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ETHYL VINYL ETHER - AN AGENT FOR PROTECTION OF THE PYRAZOLE NH-FRAGMENT. A CONVENIENT METHOD FOR THE PREPARATION OF *N*-UNSUBSTITUTED 4-ALKYNYLPYRAZOLES

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Abstract – *N*-Unsubstituted 4-iodopyrazole (**1**) is easily converted into 4-alkynyl derivatives (**5**) in moderate to good overall yields by using intermediate protection of the nitrogen atom of the pyrazole ring by ethyl vinyl ether.

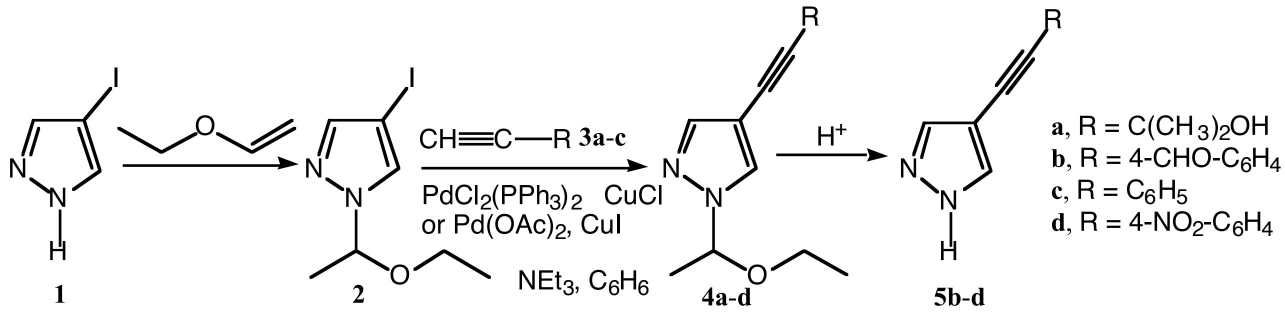
INTRODUCTION

Acetylenic derivatives of pyrazoles are attractive synthons as well as promising biologically active compounds.[1,2] Special interest is shown by pyrazolylacetylenes bearing a formyl group, which gives the possibility to create stable radicals, such as nitronylnitroxides derived from 2-imidazolines.[3,4] We have reported the synthesis of some acetylenyl-*N*-alkylpyrazolylnitronylnitroxides, which showed interesting optical and magnetic properties.[3,4] However, more promising for the design of high dimension molecular ferromagnetics are *N*-unsubstituted pyrazolyl halides due to the possibility to use the NH-fragment, for instance to form N–H···N aggregates in the solid state. From the various papers dealing with the synthesis of alkynylpyrazoles it may be concluded that the Pd-Cu-catalyzed cross-couplings of 1-alkynes with pyrazolyl halides is the most convenient method for synthesizing the above mentioned compounds.[1,5]

RESULTS AND DISCUSSION

The cross-coupling of *N*-substituted pyrazolyl halides with 1-alkynes proceeds without complication in the presence of bis(triphenylphosphine)palladium(II) dichloride or tetrakis(triphenylphosphine)-palladium(0) (1-2 mol. %), CuI and alkylamines.[1,2] On the other hand, there are only two examples for obtaining N-1 unsubstituted 4-alkynylpyrazoles by direct cross-coupling of 4-iodopyrazole with the corresponding 1-alkynes. Special conditions (a larger amount of palladium catalyst, Pd/C, 10 % and a more strong inorganic base, K_2CO_3 in DME/H_2O) are necessary for the preparation of *N*-unsubstituted alkynylpyrazoles.[6,7] This is related to the deactivating influence of the +M-effect of the negatively charged nitrogen atom in the pyrazolate anion on the reactivity of the halogen atom in 4 position of the pyrazole ring. According to our experience, this procedure has another limitation,[6] it can only be applied to water-soluble acetylenes, like 2-propyn-1-ol and 3-butyn-1-ol. Our attempts to introduce phenylacetylene in pyrazole 4-position using 4-iodopyrazole and the De la Rosa method failed.[6-8] To avoid these problems, a possibility to synthesize unsubstituted 4-acetylenylpyrazoles is to use *N*-protecting groups. In fact, 2,4,6-trimethylbenzoyl,[9] *t*-Boc and MEM,[10] phenacyl, *p*-tosyl,[11] OBn,[12] trityl,[13] and acetyl groups,[14] have been successfully applied for Stille and Heck-Sonogashira cross-couplings. Unfortunately, deprotection of the above-mentioned groups occurs in rather hard conditions such as heating in the presence of strong bases or acids.

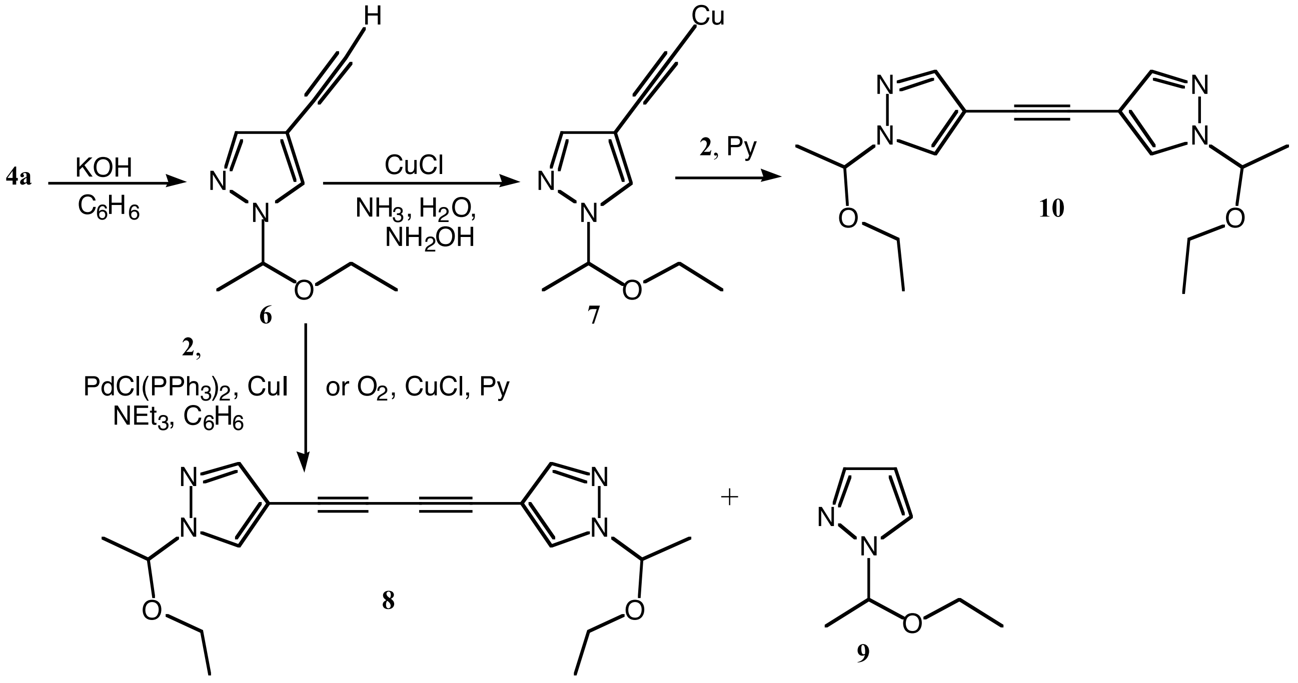
In search for groups which satisfied the criterion of easiness of protection and deprotection, we found a new protecting group for *NH*-pyrazoles: ethyl vinyl ether. We observed that alkylation of 4-iodopyrazole (**1**) by ethyl vinyl ether in benzene at 30-40 °C in the presence of traces of concentrated HCl leads to compound (**2**) in 95 % yield. The cross-coupling of iodide (**2**) with 1-alkynes (**3a**,**c**,**d**) in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in benzene at 60-70 °C gave pyrazolylacetylenes (**4a**) (in 91 % yield) and (**4c**,**d**) (that were used in next step without purification). It should be noted that when the starting material contains a formyl group another catalytic system is required;[15] thus, the synthesis of alkynylaldehyde (**4b**) was performed by cross-coupling of iodide (**2**) with 4-ethynylbenzaldehyde (**3b**) (in 80 % yield) or by cross-coupling of alkynylpyrazole (**6**) with 4-bromobenzaldehyde in the presence of $Pd(OAc)_2$, CuI, PPh_3, and Et_3N. The reason for the necessity of such catalytic system has been previously described.[16]



Scheme 1

We also found that deprotection could be carried out easily by the acid-catalyzed hydrolysis of the alkynylpyrazoles (**4b-d**) to form the desired products (**5b-d**) in 67-88 % yield (Scheme 1). The alcohol (**4a**) underwent cleavage by retro-Favorsky reaction with dry potassium hydroxide in boiling benzene to give 4-ethynylpyrazole (**6**) in 66 % yield. The ethynylpyrazole (**6**) was used in a cross-coupling reaction with *N*-protected iodopyrazole (**2**) in the presence of bis(triphenylphosphine)palladium(II) dichloride and CuI in Et_2NH. However, we did not find the expected product of replacement of iodine by the acetylenic group. The reaction leads to by-products, disubstituted butadiyne (**8**), accompanied by reductive deiodination of **2** and formation of 1-(1-ethoxyethyl)-*1H*-pyrazole (**9**). We have already reported some examples of such unusual direction of the Sonogashira-Heck reaction even in the case of *N*-alkylated 4-iodopyrazoles.[17] Structure of **8** was confirmed additionally by independent oxidative coupling of **6** according to the Hay method.[18]

Previously, we established that it is possible to avoid these complications by using the Stephens-Castro method, *i.e.* cross-coupling of 4-iodopyrazoles with copper(I) acetylides.[17] Therefore, pyrazolyl iodide (**2**) was treated with copper acetylide (**7**) in pyridine at 110-115 °C (7 h) to give the desired product 1,4-bis[l-(l-ethoxyethyl)pyrazol-4-yl]ethyne (**10**) in 74 % yield.



Scheme 2

In summary, we have established that ethyl vinyl ether is a very convenient reagent for the protection of *N*-unsubstituted pyrazoles. The easiness of introduction and removal of the protecting group as well as the low cost of the reagent makes this procedure a convenient method for preparing *N*-unsubstituted 4-alkynylpyrazoles. From 4-iodopyrazole, a series of 4-alkynylpyrazoles have been synthesized by Stephens-Castro or Heck-Sonogashira cross-couplings, using this protecting group.

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EXPERIMENTAL

4-Ethynyl(nitrobenzene)[19] and 4-ethynylbenzaldehyde[15] were prepared by previously reported methods. Copper(I) acetylide (**7**) was prepared from l-(l-ethoxyethyl)-4-ethynylpyrazole (**6**) according to the published procedure.[20]

All commercial reagents were used without additional purification. Analytical TLC plates were Silufol® UV-254 (Silpearl on aluminum foil, Czechoslovakia). Silica gel "KSK" (Russia, 100-200 mesh, air dried and activated at 130 °C for 5 h) was used for column chromatography. IR spectra were obtained for KBr pellets using a Bruker IFS 66 IR-spectrophotometer. Melting points were obtained using a Kofler melting point apparatus. ^{1}H NMR spectra were recorded on a Varian XL 200 or Bruker Avance 300 spectrometer locked to the deuterium resonance of the solvent. Chemical shifts were calculated relative to solvent signals used as the internal standards δ_H 7.240 ppm for $CDCl_3$ and δ_H 2.50 ppm for DMSO-d_6.

4-Iodopyrazole (**1**). Pyrazole (3.4 g, 0.05 mol), I_2 (5.1 g, 0.02 mol), HIO_3 (1.8 g, 0.01 mol) and 30 % H_2SO_4 (2 mL) in AcOH (30 mL) were stirred at 70 °C for 15 min until discoloration of the reaction mixture. A saturated solution of $NaHCO_3$ (10 mL) was added to the reaction mixture. The reaction mixture was concentrated in *vacuo*, neutralized with 20 % Na_2CO_3, and extracted with chloroform. The combined organic solution was dried ($MgSO_4$) and concentrated in *vacuo.* The residue was purified by crystallization from a mixture of benzene-hexane to give 9.36 g (97.5 %) of **1**. mp 106-108 °C (lit.,[21] mp 108.5 °C).

Protection: Preparation of l-(l-ethoxyethyl)-4-iodopyrazole (**2**). 4-Iodopyrazole (3.2 g, 16 mmol) (**1**), ethoxyethene (3.0 g, 42 mmol) and one drop of conc. HCl in benzene (20 mL) were stirred at 30-40°C for 2 h. A saturated solution of $NaHCO_3$ (5 mL) was added to the reaction mixture. The reaction mixture was dried over K_2CO_3, filtered through $A1_2O_3$, and concentrated in *vacuo*. The final yellow oil was purified by vacuum distillation to afford 4.7 g (95 %) of the title compound as a yellowish oil, bp 74-76 °C/0.5 torr, $n_d^{23} = 1.5272$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (t, 3H, $J = 10.4$, CH_3-CH_2), 1.69 (d, 3H, $J = 9.2$, CH_3-CH), 3.38, 3.44 (two q, 2H, $J = 10$, CH_2-CH_3), 5.54 (q, 1H, $J = 9.2$, CH-CH_3), 7.55 (s, 1H, H-3), 7.68 (s, 1H, H-5); HRMS, *m/z* (%): 265.99160 (calcd for $C_7H_{11}N_2OI$ 265.99179), MS 266 (M^+ 24), 222 (27), 221 (15), 207 (11), 194 (39), 94 (11), 73 (43), 72 (63), 67 (14).

General procedure of cross-coupling of iodopyrazole (**2**) **with 1-alkynes** (**3a**,**c**,**d**). A mixture of iodopyrazole (**2**) (2.65 g, 0.01 mol), alkyne (**3a**,**c**,**d**) (0.011 mol), $Pd(PPh_3)_2Cl_2$ (0.1 g, 0.56 mmol), CuI (50 mg, 0.26 mmol), triethylamine (2.5 mL) in benzene (50 mL) was stirred at 80 °C in an argon stream until the disappearance of the starting product, cooled, diluted with chloroform (30 mL), filtered through a column of Al_2O_3 (3 x 2.5 cm) and concentrated on a rotary evaporator.

4-[l-(l-Ethoxyethyl)-l*H*-pyrazol-4-yl]-2-methylbut-3-yn-2-ol (**4a**). Reaction time 2.5 h. The alkynylpyrazole (**4a**) was purified by column chromatography on silica gel (elution with chloroform) or distilled in *vacuo*. Yield 91 %. bp 138-140 °C/ 0.5 torr, $n_d^{23} = 1.5140$. IR, ν_{max} = 853, 891, 958, 1021, 1063, 1121, 1164, 1209, 1256, 1337, 1361, 1441, 1556, 1631, 1729, 2232, 2933, 2981, 3380 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ, 1.18 (t, 3H, *J* = 10.4, *CH_3*-CH_2), 1.55 [s, 6H, *C*(CH_3)$_2$], 1.66 (d, 3H, *J* = 9.2, *CH*-CH_3), 2.12 (s, 1H, OH), 3.34, 3.48 (two q, 3H, *J* = 10.4 Hz, *CH_2*-CH_3), 5.47 (q, 3H, *J* = 9.2 Hz, *CH*-CH_3), 7.60 (s, 1H, H-3), 7.73 (s, 1H, H-5); HRMS, *m/z* (%): 222.13530 (calcd for $C_{12}H_{18}N_2O_2$ 222.13682), MS 222 (M^+ 23), 177 (11), 151 (16), 150 (13), 135 (100), 133 (22), 132 (22), 105 (12), 93 (14). The alkynylpyrazoles (**4c,d**) were deprotected without further purification.

4-[l-(l-Ethoxyethyl)-1*H*-pyrazol-4-ylethynyl]benzaldehyde (**4b**). The compound was prepared according to the procedure described in ref. 15 with some modification. Copper(I) iodide (0.05 g, 0.26 mmol) was added to a stirred solution of 4-ethynylbenzaldehyde (2.65 g, 20.4 mmol), 4-iodopyrazole (**2**) (5.32 g, 20 mmol), $Pd(OAc)_2$ (0.1 g, 0.56 mmol), triphenylphosphine (0.2 g, 0.8 mmol) and (**3b**) (0.25 g, 0.95 mmol) and triethylamine (5 mL) in benzene (50 mL) under an argon atmosphere. The mixture was stirred at 60-70 °C for 1.5 h and then filtered through silica gel. The solvent was distilled off in vacuum and the residue was chromatographed on silica gel (elution with chloroform) and following recrystallization from a mixture of benzene with hexane to afford compound (**4b**) (4.31 g, 80 %). Yellowish powder, mp 148-149 °C; IR, ν_{max} = 831, 861, 944, 979, 1006, 1067, 1123, 1160, 1211, 1252, 1295, 1318, 1379, 1408, 1429, 1483, 1502, 1555, 1602, 1686, 2216, 2902, 2976, 3080 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ, 1.19 (t, 3H, *J* = 10.5, *CH_3*-CH_2), 1.69 (d, 3H, *J* = 9.3, *CH_3*-CH), 3.39, 3.50 (two q, 2H, *J* = 10.5, *CH_2*-CH_3), 5.56 (q, 1H, *J* = 9.3, *CH*-CH_3), 7.61 (d, 2H, *J* = 8.3, H-3 and H-5), 7.73 (s, 1H, H-3'), 7.86 (s, 1H, H-5'), 8.08 (d, 2H, *J* = 8.3 Hz, H-2 and H-6), 10.03 (s, 1H, CHO). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.41; H, 6.23; N, 10.22.

l,4-Bis[l-(l-ethoxyethyl)pyrazol-4-yl]butadiyne (**8**). The general procedure of cross-coupling was used: starting from **2** and **6** and with 2.5 h of reaction time, two compounds were separated by column chromatography on SiO_2 [butadiyne (**8**) (yield 79 %) and 1-(1-ethoxy-ethyl)-*1H*-pyrazole (**9**) (30 %)]. Compound (**8**) was also synthesized by oxidative coupling of alkyne (**6**) in condition of Hay's reaction. Air was bubbled into a mixture of acetylene (**6**) (0.28 g, 3.5 mmol) and CuCl (50 mg, 0.5 mmol) in 5 mL of pyridine (Py in Scheme2) at 35-40 °C for 6.5 h. The reaction mixture was poured into 50 mL of water, and the product was extracted with $CHCl_3$ (2 x 25 mL). The extract was washed with 25 % NH_4OH (3 x 15 mL) and water (50 mL), dried ($MgSO_4$), and filtered through a layer of Al_2O_3 (2.5 x 2 cm). The solvent was removed, and the residue was crystallized from a mixture of benzene-hexane. 0.1 g (36 %), mp 120-122 °C; IR, ν_{max} = 884, 864, 945, 979, 1004, 1065, 1093, 1121, 1168, 1244, 1344, 1381, 1441, 1438, 1540, 1634, 1705, 2106, 2879, 2908, 2925, 2977, 3077, 3104, 3121, 3431 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ, 1.12 (t, 3H, *J* = 7, *CH₃*-CH₂), 1.62 (d, 3H, *J* = 6, *CH*-CH₃), 3.24-3.65 (m, 2H, *CH₂*-CH₃), 5.37 (q, 1H, *J* = 6, *CH*-CH₃), 7.47 (s, 1H, H-3), 7.68 (s, 1H, H-5); HRMS, *m/z* (%): 326.1741 (calcd for $C_{18}H_{22}N_4O_2$ 326.1743).

General procedure for deprotection [synthesis of *N*-unsubstituted 4-alkynylpyrazoles (5b-d)]. To a solution of alkynylpyrazole (**4b**) (or the crude products in the case of **4c**,**d**) in chloroform (~ 20 mL), water (5 mL) and conc. HCl (1 mL) were added. The solution was stirred at room temperature for 1 h and was then neutralized with $NaHCO_3$. The organic layer was separated and the water solution was extracted with chloroform (3 x 20 mL). The combined organic solution was dried ($MgSO_4$) and concentrated in *vacuo.* The residue was purified by crystallization to give alkynylpyrazoles (**5b-d**).

4-(1*H*-Pyrazol-4-ylethynyl)benzaldehyde (**5b**). Yield 88 %, mp ~164 °C with decomp (ethanol); IR, ν_{max} = 927, 997, 1040, 1106, 1156, 1212, 1283, 1301, 1374, 1393, 1413, 1488, 1557, 1598, 1673, 2215, 2962, 3244 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ, 7.68 (d, 2H, *J* = 9.1, H-2 and H-6), 7.80 (s, 1H, H-3'), 7.93 (d, 2H, *J* = 9.1, H-3 and H-5), 8.22 (s, 1H, H-5), 10.03 (s, 1H, CHO). Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.31; H, 4.23; N, 14.24.

4-Phenylethynyl-1*H*-pyrazole (**5c**). Yield 67 %, mp 131-132°C (benzene) (lit.,[11] mp 134-134.5 °C); IR, ν_{max} = 851, 941, 1000, 1053, 1108, 1154, 1173, 1252, 1285, 1342, 1377, 1516, 1562, 1597, 2214, 2930, 3061, 3121 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ, 7.34-7.43 (m, 3H, H-2', H-4' and H-6'), 7.48 (t, 2H, *J* = 9.1, H-3' and H-5'), 7.74 (br s, 1H, H-3), 8.14 (br s, 1H, H-5).

4-(4-Nitrophenylethynyl)-l*H*-pyrazole (**5d**). Yield 72 %, mp 185-186 °C (benzene-chloroform); IR, ν_{max} = 815, 862, 917, 1001, 1027, 1071, 1140, 1168, 1378, 1484, 1565, 2225, 2826, 2878, 2955, 3120, 3155 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ, 7.92 (br s, 2H, H-3 and H-5), 7.75 (d, 2H, *J* = 9, H-2' and H-6'), 8.24 (d, 2H, *J* = 9, H-3' and H-5'); HRMS, *m/z* (%): 213.0592 (calcd for $C_{11}H_7N_3O_2$ 213.0538). Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.08; H, 3.42; N, 19.51.

l-(l-Ethoxyethyl)-4-ethynyl-1*H*-pyrazole (**6**). A mixture of alkyne (**4a**) (4.6 g, 21 mmol) and dried KOH (0.6 g, 12 mmol) in 20 mL of C_6H_6 was refluxed 3.5 h. The reaction mixture was cooled and filtered through a layer of Al_2O_3. The solvent was removed and the final yellow oil was purified by vacuum distillation to afford 2 g (59 %) as a yellowish oil, bp 78-80 °C/2 torr, n_d^{23} = 1.5126; IR, ν_{max} = 815, 854, 942, 978, 1006, 1064, 1121, 1247, 1302, 1346, 1381, 1441, 1545, 1630, 1694, 2115, 2931, 2981, 3070, 3130, 3292 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm; *J*, Hz: 1.16 (t, 3H, *J* = 10.4, *CH₃*-CH₂), 1.67 (d, 3H, *J* = 9.4, *CH₃*-CH), 3.04 (s, 1H, C≡C-H), 3.35, 3.48 (two q, 2H, *J* = 10.4, *CH₂*-CH₃), 5.52 (q, 1H, *J* = 9.4, *CH*-CH₃), 7.63 (s, 1H, H-3), 7.77 (s, 1H, H-5); HRMS, *m/z* (%): 164.09630 (calcd for $C_{11}H_7N_3O_2$ 164.09496), MS 164 (M^+ 22), 136 (10), 135 (18), 120 (19), 119 (18), 92 (34), 73 (40), 72 (27).

1,2-Bis[l-(l-ethoxyethyl)pyrazol-4-yl]ethyne (**10**). A mixture of iodopyrazole (**2**) (1.50 g, 5.4 mmole) and copper(I) salt of l-(l-ethoxyethyl)-1*H*-pyrazole-4-acetylene (**7**) (1.04 g, 6.0 mmol) in pyridine (40 mL) was refluxed in an argon stream for 7 h, cooled, diluted with chloroform (50 mL). The resulting mixture was passed through a neutral alumina column (2 x 2.5 cm). The solvent was removed under vacuum, and the residue was taken up in chloroform. The solution was washed with 25 % aqueous solution of ammonia and water, and dried over potassium carbonate. After distilling off the solvent the crude product was purified by column chromatography on silica gel (elution with chloroform) and following recrystallization from benzene/hexane to afford 1.04 g (74 %) of **10** as a white powder, mp 112-114 °C. IR, □$_{max}$ = 640, 662, 721, 754, 800, 848, 864, 979, 1003, 1065, 1092, 1120, 1168, 1244, 1344, 1382, 1441, 1482, 1540, 1706, 2160, 2874, 2925, 2976, 3077, 3103, 3463 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) □, 1.09 (t, 3H, *J* = 6.6, *CH_3*-CH_2*)*, 1.55 (d, 3H, *J* = 5, *CH_3*-CH) 3.21-3.41 (m, 2H, *CH_2*-CH_3), 5.37 (q, 1H, *J* = 5, *CH*-CH_3), 7.44 (s, 1H, H-3), 7.65 (s, 1H, H-5). Anal. Calcd for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.33; H, 7.50; N, 18.31.

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