ORGANIC LETTERS

2000
Vol. 2, No. 5
633−634

An Efficient Synthesis of Pyrimidines from β-Amino Alcohols

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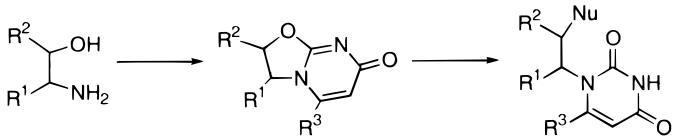
Received December 22, 1999

ABSTRACT

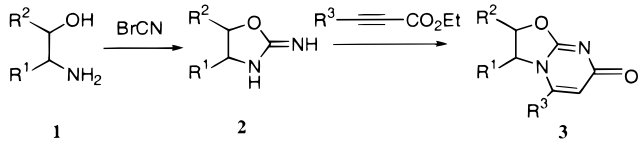


Pyrimidinones 3 were chemoselectively reduced by using metal-catalyzed hydrogenation and stereoselectively substituted by various nucleophiles. Starting from β-amino alcohols 1, the overall process allows efficient access to substituted pyrimidines 4 and 6.

The emergence of Acyclovir[1] as a successful antiviral agent has stimulated the synthesis of a wide variety of acyclic nucleosides.[2] However, no structure−activity relationship has been reported so far for this new potential antiviral agent. Therefore, new pyrimidine acyclonucleosides are of great interest.

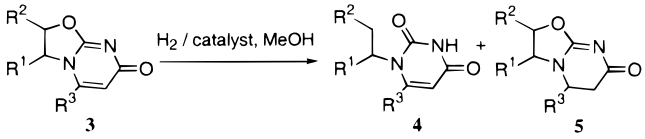
We present here an efficient access to acyclonucleosides **4** and **6** starting from β-amino alcohols **1** in three high-yielding steps. Reaction of the β-amino alcohol with cyanogen bromide followed by condensation of the resulting heterocycle **2** with ethyl propiolate or ethyl butynoate led to pyrimidinones **3** (Scheme 1).[3]

Scheme 1



We first studied catalytic hydrogenation of substituted pyrimidinones **3** according to the experimental conditions; this reaction afforded either pyrimidines **4** or dihydropyrimidines **5** (Scheme 2). Results are collected in Table 1.

Scheme 2



3a: R^1=Ph, R^2= H, R^3=H

3b: R^1=Me, R^2= H, R^3=H

3c: R^1=CH_2Ph, R^2= H, R^3=Me

3d: R^1=H, R^2= Me, R^3=H

3e: R^1=Ph, R^2=H, R^3=Me

Palladium- and rhodium-mediated catalysis was investigated in order to cleave the oxazolidine C−O bond. When rhodium was used (entries 7 and 8), hydrogenation affected only the ethylenic double bond, affording compound **5**, thus leaving the C−O bond untouched. On the other hand, palladium catalysis[4] was satisfactory except in the case of

(1) Shaeffer, H. J.; Beauchamp, L.; De Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* **1978**, *272*, 583.

(2) (a) Campos, J.; Pineda, M. J.; Gomez, J. A.; Entrena, A.; Trujillo, M. A.; Gallo, M. A.; Espinosa, A. *Tetrahedron* **1996**, *52*, 8907. (b) Gomez, J. A.; Campos, J.; Marchal, J. A.; Trujillo, M. A.; Melguizo, C.; Prados, J.; Gallo, M. A.; Aranega, A.; Espinosa, A. *Tetrahedron* **1997**, *53*, 7319. (c) Chu, C. K.; Cutler, S. *J. Heterocycl. Chem.* **1986**, *23*, 289. (d) Hossain, N.; Rozenski, J.; De Clercq, E.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 13655.

(3) (a) Agami, C.; Cheramy, S.; Dechoux, L.; Kadouri-Puchot, C. *Synlett* **1999**, 727. (b) Agami, C.; Cheramy, S.; Dechoux, L. *Synlett* **1999**, 1838. Selected data for compound **3a**: ^{1}H NMR (250 MHz, $CDCl_3$) 4.49 (dd, J = 7.8 and 9.2 Hz, 1H), 5.01 (t, J = 9.2 Hz, 1H), 5.23 (dd, J = 7.8 and 9.2 Hz, 1H), 5.95 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 7.23−7.31 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) 61.9, 73.9, 109.8, 127.1, 129.7, 130.1, 135.1, 135.8, 160.9, 172.0; mp 186 °C.

10.1021/ol991385x CCC: $19.00
Published on Web 02/05/2000

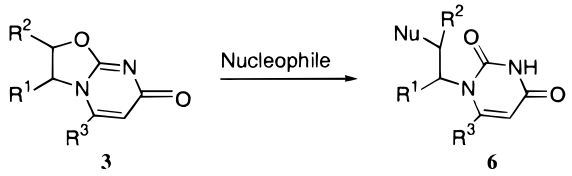
Table 1. Chemoselective Reductions of Pyrimidinones **3**

entry	substrate	catalyst	yield (%)	ratio **4**/**5**
1	**3a**	Pd/C	70	>95/5
2	**3a**	$Pd/BaSO_4$	91	>95/5
3	**3a**	$Pd(OH)_2$	84	>95/5
4	**3b**	$Pd/BaSO_4$	95	>95/5
5	**3c**	$Pd/BaSO_4$	95	>95/5
6	**3d**	$Pd/BaSO_4$	65	<5/95
7	**3a**	Rh, Al_2O_3	74	<5/95
8	**3e**	Rh, Al_2O_3	78	<5/95

substrates **3d** and **3e**. Substrate **3d** was stable unless the experimental conditions are forced:[5] in that case the ethylenic bond was hydrogenated (entry 6). This result indicates that a methylene group α to the oxazolidine C−O bond is necessary to achieve the formation of pyrimidines **4**. Palladium catalysis applied to substrate **3e** resulted in hydrogenolysis of the benzylic carbon−nitrogen bond.

Perusal of the literature showed that 2,2′-anhydronucleosides can be substituted with nucleophiles such as azide anion[6] and halides.[7] To obtain functionalized pyrimidines **6**, we investigated the reactivity of compounds **3** with such nucleophiles in acidic conditions (Scheme 3). To this aim,

Scheme 3



3 **6**

H_2O, MeOH, thiophenol, and trimethylsilyl halides were reacted with pyrimidinones **3**. Results are presented in Table 2.[8]

As shown in Table 2, the reaction was effective for all substrates in nearly quantitative yields (>90%). These nucleophilic substitutions are chemo- and diastereoselective as well. The stereoselectivity was proven for substrate **3f**,

Table 2. Regioselective Reactions of Pyrimidinones **3**

entry	substrate	R^1	R^2	R^3	conditions	Nu
1	**3a**	Ph	H	H	TMSCl/THF	Cl
2	**3a**	Ph	H	H	MeOH/PTSA	OMe
3	**3a**	Ph	H	H	H_2O/THF/PTSA	OH
4	**3a**	Ph	H	H	TMSI/THF	I
5	**3a**	Ph	H	H	PhSH/THF/PTSA	PhS
6	**3e**	Ph	H	Me	TMSCl/THF	Cl
7	**3f**	Me	Ph	H	TMSCl/THF	Cl
8	**3f**	Me	Ph	H	H_2O/THF/PTSA	OH
9	**3f**	Me	Ph	H	MeOH/PTSA	OMe

whose substitution with three nucleophiles (entries 7−9) afforded only one diastereoisomer. In contrast, trimethylsilyl azide and cyanide were ineffective in these experimental conditions, even in the presence of added fluoride ion.

In summary, a concise and practical synthesis of pyrimidines **4** and **6** has been developed starting from β-amino alcohols. This procedure has a wide scope and should allow for the synthesis of a large variety of acyclonucleosides which are potential antiviral and antitumoral agents.

OL991385X

(4) . **General procedure for the hydrogenolysis on palladium**. Pd/$BaSO_4$ (100 mg) was added, at room temperature, to a solution of compound **3a** (0.47 mmol) in MeOH (10 mL) under an atmosphere of hydrogen. The reaction mixture was stirred at room temperature for 4 h. The suspension was then filtered on Celite and methanol was evaporated. The residue was chromatographed on silica gel (AcOEt/MeOH 98/2) to afford compound **4a** (91 mg). Selected data for **4a**: ^{1}H NMR (250 MHz, $CDCl_3$) 1.63 (d, J = 7.1 Hz, 3H), 5.58 (d, J = 8.0 Hz, 1H), 5.91 (q, J = 7.1 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.26 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): 18.4, 53.3, 102.7, 127.2, 128.5, 129.1, 138.6, 141.1, 151.2, 163.0

(5) Reaction was performed with Pd/$BaSO_4$ (5 equiv) over 2 days.

(6) Costa, A. M.; Faja, M.; Farras, J.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 1835.

(7) (a) Mercer, J. R.; Knaus, E. E.; Wiebe, L. I. *J. Med. Chem*. **1987**, *30*, 670. (b) Kumar, A.; Walker, R. T. *Tetrahedron* **1990**, *46*, 3101.

(8) **General procedure for the substitution of 3a by trimethylsilyl halides.** To a solution of **3a** (100 mg, 0.47 mmol) in 10 mL of THF was added TMSCl (0.09 mL, 0.70 mmol). The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated solution of $NaHCO_3$ and extracted twice with 20 mL of dichloromethane. The organic phase was concentrated at reduced pressure to afford quantitatively compound **6a** (Nu = Cl). Selected data for **6a** (Nu = Cl): ^{1}H NMR (250 MHz, $CDCl_3$) 4.07 (m, 2H), 5.63 (d, J = 8.3 Hz, 1H), 5.94 (t, J = 6.5 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) 43.2, 59.1, 102.5, 128.6, 129.2, 129.4, 134.7, 141.7, 151.2, 163.1.