FACILE SYNTHESIS OF 5H-[1]BENZOPYRANO[2,3-b]-1,2,3,4-TETRAHYDROPYRIDIN-5-ONES

Franco M. Pasutto*, Syed Abuzar, and Srinivasamurthy Satyamurthy
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada, T6G 2N8

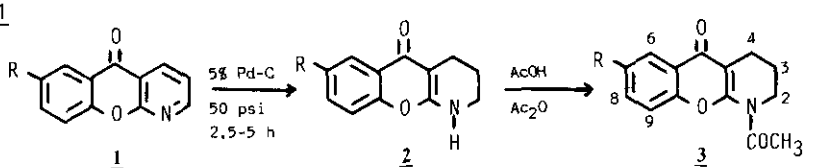
Abstract - A facile synthesis of 7-substituted-5H-[1]benzopyrano[2,3-b] -1,2,3,4-tetrahydropyridin-5-ones is described. Catalytic hydrogenation of 7-substituted 5H-[1]benzopyrano[2,3-b]pyridin-5-ones affords the title compounds in greater than 90% yields. Facile, high yield, N^1-acetylation is achieved by reaction with acetic anhydride.

The reduced pyridine moiety continues to be of interest as a component of pharmacologically active agents[1,2] as well as in natural product chemistry for the synthesis of alkaloids[3]. We are particularly interested in the development of agents inhibitory towards enzymes, such as cyclooxygenase and lipoxygenase, involved in the metabolism of arachidonic acid. Inhibition of these enzymes provides a means of controlling prostaglandin-associated inflammation and leukotriene-associated immediate hypersensitivity reactions[4-6]. During the course of these studies, we required quantities of tetrahydropyridin-5-ones 2 sufficient for pharmacological evaluation and further chemical modification. Benzopyranopyridin-5-ones 1, the immediate precursors, are prepared in generally good yields by reaction of 2-chloronicotinic acid with an appropriately substituted phenol[7]. A reported procedure[8] for the synthesis of 2a from 1a involved hydrogenation over Raney-nickel catalyst at a pressure of 735 psi (50 atm), temperature of 70-80°C, with a yield of 50%.

We describe here an improved synthesis of 2 in excellent yield using 5% palladium-charcoal as the hydrogenation catalyst. A catalyst/compound ratio of 1/10 (w/w) was used except for the reduction of 1i. Reduction of 1 takes place at the significantly lower pressure of 50 psi (3.4 atm), at room temperature and reaction time of 2.5-5 h. The choice of reaction solvent did not significantly affect product yield and ethanol, methanol, or acetic acid gave satisfactory results. Similarly, 10% palladium-charcoal or platinum oxide were equally effective in affording compounds 2.

Reduction of compounds 1a-h gave 2a-h respectively. The reaction appears to be general insofar as the nature of the R-substituent, whether electron-withdrawing or donating, does not affect the course of the reaction at the pyridine ring. The nitro substituent of 1i, however, was reduced

Scheme 1



1	R	2	R	3	R
1a	H	2a	H	3a	H
b	CH_3	b	CH_3	d	OCH_3
c	NH_2	c	NH_2	e	$NHCOCH_3$
d	OCH_3	d	OCH_3		
e	$NHCOCH_3$	e	$NHCOCH_3$		
f	$CH_2COOCH_2CH_3$	f	$CH_2COOCH_2CH_3$		
g	$COOCH_2CH_3$	g	$COOCH_2CH_3$		
h	COOH	h	COOH		
i	NO_2				
j	Br				
k	Cl				

with the pyridine ring to give 2c. Interestingly, reduction of 1i under conditions similar to those described above, afforded 1c in 91% yield; compound 2c was apparently not detected [7]. We prepared 1c from 1i by reduction with ferrous sulfate-ammonia. The versatility of the reduction procedure is hampered by concomitant hydrogenolysis of C-7 halogen substituents. Thus, catalytic reduction of 1j did not afford the corresponding brominated compound 2; under these reaction conditions, 1j undergoes hydrogenolysis [9] and is obtained as the hydrobromide salt of 2a (90% yield, mp 280°C from n-propanol). Basification of this salt gave a compound identical to authentic 2a. Analysis of the hydrobromide salt by chemical ionization mass spectrometry (ammonia as reactant gas) gave an M+1 fragment of m/e 202, corresponding to 2a; the 2M+1 fragment (m/e 403) was also observed. Compound 1k behaves similarly.

Compounds 2 are resistant to further reduction even with reaction times of 20 h. It has been reported [3] that the β-aminoacryl grouping in reduced 3-acylpyridines is stable under palladium-catalyzed hydrogenation conditions.

Compound 2a undergoes N-alkylation with dialkylaminoalkyl chlorides and benzyl chlorides in the presence of sodium ethoxide [8]. The N-acetyl derivatives 3a, 3d, and 3e were prepared in excellent yields by reaction with acetic anhydride/acetic acid (1/10, v/v). They may also be obtained in comparable yields by overnight reflux in a toluene solution containing acetyl chloride and triethylamine (one equivalent).

Table 1. Yields, mp, IR and ^{1}H NMR Spectral Data of 2 and 3

Compd. No.	Yield %	mp (°C)[a]	IR(KBr) ν[cm^{-1}]	^{1}H NMR δ[ppm][b]
2a	92[c]	232°	3416,1638,1605	1.94(quint,2H,$CH_2CH_2CH_2NH$,J=6.2 Hz);2.70(t,2H,$CH_2CH_2CH_2NH$, J=6.2 Hz);3.46(m,2H,$CH_2CH_2CH_2NH$);6.56(br.s,1H,NH,exch.);7.26 (dd,1H,9-H,J=8.1,1.1 Hz);7.34(m,1H,7-H);7.54(ddd,1H,8-H,J= 8.1,7.0,1.6 Hz);8.20(dd,1H,6-H,J=8.1,1.6 Hz)
b	93	292°	3410,1614,1556	1.80(quint,2H,$CH_2CH_2CH_2NH$,J=6.3 Hz);2.43(s,3H,CH_3);2.66(t, 2H,$CH_2CH_2CH_2NH$,J=6.3 Hz);3.44(br.m,2H,$CH_2CH_2CH_2NH$);6.84(br. s,1H,NH,exch.);7.14(d,1H,9-H,J=10.8 Hz);7.30(dd,1H,8-H,J= 10.8,3.6 Hz);7.94(d,1H,6-H,J=3.6 Hz)
c	93[d]	280°	3419,3306,1626, 1608	1.75(quint,2H,$CH_2CH_2CH_2NH$,J=6.3 Hz);2.46(t,2H,$CH_2CH_2CH_2NH$, J=6.3 Hz);3.28(br.m,2H,$CH_2CH_2CH_2NH$);5.20(s,2H,NH_2,exch.); 6.82(dd,1H,8-H,J=9,2.8 Hz);7.05(d,1H,9-H,J=9 Hz);7.14(d,1H, 6-H,J=2.8 Hz);7.66(br.t,1H,NH,exch.)
d	95	235°	3400,1622,1607	1.90(quint,2H,$CH_2CH_2CH_2NH$,J=6 Hz);2.66(t,2H,$CH_2CH_2CH_2NH$,J= 6 Hz);3.42(m,2H,$CH_2CH_2CH_2NH$);3.90(s,3H,OCH_3);7.08(dd,1H, 8-H,J=9, 3 Hz);7.18(br.s, 1H,NH,exch.);7.20(d,1H,9-H,J=9 Hz);7.57(d,1H,6-H,J=3 Hz)
e	95	315°	3238,3213,1688, 1622	1.82(m,2H,$CH_2CH_2CH_2NH$);2.08(s,3H,$COCH_3$);2.54(t,2H,CH_2CH_2-CH_2NH,J=6.1 Hz);3.36(br.m,2H,$CH_2CH_2CH_2NH$);7.28(d,1H,9-H,J= 8.8 Hz);7.80(br.m,1H,NH,exch.);7.94(dd,1H,8-H,J=8.8,2.6 Hz); 8.13(d,1H,6-H,J=2.6 Hz);10.10(s,1H,$NHCOCH_3$,exch.)
f	95	177°	3430,1728,1625	1.24(t,3H,CH_2CH_3,J=7.2 Hz);1.90(m,2H,$CH_2CH_2CH_2NH$);2.67(t, 2H,$CH_2CH_2CH_2NH$,J=6.3 Hz);3.43(m,2H,$CH_2CH_2CH_2NH$);3.69(s,2H, $COCH_2$);4.15(q,2H,CH_2CH_3,J=7.2 Hz);6.40(br.s,1H,NH,exch.); 7.16(d,1H,9-H,J=8.9 Hz);7.42(dd,1H,8-H,J=8.9,2.2 Hz);8.03 (d,1H,6-H,J=2.2 Hz)
g	90	238°	3328,1720,1622	1.4(t,3H,CH_2CH_3,J=7.1 Hz);1.92(quint,2H,$CH_2CH_2CH_2NH$,J=6.4 Hz);2.68(t,2H,$CH_2CH_2CH_2NH$,J=6.4 Hz);3.46(m,2H,$CH_2CH_2CH_2NH$); 4.39(q,2H,CH_2CH_3,J=7.1 Hz);6.80(br.s,1H,NH,exch.);7.26(d, 1H,9-H,J=8.9 Hz);8.16(dd,1H,8-H,J=8.9,2.3 Hz);8.83(d,1H, 6-H,J=2.3 Hz)
h	90	355-7°	3435,1687,1614, broad 2200-3600	1.78(quint,2H,$CH_2CH_2CH_2NH$,J=6.2 Hz);2.50(t,2H,$CH_2CH_2CH_2NH$, J=6.2 Hz);3.36(m,2H,$CH_2CH_2CH_2NH$);7.47(d,1H,9-H,J=8.6 Hz); 8.13(dd,1H,8-H,J=8.6,2.1 Hz);8.17(br.s,1H,NH,exch.);8.53(d, 1H,6-H,J=2.1 Hz);13.07(br.s,1H,COOH)
3a	94	184°	1696,1614	1.94(m,2H,$CH_2CH_2CH_2N$);2.56(s,3H,$COCH_3$);2.62(t,2H,$CH_2CH_2CH_2$-N,J=6.8 Hz);3.90(m,2H,$CH_2CH_2CH_2N$);7.47(m,1H,7-H);7.55(dd, 1H,9-H,J=8.3, 1.2 Hz);7.75(ddd,1H,8-H,J=8.3,7.2,1.7 Hz); 8.13(dd,1H,6-H,J=8, 1.7 Hz)
3d	95	202°	1687,1605	1.96(quint,2H,$CH_2CH_2CH_2N$,J=6.7 Hz);2.58(s,3H,$COCH_3$);2.74 (t,2H,$CH_2CH_2CH_2N$,J=6.7 Hz);3.96(t,2H,$CH_2CH_2CH_2N$,J=6.7 Hz); 7.28(dd,1H,8-H,J=9.1, 3 Hz);7.37(d,1H,9-H,J=9.1 Hz);7.65 (d,1H,6-H,J=3 Hz)
3e	93	251°	3295,1716,1694, 1615	1.85(quint,2H,$CH_2CH_2CH_2N$,J=5.7 Hz);2.10(s,3H,$NHCOCH_3$);2.52 (m,5H,$CH_2CH_2CH_2N$,$COCH_3$);3.82(t,2H,$CH_2CH_2CH_2N$,J=5.7 Hz);7.68 (d,1H,9-H,J=8.8 Hz);7.96(dd,1H,8-H,J=8.8,2.8 Hz);8.21(d,1H, 6-H,J=2.8 Hz);10.29(s,1H,NH,exch.)

a) Compounds 2a-d and 3d were recrystallized from ethanol; 2e,2g,3a and 3e from methanol; 2h from dioxane-methanol; 2f from acetone.
b) Due to poor sample solubility, a solvent mixture of $CDCl_3$/DMSO-d_6 was used for compounds 2a-g; compounds 2h,3e and 3a,3d were dissolved in DMSO-d_6 and $CDCl_3$ respectively.
c) Yield of 2a from 1j and 1k was 90% and 87% respectively.
d) Yield of 2c from 1i was 85%.

Table 2. Mass Spectral and Analytical Data of 2 and 3

Compd. No.	Formula	MS M^+ m/e(%)	Microanalyses (Calcd.) C (%)	H (%)	N (%)
2a	$C_{12}H_{11}NO_2$	201(32)	71.50 (71.63)	5.54 (5.51)	6.91 (6.96)
2b	$C_{13}H_{13}NO_2$	215(84)	72.51 (72.54)	6.01 (6.09)	6.79 (6.51)
2c	$C_{12}H_{12}N_2O_2$	216(66)	66.38 (66.65)	5.64 (5.59)	12.75 (12.95)
2d	$C_{13}H_{13}NO_3$	231(50)	67.44 (67.52)	5.68 (5.67)	6.04 (6.06)
2e	$C_{14}H_{14}N_2O_3$	258(1)	64.66 (65.11)	5.43 (5.46)	10.70 (10.85)
2f	$C_{16}H_{17}NO_4$	287(100)	66.65 (66.89)	5.91 (5.96)	4.83 (4.87)
2g	$C_{15}H_{15}NO_4$	273(100)	66.02 (65.93)	5.58 (5.53)	5.17 (5.13)
2h	$C_{13}H_{11}NO_4$	245(100)	63.65 (63.67)	4.50 (4.52)	5.67 (5.71)
3a	$C_{14}H_{13}NO_3$	243(44)	69.07 (69.12)	5.41 (5.39)	5.59 (5.76)
3d	$C_{15}H_{15}NO_4$	273(46)	65.73 (65.93)	5.46 (5.53)	5.07 (5.13)
3e	$C_{16}H_{16}N_2O_4$	300(46)	63.37 (63.99)	5.46 (5.37)	9.06 (9.33)

EXPERIMENTAL

Melting points were obtained on a Thomas Hoover capillary apparatus and are uncorrected. The IR spectra (KBr pellet) were recorded on a Nicolet 5DX fourier transform spectrometer. ^{1}H Nmr spectra were measured on a Bruker AM 300 fourier transform spectrometer using Me_4Si as the internal standard. Mass spectra were obtained on a Hewlett Packard 5980A spectrometer equipped with a 5934A data system. Elemental analyses were carried out on a Perkin Elmer 240B analyzer.

General Procedure for the preparation of 2 and 3

A suspension of 5H-[1]benzopyrano[2,3-b]pyridin-5-one (1a, 3.9 g, 20 mmol) in ethanol (100 ml) was shaken in a Parr hydrogenator with a hydrogen pressure of 50 psi in the presence of 5% Pd-C (0.4 g) for 4 h. The catalyst was collected on a filter and washed with hot ethanol. The filtrate was evaporated *in vacuo* and the residue recrystallized from ethanol to give the product 2a as colorless crystals. A solution of 2a (0.98 g, 4.9 mmol) in glacial acetic acid (20 ml) and acetic anhydride (2 ml) was then refluxed for 4-5 h. The reaction mixture was cooled and poured into cold water (100 ml). The precipitated solid was filtered, washed with water several times, dried, and recrystallized from methanol to give the product 3a as colorless crystals.

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