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Pyrazine- and pyridine-substituted prop-2-yn-1-ols, but-3-yn-2-ols, and but-3-yn-2-ones – purification, stability, and handling revised

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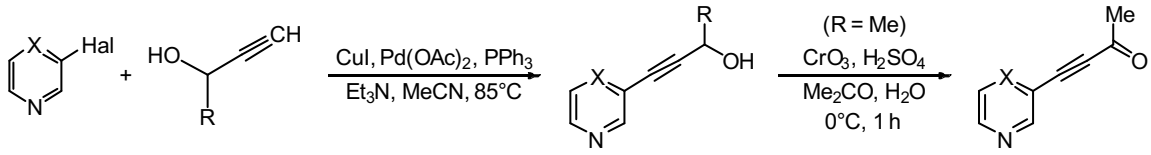


Hal = Br, Cl; R = H, Me

A short series of alkynyl-substituted pyrazine and pyridine derivatives was synthesized by the palladium-catalyzed Sonogashira cross-coupling reactions between aryl halides and alkynes. All the products are either white solids or colorless liquids, which is partly in contrast to previous reports. After purification, a color change or intense darkening was observed, in some cases starting almost immediately. Both, the nature of the heteroaromatic ring and the substituents of the alkyne moiety affect their stability. Herein details of synthesis, characterization, and, most importantly, purification and handling are reported.

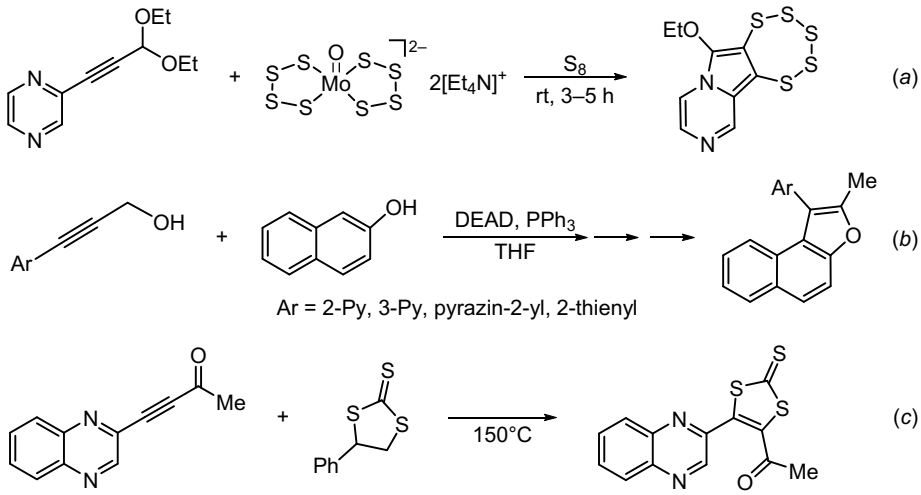
Keywords: alkynylpyrazines, alkynylpyridines, alcohol oxidation, purification, Sonogashira cross-coupling reactions, stability.

Pyrazine- and pyridine-substituted prop-2-yn-1-ols, but-3-yn-2-ols, and but-3-yn-2-ones are mostly known as key intermediates in synthetic reaction series, i.e., they are predominantly used as building blocks for the construction of target molecules. Reports about these very reactive compounds are actually rather scarce in the literature, and those that are available fall into quite different areas of research, mostly in the organic and pharmaceutical chemistry field, where they are used as attractive precursors to a number of heterocyclic compounds. These alkynyl-substituted nitrogen heterocycles have been used in the preparation of pentathiepins with potential anticancer and antibacterial activities (Scheme 1*a*),[1] the preparation of neuronal acetylcholine-gated ion channel agonists,[2] and the synthesis of naphthofurans (Scheme 1*b*)[3] and γ-butyrolactol ether derivatives.[4] They are part of investigations regarding the synthesis of α,β-acetylenic aldehydes from terminal alkynes,[5] new solid state procedures/immobilization methods,[6] novel Sonogashira catalysts,[7] and the regiochemistry of Mitsunobu alkylations.[8] Pyrazine-substituted but-3-yn-2-ones also play an important role in the context of bioinorganic model chemistry of molybdenum-dependent oxidoreductases,[9] which is in fact our main interest in respect to this class of compounds, where they are used for mimicking a complex organic ligand (molybdopterin) in the respective active sites (an example[9b] see in Scheme 1*c*).

Nevertheless, when searching the literature for analogous compounds with further substituents on both ends of the alkyne moiety, i.e., on the heterocycle and/or on the oxygen-bearing carbon, only a moderate number of results could be found. The available literature is dominated by patents with a focus on pharmaceutical applications including inhibiting a checkpoint kinase 1 (CHK1) function relevant to cancer growth,[10] treating and/or preventing allergic and immune diseases, inflammatory dermatosis and neurodegenerative disorders,[11] the use as antiulcer agents,[12] cyclooxygenase-2 (COX-2) inhibitors for treating inflammatory diseases[13] and glucokinase activators for the treatment of type II diabetes.[14]

This diversity emphasizes the significant and general potential of heterocycle-substituted prop-2-yn-1-ols, but-3-yn-2-ols, and but-3-yn-2-ones with respect to a broad range of available chemical transformations and medicinal applications of the respective products. Bearing a reactive alkynyl function in conjugation to a heteroaromatic ring, these compounds can undergo various cycloaddition and intramolecular cyclization reactions to produce derivatives of fused heterocycles of pharmaceutical interest. There are several reports on the biological activity of fused aromatic

Scheme 1



compounds with pyrazine functionalities.[10–15] However, despite their promising chemical structures, the synthetic potential of alkynylpyridines/pyrazines has not been fully exploited in the past, possibly due to difficulties of purification and handling. Few of these N-heterocyclic alkynes have ever been properly characterized. One reason might be that in the course of most research projects such compounds were not necessarily isolated as intermediates, but used immediately for the following reaction steps. As we needed to obtain alkynylpyrazines as precursors for quite ambitious synthetic undertakings we, in the present work, have reinvestigated the synthesis of some known or at least "literature-mentioned" alkyne-substituted pyridines and pyrazines, optimized the respective purification and handling protocols, and even amended some characterizations of these compounds from previous reports. This knowledge might lead to a more frequent use of this class of compounds in the future and hence broaden the spectrum of easily accessible yet complex N-heterocyclic reagents.

In the present study, N-heterocycle-substituted alkynes served as intermediates in a reaction series adapted from procedures developed by Joule, Garner, and Taylor for the generation of bioinorganic model compounds.[9a,b,d,16] Our aim was the synthesis of pyrazine- or pyridine-substituted prop-2-yn-1-ols and but-3-yn-2-ols and, in a subsequent synthetic step, the corresponding aldehydes or ketones. For comparison, the corresponding pyridine derivatives were also investigated. The pyridine alkynes are much more stable and it is, hence, considerably easier to work with them. Heteroaryl halides **1**, **2** and propargylic alcohol **3a** or 3-butyn-2-ol **3b** were subjected to the common palladium-catalyzed Sonogashira coupling reaction conditions[17] yielding the corresponding alkynyl-substituted N-heterocycles **4a**,**b** and **5a**,**b** (Scheme 2, Table 1).

For the synthesis of pyrazine derivatives, 2-chloropyrazine (**1**) could be used as the heterocyclic starting material. 3-Chloropyridine was not active under the same reaction conditions. Instead, 3-bromopyridine (**2**) had to be used, and the reaction times needed to be extended from

Scheme 2

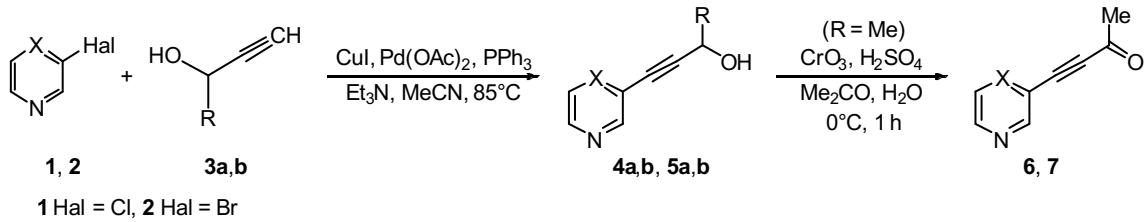


Table 1. Yields and properties of alkynyl-substituted pyrazines **4a**,**b**, **6** and pyridines **5a**,**b**, **7**

Halide	Alcohol	Product	X	R	Yield, %	Look	Timespan of stability (at rt in air)
1	**3a**	**4a** (primary alcohol)	N	H	32	White solid	Days
1	**3b**	**4b** (secondary alcohol)	N	Me	43	Colorless liquid	Hours
–	–	**6** (ketone)	N	Me	42	White solid	Minutes to hours
2	**3a**	**5a** (primary alcohol)	CH	H	71	White solid	Days
2	**3b**	**5b** (secondary alcohol)	CH	Me	78	Colorless liquid	Days
–		**7** (ketone)	CH	Me	48	Colorless liquid	Minutes to hours

6 to 20 h. The lower reactivity of the 3-chloropyridine compared to 2-chloropyrazine (**1**) is due to the lack of –M and –I effects based on the absence of the second nitrogen, as observed and described previously.[17f] Besides the N-heterocyclic reagent, the alkyne precursor, too, has an effect on the reaction course. The yields summarized in Table 1 show that under the same conditions better yields were observed for but-3-yn-2-ol (**3b**) compared to unsubstituted propargylic alcohol (**3a**); i.e., the reaction yield using a secondary alcohol as the reactant was better than using a primary alcohol, which is typical for palladium-catalyzed coupling reactions.[17f]

Ketones **6** and **7** were synthesized from secondary alcohols **4b** and **5b** using Jones' reagent in acetone at 0°C The attempted oxidation of compounds **4a** and **5a** to the corresponding aldehydes could not be achieved neither under the same conditions (Jones' reagent in acetone at 0°C) nor with any of the various oxidation agents tested (MnO_2, CrO_3/H_2SO_4, *N*-chlorosuccinimide/*N*-(*tert*-butyl)benzenesulfenamide, DMSO/cyanuric chloride).[15a,18] The reason for this may be an increased instability of the oxidation products of the primary alcohols compared to the secondary alcohols, in accordance with the already comparably lower yields of the respective primary products **4a** and **5a**.

The crude products **4a**,**b**, **5a**,**b** obtained by extraction are brown oils. Even after purification by column chromatography, it was only possible to obtain brownish-stained or brown-colored products. This was the case even with compound **4a**, which is described in literature as a "red amorphous solid".[19]

After trying several different methods, the purification of products **4a**,**b**, **5a**,**b**, **6**, **7** eventually succeeded by rather convenient sublimation or microdistillation at a temperature around 40°C under reduced pressure (0.02 mbar). Notably, a simple isolation process, such as sublimation or distillation is for these pyridine- and pyrazine-containing alkyne alcohols and ketones much more efficient and reliable than using the rather tedious (and costly) separation by a column; a fact which to date went unnoticed. All products, purified in such way, are colorless or white and, depending on the nature of the substituents, are either viscous liquids or solids. Upon standing, however, they change their color to brown or even black (compound **6**). Depending on the structure the color change is more or less rapid. In general, pyridyl alkynes are more stable than pyrazinyl alkynes. A possible reason for this could be the π-electron deficiency of the pyridines compared to pyrazines. The oxidized forms **6**, **7** are generally the least stable ones. The rapidity of the color change also depends on whether the compound is in its pure form or in solution.

Compound **6** decomposes after a few minutes in air accompanied by a color change to brown and, after some hours, to even black. In solution, this process takes somehow longer; the color change from colorless to intense brown takes place within a couple of days. Compound **4a** changes its color to brown within a few days. Notably, this process is faster in solution as opposed to compound **6**. Compound **4b** behaves like compound **6**, but it is significantly more stable. Common to all synthesized compounds is that once dissolved in chloroform the color change is accompanied by the formation of an insoluble residue which could not be identified despite all efforts. In DMSO, however, no residue is formed, i.e., in this solvent only the color change serves as an indicator of decomposition. For the corresponding pyridine compounds, the decomposition time relations are similar (in the same order depending on the substituents), but they are generally more stable. In the NMR spectra of all the products, a distinct signal broadening can be observed with time, which indicates radical formation[20] and/or the formation of polymers, possibly with extensive double bond conjugation. This assumption is also supported by an increasingly intense coloration, as the presence of unpaired electrons and extensive conjugation result in a dark or intensely colored material based on allowed electron transitions between orbitals.[21] The IR spectrum of compound **4b**, for instance, displays broad absorption bands in the region 1718–1653 cm^{-1}. The number and intensity of these bands increase with time when compound **4b** is kept as isolated pure substance in air (see Fig. 1), suggesting that carbonyl species are prevalent in the decomposed material. Simultaneously, some changes were observed at around 3300 cm^{-1}, the region of OH groups and hydrogen bonding in general.

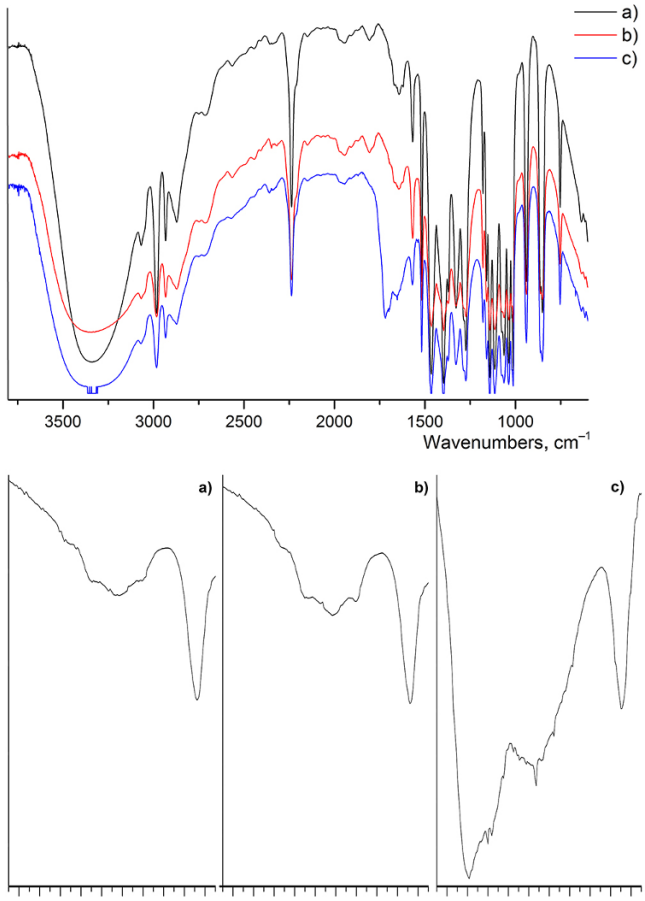


Figure 1. Top: IR spectra of 4-(pyrazin-2-yl)-but-3-yn-2-ol (**4b**); (a) freshly prepared, (b) after 4 days, and (c) after 6 months; bottom: the same IR spectra in the range of 1750–1550 cm^{-1}. Here transmissions were corrected to ensure comparability.

None of the investigated compounds **4a**,**b**, **5a**,**b**, **6**, **7** had a considerably long shelf life even when purified and stored at low temperature. Apparently they inevitably undergo decomposition. This is most likely due to polymerization into a material bearing conjugated double bonds, as discussed above. The decomposition products, unfortunately, could not be characterized unequivocally, as they likely form complex mixtures together with non-decomposed material. Compounds **4a**,**b**, **5a**,**b**, **6**, **7**, and likely other compounds of this class, should be used either *in situ*, where possible, or they should be used for a following consecutive reaction as soon as possible after isolation. Any kind of coloration is evident of a beginning decomposition, and this should be kept in mind when adjusting the respective stoichiometries for the following reactions. When an interruption of the reaction series cannot be avoided, keeping in a deep freezer at –78°C under inert gas is highly recommended, though even these quite drastic measures do not keep the compounds stable for more than a few days.

In conclusion, pyrazine- and pyridine-substituted alkynes which have been mentioned in the literature before as intermediate products in multistep reactions were reinvestigated with respect to their synthesis. More importantly, optimized methods for their isolation and purification were developed and the stability of compounds was studied, as this has not been done before. Notably, we could show that sublimation or microdistillation yield much purer products than column chromatography and is certainly less laborious and time-consuming. Because of the presence of N-heterocyclic moieties and their substantial reactivity alkynylpyrazines do have a great potential for synthetic developments in different fields of research. Predominantly, their use in a pharmaceutical context can be envisioned, as they can be relatively easy obtained using the Sonogashira reaction. The most important finding was that even under inert gas in a deep freezer it is only possible to store these compounds for a limited time due to their high intrinsic reactivity. Instead, it is requisite to continue with any following reaction steps immediately or at least as soon as possible, until the alkyne function has been transformed. These findings will hopefully encourage an increased use of this group of reactive compounds, since now they can be isolated more conveniently and have been characterized in pure form.

Experimental

IR spectra were recorded on a Perkin-Elmer System 2000 Fourier-transform infrared spectrophotometer or a Shimadzu IR Affinity-1 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 300 spectrometer (300 and 75 MHz, respectively). All chemical shifts are quoted in respect to TMS for the ^{1}H signals and deuterated solvent for the ^{13}C signals ($CDCl_3$ δ 77.0 ppm, DMSO-d_6 δ 39.5 ppm). ^{13}C NMR signals were assigned using the DEPT experiment. Electron ionization mass spectra were recorded on a single focussing sector-field Waters AMD40 spectrometer. Elemental analyses (C, H, N, and S) were carried out with an Elementar Vario MICRO elemental analyzer. Melting points were determined with a Sanyo Gallenkamp melting point apparatus. Acetonitrile was dried over 0.3 nm molecular sieves. Other chemicals were used as purchased.

Synthesis of alkynyl-substituted pyrazines and pyridines 4a,**b and 5a**,**b** (General method). Palladium acetate (92.1 mg, 0.41 mmol), triphenylphosphine (640.0 mg, 2.44 mmol), and copper(I) iodide (465.0 mg, 2.44 mmol) were added to a degassed solution of aryl halide **1**, **2** (45 mmol), alkyne **3a**,**b** (49 mmol), triethylamine (20 ml), and acetonitrile (50 ml). The reaction mixture was stirred at 85°C for 6 h (synthesis of products **4a**,**b**) or 20 h (synthesis of products **5a**,**b**) under a nitrogen atmosphere. The mixture was allowed to cool to room temperature and the solvent was evaporated. Then the residue was extracted with water (80 ml) and ethyl acetate (100 ml). The resulting mixture was filtered through silica, the layers were separated and the aqueous layer extracted with ethyl acetate (3×50 ml). The combined organic extracts were washed with brine (50 ml), dried over sodium sulfate, and evaporated to yield brown oil. After microdistillation or sublimation at 40°C with the use of a cooling finger under vacuum (0.02 mbar), the pure product was obtained.

3-(Pyrazin-2-yl)prop-2-yn-1-ol (4a).[1] Yield 1.93 g (32%). White solid. Mp 71–73°C. IR spectrum (KBr), ν, cm^{-1}: 642 (w), 711 (s br), 1014 (vs), 1030 (vs), 1063 (s), 1141 (s), 1159 (w), 1183 (w), 1226 (w), 1276 (s), 1360 (m), 1399 (s), 1460 (vs), 1515 (m), 1573 (vw), 1641 (vw br), 2214 (m), 2246 (w), 2408 (vw), 2660 (vw), 2857 (vw), 2915 (vw), 3257 (vs). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.64 (1H, br. s, OH); 4.58 (2H, s, CH_2); 8.51 (1H, d, ^3J = 2.6, H-5); 8.56 (1H, dd, ^3J = 2.6, ^4J = 1.6, H-6); 8.69 (1H, d, ^4J = 1.5, H-3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 50.9 (CH_2); 81.6 (C≡C); 92.4 (C≡C); 139.6 (C-2); 143.1 (CHN); 144.3 (CHN); 147.6 (C-3). Mass spectrum (EI, 70 eV, 350°C), *m*/*z* (I_{rel}, %): 134 $[M]^+$ (55), 105 (100). Found, %: C 62.85; H 4.47; N 20.53. $C_7H_6N_2O$. Calculated, %: C 62.68; H 4.51; N 20.88.

4-(Pyrazin-2-yl)but-3-yn-2-ol (4b).[8] Yield 2.87 g (43%). Colorless liquid. IR spectrum (thin film), ν, cm^{-1}: 754 (w), 852 (m), 940 (m), 1013 (s), 1038 (s), 1064 (s), 1115 (s), 1142 (s), 1180 (m), 1273 (m), 1328 (m), 1371, 1397 (s), 1465 (s), 1518 (m), 1568 (w), 1641 (vw br), 2238 (m), 2872, 2934, 2983, 3069, 3340 (s br). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.60 (3H, d, ^3J = 6.6, CH_3); 3.36 (1H, br. s, OH); 4.82 (1H, q, ^3J = 6.7, CH); 8.50 (1H, d, ^3J = 2.5, H-5); 8.55 (1H, dd, ^3J = 2.5, ^4J = 1.6, H-6); 8.67 (1H, d, ^4J = 1.5, H-3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 23.8 (CH_3); 58.1 (CH); 80.1 (C≡C); 95.9 (C≡C); 139.6 (C-2); 143.0 (CHN); 144.2 (CHN); 147.5 (C-3).

3-(Pyridin-3-yl)prop-2-yn-1-ol (5a).[2,7] Yield 4.25 g (71%). White solid. Mp 100–101°C (mp 99–100°C[2]; mp 101–102°C[7]). IR spectrum (KBr), ν, cm^{-1}: 636 (s), 704 (vs), 742 (s), 806 (s), 951 (m), 1027 (vs), 1188 (m), 1232 (m), 1264 (m), 1354 (m), 1407 (s), 1478 (vs), 1562 (m), 1588 (m), 2848 (w), 2937 (vw), 3045 (m), 3195 (s), 3381 (m). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.34 (2H, d, ^3J = 5.9, CH_2); 5.42 (1H, t, ^3J = 5.9, OH); 7.42 (1H, ddd, ^3J = 7.9, ^3J = 4.9, ^4J = 0.7, H-5); 7.85 (1H, dt, ^3J = 7.9,

^4J = 1.9, H-4); 8.56 (1H, br. d, $^3J \approx 4$, H-6); 8.63 (1H, br. s, H-2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 49.4 (CH_2); 80.4 (C≡C); 93.2 (C≡C); 119.5 (C-3); 123.6 (C-5); 138.7 (C-4); 148.7 (C-6); 151.4 (C-2). Mass spectrum (EI, 70 eV, 300°C), *m*/*z* (I_{rel}, %): 133 $[M]^+$ (17), 79 (100). Found, %: C 71.72; H 5.15; N 10.52. C_8H_7NO. Calculated, %: C 72.16; H 5.30; N 10.52.

4-(Pyridin-3-yl)but-3-yn-2-ol (5b).[4] Yield 5.17 g (78%). Colorless liquid. IR spectrum (thin film), ν, cm^{-1}: 705 (m), 807 (m), 856 (m), 935 (m), 1028, 1049, 1077, 1112 (s), 1188 (m), 1262, 1330 (m), 1370 (m), 1409 (s), 1478 (m), 1566 (m), 1588 (w), 1668 (vw), 2869, 2932, 2982, 3300 (s br). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.42 (3H, d, ^3J = 6.6, CH_3); 4.65 (1H, dq, ^3J = 6.6, ^3J = 5.4, CH); 5.59 (1H, d, ^3J = 5.4, OH); 7.42 (1H, ddd, ^3J = 7.9, ^3J = 4.9, ^5J = 0.9, H-5); 7.84 (1H, dd, ^3J = 7.9, ^4J = 1.9, H-4); 8.56 (1H, dd, ^3J = 4.9, ^4J = 1.7, H-6); 8.62 (1H, dd, ^4J = 2.1, ^5J = 0.8, H-2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 24.4 (CH_3); 56.7 (CH); 79.1 (C≡C); 96.6 (C≡C); 119.5 (C-3); 123.6 (C-5); 138.5 (C-4); 148.7 (C-6); 151.5 (C-2).

Preparation of the oxidation products 6 and 7 (General method). Jones' reagent (2.5 g CrO_3, 2.5 ml H_2SO_4, 7.5 ml H_2O) was added dropwise to a stirred solution of the alcohol **4b** or **5b** (18.51 mmol) in acetone (30 ml) at 0°C over 20 min. The mixture was stirred for 1 h and then allowed to warm to room temperature. Water (80 ml) and diethyl ether (80 ml) were added, the layers were separated, and the aqueous layer extracted with diethyl ether (3×50 ml). The combined organic layers were washed with saturated aq. $NaHCO_3$, brine (50 ml), dried over sodium sulfate, and the solvent was evaporated to yield brown oil. After sublimation at 40°C with the use of a cooling finger under vacuum (0.02 mbar), the pure product was obtained.

4-(Pyrazin-2-yl)but-3-yn-2-one (6).[16a] Yield 1.14 g (42%). White solid. Mp 36–37°C (mp 36°C[16a]). IR spectrum (KBr), ν, cm^{-1}: 726 (m), 753 (m), 865 (s), 991 (m), 1014 (s), 1054 (m), 1146 (m), 1159 (m), 1184 (s), 1282 (s), 1296 (s), 1369 (s), 1404 (s), 1466 (s), 1519 (w), 1675 (vs), 2152 (w), 2218 (vs), 2921 (w), 3007 (w), 3043 (w), 3075 (w), 3438 (m br). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 8.63 (1H, d, ^3J = 2.5, H-5); 8.66 (1H, dd, ^3J = 2.5, ^4J = 1.5, H-6); 8.81 (1H, d, ^4J = 1.4, H-3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 32.7 (CH_3); 84.1 (C≡C); 89.0 (C≡C); 137.8 (C-2); 144.7 (CHN); 144.9 (CHN); 148.7 (C-3); 183.6 (C=O). Found, %: C 65.32; H 4.04; N 18.84. $C_8H_6N_2O$. Calculated, %: C 65.75; H 4.14; N 19.17.

4-(Pyridin-3-yl)but-3-yn-2-one (7).[5] Yield 1.29 g (48%). Colorless liquid. IR spectrum (thin film), ν, cm^{-1}: 704 (s), 808 (s), 979 (s), 1023 (s), 1122 (m), 1162 (vs), 1190 (s), 1280 (s), 1360 (s), 1409 (s), 1478 (s), 1564 (s), 1584 (s), 1674 (vs), 2132 (m), 2207 (vs), 2918 (w), 3007 (w), 3047 (w), 3332 (w), 3380 (w br). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.48 (3H, s, CH_3); 7.54 (1H, ddd, ^3J = 7.9, ^3J = 4.9, ^5J = 0.8, H-5); 8.10 (1H, dt, ^3J = 7.9, ^4J = 1.9, H-4); 8.72 (1H, dd, ^3J = 4.8, ^4J = 1.4, H-6); 8.84 (1H, d, ^4J = 1.3, H-2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 32.7 (CH_3); 85.7 (C≡C); 90.4 (C≡C); 116.4 (C-3); 123.8 (C-5); 140.1 (C-4); 151.1 (C-6); 152.8 (C-2); 184.0 (C=O).

Supplementary information to this article containing ^{1}H, ^{13}C NMR, and IR spectra of the synthesized compounds is available online at http://link.springer.com/journal/10593.

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