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A NEW SYNTHESIS OF C-NUCLEOSIDES BY 1,3-DIPOLAR CYCLOADDITION OF CHIRAL AZOMETHINE IMINES TO METHYL ACRYLATE THE STEREOSELECTIVE SYNTHESIS OF FUSED PYRAZOLES

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Abstract

A new stereoselective synthesis of C-nucleosides is described. The fused NH,NH-dihydro pyrazole derivative 1 was transformed with carbohydrates into chiral azomethine imines 2-4. The 1,3-dipolar cycloaddition of these to methyl acrylate affords the nucleosides 5-7. The compound 8 was prepared from 1, unprotected D-ribose and methyl acrylate in a one-pot procedure. The synthesis is highly stereoselective to give products in >95% ee, except for 5.

There are four types of carbohydrate derivatives, which react as 1,3-dipoles in cycloaddition reactions, described in the literature. They are azides,[1,2] nitrones,[3-5] nitrile oxides,[6] and diazo derivatives.[7-9] Only azides and acyclic diazo carbohydrates have been isolated in pure form, while the corresponding nitrones and nitrile oxides have been prepared "in situ" and used in further transformations.

On the other hand, azomethine imines are important intermediates which react as 1,3-dipoles in cycloaddition and electrocyclic reactions, in which five, six and seven-membered heterocyclic systems are formed.[10-13]

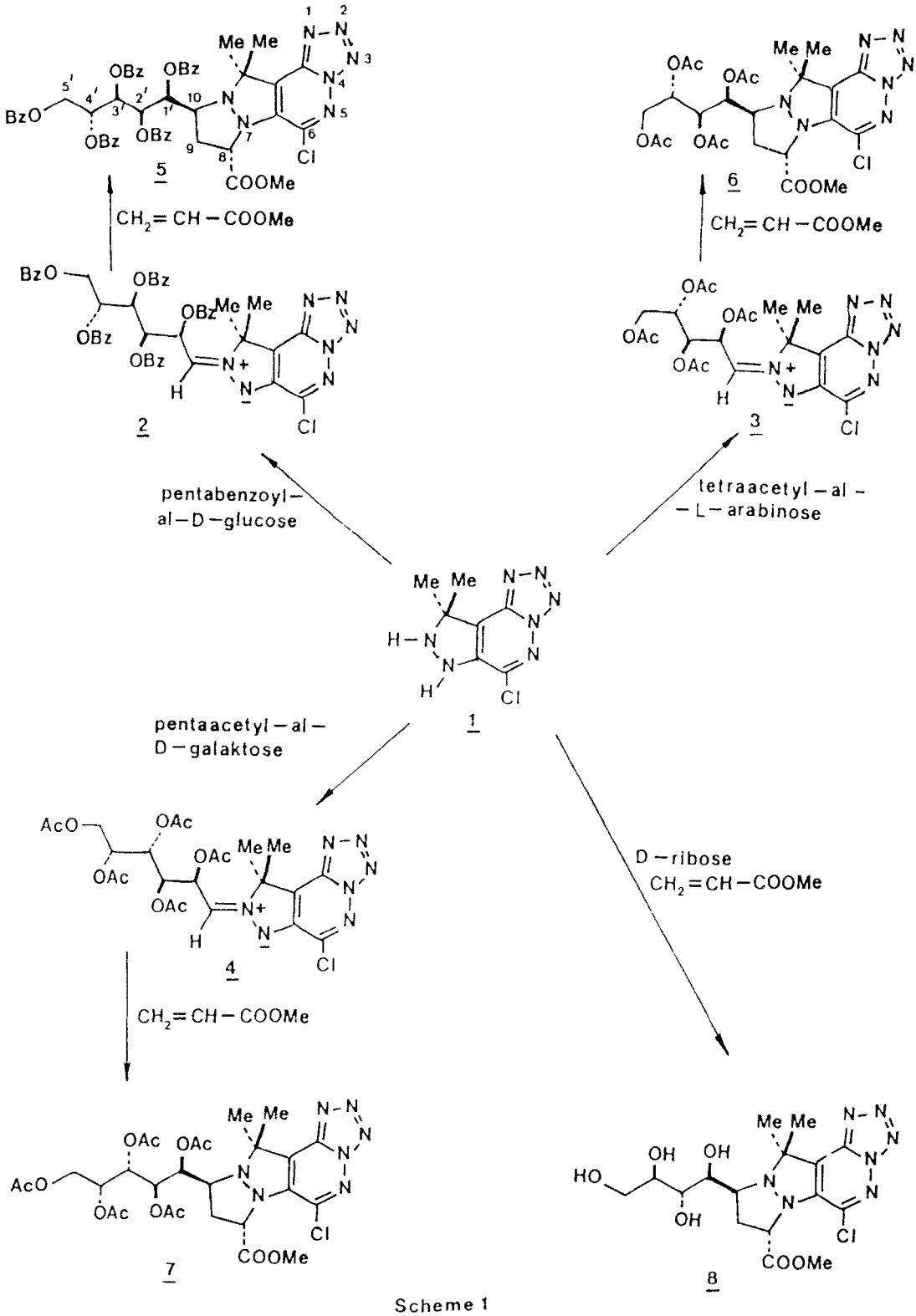
While studying the 1,3-dipolar cycloaddition reactions of diazoalkanes to heteroaromatic systems, especially to pyridazines and fused pyridazines, we have observed that primary CH,CH-dihydro cycloadducts easily rearrange into NH,NH-dihydro cycloadducts. These react with aldehydes,

dimethylformamide dimethyl acetal and dimethyl acetylenedicarboxylate to give the corresponding stable azomethine imines, the structure of which has been determined by X-ray analysis.[14] They rearrange easily by thermal 6π-electron ring-opening followed by a 1,5-sigmatropic hydrogen shift and electrocyclization into the corresponding fused 1,2-diazepines.[15] They react also as 1,3-dipoles with unsaturated compounds, such as olefins, acetylenes and arynes, forming new pyrazole ring fused to other heterocyclic systems. Since naturally occuring C-nucleosides, such as Pseudouridin, Formycin B, Oxoformycin B, Pyrazomycin and other antibiotics,[16,17] contain heterocyclic structural element, we tried to apply this latter reaction for the stereoselective synthesis of fused pyrazole C-nucleosides.

In this communication we report on the synthesis of azomethine imines as a new type of stable 1,3-dipoles derived from carbohydrates. They were prepared from 7,8-dihydro-6-chloro-9,9-dimethyl-9H-pyrazolo[4,3-d] tetrazolo[1,5-b]pyridazine (1) and tetra- or penta-O'-substituted aldehydo sugars, such as pentabenzoyl-al-*D*-glucose, tetraacetyl-al-*L*-arabinose and pentaacetyl-al-*D*-galactose to give the compounds 2-4, respectively.

In the reaction of azomethine imines 3 and 4 with methyl acrylate as the dipolarophile by heating in benzene or acetonitrile under reflux the corresponding O'-acetylated compounds 6 and 7 were isolated as pure (>95% ee) stereoisomers in 60-67% yield. On the other hand, the reaction of the benzoylated azomethine imine 2 with methyl acrylate gave the compound 5, which contains around 10% of another isomer, determined by ^{1}H nmr. The absolute configuration of this isomer was not determined. The reaction can be carried out also as a one-pot synthesis. In this manner, the compound 1 was treated with *D*-ribose and methyl acrylate by heating in methanol in the presence of a catalytic amount of trifluoroacetic acid under reflux to give the compound 8. (Scheme 1).

The determination of configurations at the newly formed chiral centers C_8 and C_{10} in the compounds 5-7 is based on the following characteristics. The relative configuration was determined from ^{1}H nmr spectra, since the chemical shift for H_8 is dependent on the structure of the carbohydrate component at C_{10}. This points out that H_8 and carbohydrate residue are on the same side of the ring system, and consequently, that other substituents, i.e. the methoxycarbonyl group at C_8 and carbohydrate residue at C_{10}, are trans in respect to each other. The relative configurations at C_{10} and C_1, were determined on the basis of the magnitude of the coupling constants, $J_{10-H,1'-H}$ = 2-3 Hz. This is consistent with the proposed structures. Since the absolute configuration at C_1, is given by the carbohydrate component used in the preparation of the azomethine imi-


pentabenzoyl–al–D–glucose
tetraacetyl–al–L–arabinose
pentaacetyl–al–D–galaktose
D–ribose
CH2=CH–COOMe
CH2=CH–COOMe
CH2=CH–COOMe
CH2=CH–COOMe
1
2
3
4
5
6
7
8

Scheme 1

ne, the absolute configuration of all three centers in compounds 5-7 is therefore (1'*S*,8*S*,10*S*). The structure of the compound 8, including the absolute configurations at C_1, ,C_8 and C_{10} (1'*S*,8*S*,10*S*) was determined by X-ray analysis.[18] The dipolarophile reacts with azomethine imine from the less hindered side of the azomethine. A similar stereochemistry has been observed earlier in the cycloadditions of nitrones to monosubstituted olefins.[3,4]

The method, in comparison to other known methods which are mostly tedious multistep procedures, is superior for the following reasons. In this synthetic procedure,protected or unprotected sugars can be used. The reactions can be carried out in a one-pot synthesis, since azomethine imines are formed "in situ". The syntheses are highly stereospecific. Since the orientation around the double bond in azomethine imines is known from the X-ray studies, the absolute configuration at positions 8 and 10 of the newly formed pyrazoline system is determined by the configuration of the sugar. These reactions can also be applied generally for the preparation of many C-nucleosides from various azomethine imines.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope. ^{1}H nmr spectra were recorded on a JEOL FX 90Q FT spectrometer with TMS as internal standard. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. Elemental analyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. The reactions were followed by tlc (DC-Fertigplatten Kiselgel 60 F_{254}, E.Merck, and a mixture chloroform/methanol, 10:1, as solvent). The following compounds were prepared according to the procedures described in literature: 6-chloro-9,9-dimethyl-7,8-dihydro-9H-pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine (1),[19] pentabenzoyl-al-*D*-glucose,[20] tetraacetyl-al-*L*-arabinose,[21] and pentaacetyl-al-*D*-galactose.[22]

Substituted 9H-Pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine(8*E*)-Azomethine Imines. General Procedure.

A mixture of 1 (0.001 mole) and carbohydrate derivative (0.0011 mole) in an appropriate solvent was heated for 50-90 min. The reaction mixture was left in a regrigerator for several hours. The precipitate was collected by filtration and recrystallized to give the corresponding azomethine imine. The following compounds were prepared in this manner:

9,9-Dimethyl-8-(*D-gluco*-2',3',5',6'-pentabenzoyloxyhex-1'-ylidene)-6-chloro-9H-pyrazolo[4,3-d]tetrazolo[2,5-b]pyridazine (8*E*)-Azomethine Imine (2): from 1 and pentabenzoyl-al-*D*-glucose in ethanol (6 ml) and trifluoroacetic acid (0.1 ml) under reflux (1.5 hours), yield 451 mg (50 %), mp 110-113°C (methanol); ^{1}H NMR($CDCl_3$, 60°C, 90 MHz): δ_{ppm} = 1.61-2.06 (m,9Me_2,6H); 4,68(dd,6'-HCH,1H); 4.98(dd,6'-HCH,1H); 6.87(m,2'-H,3'-H,4'-H,5'H,4H); 7.06-7.64(m,5xPh/3"-H,4"-H,5"-H/,14H); 7.74-8.18(m,5xPh/2"-H,6"-H/1'-H, 11H, J_{gem} = 12Hz, $J_{5',6'a}$ = 3Hz, $J_{5',6'}$ = 5.5Hz.

Anal. Calcd. for $C_{48}H_{38}ClN_7O_{10}$: C, 63.47; H, 4.22; N, 10.79; Found: C, 63.37; H, 4.43; N, 10.58.

9,9-Dimethyl-8-(*L-arabino*-2',3',4'-5'-tetraacetyloxypent-1'-ylidene)-6-chloro-9H-pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine (8*E*)-Azomethine Imine (3): from 1 and tetraacetyl-al-*L*-arabinose in aqueous acetic acid (30 %, 5 ml) at 60°C (30 min), yield 970 mg (62 %), mp 99-101°C (benzene); $[\alpha]_D^{24}$ = -60 ± 5° ($CHCl_3$, c=4.19.10^{-3}g/ml); ^{1}H NMR($CDCl_3$, 24°C, 90 MHz): δ_{ppm} = 1.88 (s,9-Me,3H); 1.90(s,9-Me,3H); 2.07(s,MeCO,3H); 2.13(s,MeCO,3H); 2.15(s,MeCO,3H); 2.19(s,MeCO,3H); 4.22(dd,5"-H,1H); 4.42(dd,5'-H,1H); 5.15-5.39(m,4'-H,1H); 5.79(dd,3'-H,1H); 6.18(dd,2'-H,1H); 6.60(d,1'-H,1H), $J_{1',2'}$ = 5.9Hz, $J_{2',3'}$ = 2.9Hz, $J_{3',4'}$ = 8.0Hz, $J_{4',5'}$ = 2.8Hz, $J_{4',5"}$= 4.9Hz, $J_{5',5"(gem)}$ = 12.3Hz.

Anal. Calcd. for $C_{20}H_{24}ClN_7O_8$: C, 45.68; H, 4.60; N, 18.64; Found: C, 45.85; H, 4.79; N, 18.64.

9,9-Dimethyl-8-(*D-galacto*-2',3',4',5',6'-pentaacetyloxyhex-1'-ylidene)-6-chloro-9H-pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine (8*E*)-Azomethine Imine (4): from 1 and pentaacetyl-al-*D*-galactose in methanol (5 ml) at 60°C (5 min), yield 83 %), mp 115-118°C (methanol); $[\alpha]_D^{26}$ = -15 ± 3° ($CHCl_3$, C=1.26.10^{-2}g/ml); ^{1}H NMR($CDCl_3$, 24°C, 90 MHz); δ_{ppm} = 1.82(s,9-Me, 3H); 1.87(s,9-Me,3H); 2.03(s,MeCO,3H); 2.05(s,MeCO,3H); 2.07(s,MeCO,3H); 2.20(s,MeCO,6H);3.89(dd,6'-H,1H); 4.32(dd,6"-H,1H); 5.20-5.88(m,3'-H,4'-H, 5'-H,3H); 5.97(dd,2'-H,1H); 6.50(d,1'-H,1H); $J_{1',2'}$ = 5.6Hz, $J_{5',6'}$ = 8.0Hz , $J_{5',6"}$ = 4.5Hz, $J_{2',3'}$ = 1.2Hz, $J_{6',6"(gem)}$ = 11.0Hz.

Anal. Calcd. for $C_{23}H_{28}ClN_7O_{10}.H_2O$: , 46.20; H, 4.72; N, 16.40. Found: C, 45.90; H, 4.96; N, 16.19.

1,3-Dipolar Cycloadditions of methyl acrylate to Azamethine Imines 2-4. Asymetric Synthesis of Fused Prazoles 5-7. General Procedure.

A mixture of azamethine imine (0.003 mole) and methyl acrylate

(0.01 mole) in benzene or acetonytrile (1.5-2.5 ml) 30-50 minutes under reflux. The solvent was evaporated in vacuo and the solid residue was recrystallized from appropriate solvent. In this manner the following compounds were prepared:

(1'*S*,8*S*,10*S*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-10-(penta-O'-benzoyl-*D*-arabitol-1'-yl)-10H,12H-pyrazolo[1',2':1,2]pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine (5): from 2 and methyl acrylate in benzene (1,5 ml) by heating under reflux (30 min), yield 61 %, mp 99-104°C (ethanol); ^{1}H NMR($CDCl_3$, 24°C, 90 MHz); δ_{ppm} = 1.60(s,12-Me,3H); 1.88(s, 12-Me,2H); 2.45-3.23(m,9-H_2,2H); 3.46(s,COOMe,3H); 3.93-4.26(m,10H,1H); 4.50(dd,5"-H,1H); 4.91(dd,5'-H,1H); 4.33-5.08(m,5'-CH_2,8-H,3H); 5.60 (m, 1'-H,2'-H,3'-H,4'-H,4H); 7.16-7.74(m,5xPh/3"-H,4"-H/,15H); 7.79-8.52 (m, 5xPh/2"-H,6"-H,10H); $J_{5',5"(gem)}$ = 12.0Hz, $J_{5',4'}$ = 2.8Hz, $J_{5",4'}$ = 5.7Hz.

Anal. Calcd. for $C_{52}H_{44}ClN_7O_{12}$: C, 62.81; H, 4.46; N, 9.86. Found: C, 63.04; H, 4.62; N, 9.63.

(1'*S*,8*S*,10*S*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-10-(tetra-O'-acetyl-*L*-erytrithol-1'-yl)-10H,12H-pyrazolo[1',2':1,2]pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine (6): from 3 and methyl acrylate in benzene (1.5 ml) by heating under reflux (50 min), yield 60 %, mp 160-162°C (methanol); $[\alpha]_D^{19}$ = +347 ± 5° ($CDCl_3$, c=4.18.10^{-3}g/ml); ^{1}H NMR($CDCl_3$, 24°C, 90 MHz): δ_{ppm} = 1.73 (s,12-Me,3H); 1.87(s,12-Me,3H); 2.05(s,MeCO,3H); 2.07(s,MeCO,3H); 2.11(s,MeCO,3H); 2.13(s,MeCO,3H); 2.353.39(m,9-H_2,2H); 3.73(s,COOMe,3H); 3.53-3.90(m,10-H,1H); 3.73(dd,5'-H,1H); 4.03(dd,5"-H,1H); 4.73(dd,8-H,1H), 4.90-5.17(m,2'-H,3'-H,4'-H,3H), $J_{5',5"(gem)}$ = 17.0Hz, $J_{4',5'}$ = 3.5Hz, $J_{8,9'(trans)}$ = 2.0Hz, $J_{8,9(cis)}$ = 7.8Hz, $J_{4',5"}$ = 5.0Hz.

Anal. Calcd. for $C_{24}H_{30}ClN_7O_{10}$: C, 47.10; H, 4.94; N, 16.02. Found: C, 47.22; H, 5.20; N, 16.24.

(1'*S*,8*S*,10*S*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-10-(penta-O'-acetyl-*D*-lyxitol-1'-yl)-10H,12H-pyrazolo[1',2':1,2]pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine (7): from 4 and methyl acrylate in benzene (6 ml) by heating under reflux (45 min), yield 66 %, mp 215-217°C (chlorobenzene); ^{1}H NMR($CDCl_3$, 23°C, 300MHz): δ_{ppm} = 1.726(s,12-CH_3,3H); 1.937(s,12-CH_3); 2.028(s,CH_3CO,3H); 2.085(s,CH_3CO,3H); 2.120(s,CH_3CO,3H); 2.153(s,CH_3CO,3H); 2.180(s,CH_3CO,3H); 2.324(ddd,9A-H,1H); 2.922(ddd,9B-H); 3.695(ddd,10H,1H); 3.730(s,$COOCH_3$3H); 3.809(dd,5A,-H,1H); 4.347(dd,5B,1H); 4.707(dd,8-H); 5.24-5.37(m,1'-H,2'-H,3'-H,4'-H,4H); $J_{8,9A}$ = 2.0Hz, $J_{4',5A}$ = 5.2Hz, $J_{9A,10}$ = 5.5Hz, $J_{8,9B}$ = 8.2Hz, $J_{4',5B}$ = 4.4Hz, $J_{9B,10}$ = 9.3 Hz,

$J_{1',10}$ = 2.3Hz, $J_{5A,5B(gem)}$ = 11.8Hz, $J_{9A,9B(gem)}$ = 13.0Hz.

Anal. Calcd. for $C_{27}H_{34}ClN_7O_{12}$: C, 47.41; H, 5.01 ; N, 14.33. Found: C, 47.61; H, 5.32; N, 13.93.

(1'*S*,8*S*,10*S*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-(*D*-erytrithol-1'-yl)-10H,12H-pyrazolo[1',2':1,2]pyrazolo[4,3-d]tetrazolo[1,5-b]pyridazine (8): To a mixture of 1 (450 mg, 0.002 mole) and *D*-ribose (370 mg, 0.0027 mole) in methanol (4 ml) methyl acrylate (258 mg, 0.003 mole) and trifluoroacetic acid (1 drop) were added. The mixture was heated under reflux (1 hour). The precipitate was, after standing in refrigerator for several hours, collected by filtration and recrystallized from methanol to give 8, yield 41 %, mp 167-169°C; $[\alpha]_D^{26}$ = +742 ± 5° (methanol, c=7.06.10^{-3}g/ml); ^{1}H NMR(DMSO-d_6, 23°C, 90 MHz): δ_{ppm} = 1.63 (s,12-CH_3,3H); 1.85(s,12-CH_3,3H); 2.27-3.18(m,O-H_2); 3.18-4.02 (m,10-H, 1'-H,2'-H,3'-H,4'-H,$COOCH_3$(δ=3.70(s)),H_2O); 4.43(t,4'-OH,1H)*; 4.70(d, 3'-OH,1H)*; 4.85(d,2'-OH,2'-OH,2H)*; 4.93(d,8-H,1H); $J_{5',OH}$ = $J_{1',OH}$ = $J_{2',OH}$ = 4.2Hz, $J_{3',OH}$ = 3.0Hz, $J_{8,9}$ = 7.6Hz.

Anal. Calcd. for $C_{16}H_{22}ClN_7O_6$: C, 43.30; H, 5.00; N, 22.09. Found: C, 43,51; H, 5.26; N, 21.87.

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