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Chemoselective reduction of pyrimidines. An access to enantiopure tetrahydropyrimidinones

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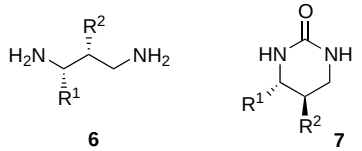
Abstract—A synthesis of substituted 1,3-tetrahydropyrimidinones **8** starting from homochiral synthon **2** is described. Chemoselective reduction of pyrimidines **4** using BH_3·THF provides an access to regioselective *N*-protected tetrahydropyrimidinones **8**.

In the course of our studies concerning the enantioselective synthesis of α,β-substituted β-amino acids **5** we made use of a new chiral synthon **2**.[1] Conjugate additions of different organocuprate reagents to this chiral Michael acceptor occurred with complete diastereoselectivity and afforded compounds **3**, which furnished products **4** in good yields after hydrogenolysis[2] of the labile homobenzylic C–O bond[3] (Scheme 1).

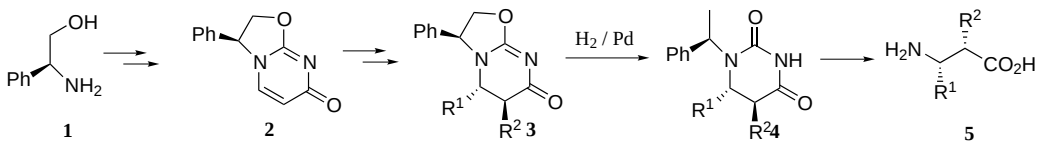
Herein, we wish to report a new entry to enantiopure *N*-protected tetrahydropyrimidinones **8** starting from homochiral template **2**. Tetrahydropyrimidinones **7**, which formally would lead to 1,3-diamines **6**, are potential anti-HIV agents[4] (Scheme 2). The synthesis of such 1,3-diamines has attracted some attention in recent years.[5] Although less described than their 1,2-analogues, which play an important role as chiral auxiliaries and catalysts in asymmetric synthesis,[6] they are of interest in medicinal chemistry (i.e. in cancer research).[7]

This paper presents our results concerning the chemoselective reduction of pyrimidines **4** and describes the synthesis of homochiral tetrahydropyrimidinones **8**. The reduction of pyrimidines into tetrahydropyrimidinones was the subject of but a few studies: $LiAlH_4$ reductions of two pyrimidines analogous to compounds **4** were reported[8] and the yields were really unsatisfactory in both cases.

In order to synthesize enantiopure tetrahydropyrimidinones **8**, pyrimidines **4** were reduced with an excess of $LiAlH_4$ in THF or diethylether. In these conditions, pyrimidine **4c** afforded 4-hydroxypyrimidinone **12c** (46% yield): only traces of the expected compound **8c** was observed in the NMR spectrum of the crude material (Scheme 3). Moreover, the reduction of pyrimidines **4c** with DIBAL-H gave rise to compound **12c** in 43% yield (Scheme 3). It is noteworthy that *N*-substituted hydantoins have already been shown to undergo similar $LiAlH_4$ reductions to give 4-hydroxy-2-imidazolidinones in good yields.[9]



Scheme 2.



Scheme 1.

Keywords: 1,3-diamines; tetrahydropyrimidinones; chemoselective reduction; pyrimidines.
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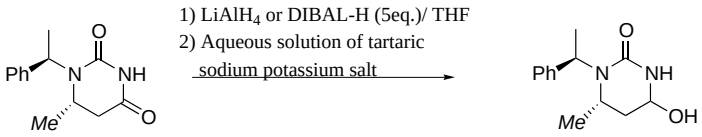


4c **12c**

Scheme 3.

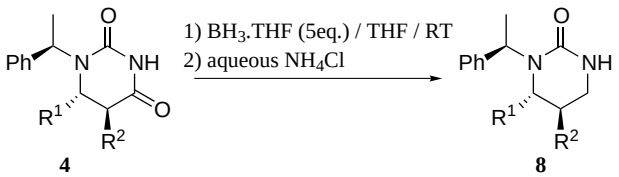
In order for the expected reaction to succeed another reducing agent was used. Reduction with BH_3·THF afforded the tetrahydropyrimidinones **8** in good yields. The results are presented in Table 1.

All reactions were performed with an excess of BH_3·THF (5 equiv.). Tetrahydropyrimidinones **8** were obtained in good yields by chemoselective reduction of the carbonyl on C-4 using BH_3·THF at room temperature. Compound **8a** was also obtained in good yield by using 1.2 equiv. of BH_3·THF in the same experimental conditions. No epimerization could be detected when the reaction was applied to substrates **4d** and **4e** bearing a stereogenic center α to the carbonyl function. When the reaction was conducted at reflux with the same reducing agent, pyrimidine **4b** led to the *N*-methylated diamine **9** (Scheme 4). It is noteworthy that in this case, the carbon–nitrogen bond was selectively cleaved and no 1,3-diazepine **10** could be obtained (Scheme 4) as observed in the reduction of cyclic ureas with $LiAlH_4$.[10]

The regioselectivity of formation of the *N*-methylated products **9** was determined by converting the 1,3-diamines **9** into the *N*-methylated dihydropyrimidinone **11**, using triphosgene in basic medium (Scheme 4). Compound **11** was correlated with the product arising from *N*-methylation of tetrahydropyrimidinone **4b**.

In order to synthesize 1,3-diamine **13**, pyrimidinones **8b** was submitted to hydrolysis under basic conditions (NaOH, reflux), but these conditions leave the starting material unreacted. In contrast acidic hydrolysis provides debenzylated tetrahydropyrimidinone **7b** (Scheme 5).[11]

Table 1. Chemoselective reduction of pyrimidines **4**



4 **8**

Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**4a**	H	H	**8a**	87
2	**4b**	*n*-Bu	H	**8b**	61
3	**4c**	Me	H	**8c**	69
4	**4d**	Me	Me	**8d**	76
5	**4e**	H	Me	**8e**	64

In conclusion, it was found that BH_3·THF reduces chemoselectively pyrimidines **4** into tetrahydropyrimidinones **8**. The homochiral template **2** affords an easy access to enantiopure mono- and disubstituted tetrahydropyrimidinones **8** in three or four steps, respectively.

The introduction of a third substituent by diastereoselective alkylation of α-hydroxypyrimidinones **12**, which are masked acyliminium ions, is currently underway.

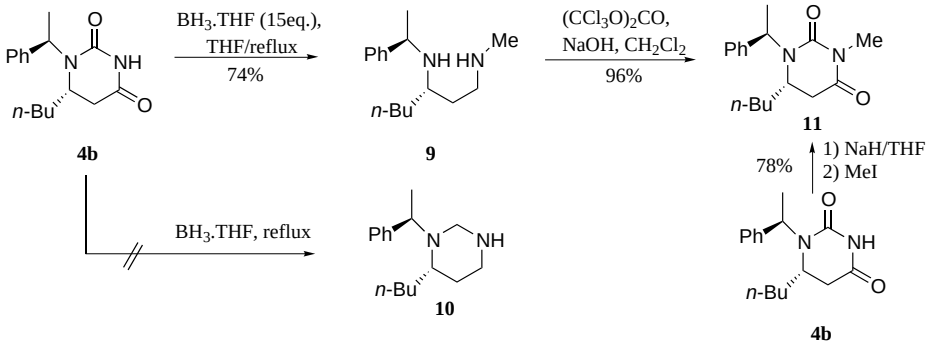
Experimental procedure for the preparation of tetrahydropyrimidinones 8

A typical experimental procedure is provided for the synthesis of tetrahydropyrimidinone **8b**. To a solution of pyrimidine **4b** (160 mg, 0.58 mmol) in THF (10 mL) was added dropwise, at room temperature, a solution of BH_3·THF (2.9 mL of a 1 M solution in THF). The reaction mixture was stirred for 4 h and then quenched with a saturated solution of ammonium chloride. The resulting mixture was extracted with dichloromethane (3×20 mL). The combined organic phases were then dried over magnesium sulfate. After filtration and concentration under vacuum, chromatography on silica gel (EtOAc/MeOH 95/5) afforded 92 mg (61%) of compound **8b**.

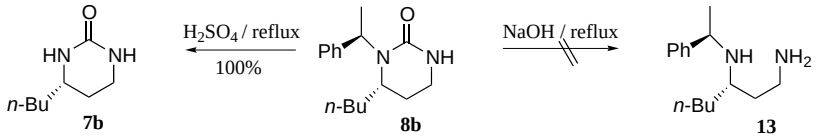
$[\alpha]_D^{20}=+84$ (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.58 (t, 3H, $J=6$ Hz), 0.87 (m, 4H), 1.11 (m, 2H), 1.43 (d, 3H, $J=7$ Hz), 1.58 (m, 1H), 1.72 (m, 1H), 3.21 (m, 3H), 4.98 (sl, 1H, NH), 5.68 (q, 1H, $J=7$ Hz), 7.22 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 13.8, 16.1, 22.1, 24.2, 28.1, 31.2, 36.6, 49.8, 52.0, 127.3, 128.2, 141.5, 155.8.

Experimental procedure for the preparation of 4-hydroxydihydropyrimidinones 12c

To a solution of pyrimidine **4c** (120 mg, 0.517 mmol) in THF (5 mL) was added dropwise, at room temperature, a solution of DIBAL-H (2.58 mL of a 1 M solution in hexanes). The reaction mixture was stirred for 4 h and then quenched with an aqueous solution of tartaric acid sodium potassium salt and further stirred for 1 h. The resulting mixture was extracted with dichloromethane (3×20 mL). The combined organic phases were then dried over magnesium sulfate. After filtration and concentration under vacuum, chromatography on silica gel (CH_2Cl_2/MeOH 95/5) afforded 52 mg (43%) of compound **12c**.



Scheme 4.



Scheme 5.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.78 (d, 3H, $J=6.75$ Hz), 1.44 (d, 3H, $J=7$ Hz), 1.81 (m, 2H), 3.52 (m, 1H), 4.62 (ls, 1H, NH), 5.23 (m, 1H), 5.65 (q, 1H, $J=7$ Hz), 6.51 (ls, 1H, OH), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 16.4, 20.5, 35.1, 45.6, 52.0, 73.9, 127.2, 127.7, 128.1, 141.2, 154.6.

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