Asymmetric Synthesis of α-Alkyl-α-phenylglycine Derivatives

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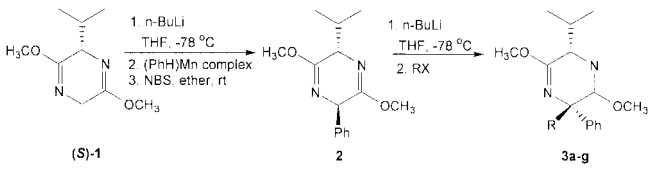
The development of new methods for stereoselective synthesis of α-quarternary α-amino acids has gained importance in recent years. These substances are popular replacements for amino acids in peptides because their presence often leads to enhanced proteolytic stability and a restriction in the number of allowed conformations.[1] Also, α-quarternary α-amino acids are known to display inhibitory activity toward enzymes and to serve as components of biologically active natural products. For example, some members of this family have recently been found to act as selective antagonists of the metabotropic glutamate receptor.[2]

Although a number of approaches for the synthesis of chiral α,α-dialkyl-substituted α-amino acids have been reported,[3] general methods for asymmetric synthesis of α-alkyl-α-aryl glycines have yet to be developed owing to the absence of procedures for introduction of the aryl moiety.[4] Below, we describe the results of recent studies in our laboratory on the asymmetric synthesis of α-alkyl-α-phenylglycine derivatives. The sequence developed for this purpose begins with arylation of the bislactim ether, (*S*)-**1**, which is a chiral glycine equivalent. This is followed by alkylation to form 3-alkyl-3-phenylpyrazines **3** and subsequent hydrolysis to generate the target amino acid esters.

(3*R*)-3-Phenylpyrazine **2** is prepared by treatment of the lithio anion of the bislactim ether **1** with the previously described benzene-$Mn(CO)_3$ complex.[5] Treatment of **2** with *n*-BuLi at -78 °C followed by addition of an alkyl halide leads to highly stereoselective (> 99 : 1) formation of the pyrazines **3** in which the alkyl and isopropyl substituents are *trans*-disposed (Scheme 1, Table 1).[6] The only exception to this general trend is with methyl iodide where an inseparable mixture (11 : 1) of diastereomeric products **3a** is obtained (Table 1, entry 1). The diastereomer ratio in this case was determined by analysis of the ^{1}H NMR spectrum which contains the two sets of the methoxy methyl resonances at 3.71 and 3.63 ppm (major) and at 3.66 and 3.57 ppm (minor). Methyloxymethyl chloride did not react with the anion of **2** at -78 °C but it smoothly gives adduct **3e** when reaction is performed at -30 °C (Table 1, entry 5). Finally, *n*-butyl bromide did not participate in this reaction but the corresponding iodide, prepared by treatment of the bromide with NaI in acetone, did to give adduct **3g** (Table 1, entry 8).



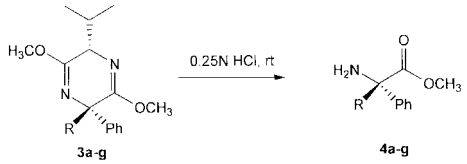
Scheme 1

Table 1. Alkylation reactions of 3-phenylpyrazine

Entry	Product	RX	Yield (%)[a]	% de
1	**3a**	CH_3I	90	83
2	**3b**	$PhCH_2Br$	80	>99
3	**3c**	$H_2C{=}CHCH_2Br$	85	>99
4	**3d**	$HC{\equiv}CCH_2Br$	80	>99
5[b]	**3e**	CH_3OCH_2Cl	77	>99
6	**3f**	$BrCH_2CO_2CH_2CH_3$	79	>99
7	**3g**	C_4H_9Br	no reaction	–
8	**3g**	C_4H_9I	86	>99

[a]Isolated yields. [b]The reaction was performed at -30 °C.

The 3-alkyl-3-phenylpyrazines **3** undergo slow hydrolysis under mild conditions (0.25N HCl, 25 °C) to yield the desired α-alkyl-α-phenylglycine methyl esters **4** (Scheme 2, Table 2).[7] While the pyrazines containing small alkyl substituents required 2-3 day hydrolysis periods for completion, the benzyl substituted pyrazine **3b** gave only a 25% yield of **4b** (50% recovered **3b**) after treatment with 0.25N HCl for 30 days (Table 2, entry 2).[8] The hydrolysis products were contaminated with trace amounts of dipeptide methyl esters which could not be separated by column chromatography. When more highly concentrated HCl solutions are used for

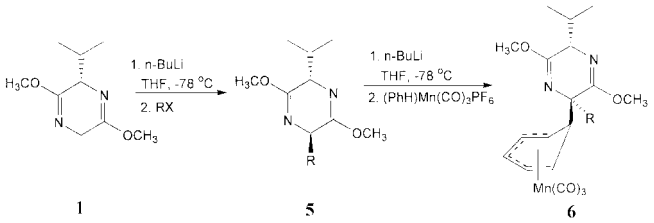


Scheme 2

Table 2. Hydrolysis reactions of 3-alkyl-3-phenylpyrazines

Entry	Products	R	Time (d)	% Yield[a]
1	**4a**	CH_3	3	89
2	**4b**	$PhCH_2$	30	25
3	**4c**	$H_2C{=}CHCH_2$	7	84
4	**4d**	$HC{\equiv}CCH_2$	14	80
5	**4e**	CH_3OCH_2	2	79
6	**4f**	$CH_2CO_2CH_2CH_3$	9	80
7	**4g**	C_4H_9	20	82

[a]Isolated yields.



Scheme 3

the hydrolysis process, the yield diminished due to the formation of unreactive 2,5-dioxohexahydropyrazines.

In order to determine if racemization is occurring under the conditions used for the hydrolysis reactions, synthesis of the diastereomers of the 3-alkyl-3-phenylpyrazines with opposite C-3 stereochemistry was attempted by using the reverse alkylation-phenylation sequence (Scheme 3). Although reactions of the anions of the 3-alkylpyrazines **5** with the benzene-Mn complex were successful, all attempts to oxidatively demetallate the (cyclohexadienyl)Mn complexes **6** by using NBS, CAN, iodine, Ph_3CPF_6, or Jones reagent failed to give the 3-alkyl-3-phenylpyrazine products.

However, this problem was solved by employing a route starting with the (*R*)-enantiomer of pyrazine **1**. (*R*)-α-Methyl-α-phenylglycine methyl ester was prepared from (*R*)-**1** by using the chemistry shown in Scheme 1. The enantiomeric excess for α-methyl-α-phenylglycine methyl ester was the determined by ^{1}H NMR analysis using Eu(hfbc)$_3$ as a chiral shift reagent. The enantiomer ratio in **4a** was found to be 11 : 1, the same as the 3-methyl-3-phenylpyrazine **3a** diastereomer ratio, indicating that no racemization attends the hydrolysis process.

In conclusion, 3-alkyl-3-phenylpyrazines can be prepared in high yields and high diastereoselectivities by alkylations of chiral 3-phenylpyrazine. Also, mild hydrolysis of the pyrazine ring liberates α-alkyl-α-phenylglycine methyl esters again in high yields and without racemization.

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6. General Alkylation Procedure: To a stirred solution of pyrazine **1** (0.35 mmol, 1.0 equiv) in THF (3 mL) under an N_2 atmosphere was added *n*-BuLi (0.42 mmol, 1.2 equiv) at -78 °C and the mixture was stirred for 30 min before adding a solution of the alkyl halide (0.39 mmol, 1.13 equiv) in THF (1 mL). After stirring for 30 min, the mixture is cooled to -78 °C, diluted with satd NH_4Cl, and extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* giving a residue which was subjected to chromatography on silica gel (ether-hexane, 1 : 10) to yield the pyrazines **3**. General Spectroscopic Data: (3*S*,6*R*)-6-Isopropyl-2,5-dimethoxy-3-benzyl-3-phenylpyrazine (**3b**): $[\alpha]_D^{25}$ = +53.7 (c 1.9, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 11.0 Hz, 2H), 7.09-7.34 (m, 8H), 3.78 (s, 3H), 3.70 (d, *J* = 12.6 Hz, 1H), 3.67 (s, 3H), 3.14 (d, *J* = 3.3 Hz, 1H), 3.10 (d, *J* = 12.6 Hz, 1H), 2.07 (dhept, *J* = 6.7, 3.6 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.55 (d, *J* = 6.6 Hz, 3H); IR (KBr) 3296, 2965, 1694, 1434, 1241, 1186 cm^{-1}.
7. General Hydrolysis Procedure: A suspension of the 3-alkyl-3-phenylpyrazine **3** (0.34 mmol) in 0.25N HCl solution (10 mL) and stirred for 2-30 days at 25 °C. The mixture was washed with ether and the aqueous layer was concentrated. The residue was diluted with ether and conc. NH_4OH was added until pH reached 8-10. The ethereal layer was separated and aqueous layer was extracted with ether. The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* giving a residue which was subjected to chromatography on silica gel (ethyl acetate-hexane, 1 : 2) to yield the amino acid esters **4**. General Spectroscopic Data: for (*S*)-α-Benzylphenylglycine methyl ester (**4b**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.04 (m, 10H), 3.37 (s, 3H), 3.64 (d, *J* = 13.0 Hz, 1H), 3.15 (d, *J* = 13.0 Hz, 1H), 1.89 (s, 2H); IR (KBr) 3323, 3034, 2951, 1724, 1599, 1434, 1255, 1186 cm^{-1}.
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