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Insertion of 1,3-diphenylprop-2-yn-1-one into imidazo[4,5-*b*]pyridines in the presence of water: one-pot synthesis of pyrido[2,3-*b*][1,4]diazocin-9-ones

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1,3-Diphenylprop-2-yn-1-one is inserted into 3-substituted imidazo[4,5-*b*]pyridines upon refluxing in MeCN in the presence of equimolar amount of water to afford pyrido[2,3-*b*][1,4]diazocin-9-ones in up to 61% yield.

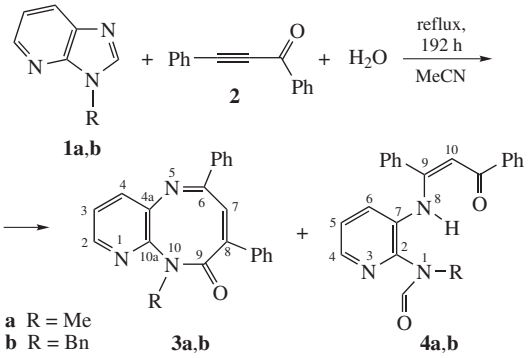
Diazocinones fused with aromatic or heteroaromatic cycles, though hardly accessible, attract attention due to their potential physiological activity. Among them, 5-hydroxymethyl-2-isopropyl-1-methyl-1,4,5,6-tetrahydro-1,4-benzodiazocin-3(2*H*)-one (BL-V8) exhibits the properties of selective modulators for protein kinase C,[1] while diazocinones annelated with the pyridine ring were claimed to be HIV integrase inhibitors.[2] No wonder that the synthesis of condensed diazocinones are under steady progress.[3] For this purpose, intramolecular condensation,[3(a)] N-arylation,[3(b)] Friedel–Crafts,[3(c)] or three-component reactions[3(d)] have been employed, but, as a rule, these methods are multi-step and do not provide good yields.

More than 30 years ago, benzodiazocinones were isolated in 7–9% yields, when 1-substituted benzimidazoles were boiled with 4-phenylbut-3-yn-2-one under anhydrous conditions for 3–8 days.[4,5] Any further investigations of this reaction were not continued, obviously because of the impractical yields of benzodiazocinones.

Recently, we have found that the reaction between substituted benzimidazoles, acylacetylenes and water delivered products of imidazole-ring cleavage, β-arylaminovinyl ketones, in up to 75% yield.[6] The minor products of this reaction appeared to be benzodiazocinones (13% yield,[6(a)] which increased up to 28% yield in the presence of D_2O[6(b)]) resulted from imidazole-ring expansion.

Here we report the preliminary results concerning our attempt to extend this reaction over another type of condensed imidazoles, namely imidazo[4,5-*b*]pyridines, in hope to shift the products ratio in favor of diazocinones. Indeed, unlike benzimidazoles, in imidazopyridines, the proton in C-2 position should be expected to be more acidic due to a stronger electron-withdrawing effect of the fused pyridine moiety as compared with the benzene ring.

The experiment, carried out with 3-methylimidazo[4,5-*b*]-pyridine **1a** and 1,3-diphenylprop-2-yn-1-one **2** in the presence of water (1:1:1 molar ratio), confirmed these expectations. The yield of the ring-expansion product **3a** was 61%, while the yield of ring-opening product, β-aminovinyl ketone **4a**, was 3% (^{1}H NMR), *i.e.*, **3a**:**4a** ratio reached 95:5. The reaction was implemented in boiling MeCN (192 h, Scheme 1).†



Scheme 1

† ^{1}H, ^{13}C, ^{15}N and 2D NMR spectra were recorded with an AV-400 Bruker BioSpin spectrometer with HMDS (^{1}H NMR) and $MeNO_2$ (^{15}N NMR) as internal standards. IR spectra were recorded on a Bruker Vertex-70 instrument. 3-Substituted imidazo[4,5-*b*]pyridines **1a**,**b**[9] and 1,3-diphenylprop-2-yn-1-one **2**[10] were prepared by described methods. Column and thin-layer chromatography were carried out on neutral Al_2O_3 with chloroform–benzene–ethanol (20:4:1) mixture as eluent.

Synthesis of compounds **3a** *and* **4a**. 3-Methylimidazo[4,5-*b*]pyridine **1a** (0.133 g, 1.00 mmol) in MeCN (1.5 ml) was added to a mixture of alkyne **2** (0.206 g, 1.00 mmol) and H_2O (0.018 g, 1.00 mmol) in MeCN (1.5 ml). The mixture was stirred at 82 °C for 192 h. The solvent was removed, column chromatography afforded pyridodiazocinone **3a** and β-aminovinylketone **4a**. Conversion of initial 3-methylimidazo[4,5-*b*]-pyridine **1a** was 82%.

*10-Methyl-6,8-diphenylpyrido[2,3-*b*][1,4]diazocin-9(10*H*)-one* **3a** was obtained as a beige powder (0.170 g, 61%), mp 192–193 °C (ethanol). IR (microlayer, ν/cm^{-1}): 1655 (C=O), 1624, 1609 (C=C). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 8.29 (dd, 1H, H-2, $^3J_{H^2,H^3}$ 4.4 Hz), 8.03 [m, 2H, *o*-H, C(8)-Ph], 7.50–7.40 [m, 3H, *m*,*p*-H, C(8)-Ph; 2H, *o*-H, C(6)-Ph], 7.44 (dd, 1H, H-4, $^3J_{H^3,H^4}$ 7.5 Hz, $^4J_{H^2,H^4}$ 1.5 Hz), 7.36 [m, 3H, *m*,*p*-H, C(6)-Ph], 7.25 (dd, 1H, H-3, $^3J_{H^2,H^3}$ 4.4 Hz), 6.49 (s, 1H, H-7), 3.36 [s, 3H, N(10)-Me]. ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 168.4 (C-6), 168.3 (C-9), 145.8 (C-10a), 145.2 (C-2), 144.8 (C-8), 143.5 (C-4a), 136.5 [*i*-C, C(6)-Ph], 134.6 [*i*-C, C(8)-Ph], 132.1 [*p*-C, C(6)-Ph], 131.7 (C-4), 129.4 [*p*-C, C(8)-Ph], 128.9 [*m*-C, C(8)-Ph], 128.8 [*m*-C, C(6)-Ph], 128.5 [*o*-C, C(6)-Ph], 126.7 [*o*-C, C(8)-Ph], 123.0 (C-3), 119.4 (C-7), 34.2 [N(10)-Me]. ^{15}N NMR (40.55 MHz, $CDCl_3$) δ: –62.0 (N-5), –77.1 (N-1), –248.5 (N-10). Found (%): C, 77.53; H, 4.98; N, 12.09. Calc. for $C_{22}H_{17}N_3O$ (339.39) (%): C, 77.86; H, 5.05; N, 12.38.

N-*Methyl*-N-*(3-{[(Z)-3-oxo-1,3-diphenylprop-1-enyl]amino}pyridin-2-yl)formamide* **4a** (3% according to ^{1}H NMR spectrum of reaction mixture). IR (microlayer, ν/cm^{-1}): 1685 (C=O), 1605 (C=C). *syn*/*anti* Rotamers, ratio 85:15. *syn*-**4a**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.79 [s, 1H, N(8)H], 8.30 [s, 1H, N(1)CHO], 8.16 (m, 1H, H-4), 7.95 (m, 2H, *o*-H, Ph in Bz), 7.50–7.25 [m, 5H, *o*,*m*,*p*-H, C(9)-Ph; 3H, *m*,*p*-H, Ph in Bz;

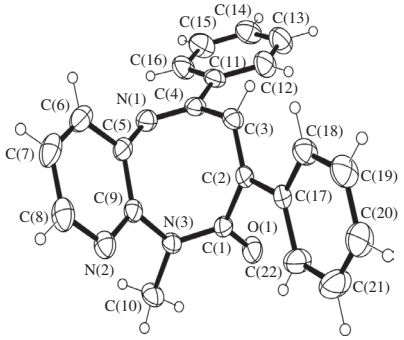


Figure 1 Molecular structure of pyridodiazocinone **3a**.

The process was controlled by IR spectroscopy and stopped after disappearance of the absorption band at 2198 cm^{-1} (the stretching vibrations of the triple bond in acylacetylene **2**).

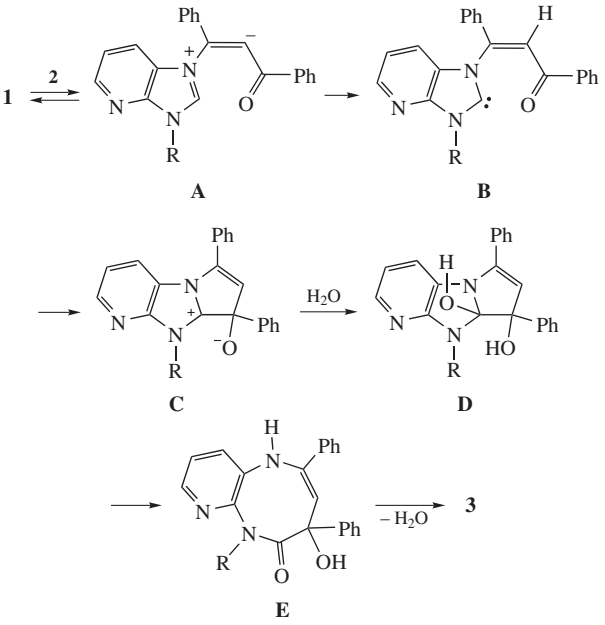
The structure of pyridodiazocinone **3a** has been unambiguously assigned by the X-ray analysis‡ of single crystals of product (Figure 1) and confirmed by ^{1}H, ^{13}C, ^{15}N NMR, 2D (NOESY, COSY, HMBC, HSQC), and IR spectroscopy.

The structure of compound **3a** is formed by two crystallographically independent molecules, one of which is shown in Figure 1. The conformation of 8-membered ring in molecule of pyridodiazocinone **3a** is very similar to the boat.

In the NOESY spectrum of pyridodiazocinone **3a**, there are cross-peaks between H-7 and *ortho*-protons of the phenyl rings. In the ^{1}H NMR spectrum of adduct **3a**, singlet of olefinic proton H-7 resonates at 6.49 ppm. The ^{13}C NMR spectrum is presented by resonance of the C=O group at 168.3 ppm. There are three signals of nitrogen in ^{15}N NMR spectrum of compound **3a**: –62.0 (N-5), –77.1 (N-1), –248.5 (N-10) ppm. In the IR spectrum, absorption band of the C=O group appears at 1655 cm^{-1}.

Noteworthy, the reaction is strictly regioselective: while both nitrogen atoms of **1** (N-1 and N-4) could form zwitterionic species (as shown previously for diverse pyridine[7] and imidazole[8] systems), in this case, only imidazole nitrogen N-1 triggers the cascade transformations *via* intermediate **A** (*vide infra*).

According to the previous mechanistic rationalizations,[8] the assemblage of pyridodiazocinone may involve the following domino sequence. Carbanionic site of zwitterion **A**, the adduct of nucleophilic addition of imidazopyridine **1** to alkyne **2**, is quenched by proton transfer from C-2 position of the imidazole ring. The following insertion of the carbene intermediate **B** into the carbonyl group generates intermediate **C**. The latter uptakes molecules of water to give intermediate **D** rearranging *via* C(2)–N(1) bond cleavage to intermediate **E**. The prototropic shift and dehydration in intermediate **E** furnish pyridodiazocinone **3** (Scheme 2).



Scheme 2

This mechanism is in agreement with the strong substituent effect on the products ratio. Indeed, when 3-methyl group is replaced by benzyl substituent (substrate **1b**), **3b**:**4b** ratio becomes 31:69 thus being inverted in favor of the ring-opening product **4b**.§ This inversion may result from the expected steric screening of the 2-position by the *ortho*-hydrogen of benzyl substituent that interfers the formation of carbene **B** and its further intramolecular addition to the carbonyl group. Consequently, the probability of the ring cleavage to form product **4b** augments.

The characteristic signals in the ^{1}H NMR and IR spectra of compounds **4a** and **4b** are close to those of β-arylaminovinyl ketones obtained from benzimidazole, 1,3-diphenylprop-2-yn-1-one and water under similar conditions.[6]

1H, H-6], 7.06 (m, 1H, H-5), 6.23 (s, 1H, H-10), 3.12 [s, 3H, N(1)Me]. *Anti*-**4a**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.53 [s, 1H, N(8)H], 8.48 [s, 1H, N(1)CHO], 8.14 (m, 1H, H-4), 8.04 (m, 2H, *o*-H, Ph in Bz), 7.50–7.25 [m, 5H, *o*,*m*,*p*-H, C(9)-Ph; 3H, *m*,*p*-H, Ph in Bz; 1H, H-6], 7.06 (m, 1H, H-5), 6.16 (s, 1H, H-10), 3.53 [s, 3H, N(1)Me]. The ^{13}C NMR spectrum and elemental analysis were not obtained due to small amounts of product **4a** in reaction mixture.

‡ *Crystal data for pyridodiazocinone* **3a**. Single crystals of **3a** ($C_{22}H_{17}N_3O$, M = 339.39) were grown from ethanol, monoclinic, space group $P2_1/n$ (no. 14), a = 18.588(2), b = 9.0500(7) and c = 21.296(2) Å, β = 100.020(4)°, V = 3527.9(5) Å^3, Z = 8, T = 296 K, μ(MoKα) = 0.080 mm^{-1}, d_{calc} = = 1.278 g cm^{-3}, 57680 reflections collected, 6941 unique (R_{int} = 0.052) which were used in all calculations. The final R_1 was 0.0515 [$I > 2\sigma(I)$] and wR_2 was 0.1416 (all data). The XRD data were collected with a Bruker Kappa Apex II diffractometer, using MoKα (λ = 0.71073 Å) radiation with a graphite monochromator. Absorption corrections were applied using the empirical multiscan method with the SADABS program.[11] The structures were solved by direct methods using the SHELXS-97 program[12] and refined by the least-squares method in the fullmatrix anisotropic approximation using the SHELXL-97 program.[12] The H atom positions were located geometrically and refined using a riding model. The obtained structures were analyzed for exposing shortened contacts between nonbonded atoms with the programs PLATON[13] and MERCURY.[14]

CCDC 1032968 contains 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.

For more details, see Online Supplementary Materials.

§ *Synthesis of compounds* **3b** *and* **4b**. Analogously from alkyne **2** (0.206 g, 1.00 mmol), H_2O (0.018 g, 1.00 mmol) and 3-benzylimidazo[4,5-*b*]pyridine **1b** (0.209 g, 1.00 mmol) in MeCN (2.5 ml) (82 °C, 194 h), pyridodiazocinone **3b** and β-aminovinylketone **4b** were obtained. Conversions of initial 3-benzylimidazo[4,5-*b*]pyridine **1b** and alkyne **2** were 50 and 54%, respectively.

*10-Benzyl-6,8-diphenylpyrido[2,3-*b*][1,4]diazocin-9(10*H*)-one* **3b** was obtained as a dark-yellow oil (0.050 g, 24%). IR (microlayer, ν/cm^{-1}): 1661 (C=O), 1607, 1597 (C=C). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 8.24 (m, 1H, H-2), 7.94 [m, 2H, *o*-H, C(8)-Ph], 7.50–7.10 [m, 3H, *m*,*p*-H, C(8)-Ph; 5H, *o*,*m*,*p*-H, C(6)-Ph; 5H, *o*,*m*,*p*-H, N(10)-Bn, 1H, H-4; 1H, H-3], 6.50 (s, 1H, H-7), 5.62 and 4.71 [d, 2H, CH_2 in N(10)-Bn, $^{2}J_{H,H}$ 14.7 Hz]. ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 168.1 (C-6), 167.4 (C-9), 144.6 (C-10a), 145.1 (C-2), 144.5 (C-8), 144.3 (C-4a), 136.8 [*i*-C, N(10)-Bn], 136.6 [*i*-C, C(6)-Ph], 134.7 [*i*-C, C(8)-Ph], 132.1 [*p*-C, C(6)-Ph], 131.0 (C-4), 129.5 [*p*-C, C(8)-Ph], 128.9 [*m*-C, N(10)-Bn], 128.8 [*m*-C, C(6)-Ph], 128.5 [*m*-C, C(8)-Ph], 128.4 [*o*-C, C(6)-Ph], 128.2 [*o*-C, N(10)-Bn], 127.4 [*p*-C, N(10)-Bn], 126.7 [*o*-C, C(8)-Ph], 123.0 (C-3), 119.6 (C-7), 50.9 [CH_2, N(10)-Bn]. Found (%): C, 81.32; H, 5.33; N, 9.92. Calc. for $C_{28}H_{21}N_3O$ (415.49) (%): C, 80.94; H, 5.09; N, 10.11.

Based on the results obtained the following conclusions can be made. (i) Unlike 1-substituted benzimidazoles, 3-methylimidazo[4,5-*b*]pyridine reacts with alkyne **2** and water *via* insertion of the alkyne into the imidazole counterpart to mainly afford pyridodiazocinone in 61% yield, while the yield of the ring-cleavage product is just 3%. This suggests a general character of the reaction found for the series of imidazopyridines. (ii) A strong influence of substituent structure at the 3-position of the imidazopyridine ring on the expansion/cleavage ratio has been observed. This fact supports the proposed mechanism with participation of carbene intermediate. (iii) Chemoselectivity of the three-component reaction between condensed imidazoles, electrophilic alkynes and water (ring-opening *vs*. alkyne insertion) is strongly controlled by structure of the annelated counterpart of the molecule that opens new wide possibilities for the synthesis of earlier inaccessible diazocinones and functionalized β-aminovinylketones.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.01.007.

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N-*Benzyl*-N-*(3-[(Z)-3-oxo-1,3-diphenylprop-1-enyl]aminopyridin-2-yl)formamide* **4b** was obtained as a light-yellow powder (0.117 g, 54%), mp 62–65 °C (hexane). IR (microlayer, ν/cm^{-1}): 1687, 1683 (C=O), 1605, 1596 (C=C). *syn*/*anti* Rotamers, ratio 55:45. *syn*-**4b**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.87 [s, 1H, N(8)H], 8.45 [s, 1H, N(1)CHO], 8.11 (s, 1H, H-4), 7.99 (m, 2H, *o*-H, Ph in Bz), 7.50–7.00 [m, 4H, *o*,*m*-H, C(9)-Ph; 3H, *m*,*p*-H, Ph in Bz; 5H, *o*,*m*,*p*-H in N(1)-Bn], 6.90 (m, 1H, *p*-H, Ph in Bz), 6.71 (m, 2H, H-5, H-6), 6.22 (s, 1H, H-10), 5.12 [s, 2H, CH_2 in N(1)-Bn]. ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 190.0 [N(1)-CHO], 162.9 [C=O, Bz], 160.4 (C-9), 146.7 (C-2), 144.7 (C-4), 139.4 (*i*-C, Bz), 136.5 (*p*-C, Bz), 135.8 [*i*-C, C(9)-Ph], 134.9 [*i*-C, N(1)-Bn], 134.0 (C-6), 131.6 (C-7), 130.3 (*p*-C, Bz), 129.1 [*p*-C, C(9)-Ph], 128.9 [*m*-C, C(9)-Ph], 128.6 [*m*-C, N(1)-Bn; *o*-C, C(9)-Ph; *m*-C, Bz; *o*-C, Bz], 46.8 [CH_2, N(1)-Bn]. *anti*-**4b**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.25 [s, 1H, N(8)H], 8.77 [s, 1H, N(1)CHO], 8.13 (s, 1H, H-4), 8.01 (m, 2H, *o*-H, Ph in Bz), 7.50–7.00 [m, 4H, *o*,*m*-H, C(9)-Ph; 3H, *m*,*p*-H, Ph in Bz; 5H, *o*,*m*,*p*-H in N(1)-Bn], 6.90 (m, 1H, *p*-H, Ph in Bz), 6.72 (m, 1H, H-5), 6.60 (m, 1H, H-6), 6.10 (s, 1H, H-10), 5.15 [s, 2H, CH_2 in N(1)-Bn]. ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 190.7 [N(1)CHO], 162.2 (C=O, Bz), 160.0 (C-9), 146.7 (C-2), 143.9 (C-4), 139.4 (*i*-C, Bz), 135.8 [*i*-C, C(9)-Ph], 134.0 [*p*-C, Bz; *i*-C, N(1)-Bn], 132.0 (C-6), 131.7 (C-7), 129.6 (*p*-C, Bz), 129.1 [*p*-C, C(9)-Ph], 128.9 [*m*-C, C(9)-Ph; *m*-C, N(1)-Bn], 128.6 [*o*-C, C(9)-Ph; *m*-C, Bz], 128.1 (*p*-C, Bz), 52.0 [CH_2, N(1)-Bn]. Found (%): C, 77.47; H, 4.92; N, 9.27. Calc. for $C_{28}H_{23}N_3O_2$ (%): C, 77.58; H, 5.35; N, 9.69.