Intramolecular Hyrdide Addition to Pyridinium Salts: New Routes to Enantiopure Dihydropyridones

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Abstract

The transformation of a simple disubstituted pyridine into a pyridinium ion bearing an exocyclic hyrdoxyl group protected as a silane, enabled an intramolecular hydride transfer reaction to take place when fluoride was used as a nucleophile. The addition was both regio- and stereoselective and enabled the formation of enantiopure dihydropyridones when enantiopure pyridine derivatives were used in this sequence. The heterocyclic products contain ample functionality for further elaboration reactions and subsequent derivatisation.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). J. Appl. Cryst. 27, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). J. Appl. Cryst. 36, 1487.

Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). Methods in Enzymology, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*, Chemical Crystallography Laboratory, Oxford, UK.

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Crystal data

$C_{17}H_{18}N_2O_5$	$F(000) = 1392$
$M_r = 330.34$	$D_x = 1.363$ Mg m^{-3}
Monoclinic, *C*2/*c*	Mo *K*α radiation, λ = 0.71073 Å
Hall symbol: -C 2yc	Cell parameters from 3720 reflections
a = 35.6530 (8) Å	θ = 5–27°
b = 6.9183 (2) Å	μ = 0.10 mm^{-1}
c = 14.1033 (4) Å	*T* = 150 K
β = 112.2564 (12)°	Plate, Yellow
V = 3219.53 (15) Å^3	0.28 × 0.20 × 0.16 mm
Z = 8	

Data collection

Nonius KappaCCD diffractometer	2870 reflections with $I > 2.0\sigma(I)$
graphite	$R_{int} = 0.000$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.1°$
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -45 \rightarrow 46$
$T_{min} = 0.98$, $T_{max} = 0.98$	$k = -6 \rightarrow 8$
14302 measured reflections	$l = -18 \rightarrow 18$
3651 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.041$	No H atoms present
$wR(F^2) = 0.097$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.03P)^2 + 2.78P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$S = 0.95$	$(\Delta/\sigma)_{max} = 0.001$
3651 reflections	$\Delta\rho_{max} = 0.31$ e Å^{-3}
217 parameters	$\Delta\rho_{min} = -0.27$ e Å^{-3}
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.62466 (3)	0.24213 (13)	0.53786 (7)	0.0280
C2	0.66187 (4)	0.12945 (18)	0.58770 (10)	0.0255
C3	0.68276 (3)	0.11162 (18)	0.51093 (9)	0.0236
N4	0.65381 (3)	0.04791 (15)	0.41024 (8)	0.0257
C5	0.64665 (4)	−0.14189 (19)	0.39355 (10)	0.0300
C6	0.66811 (4)	−0.2837 (2)	0.45775 (11)	0.0336
C7	0.70521 (4)	−0.24129 (19)	0.54065 (10)	0.0291
C8	0.71818 (4)	−0.03096 (19)	0.55054 (10)	0.0278
O9	0.72760 (3)	−0.36476 (15)	0.59775 (8)	0.0395

C10	0.63350 (4)	0.1892 (2)	0.33028 (10)	0.0316
C11	0.65944 (4)	0.2704 (2)	0.27763 (10)	0.0339
C12	0.69680 (4)	0.2197 (2)	0.29326 (11)	0.0363
C13	0.68686 (4)	0.2404 (2)	0.68302 (10)	0.0327
C14	0.58905 (4)	0.1526 (2)	0.51007 (11)	0.0315
O15	0.58434 (3)	−0.01547 (16)	0.52495 (10)	0.0537
C16	0.55477 (4)	0.2887 (2)	0.45727 (10)	0.0292
C17	0.56094 (4)	0.4855 (2)	0.44928 (10)	0.0301
C18	0.52809 (4)	0.6063 (2)	0.40158 (10)	0.0316
C19	0.48977 (4)	0.5253 (2)	0.36303 (10)	0.0296
N20	0.45456 (4)	0.65331 (18)	0.31462 (9)	0.0354
O21	0.42074 (3)	0.58148 (18)	0.28589 (9)	0.0509
O22	0.46069 (3)	0.82478 (16)	0.30556 (9)	0.0523
C23	0.48280 (4)	0.3309 (2)	0.36951 (11)	0.0358
C24	0.51587 (4)	0.2121 (2)	0.41732 (12)	0.0364
H21	0.6548	−0.0019	0.6046	0.0290*
H31	0.6926	0.2425	0.5016	0.0271*
H51	0.6241	−0.1774	0.3299	0.0370*
H61	0.6590	−0.4173	0.4450	0.0408*
H81	0.7347	−0.0159	0.5084	0.0330*
H82	0.7350	−0.0030	0.6240	0.0323*
H101	0.6232	0.2969	0.3620	0.0371*
H102	0.6094	0.1232	0.2775	0.0367*
H111	0.6466	0.3698	0.2266	0.0405*
H121	0.7111	0.2786	0.2555	0.0453*
H122	0.7105	0.1184	0.3441	0.0444*
H131	0.7123	0.1694	0.7227	0.0482*
H132	0.6938	0.3677	0.6622	0.0478*
H133	0.6703	0.2564	0.7249	0.0476*
H171	0.5880	0.5365	0.4782	0.0367*
H181	0.5313	0.7456	0.3968	0.0354*
H231	0.4555	0.2807	0.3397	0.0402*
H241	0.5120	0.0743	0.4224	0.0416*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0228 (4)	0.0235 (5)	0.0379 (5)	0.0044 (4)	0.0119 (4)	0.0026 (4)
C2	0.0238 (6)	0.0217 (6)	0.0305 (6)	0.0046 (5)	0.0096 (5)	0.0028 (5)
C3	0.0215 (6)	0.0210 (6)	0.0262 (6)	−0.0008 (5)	0.0068 (5)	−0.0016 (5)
N4	0.0242 (5)	0.0234 (5)	0.0257 (5)	−0.0007 (4)	0.0051 (4)	−0.0002 (4)
C5	0.0284 (7)	0.0282 (7)	0.0313 (7)	−0.0037 (6)	0.0088 (5)	−0.0060 (5)
C6	0.0385 (8)	0.0215 (7)	0.0402 (8)	−0.0021 (6)	0.0142 (6)	−0.0042 (6)
C7	0.0332 (7)	0.0269 (7)	0.0313 (7)	0.0089 (6)	0.0169 (6)	0.0017 (5)
C8	0.0218 (6)	0.0292 (7)	0.0302 (7)	0.0034 (5)	0.0074 (5)	−0.0021 (5)
O9	0.0450 (6)	0.0343 (6)	0.0406 (6)	0.0164 (5)	0.0180 (5)	0.0085 (4)
C10	0.0284 (7)	0.0307 (7)	0.0303 (7)	0.0034 (6)	0.0051 (5)	0.0045 (5)
C11	0.0423 (8)	0.0285 (7)	0.0289 (7)	−0.0008 (6)	0.0113 (6)	0.0021 (5)
C12	0.0416 (8)	0.0366 (8)	0.0334 (7)	−0.0067 (7)	0.0172 (6)	−0.0031 (6)
C13	0.0365 (7)	0.0321 (7)	0.0291 (7)	0.0022 (6)	0.0118 (6)	−0.0032 (6)
C14	0.0263 (7)	0.0268 (7)	0.0423 (8)	0.0010 (6)	0.0141 (6)	0.0007 (6)

O15	0.0305 (5)	0.0277 (6)	0.0961 (9)	0.0001 (4)	0.0162 (6)	0.0130 (6)
C16	0.0257 (6)	0.0284 (7)	0.0348 (7)	0.0023 (5)	0.0129 (5)	−0.0013 (5)
C17	0.0246 (6)	0.0285 (7)	0.0367 (7)	0.0005 (5)	0.0110 (5)	−0.0016 (6)
C18	0.0304 (7)	0.0271 (7)	0.0356 (7)	0.0032 (6)	0.0106 (6)	0.0007 (6)
C19	0.0263 (6)	0.0331 (7)	0.0273 (6)	0.0068 (6)	0.0078 (5)	−0.0003 (5)
N20	0.0302 (6)	0.0388 (7)	0.0321 (6)	0.0072 (5)	0.0060 (5)	0.0018 (5)
O21	0.0257 (5)	0.0550 (8)	0.0602 (7)	0.0042 (5)	0.0029 (5)	0.0121 (6)
O22	0.0409 (6)	0.0338 (6)	0.0669 (8)	0.0090 (5)	0.0033 (5)	0.0043 (5)
C23	0.0251 (6)	0.0365 (8)	0.0406 (8)	−0.0015 (6)	0.0067 (6)	−0.0037 (6)
C24	0.0285 (7)	0.0279 (7)	0.0504 (8)	−0.0008 (6)	0.0121 (6)	−0.0019 (6)

Geometric parameters (Å, º)

O1—C2	1.4682 (14)	C11—H111	0.975
O1—C14	1.3311 (15)	C12—H121	0.957
C2—C3	1.5339 (17)	C12—H122	0.989
C2—C13	1.5108 (18)	C13—H131	0.996
C2—H21	0.995	C13—H132	0.989
C3—N4	1.4716 (15)	C13—H133	0.986
C3—C8	1.5314 (17)	C14—O15	1.2047 (17)
C3—H31	0.997	C14—C16	1.4985 (18)
N4—C5	1.3413 (17)	C16—C17	1.3906 (19)
N4—C10	1.4607 (16)	C16—C24	1.3892 (19)
C5—C6	1.3578 (19)	C17—C18	1.3877 (19)
C5—H51	0.983	C17—H171	0.960
C6—C7	1.425 (2)	C18—C19	1.3832 (19)
C6—H61	0.973	C18—H181	0.976
C7—C8	1.5172 (19)	C19—N20	1.4753 (17)
C7—O9	1.2363 (16)	C19—C23	1.377 (2)
C8—H81	0.989	N20—O21	1.2227 (16)
C8—H82	0.999	N20—O22	1.2217 (16)
C10—C11	1.4976 (19)	C23—C24	1.385 (2)
C10—H101	1.007	C23—H231	0.968
C10—H102	1.009	C24—H241	0.970
C11—C12	1.313 (2)		

C2—O1—C14	118.82 (10)	C10—C11—C12	126.46 (13)
O1—C2—C3	107.28 (9)	C10—C11—H111	115.3
O1—C2—C13	106.11 (10)	C12—C11—H111	118.3
C3—C2—C13	112.88 (10)	C11—C12—H121	120.9
O1—C2—H21	109.6	C11—C12—H122	120.1
C3—C2—H21	109.3	H121—C12—H122	119.0
C13—C2—H21	111.6	C2—C13—H131	110.7
C2—C3—N4	110.77 (10)	C2—C13—H132	108.5
C2—C3—C8	110.37 (10)	H131—C13—H132	109.3
N4—C3—C8	109.82 (10)	C2—C13—H133	107.8
C2—C3—H31	108.0	H131—C13—H133	110.0
N4—C3—H31	107.3	H132—C13—H133	110.6
C8—C3—H31	110.5	O1—C14—O15	125.32 (12)
C3—N4—C5	118.68 (10)	O1—C14—C16	111.20 (11)
C3—N4—C10	120.39 (10)	O15—C14—C16	123.48 (12)

C5—N4—C10	120.93 (11)	C14—C16—C17	122.07 (12)
N4—C5—C6	124.67 (12)	C14—C16—C24	117.58 (12)
N4—C5—H51	116.1	C17—C16—C24	120.34 (12)
C6—C5—H51	119.2	C16—C17—C18	119.89 (12)
C5—C6—C7	120.77 (13)	C16—C17—H171	119.3
C5—C6—H61	119.9	C18—C17—H171	120.8
C7—C6—H61	119.2	C17—C18—C19	118.27 (13)
C6—C7—C8	115.39 (11)	C17—C18—H181	121.9
C6—C7—O9	124.17 (13)	C19—C18—H181	119.8
C8—C7—O9	120.25 (12)	C18—C19—N20	118.67 (12)
C3—C8—C7	113.81 (10)	C18—C19—C23	123.05 (12)
C3—C8—H81	108.1	N20—C19—C23	118.26 (12)
C7—C8—H81	106.0	C19—N20—O21	117.96 (12)
C3—C8—H82	110.0	C19—N20—O22	118.46 (12)
C7—C8—H82	108.8	O21—N20—O22	123.57 (12)
H81—C8—H82	110.0	C19—C23—C24	118.05 (13)
N4—C10—C11	114.52 (11)	C19—C23—H231	119.9
N4—C10—H101	108.0	C24—C23—H231	122.0
C11—C10—H101	110.0	C16—C24—C23	120.39 (13)
N4—C10—H102	107.6	C16—C24—H241	119.6
C11—C10—H102	108.6	C23—C24—H241	120.0
H101—C10—H102	108.0		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H51···O21^{i}	0.98	2.45	3.352 (2)	151
C8—H81···O9^{ii}	0.99	2.50	3.419 (2)	155
C12—H121···O9^{iii}	0.96	2.58	3.480 (2)	157
C13—H132···O9^{iv}	0.99	2.56	3.513 (2)	163
C24—H241···O22^{v}	0.97	2.60	3.344 (2)	134

Symmetry codes: (i) −*x*+1, *y*−1, −*z*+1/2; (ii) −*x*+3/2, −*y*−1/2, −*z*+1; (iii) *x*, −*y*, *z*−1/2; (iv) *x*, *y*+1, *z*; (v) *x*, *y*−1, *z*.