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[1]BENZOPYRANO[4,3-c]PYRAZOLES BY INTRAMOLECULAR NITRILE IMINE ADDITION TO ACETYLENES

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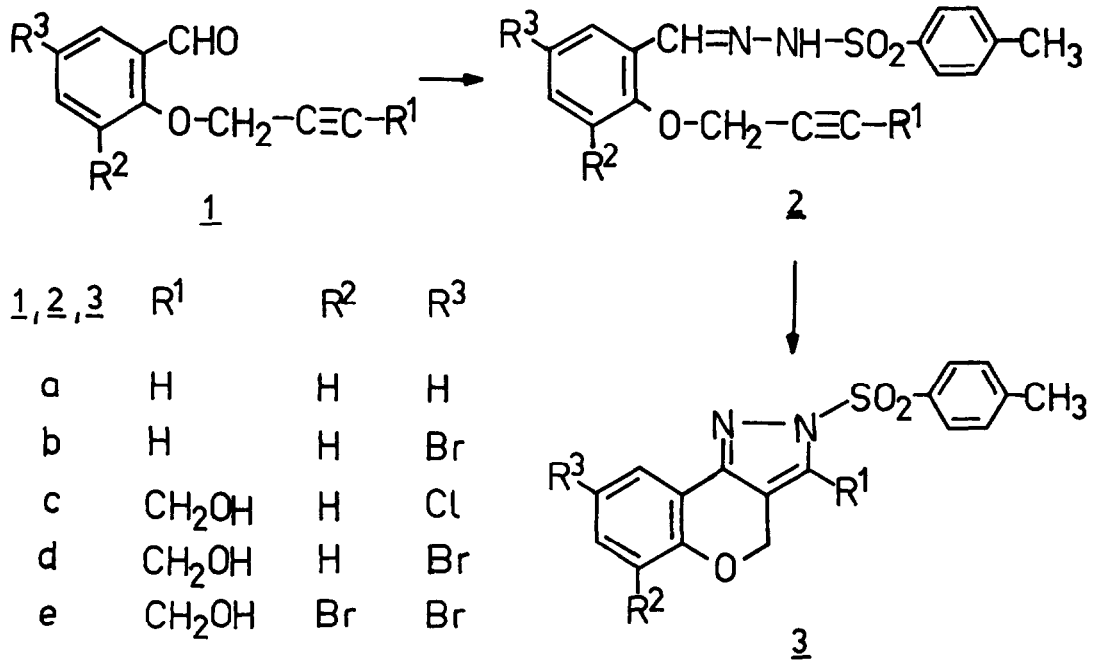
Abstract- 2-Alkynyloxy-benzaldehydes 1 are obtained by alkylation of the corresponding salicylaldehydes either with p-toluenesulfonic acid propargylester or 1-acetoxy-4-chloro-but-2-yne. The aldehydes 1 are converted into the hydrazones 2 by reaction with p-toluenesulfonylhydrazide. Dehydrogenation of 2 with lead tetraacetate yields 2,4-dihydro[1]benzopyrano[4,3-c]pyrazoles 3. In one case the acylated by-product 4 has been formed.

Nitrile imines are 1,3-dipoles reacting with dipolarophiles to yield 5-membered heterocycles. The intramolecular variant of 1,3-dipolar cycloaddition is of particular interest because the use of nonactivated multiple bond systems as a dipolarophilic side chain is possible.[1]
The dehydrogenation of aldehyde hydrazones with lead tetraacetate had already been used to prepare condensed pyrazoles.[2-4] But the utilization of hydrazones of 2-alkynyloxy-benzaldehydes has not been reported except for the single example 2a, not undergoing an intramolecular cycloaddition when subjected to the reaction conditions used in lit.[4]. The synthesis of the starting materials of type 1 is possible by alkylation of the corresponding salicylaldehydes either with p-toluenesulfonic acid propargylester [5] (R: H) or 1-acetoxy-4-chloro-but-2-yne[6] (R: CH_2OH). In the latter case the used reaction conditions also resulted in the cleavage of the acetate group previously described.[7]

The aldehydes 1 are converted into the hydrazones 2 by reaction with p-toluenesulfonylhydrazide using methanol as solvent in the presence of catalytical amounts of hydrochloric acid.
Dehydrogenation of the compounds 2b-e with lead tetraacetate at -5°C yields 2,4-dihydro[1]benzopyrano[4,3-c]pyrazoles 3b-e by intramolecular cycloaddition of the nitrile imines formed in situ.

Compound 3a could not be isolated when these reaction conditions were applied to 2a; the acylated product 4 was abtained. This kind of acetylation has already been described in reactions of 2a and of 2-alkenyloxy-benzaldehyde tosylhydrazones with lead tetraacetate.[4]

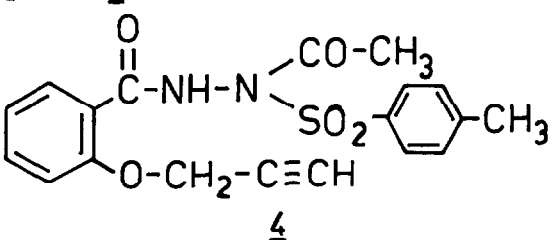
But if the dehydrogenation of 2a is carried out at -30°C the cycloaddition product 3a can be obtained well defined.



1,2,3	R^1	R^2	R^3
a	H	H	H
b	H	H	Br
c	CH_2OH	H	Cl
d	CH_2OH	H	Br
e	CH_2OH	Br	Br

Scheme 1

The ^1H NMR spectra of the hydrazones 2 show at δ = 8.1-8.2 ppm the singlet of the proton of the CH=N group. At δ = 11.3 ppm to 11.8 ppm the signal of the NH group is found. In the ^1H NMR spectra of the pyrazoles 3 the signals of the methylene groups are downfield shifted compared to the corresponding compounds 2.



Scheme 2

This synthesis of [1]benzopyrano[4,3-c]pyrazoles needs fewer steps than other possible methods using nitrile imines.[1,8,9]

The reactions show that nitrile imines are able to react with nonactivated C,C triple bond systems in intramolecular manner under mild reaction conditions.

EXPERIMENTAL

Melting pcints were determined with BOËTIUS micro melting point apparatus, and are uncorrected. IR spectra were obtained with a spectrophotometer Specord 71 IR (VEB Carl Zeiss Jena). ^{1}H NMR spectra were recorded with a Bruker AC 80 spectrometer. Chemical shifts are reported in δ from TMS as internal standard.

Synthesis of 2-(Propargyloxy)benzaldehydes (1a,b)

The corresponding salicylaldehyde (0.039 mol) is suspended in water (10ml). To the stirred mixture are dropped at room temperature p-toluenesulfonic acid propargylester (10.4 g; 0.053 mol) and sodium hydroxide solution (4.5 ml; 35%) simultaneously. After this the solution is warmed to 70°C for 2 h. After standing overnight the resulted precipitate is filtered off by suction and recrystallized using a soxhlet.

2-(1-Hydroxy-but-2-in-4-yloxy)benzaldehydes (1c-e)

The salicylaldehyde (0.02 mol) and potassium hydroxide (1.4 g; 0.024 mol) dissolved in ethanol (60 ml) are stirred under reflux for 1 h. After cooling to room temperature 1-acetoxy-4-chloro-but-2-yne (3 g; 0.02 mol) is added and the solution is stirred under reflux for 12h.The mixture is diluted with water and extracted with ether. The combined extracts are washed twice with sodium hydroxide solution (5%) and with water, dried over sodium sulfate and evaporated in vacuo. The resulting residue is purified by recrystallization.

Benzaldehyde-tosylhydrazones (2a-e)

p-Toluenesulfonylhydrazide (1.9 g; 0.01 mol) is dissolved in methanol (15 ml) and 10 drops of conc. hydrochloric acid are added. This solution is dropped at room temperature to a stirred mixture of the aldehyde 1 (0.01 mol) and methanol (30 ml). The reaction mixture is heated on a steam bath for 0.5 h and then stirred at room temperature overnight. The solvent is removed and the residue crystallized after having added a few drops of ethanol and n-hexane.

2-(p-Toluenesulfonyl)-2,4-dihydro[1]benzopyrano[4,3-c]pyrazoles (3a-e)

The hydrazone 2 (1 g) is dissolved in absolute acetonitrile (70 ml). To this mixture is dropped lead tetraacetate (1.5 mol equiv.), dissolved in abs. acetonitrile (20 ml), with stirring at -5°C (-30°C to synthesize compound 3a). The solution is stirred at the same temperature for 6 h and then stored at room temperature overnight. The precipitate is removed by filtration. The solution is filtered through a short column filled with alumina (neutral). Then the alumina is washed with methylene chloride. The combined filtrates are evaporated in vacuo.
If it is not possible to remove unreacted starting material completely the obtained residue will be dissolved in an appropriate solvent (3a,b: benzene; 3c: methylene chloride) and the filtration is repeated. After evaporation of the solvent the residue is crystallized, eventually by adding some ethanol.

Table 1: Benzaldehydes 1a-e, Benzaldehyde Tosylhydrazones 2a-e and 2,4-Dihydro[1]benzopyrano[4,3-c]pyrazoles 3a-e

Comp.	Yield (%)	M.p. (°C) (recryst.)	Formula (mol.wt.)	C Calc./Found	H Calc./Found	N Calc./Found	MS m/z (%)
1a[5]	80	66-68 (petroleum ether) (m.p.$_{lit.}$ 72-74)	$C_{10}H_8O_2$ (160.2)	74.99 74.61	5.03 5.02		
1b	55	89-91 (n-hexane)	$C_{10}H_7BrO_2$ (239.1)	50.24 50.25	2.95 2.94		
1c	65	77-79 (benzene/n-heptane)	$C_{11}H_9ClO_3$ (224.7)	58.81 58.97	4.04 4.05		
1d	74	104-106 (benzene)	$C_{11}H_9BrO_3$ (269.1)	49.10 49.15	3.37 3.39		
1e	43	104-106 (benzene/n-heptane)	$C_{11}H_8Br_2O_3$ (348.0)	37.97 38.12	2.32 2.30		
2a[1]	61	139-141 (methanol/H_2O) (m.p.$_{lit.}$ 139.5-141)	$C_{17}H_{16}N_2O_3S$ (328.4)	62.18 62.23	4.91 4.86	8.53 8.52	
2b	70	125-128 (ethanol/H_2O)	$C_{17}H_{15}BrN_2O_3S$ (407.3)	50.13 50.50	3.71 3.85	6.88 6.81	
2c	71	157-160 (ethanol/H_2O)	$C_{18}H_{17}ClN_2O_4S$ (392.9)	55.03 55.05	4.36 4.35	7.13 7.24	
2d	69	153-156 (ethanol/H_2O)	$C_{18}H_{17}BrN_2O_4S$ (437.3)	49.44 49.39	3.92 3.92	6.41 6.53	
2e	56	107-110 (ethanol/H_2O)	$C_{18}H_{16}Br_2N_2O_4S$ (516.2)	41.88 41.56	3.12 3.17	5.43 5.13	
3a	37	138-140 (ethanol/H_2O)	$C_{17}H_{14}N_2O_3S$ (326.4)	62.56 62.46	4.32 4.27	8.58 8.56	326 (M^+;100)
3b	25	175-177 (ethanol)	$C_{17}H_{13}BrN_2O_3S$ (405.3)	50.38 50.41	3.23 3.31	6.91 6.90	404 (M^+;100)
3c	52	149-151 (ethanol/H_2O)	$C_{18}H_{15}ClN_2O_4S$ (390.9)	55.32 55.62	3.87 4.11	7.17 6.86	390 (M^+;100)
3d	41	146-149 (ethanol/H_2O)	$C_{18}H_{15}BrN_2O_4S$ (435.3)	49.67 49.82	3.47 3.58	6.44 6.02	434 (M^+;9)
3e	15	187-189 (ethanol/H_2O)	$C_{18}H_{14}Br_2N_2O_4S$ (514.2)	42.05 42.33	2.74 3.03	5.45 5.29	512 (M^+;29)

Table 2: IR and ^{1}H NMR Data of Compounds 1, 2 and 3

Comp.	IR (Nujol) ν (cm^{-1})	^{1}H NMR[a] δ (ppm)
1a	3260,1680,1220	2.56(1H,t,CH,J=2.4Hz); 4.80(2H,d,CH_2,J=2.4Hz); 6.94-7.89(4H,m,arom.); 10.46(1H,s,CHO)
1b	3220,1685,1595, 1220,1190	2.58(1H,t,CH,J=2.4Hz); 4.81(2H,d,CH_2,J=2.4Hz); 6.96-7.94(3H,m,arom.); 10.37(1H,s,CHO)
1c	3500,1680,1120	2.14(1H,m,OH); 4.25(2H,m,CH_2); 4.80(2H,t,CH_2,J=2Hz); 6.95-7.72(3H,m,arom.);10.29(1H,s,CHO)
1d	3440,1680,1130	2.46(1H,m,OH); 4.25(2H,m,CH_2); 4.80(2H,t,CH_2,J=2Hz); 6.90-7.85(3H,m,arom.); 10.25(1H,s,CHO)
1e	3200,1680,1140	2.72(1H,s,OH); 4.16(2H,t,CH_2,J=2Hz); 4.84(2H,t,CH_2, J=2Hz); 7.80-7.92(2H,m,arom.); 10.24(1H,s,CHO)
2a	3280,3160,1610, 1325, 1160	2.34(3H,s,CH_3); 3.55(1H,t,CH,J=2.4Hz); 4.84(2H,d,CH_2, J=2.4Hz); 6.89-7.81(8H,m,arom.); 8.21(1H,s,CH); 11.37 (1H,s,NH)
2b	3230,3180,1600, 1325,1170	2.34(3H,s,CH_3); 3.57(1H,t,CH,J=2.4Hz); 4.85(2H,d,CH_2, J=2.4Hz); 7.03-7.79(7H,m,arom.); 8.12(1H,s,CH); 11.55(1H,s,NH)
2c	3180,1595,1310, 1155	2.34(3H,s,CH_3); 2.49(1H,m,OH); 4.09(2H,s,CH_2); 4.88 (2H,s,CH_2); 7.06-7.80(7H,m,arom.); 8.14(1H,s,CH); 11.56(1H,s,NH)
2d	3520,3160,1600, 1320,1160	2.34(3H,s,CH_3); 2.51(1H,m,OH); 4.08(2H,s,CH_2); 4.88(2H,s,CH_2); 7.01-7.80(7H,m,arom.); 8.13 (1H,s,CH); 11.56(1H,s,NH)
2e	3400,3270,1315, 1160	2.35(3H,s,CH_3); 2.49(1H,m,OH); 3.99(2H,s,CH_2); 4.70 (2H,s,CH_2); 7.34-7.90(6H,m,arom.); 8.11(1H,s,CH); 11.76(1H,s,NH)
3a	1600,1300,1190	2.40(3H,s,CH_3); 5.19(2H,d,CH_2,J=1Hz); 6.86-7.96(m, with t at 7.35,J=1Hz; 8H arom. and CH)
3b	1600,1300,1180	2.42(3H,s,CH_3); 5.20(2H,d,CH_2,J=1Hz); 6.75-7.97(m, with t at 7.38,J=1Hz; 7H arom. and CH)
3c	3340,1600,1300, 1160	2.41(3H,s,CH_3); 4.88(2H,s,CH_2); 5.22(2H,s,CH_2); 6.78-7.95(7H,m,arom.)
3d	1595,1155	2.77[1H,s (br),OH]; 2.41(3H,s,CH_3); 4.88(2H,s,CH_2); 5.22(2H,s,CH_2); 6.72-7.94(7H,m,arom.)
3e	3400,1595,1300, 1165	2.22[1H,s (br),OH]; 2.43(3H,s,CH_3); 4.91(2H,s,CH_2); 5.35(2H,s,CH_2); 7.26-7.97(6H,m,arom.)

[a] solvent for compounds 1 and 3: $CDCl_3$; for compounds 2: DMSO-d_6

2-(Propargyloxy)-N'-acetyl-N'-(p-toluenesulfonyl)-benzoylhydrazine (4)

Compound 2a (1 g; 0.003 mol) is dissolved in abs. acetonitrile (70 ml) and cooled to -5°C. With stirring lead tetraacetate (2.1 g; 0.0047 mol), dissolved in abs. acetonitrile (30 ml) is dropped to this solution. The reaction mixture is stirred at -5°C for 5 h and stored at room temperature overnight. The resulting precipitate is filtered off and the mother liquor after standing at room temperature for 24 h is filtered over alumina (neutral). After washing the alumina with acetone the combined filtrates are concentrated in vacuo. The oily residue is crystallized by adding a few drops of ethanol in 30% yield.-m.p. 166-169°C (EtOH).- $C_{19}H_{18}N_2O_5S$ (386.4) calc. C, 59.06; H, 4.70; N, 7.25.-found C, 59.02; H, 4.70; N, 7.13%.-MS: m/z = 344 (M^+-42, $H_2C=C=O$; 57%); 326 (6); 278 (8); 231 (M^+-155, $CH_3-C_6H_4-SO_2$; 10); 215 (8); 189 (24); 171 (7); 159 (100); 139 (28); 131 (41); 121 (29); 103 (15); 91 (30).-IR (Nujol): ν = 3320, 3220, 1730, 1710, 1680, 1605, 1310, 1170 cm^{-1}.-^1H NMR ($CDCl_3$): δ = 2.14 (3H,s,CH_3); 2.42 (3H,s, CH_3); 2.65 (1H,t,CH, J = 2.4Hz); 4.94 (2H,d,CH_2, J = 2.4Hz); 7.06-8.22 (8H, m,arom.); 9.98 (1H,s,NH) ppm.

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