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2,4-Diphenylpyrido[2,1-*a*]isoquinolinium nitrite from the domino reaction between isoquinoline, 1,3-diphenylprop-2-yn-1-one and nitromethane

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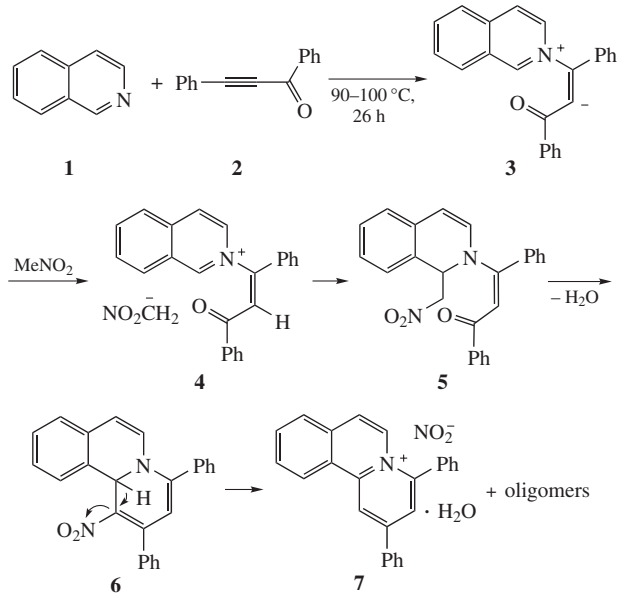
The three-component reaction between isoquinoline, 1,3-diphenylprop-2-yn-1-one and nitromethane (90–100 °C, 26 h) affords 2,4-diphenylpyrido[2,1-*a*]isoquinolinium nitrite in 23% yield along with oligomers.

Quinolizinium salts were first obtained by the reaction of isoquinoline with dimethyl acetylenedicarboxylate under oxidative conditions.[1,2] Meanwhile, the data on benzoquinolizine cations and some related systems were shortly reviewed.[3,4] An original synthesis of 2,4-diphenylpyrido[2,1-*a*]isoquinolinium tetrafluoroborate was described by Katritzky *et al*.[5] A decade ago we initiated a general methodology of functionalization of azines[6–10] and azoles[11,12] *via* zwitterionic intermediates, the adducts of such heterocycles to electron-deficient acetylenes, which were actually the iminium cations with carbanionic counterions. Now this methodology keeps successfully developing by both our[13,14] and other[15–23] groups. The adducts of isoquinoline and other azines with electron-deficient acetylenes have been used for further reactions with other electrophiles such as hexachloroacetone,[17] 1,3-dicarbonyl compounds,[18] benzoyl cyanide,[19] diketone and water,[20] 1,3-dimethylalloxane,[21] aroylnitromethanes,[22] and diphenyl phosphite.[23]

In this communication, we describe the three-component reaction between isoquinoline **1**, 1,3-diphenylprop-2-yn-1-one **2** and nitromethane (90–100 °C, 26 h, Scheme 1). According to the previous results[20,23–25] we expected the deprotonation of nitromethane with the zwitterion **3** to deliver *N*-vinylisoquinolinium cation accompanied by nitromethylene counteranion (intermediate **4**), which then forms the covalent bond between the 1-position and the CH_2 group thus affording *N*-2-benzoyl-1-phenylethenyl-1-nitromethylisoquinoline **5**. However, instead of isoquinoline **5**, 2,4-diphenylpyrido[2,1-*a*]isoquinolinium nitrite **7** monohydrate was isolated in 23% yield, the other products being oligomers. Unlike most functionalizations of azines or azoles *via* the zwitterionic adducts with electron-deficient acetylenes usually proceeding at room temperature,[13–25] in this case a prolonged (26 h) heating (at 90–100 °C) was required. No reaction at ambient temperature occurred, while under microwave irradiation (150 °C, 1 h), only oligomers were formed. The reaction was monitored with IR spectroscopy by disappearance of the C≡C absorption band at 2200 cm^{-1}.



Scheme 1

Apparently, the reaction does not stop at the stage of intermediate **5** but continues in a domino manner involving intramolecular Claisen-like condensation with elimination of a molecule of water to close the six-membered ring (intermediate **6**). The elimination of nitrite anion from this intermediate produces carbocation located in the outer six-membered ring which is further stabilized by the hydride ion transfer from the 1-position of the isoquinoline cycle to give the cation **7**.†

The structure of salt **7** has been assigned using NMR technique, 2D COSY, NOESY, HSQC, HMBC experiments, IR and MALDI-TOF spectra, as well as quantum-chemical calculations.

† ^1H, ^{13}C, ^{15}N NMR and 2D NOESY spectra were recorded on an AV-400 Bruker BioSpin spectrometer with HMDS (^1H, ^{13}C) or nitromethane (^{15}N) as internal standards. IR spectra were recorded on a Bruker Vertex 70 instrument. Mass spectra MALDI were obtained in reflectron mode, MS/MS spectra were obtained in lift mode on a Bruker ultrafleXtreme TOF/TOF instrument, a nitrogen laser operating at 337 nm. The analyte (5 pmol) was deposited onto the NALDI target in 1–2 μl droplets from the sample solution in $CHCl_3$. The spectrum was recorded in the mode of positive ions by summing the signals from several points of the sample. Melting points were determined using a Kofler micro hot stage apparatus. Elemental analyses were performed with a FLASH EA 1112 Series instrument. Isoquinoline and nitromethane were commercial reagents, 1,3-diphenylprop-2-yn-1-one was prepared as described.[30]

*2,4-Diphenylpyrido[2,1-*a*]isoquinolinium nitrite monohydrate* **7**. Isoquinoline (0.064 g, 0.5 mmol) was added to a solution of 1,3-diphenylprop-2-yn-1-one (0.103 g, 0.5 mmol) in nitromethane (5 ml) with stirring. The mixture was stirred at 90–100 °C for 26 h. The solvent was distilled off *in vacuo* and the residue was washed with acetone to give the product **7** (0.036 g, 23%) as a light-pink powder, mp 226–228 °C. Light-brown oligomers (0.062 g, 21%), which were dissolved in acetone, then were obtained by column chromatography (Al_2O_3, chloroform–benzene–ethanol, 20:4:1), mp 87–109 °C (decomp.). Initial isoquinoline was recovered (0.015 g, conversion was 77%).

In the ^{1}H and ^{13}C NMR spectra of product **7**, all peaks are observed in the regions characteristic of the ^{1}H and ^{13}C resonances of aromatic and heteroaromatic fragments, *i.e.* they contain no signals corresponding to the aliphatic CH_2 and CH groups (structures **5** and **6**). In the ^{15}N NMR spectrum, a signal of quaternized nitrogen atom is present at –181.3 ppm.

Quantum-chemical calculations of the ^{13}C chemical shifts in cation **7** in singlet state for optimized geometry have been performed. The geometry was optimized using GAUSSIAN-09[26] package at B3LYP/6-311+G(2d,p) basis set, shielding constants were computed at the same theoretical level and basis set using the GIAO method.[27] The shielding constants σ were converted to the chemical shifts δ according to the equation $\delta = (\sigma - B)/A$, where empirical coefficients $A = -1.023$ and $B = 181.38$ were taken from ref. 28.

The values of experimental and theoretically calculated chemical shifts ^{13}C for compound **7** are given in Table 1. It is evident that the values of calculated chemical shifts ^{13}C of the cation correlate well with those of product **7**. Maximum deviation of theoretical value from experimental one is 5.4 ppm, while average absolute deviation equals only 1.9 ppm that is below the deviation value observed during the calculation of chemical shifts ^{13}C at the indicated theoretical level.[28]

Moreover, some other spectral effects support the structure of compound **7**. First, in the NOESY spectrum, the equal in intensity cross-peaks between protons H^1 and H^3 of the pyridine moiety and *ortho*-protons of a phenyl ring are observed thus indicating that this substituent is located at the 2-position. Besides, the signal H^1 shows additional cross-peak with the signal H^{11}, and H^3 has a cross-peak with the signal of *ortho*-proton of second phenyl ring at the 4-position. Second, the found constants $^4J_{H^1,H^3} = 1.7$ Hz and $^1J_{C^1,H^1} = {}^1J_{C^3,H^3} = 160$ Hz are common to spin–spin interactions in the pyridine ring.[29]

Notably, all the ^{1}H NMR signals of cation **7** are very close by their values and multiplicity to those of exactly the same cation (but with BF_4 anion) synthesized by Katritzky *et al. via* entirely different transformation (from a pyrylium salt and β,β-dimethoxyethylamine).[5]

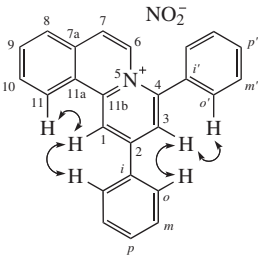
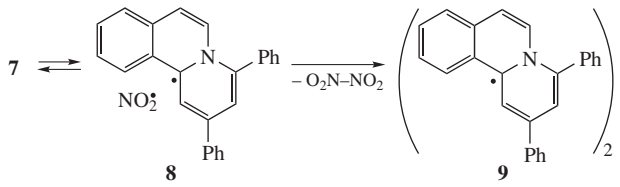


Table 1 Experimental and calculated chemical shifts ^{13}C of compound **7**.[a]

Carbon atom	δ/ppm		
	Experimental	Calculated	Deviation
C^1	118.43	117.77	–0.66
C^2	149.14	154.53	5.39
C^3	123.93	125.61	1.68
C^4	148.99	152.77	3.78
C^6	127.55	126.26	–1.29
C^7	122.43	123.79	1.36
C^{7a}	131.10	131.69	0.59
C^{11a}	125.38	125.67	0.29
C^{11b}	143.94	143.93	–0.01

[a] Chemical shifts of the aromatic fragments (calculated values are given in parentheses) are as follows: C^8, 128.07 (129.81); C^9, 134.01 (137.30); C^{10}, 130.88 (133.93); C^{11}, 126.65 (124.94); C^i, 134.09 (134.70); C^o, 128.70 (128.61); C^m, 129.52 (132.08); C^p, 131.70 (135.76); $C^{i'}$, 132.38 (132.63); $C^{o'}$, 129.89 (128.74); $C^{m'}$, 129.61 (132.37); $C^{p'}$, 131.10 (134.12).

The MALDI-TOF MS spectrum of product **7**, apart from the peak corresponding to mass of compound **7** ($[M-NO_2]^+$, *m*/*z* 332.30), contains second peak (*m*/*z* 663.29) attributable to the double mass of cation **7** without nitrite anion and hydrogen atom (Scheme 2).



Scheme 2

It may be assumed that in salt **7** the electron transfer from nitrite anion to the cationic heterocyclic moiety occurs and the heterocyclic radical **8** thus generated recombinates to form 'dimeric' species **9**. Simultaneously, NO_2 radical dimerizes to dinitrogen tetroxide (see Scheme 2).

The oligomers, according to their NMR, IR and MALDI-TOF MS/MS spectra, are mixed aromatic, dihydroaromatic and heteroaromatic systems corresponding to the molecules mainly composed of two cations **7**, additionally methylenated/deprotonated (molecular ions in the MALDI spectrum *m*/*z* 566.39, 668.38, 677.35 and 692.43).

The study of the scope of this reaction is under way though our first attempts to implement this transformation with pyridine and quinoline have so far no success.

In conclusion, a three-component reaction between isoquinoline, 1,3-diphenylprop-2-yn-1-one and nitromethane starts with deprotonation of nitromethane with carbanionic site of the primary zwitterion (the adduct of isoquinoline with 1,3-diphenylprop-2-yn-1-one). The reaction proceeds further in a domino manner *via* intramolecular cyclization with the participation of CH_2NO_2 and carbonyl groups followed by elimination of the nitrite anion and hydride shift to result in 2,4-diphenylpyrido[2,1-*a*]isoquinolinium nitrite and oligomers. Thus, the zwitterions generated from nitrogen aromatic heterocycles and electron-deficient acetylenes in combination with nitromethane have been shown to be useful intermediates for the synthesis of iminium salts.

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For **7**: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 7.69 (m, 3H, *p*-H_{Ph}, *m*-H_{Ph}), 7.77 (m, 3H, *p'*-H_{Ph}, *m'*-H_{Ph}), 7.85 (m, 2H, *o'*-H_{Ph}), 8.12 (m, 1H, H^{10}), 8.15 (d, 1H, H^7, $^3J_{H^7,H^6}$ 7.6 Hz), 8.16 (m, 1H, H^9), 8.28 (m, 1H, H^8), 8.42 (m, 2H, *o*-H_{Ph}), 8.53 (d, 1H, H^6, $^3J_{H^6,H^7}$ 7.6 Hz), 8.59 (d, 1H, H^3, $^4J_{H^3,H^1}$ 1.7 Hz), 9.56 (d, 1H, H^{11}, $^3J_{H^{11},H^{10}}$ 8.3 Hz), 9.77 (d, 1H, H^1, $^4J_{H^1,H^3}$ 1.7 Hz). ^{13}C NMR (100.62 MHz, DMSO-d_6), see Table 1. ^{15}N NMR (40.55 MHz, DMSO-d_6) δ: –181.3 (N^+). IR (KBr, ν/cm^{-1}): 3053, 3032, 1647, 1631, 1599, 1516, 1489, 1457, 1417, 1371, 1337, 1322, 1296, 1245, 1209, 1144, 884, 812, 781, 768, 756, 712, 702, 686, 592, 464. MS, *m*/*z* (%): 663.29 (100) $[2(M - NO_2) - H]^+$, 332.30 (4) $[M - NO_2]^+$. Found (%): C, 75.42; H, 4.68; N, 6.94. Calc. for $C_{25}H_{20}N_2O_3$ (%): C, 75.74; H, 5.08; N, 7.07.

For oligomers: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 2.53 (m, 2H), 7.40–7.68 (m, 25H), 7.93–7.99 (m, 12H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 31.61, 119.2, 123.3, 124.3, 124.4, 125.1, 125.3, 126.3, 127.0, 127.5, 128.1, 128.3, 128.3, 128.6, 129.6, 129.8, 129.9, 130.2, 130.7, 131.1, 131.7, 132.5, 134.3. IR (KBr, ν/cm^{-1}): 3064, 3034, 1696, 1669, 1631, 1599, 1579, 1554, 1521, 1490, 1448, 1437, 1419, 1374, 1340, 1315, 1288, 1241, 1178, 1161, 1144, 1114, 1072, 1027, 1001, 911, 807, 763, 732, 698, 646. MS/MS, *m*/*z* (%): 692.43 (35) $[P+H]^+$, 346.23 (100), 677.35 (35) $[P]^+$, 346.23 (35), 332.30 (100), 668.38 (40) $[P]^+$, 358.20 (100), 345.21 (37), 332.30 (69), 566.36 (9) $[P]^+$, 345.21 (100). Found (%): C, 74.09; H, 4.81; N, 8.16. Calc. for $C_{25}H_{18}N_2O_2$ (%): C, 79.35; H, 4.79; N, 7.40.

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