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Note

Synthesis of D-allofuranos-3-ylpyrazoles

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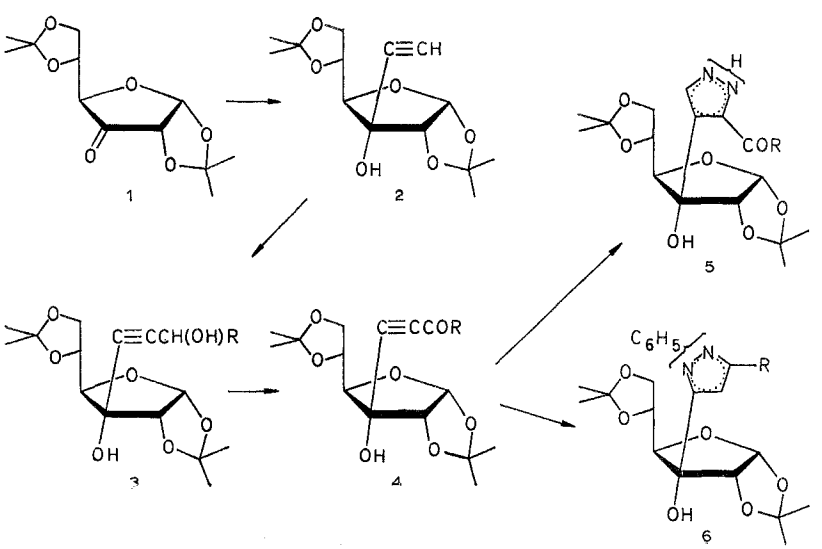
As α-acetylenic ketones are easily transformed into heterocyclic structures, ketoacetylenic sugars can be used as precursors for certain *C*-nucleosides. We now report on the utilisation of 3-*C*-ethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) [obtained[1–3] from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**)] in the synthesis of 3-substituted pyrazoles.

High yields (75–85%) of the diols **3** were obtained by treatment of **2** with lithium or sodium amide in liquid ammonia–tetrahydrofuran, followed by addition of isobutyraldehyde, 2-ethylbutanal, benzaldehyde, or tolualdehyde. Methyl sulphoxide replaced tetrahydrofuran in the reaction with *p*-chlorobenzaldehyde. The first member (**3**, R = H) of the series of diols resulted[1] from the addition of the Grignard derivative of 2-propyn-1-ol to **1**.



Oxidation of the diols **3** with chromium trioxide–pyridine–acetic acid led to the corresponding ketols **4**, which, with ethereal diazomethane, gave the pyrazoles **5** (60–80%). In at least one reaction, diazomethane probably added in both senses to the triple bond, as the n.m.r. spectrum of the pyrazole **5** ($R = CHMe_2$) contained two pairs of doublets for H-1 and H-2 of the sugar moiety, and two pairs of singlets for the pyrazole proton. T.l.c. of this product revealed two components.

When the ketols **4** were treated with phenylhydrazine in ethanol at room temperature, the pyrazoles **6** were obtained. A singlet at τ 3.33–3.7 in the n.m.r. spectra is in agreement[4] with a pyrazole H-4, but the position of the *N*-phenyl group could not be established. The direction of this type of cyclocondensation is not easily predictable[6].

EXPERIMENTAL

Melting points (uncorrected) were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded for chloroform solutions or KBr discs with a Perkin–Elmer 257 spectrophotometer. N.m.r. spectra were recorded at 60 MHz for solutions in $CDCl_3$ (internal Me_4Si) with a Perkin–Elmer R-24 spectrometer. Analyses were determined by Sección de Semimicroanálisis del Instituto de Química Orgánica de Barcelona, Spain.

T.l.c. was performed on Camag DSF-5 Silica gel with hexane–ethyl acetate (1:1), and detection with phosphomolybdic acid or with 0.05% aqueous potassium permanganate. All evaporations were carried out at $<40°/\sim12$ mmHg. Tetrahydrofuran (distilled from sodium) and methyl sulphoxide (dried over $CaSO_4$) were stored over 4 Å molecular sieve (Merck). Diazomethane was prepared from *N*-methyl-*N*-nitrosourea, and used without distillation. The chromium trioxide–pyridine–acetic acid oxidising agent was prepared[6] by slow addition of chromium trioxide (40 g) to a stirred solution of pyridine (32 g) in acetic acid (150 ml) at $<40°$, and final dilution with acetic acid (to 250 ml).

Reactions of 3-C-ethynyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**2**) *with aldehydes.* — (*a*) A solution of **2** (4.7 g) in tetrahydrofuran (10 ml) was added to a stirred solution of sodium amide (from 1.13 g of sodium) in liquid ammonia (60 ml). The volume of the mixture was slowly decreased to half at 50°. Tetrahydrofuran (90 ml) was then added slowly, and the ammonia was removed at $\sim20°/0.5$ mmHg. The volume was made up to ~90 ml with tetrahydrofuran, and a solution of isobutyraldehyde (3.65 g) in tetrahydrofuran (10 ml) was added dropwise with cooling ($\sim0°$). The mixture was stirred at room temperature for 3 h, saturated, aqueous ammonium chloride (100 ml) was added, the solvent was partially evaporated, and the resulting mixture was extracted with ether (5×20 ml). The combined extracts were dried (Na_2SO_4) and concentrated, and the syrupy residue (6.0 g) was crystallised from ethyl ether–hexane to give 3-*C*-(3-hydroxy-4-methylpent-1-ynyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**, $R = CHMe_2$) as white plates (1.13 g).

Using essentially the foregoing procedure, with the appropriate aldehyde, the 3-*C*-(4-ethyl-3-hydroxyhex-1-ynyl) (**3**, $R = CHEt_2$, from 2-ethylbutanal), 3-*C*-(3-hydroxy-3-phenylprop-1-ynyl) (**3**, R = Ph, from benzaldehyde), and 3-*C*-(3-hydroxy-

TABLE I

DATA FOR DIOLS **3** AND KETOLS **4**

Compound	*Yield* (%)	*M.p.* (*degrees*)	R_F	*Formula*	*Calc.* (%)			*Found* (%)		
					C	*H*	*Cl*	*C*	*H*	*Cl*
Diols **3**										
R = H	14	98–99	0.1	$C_{15}H_{22}O_7$	57.32	7.05	—	57.5	7.1	—
$CH(CH_3)_2$	80[a]	111–113	0.3	$C_{18}H_{28}O_7$	60.66	7.92	—	60.6	7.9	—
$CH(C_2H_5)_2$	75[a]	110–111.5	0.32							
C_6H_5	86[a]	syrup	0.34	$C_{21}H_{26}O_7$	64.62	6.67	—			
C_6H_4-*p*-CH_3	79[a]	syrup	0.27	$C_{22}H_{28}O_7$	65.33	6.95	—	65.2	6.9	—
C_6H_4-*p*-Cl	33[b]	135–136	0.31	$C_{21}H_{25}ClO_7$	59.36	5.89	8.36	59.35	5.9	8.45
Ketols **4**										
R = $CH(CH_3)_2$	14[b]	110–112	0.55	$C_{18}H_{26}O_7$	61.00	7.39	—	60.9	7.8	—
$CH(C_2H_5)_2$	83[b]	108–110[c]	0.5							
C_6H_5	50[b]	141–143	0.6	$C_{21}H_{24}O_7$	64.94	6.23	—	64.85	6.2	—
C_6H_4-*p*-CH_3	23[b]	106–107	0.51	$C_{22}H_{26}O_7$	65.66	6.51	—	65.5	6.45	—
C_6H_4-*p*-Cl	62[b]	108–109	0.53	$C_{21}H_{23}ClO_7$	59.34	5.44	8.44	59.85	5.6	8.4

[a]Crude material. [b]Crystallized product. [c]Lit.[1] m.p. 66–67°.

3-*p*-tolylprop-1-ynyl) (**3**, R = *p*-tolyl, from *p*-tolualdehyde) derivatives of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose were obtained. The physical constants and analytical data for these compounds are given in Table I. The syrupy products were purified by p.l.c.

(*b*) A solution of **2** (5 g) in methyl sulphoxide (15 ml) was added dropwise to a stirred solution of lithium amide (from 0.42 g of lithium and 100 ml of ammonia, and subsequent evaporation of solvent) in methyl sulphoxide (20 ml) under nitrogen. After stirring for 45 min at room temperature, a solution of *p*-chlorobenzaldehyde (2.82 g) in methyl sulphoxide (15 ml) was added and the mixture was stirred for 7 h. Cold water was added, the mixture was extracted with ether (4 × 50 ml), and the combined extracts were shaken with brine (3 × 40 ml) and water, dried, and concentrated. Crystallisation of the residue from ethyl ether–hexane gave 3-*C*-(3-*p*-chlorophenyl-3-hydroxyprop-1-ynyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**, R = p-chlorophenyl) as white needles (2.5 g). The physical constants and analytical data are given in Table I.

Oxidation of the diols **3**. — Chromium trioxide–pyridine–acetic acid reagent (23.8 ml) was added dropwise to a stirred solution of **3** (R = $CHMe_2$, 6.45 g) in acetic acid (20 ml) at 0°, and the mixture was stirred for 0.5 h at room temperature. Water (120 ml) was added, the mixture was extracted with ether (3 × 20 ml), and the combined extracts were washed with ice-cold 2M hydrochloric acid, saturated, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. Crystallisation of the residue from ethyl ether–hexane gave 1,2:5,6-di-*O*-isopropylidene-3-*C*-(4-methyl-3-oxopent-1-ynyl)-α-D-allofuranose (**4**, R = $CHMe_2$) as white plates (0.95 g); ν_{max} 3380 (OH), 2210 (C≡C), and 1680 cm^{-1} (C=O).

Using essentially the above procedure, the following products were obtained. 1,2:5,6-Di-*O*-isopropylidene-3-*C*-(3-oxo-3-phenylprop-1-ynyl)-α-D-allofuranose (**4**, R = Ph), ν_{max} 3340 (OH), 2230 (C≡C), and 1650 cm^{-1} (C=O).

1,2:5,6-Di-*O*-isopropylidene-3-*C*-(3-oxo-3-*p*-tolylprop-1-ynyl)-α-D-allofuranose (**4**, R = *p*-tolyl), ν_{max} 3490 (OH), 2210 (C≡C), and 1650 cm^{-1} (C=O).

3-*C*-(3-*p*-Chlorophenyl-3-oxoprop-1-ynyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**, R = *p*-chlorophenyl), ν_{max} 3490 (OH), 2210 (C≡C), and 1660 cm^{-1} (C=O).

The physical constants and analytical data for these compounds are given in Table I.

Synthesis of pyrazole derivatives **5**. — A solution of **4** (R = $CHEt_2$, 0.48 g) and diazomethane (from 6.8 g of *N*-methyl-*N*-nitrosourea) in ethyl ether (70 ml) was stored for 6.5 h. Acetic acid was then added, and the colourless solution was shaken with saturated, aqueous sodium hydrogen carbonate, dried, and concentrated. Crystallisation of the residue from ethanol–ethyl acetate gave 4-(1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)-3-(2-ethyl-1-oxobutyl)pyrazole (**5**, R = $CHEt_2$) as white prisms (0.09 g), ν_{max} 3290 (OH) and 1630 cm^{-1} (C=O).

By essentially the above procedure, the 3-benzoyl (**5**, R = Ph) and 3-*p*-chlorobenzoyl (**5**, R = *p*-chlorophenyl) derivatives of 4-(1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)pyrazole were prepared.

TABLE II

DATA FOR PYRAZOLE DERIVATIVES **5** AND **6**

Compound	*Yield*[a] (%)	*M.p.* (*degrees*)	R_F	*Formula*	*Calc.* (%)				*Found* (%)			
					C	*H*	*Cl*	*N*	*C*	*H*	*Cl*	*N*
5, R = $CH(C_2H_5)_2$	18	168–170	0.25[b]	$C_{21}H_{32}N_2O_7$	59.43	7.65	—	6.60	59.8	8.0	—	6.6
C_6H_5	35	229–230	0.1	$C_{22}H_{26}N_2O_7$	61.39	6.09	—	6.51	61.25	6.1	—	6.0
C_6H_4-*p*-CH_3	36	264	0.1	$C_{23}H_{28}N_2O_7$	62.15	6.35	—	6.30	61.85	6.35	—	6.5
6, R = $CH(CH_3)_2$	26	122–124	0.75	$C_{24}H_{32}N_2O_6$	64.85	7.26	—	6.30	64.8	7.2	—	6.3
$CH(C_2H_5)_2$	11	104–105	0.9	$C_{26}H_{36}N_2O_6$	66.08	7.68	—	5.93	66.45	7.7	—	5.95
C_6H_5	46	172–174	0.85	$C_{27}H_{30}N_2O_6$	67.77	6.32	—	5.85	67.75	6.35	—	5.8
C_6H_4-*p*-CH_3	—	158–159	0.8	$C_{28}H_{32}N_2O_6$	68.28	6.55	—	5.69	68.2	6.55	—	5.5
C_6H_4-*p*-Cl	25	149–150	0.5	$C_{27}H_{29}ClN_2O_6$	63.29	5.66	6.93	5.46	63.35	5.6	6.5	5.5

[a]Crystallized product. [b]Two spots in t.l.c.

TABLE III

P.M.R. CHEMICAL SHIFTS (τ) FOR PYRAZOLES **5** AND **6**

Compound	*H-1*	*H-2*	*H-4*	*H-5*	*H-6*	$C(CH_3)_2$	*HO-3*	$N-C_6H_5$	*Pyr-CH*	*N-H*	*Other signals*
5, R = $CH(C_2H_5)_2$	4.05d 4.1d	5.5d 5.55d	6.1–6.4m	5.75m	6.1–6.4m	8.35, 8.6, 8.8	6.0s	—	2.6s 2.8s	1.8s 1.98s	6.1–6.4m, 9.1t $-CH(C_2H_5)_2$
C_6H_5	4.1d	5.4d	6.15–6.35m	5.8m	6.15–6.35m	8.35, 8.6, 8.7, 9.01	7.5s 7.7s	—	2.98s	2.65s	1.95, 2.55 $-C_6H_5$
C_6H_4-*p*-CH_3	4.1d	5.4d	6.2–6.4m	5.8m	6.2–6.4m	8.4, 8.6, 8.7, 9.1	7.4bs	—	3.02s	2.85s	2.05d, 2.6d, 7.6s $-C_6H_4$-*p*-CH_3
6, R = $CH(CH_3)_2$	3.95d	5.22d	5.78d	6.05m	6.4dd	8.35, 8.55d, 8.7	6.75bs	2.6s	3.65s	—	6.95m, 8.82dd $-CH(CH_3)_2$
$CH(C_2H_5)_2$	3.95d	5.2d	5.8d	6.05m	6.35dd	8.35, 8.55d, 8.7	6.78s	2.6s	3.7s	—	7.38m, 9.15dd $-CH(C_2H_5)_2$
C_6H_5	3.93d	5.2d	5.75d	6.0m	6.35dd	8.35, 8.55d, 8.7	6.75s	2.78s	3.4s	—	2.78 $-C_6H_5$
C_6H_4-*p*-CH_3	3.93d	5.2d	5.7d	5.95m	6.35dd	8.35, 8.55d, 8.7	6.7s	2.78s	3.42s	—	2.96, 7.6 $-C_6H_4$-*p*-CH_3
C_6H_4-*p*-Cl	3.92d	5.17d	5.76d	6.0m	6.3dd	8.33, 8.55d, 8.7	6.72s	2.70s 2.73d 2.80d	3.33s	—	2.78d, 2.92d $-C_6H_4$-*p*-Cl

TABLE IV

P.M.R. COUPLING CONSTANTS (Hz) FOR PYRAZOLES **5** AND **6**

Compound	$J_{1,2}$	$J_{4,5}$	$J_{5,6a-6b}$	$J_{6a,6b}$
5, R = $CH(C_2H_5)_2$	3.6			
C_6H_5	3.6			
C_6H_4-*p*-CH_3	3.5			
6, R = $CH(CH_3)_2$	3.6	5.2	7.0	5.2
$CH(C_2H_5)_2$	3.6	5.3	6.4	5.0
C_6H_5	3.5	5.5	6.8	6.0
C_6H_4-*p*-CH_3	3.6	5.45	7.2	5.6
C_6H_4-*p*-Cl	3.5	5.45	7.2	5.2

The physical constants and analytical and n.m.r. data for these compounds are given in Tables II–IV.

Reaction of phenylhydrazine with the ketols **4**. – A solution of freshly distilled phenylhydrazine (0.06 ml) and ketol **4** (R = $CHMe_2$, 0.21 g) in ethanol (20 ml) was kept for 5 days at room temperature, and then concentrated. The residue was crystallised from ether–hexane to give 5(3)-(1,2:5,6-di-*O*-isopropylidene-α-D-allofuranos-3-yl)-3(5)-isopropyl-1-phenylpyrazole (**6**, R = $CHMe_2$) as white plates (0.07 g).

By essentially the above procedure, the corresponding 3(5)-(2-ethylprop-1-yl) (**6**, R = $CHEt_2$), 3(5)-phenyl (**6**, R = Ph), 3(5)-*p*-tolyl (**6**, R = *p*-tolyl), and 3(5)-*p*-chlorophenyl (**6**, R = *p*-chlorophenyl) derivatives were prepared.

The physical constants and analytical and n.m.r. data for these compounds are given in Tables II–IV.

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