Ph*), 133.3 (C^2), 131.5 (*p*-C, CO*Ph*), 130.0 (*p*-C, C^9*Ph*), 128.9 (C^3), 128.5 (*m*-C, C^9*Ph*), 128.4 (*m*-C, CO*Ph*), 128.0 (*o*-C, C^9*Ph*), 127.8 (C^6), 127.4 (*o*-C, COPh), 96.8 (C^{10}), 32.5 (N^{1}Me), 19.4 (C^5*Me*), 19.2 (C^4*Me*). *Anti*-**3**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.74 (s, 1H, N^{8}H), 8.36 (s, 1H, N^{1}CHO), 7.92 (m, 2H, *o*-H, COPh), 7.45–7.30 (m, 5H, *o*-H, *m*-H, *p*-H, C^{9}Ph; 3H, *m*-H, *p*-H, COPh), 6.91 (s, 1H, H^6), 6.24 (s, 1H, H^3), 6.13 (s, 1H, H^{10}), 3.41 (s, 3H, N^{1}Me), 2.15 (s, 3H, C^{5}Me), 2.11 (s, 3H, C^{4}Me). The carbon signals in ^{13}C NMR spectrum for *anti*-**3** were not collected due to low fraction of this rotamer. Found (%): C, 78.48; H, 6.35; N, 7.68. Calc. for $C_{25}H_{24}N_2O_2$ (%): C, 78.10; H, 6.29; N, 7.29.

reaction was controlled by IR spectroscopy and interrupted after disappearance of the absorption band at 2198 cm^{-1} belonging to the stretching vibrations of the triple bond in acylacetylene **2**.

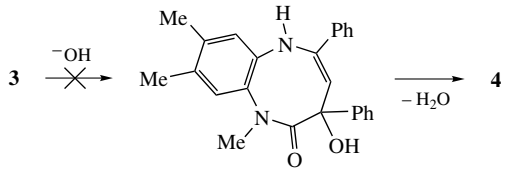
When the reaction of benzimidazole **1** with acylacetylene **2** was conducted in toluene (110 °C, 96 h), the yield of amino enone **3** dropped by about 4 times, while the yield of benzodiazocinone **4** remained approximately the same as that in MeCN. Also, with 5-fold water excess or without special addition of water, the yield of benzodiazocinone **4** almost did not change.

The ring opening of benzimidazole **1** likely involves the quenching of initial zwitterion **A** by water to deliver hemiaminal-like intermediate **B** which further rearranges with the C^2–N^3 bond cleavage (Scheme 2).



Scheme 2

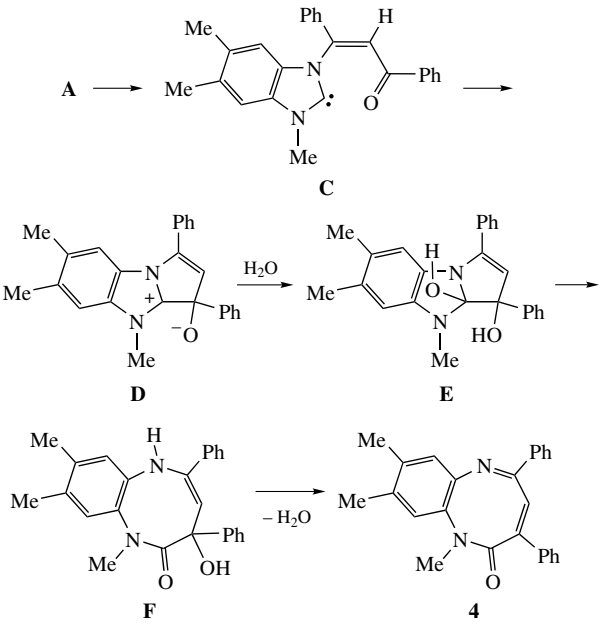
Admittedly, the ring expansion product **4** may result from the benzoin-like condensation of amino enone **3** with further elimination of water and the corresponding prototropic rearrangement (Scheme 3).



Scheme 3

However, the experiments did not confirm this assumption. Apparently, carbanionic site of zwitterion **A** is neutralized by proton from the 2-position of the imidazole ring (Scheme 4). Bearing in mind the unfavorable orientation of the carbanionic center (*anti*- relative to C^2 position), we previously assumed a similar event for the intermolecular proton transfer[9(a)] that was independently confirmed later by quantum-chemical calculations.[9(b)–(d)] Besides, the proton transfer could be mediated by the water molecule protonating the carbanion[2] and then hydroxide deprotonating the imidazolium ion. The carbene intermediate **C** should insert to the carbonyl group to generate intermediate **D**. The latter reacts with water to give intermediate **E** rearranging *via* C^2–N^3 bond cleavage to intermediate **F**. Its final dehydration with the prototropic shift leads to benzodiazocinone **4** (see Scheme 4).

The NOESY spectrum of amino enone **3** contains cross-peaks between olefinic H-10 proton and *ortho*-protons of the



Scheme 4

phenyl groups, thus unambiguously supporting the *Z*-configuration of the olefinic fragment (Figure 1). According to NMR spectra, adduct **3** is a mixture of *syn*- and *anti*-rotamers due to the hindered rotation of the formyl moiety. In the ^{1}H NMR spectrum of amino enone **3**, there are characteristic signals for olefinic protons H-10 (6.13 ppm), CHO (7.57 and 8.36 ppm) and NH (12.70 and 12.74 ppm) groups. In the ^{13}C NMR spectrum of compound **3**, carbon atom C-10 resonates at 96.8, CHO group – at 162.9 and C=O – at 190.0 ppm. The IR spectrum of adduct **3** shows absorption bands of the C=C and C=O bonds at 1603 and 1684 cm^{-1}, respectively.

The NOESY spectrum of benzodiazocinone **4** contains cross-peaks between H-4 and *ortho*-protons of phenyl rings (Figure 1). In its ^{1}H NMR spectrum, singlet of olefinic proton H-4 resonates at 6.37 ppm. The ^{13}C NMR spectrum is presented by resonance of the C=O group at 167.03 ppm. In its IR spectrum, absorption band of the C=O group appears at 1655 cm^{-1}.

In conclusion, the reaction of 1,5,6-trimethylbenzimidazole with 1,3-diphenylprop-2-yn-1-one and water affords (*Z*)-3-[2-(*N*-formyl-*N*-methylamino)-4,5-dimethylphenylamino]-1,3-diphenylprop-2-en-1-one and 1,8,9-trimethyl-3,5-diphenyl-1,6-benzodiazocin-2(1*H*)-one. This result can open a straightforward

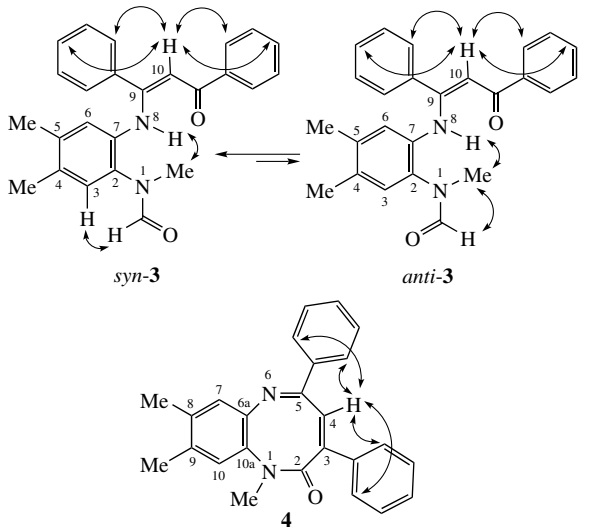


Figure 1 Cross-peaks in the NOESY spectra of amino enone **3** and benzodiazocinone **4**.

1,8,9-Trimethyl-3,5-diphenyl-1,6-benzodiazocin-2(1H)-one **4**. Beige powder (0.048 g, 13%), mp 169–170 °C (ethanol). IR (microlayer, ν/cm^{-1}): 1655 (C=O), 1620, 1610 (C=C). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 7.50–7.40 (m, 3H, *m*-H, *p*-H, C^3Ph; 2H, *m*-H, C^5Ph), 7.34 (m, 3H, *o*-H, *p*-H, C^5Ph), 6.98 (m, 2H, *o*-H, C^3Ph), 6.97 (s, 1H, H^7), 6.83 (m, 1H, H^{10}), 6.37 (s, 1H, H^4), 3.24 (s, 3H, N^1Me), 2.21 (s, 3H, C^9Me), 2.18 (s, 3H, C^8Me). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 169.1 (C^5), 167.0 (C^2), 145.8 (C^{6a}), 144.5 (C^3), 137.3 (*i*-C, C^5Ph), 134.9 (*i*-C, C^3Ph), 134.2 (C^9), 133.2 (C^8), 131.6 (*p*-C, C^5Ph), 130.9 (C^{10a}), 129.2 (*p*-C, C^3Ph), 128.8 (*m*-C, C^3Ph), 128.7 (*m*-C, C^5Ph), 128.4 (*o*-C, C^5Ph), 126.9 (C^7), 126.7 (*o*-C, C^3Ph), 123.2 (C^{10}), 120.1 (C^4), 36.2 (N^1Me), 19.6 (C^9*Me*), 19.4 (C^8*Me*). Found (%): C, 81.57; H, 5.96; N, 7.98. Calc. for $C_{25}H_{22}N_2O$ (%): C, 81.94; H, 6.05; N, 7.64.

access to rare families of densely functionalized pharmaceutically promising compounds. Despite the low non-optimized yield of the benzodiazocinone, its one-step preparation from available inexpensive starting materials may acquire synthetic value since any multi-step approaches to such compounds would hardly give higher overall yields.

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References

1 (*a*) M. Adib, M. Mollahosseini, H. Yavari, M. H. Sayahi and H. R. Bijanzadeh, *Synlett*, 2004, 1086; (*b*) I. Yavari, M. Sabbaghan and Z. Hossaini, *Synlett*, 2006, 2501; (*c*) A. Shaabani, A. H. Rezayan, A. Sarvary, M. Heidary and S. W. Ng, *Tetrahedron*, 2009, **65**, 6063; (*d*) Kh. Pourshamsian, N. Montazeri, S. Ali-Asgari, M. M. Zeydi and E. Biazar, *Orient. J. Chem*., 2011, **27**, 1017; (*e*) Y. Shen, S. Cai, C. He, X. Lin, P. Lu and Y. Wang, *Tetrahedron*, 2011, **67**, 8338; (*f*) K. V. Belyaeva, L. V. Andriyankova, L. P. Nikitina, A. G. Mal'kina, A. V. Afonin and B. A. Trofimov, *Tetrahedron Lett.*, 2012, **53**, 7040; (*g*) B. A. Trofimov, L. V. Andriyankova and K. V. Belyaeva, *Chem. Heterocycl. Compd*., 2012, **48**, 147 (*Khim. Geterotsikl. Soedin*., 2012, 153) and references cited therein; (*h*) B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, A. V. Afonin and I. A. Ushakov, *Synlett*, 2012, **23**, 2069; (*i*) K. V. Belyaeva, L. V. Andriyankova, L. P. Nikitina, A. G. Mal'kina, A. V. Afonin, I. A. Ushakov, I. Yu. Bagryanskaya and B. A. Trofimov, *Tetrahedron*, 2014, **70**, 1091.

2 B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, L. N. Sobenina, A. V. Afonin and I. A. Ushakov, *Org. Lett*., 2013, **15**, 2322.

3 M. Acheson, J. D. Wallis and J. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 1979, 584.

4 J. D. Wallis, *Acta Crystallogr*., 1992, **C48**, 897.

5 I. Shcherbakova, in *Comprehensive Heterocyclic Chemistry III*, eds. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, 2008, vol. 14, p. 255 and references cited therein.

6 (*a*) J. P. Vacca, J. S. Wai, L. S. Payne, R. C. A. Isaacs, W. Han, M. Egbertson and R. Pracitto, *PCT Int. Appl*., *WO 2006121831 A2 20061116*, 2006 (*Chem. Abstr.*, 2006, **145**, 505478); (*b*) S. Lohani, Z. Peng and A. E. Mckeown, *U.S. Pat. Appl. Publ.*, *US 20080280945 A1 20081113*, 2008 (*Chem. Abstr.*, 2008, **149**, 556676); (*c*) R. C. A. Isaacs, J. S. Wai and T. E. Fisher, *PCT Int. Appl.*, *WO 2009154870 A1 20091223*, 2009 (*Chem. Abstr.*, 2009, **152**, 97513).

7 (*a*) P. L. Reddy, D. A. Kumar, M. L. Devi, T. V. Reddy, B. V. S. Reddy and R. Narender, *Tetrahedron Lett.*, 2014, **55**, 657; (*b*) J. G. Topliss, *U.S. Pat. Office*, *US 3409608*, 1968 (*Chem. Abstr.*, 1969, **70**, 57921); (*c*) Yu. E. Ivanov, A. A. Yavolovsky, A. V. Mazepa and S. P. Krasnoshchekaya, *Chem. Heterocycl. Compd*., 2003, **39**, 250 (*Khim. Geterotsikl. Soedin.*, 2003, 281); (*d*) O. Migliara, S. Plescia, P. Diana, V. D. Stefano, L. Camarda and R. Dall'Olio, *Arkivoc*, 2004, **v**, 44; (*e*) V. V. Potapov, N. A. Fetisova, A. V. Nikitin and A. V. Ivachtchenko, *Tetrahedron Lett*., 2009, **50**, 2790; (*f*) A. Mishra and S. Batra, *Eur. J. Org. Chem*., 2010, 4832; (*g*) T. Yang, C. Lin, H. Fu, Y. Jiang and Y. Zhao, *Org. Lett.*, 2005, **7**, 4781; (*h*) S. BouzBouz and M. Sanselme, *Tetrahedron Lett.*, 2009, **50**, 5884.

8 (*a*) S. I. Miller and R. Tanaka, in *Selective Organic Transformations*, ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1970, vol. 1, p 143; (*b*) J. I. Dickstein and S. I. Miller, in *The Chemistry of the Carbon–Carbon Triple Bond*, ed. S. Patai, Wiley, New York, 1978, vol. 2, p. 814.

9 (*a*) B. A. Trofimov, L. V. Andriyankova, K. V. Belyaeva, A. G. Mal'kina, L. P. Nikitina, A. V. Afonin and I. A. Ushakov, *J. Org. Chem*., 2008, **73**, 9155; (*b*) D. Wei and M. Tang, *J. Phys. Chem. A*, 2009, **113**, 11035; (*c*) S. Li, D. Wei, Y. Zhu and M. Tang, *Comp. Theor. Chem*., 2013, **1017**, 168; (*d*) Y. Wang, J. Y. Ren, S. J. Qi, D. H. Wei and M. S. Tang, *Comp. Theor. Chem.*, 2014, **1049**, 35.

10 O. V. Starikova, G. V. Dolgushin, L. I. Larina, T. N. Komarova and V. A. Lopyrev, *Arkivoc*, 2003, **xiii**, 119.

11 A. S. Zanina, S. I. Shergina, I. E. Sokolov and R. N. Myasnikova, *Russ. Chem. Bull.*, 1995, **44**, 689 (*Izv. Akad. Nauk., Ser. Khim*., 1995, 710).

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