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The imine (+)-pseudoephedrine glycinamide: a useful reagent for the asymmetric synthesis of (*R*)-α-amino acids

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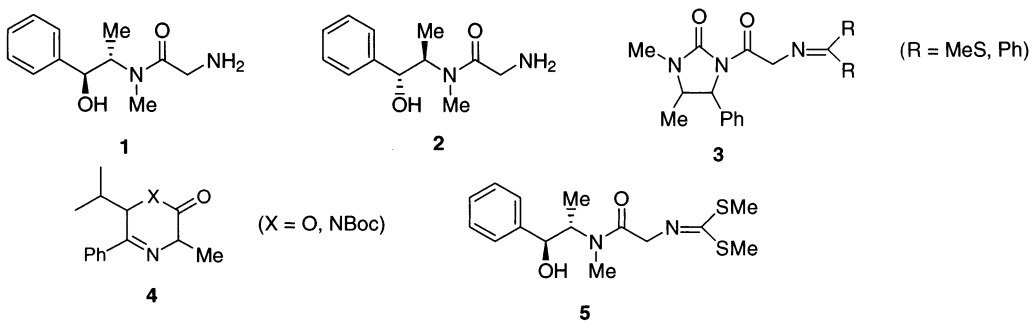
Abstract—The new imine derived from Myers (+)-pseudoephedrine glycinamide can be diastereoselectively alkylated with alkyl halides at room temperature using NaOEt or LiO-*tert*-Bu as bases under phase transfer conditions. Hydrolysis to the corresponding alkylated products was easily achieved under mild conditions to afford (*R*)-α-amino acids.

The diastereoselective electrophilic alkylation of chiral glycine-derived enolates is one of the most powerful methods for the asymmetric synthesis of α-amino acids.[1] Based on this concept, (+)- or (−)-pseudoephedrine glycinamide **1** or **2** have been alkylated with high diastereoselectivity and the alkylated products hydrolyzed to give enantiomerically enriched (*R*)- or (*S*)-α-amino acids, respectively.[2] The alkylation process requires the use of strong anionic bases such as *n*-BuLi or LDA at 0°C. Glycine or alanine imine templates are useful reagents for the synthesis of α-amino acids because they are easily enolizable and can be alkylated under very mild reaction conditions for example by phase transfer catalysis, or with organic bases.[3] Recently we reported the successful use of chiral glycinate imine **3**[4] derived from (+)- and (−)-ephedrine imidazolidinones and cyclic alaninates **4**[5] for the asymmetric synthesis of mono-alkylated α-amino acids and α-methyl α-amino acids, respectively. Those reagents can be alkylated under phase transfer conditions by using weak bases such as LiOH or K_2CO_3. Particularly, (+)- and (−)-1,5-dimethyl-4-phenylimidazolidin-2-one derived glycinates **3** present a labile imide bond and are prepared by acylation of the imidazolidinone with chloroacetyl chloride followed by amination and final imine formation. Additionally, these compounds are easily hydrolyzed under basic conditions to give the chiral auxiliary and the glycine moiety, for this reason the alkylation under phase transfer conditions must be carried out at −20°C.[4] In connection with the previous work we thought it would be of interest to prepare pseudoephedrine glycinamide imine **5** as a chiral template for the asymmetric synthesis of α-amino acids. This reagent should be more stable than the imidazolidinone derivatives **3** and could be prepared by a more direct way, furthermore it should be more easily enolizable than the *N*-unsubstituted pseudoephedrine reagent **1**.



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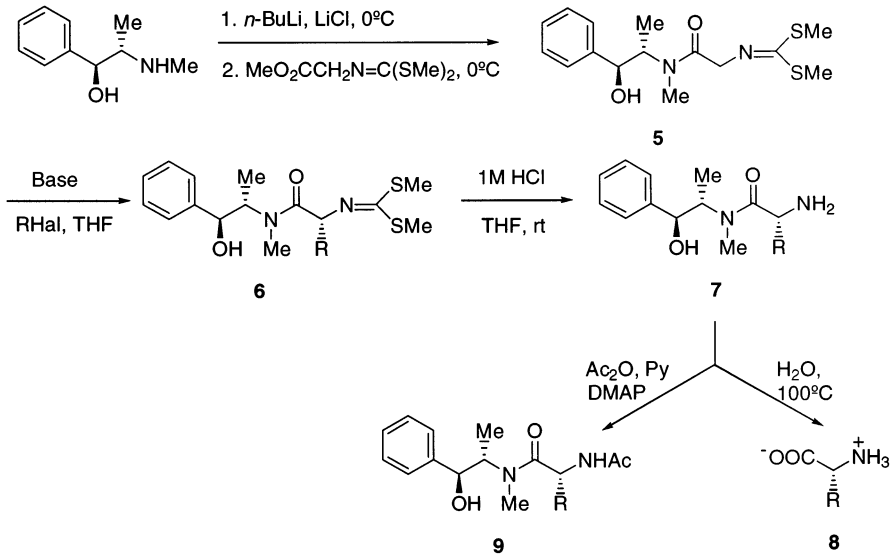

Scheme 1.

The preparation of compound **5** was carried out in 71% yield by direct condensation of *N*-[bis(methylthio)-methylene]glycine methyl ester with (+)-pseudoephedrine after deprotonation with *n*-butyllithium in the presence of lithium chloride at 0°C, conditions which have been described for compound **1**.[2a] The alkylation process of compound **5** was initially studied with allyl iodide under different reaction conditions (Scheme 1 and Table 1). Under solid–liquid PTC conditions the alkylation process in the presence of K_2CO_3, KOH or CsOH as bases and 10 mol% of tetra-*n*-butylammonium bromide (TBAB) in THF as solvent gave 1:1 mixtures of enolate and OH alkylation products. The alkylated compound **6a** was obtained in 39–45% yield with almost negligible asymmetric induction. The reaction conditions used in the case of imidazolidinone derived glycinimide **3** failed (LiOH, LiCl, TBAB or DBU, LiCl) after 24 h at rt.[4] When stronger bases such as NaH, LiOBu^t, KOBu^t or NaOEt were used in THF as solvent, the alkylation reaction took place mainly at the *C*-center with high diastereoselectivity for these alkoxide bases (Table 1, entries 1–4). In the case of NaOEt, *O*-alkylation was avoided when a 10 mol% of TBAB was added increasing simultaneously the yield and the diastereoselectivity of the *C*-alkylated products in shorter reaction times (Table 1, entry 5).

Several alkyl halides were tested using the best reaction conditions of either LiO^{t}Bu or NaOEt/TBAB in THF at rt, affording compounds **6** with good d.r.[6] The hydrolysis of the imine group by means of aqueous 1 M HCl in THF at rt gave the corresponding glycinamides **7** in 75–80% isolated yields, which have the same spectroscopic properties as those previously reported by

Table 1. Diastereoselective alkylation of imine pseudoephedrine glycinamide **5**[a]

Entry	Base (equiv.)	RHal	Reaction time (h)	*C:O* alkylation ratio[b]	Product		
					No.	Yield[c]	dr[b]
1	NaH (1.5)	CH_2=$CHCH_2I$	4	99:1	**6a**	75	63:37
2	KOBu^t (1.0)	CH_2=$CHCH_2I$	1.5[d]	99:1	**6a**	36	93:7
3	LiOBu^t (1.0)[e]	CH_2=$CHCH_2I$	24	99:1	**6a**	50	95:5
4	LiOBu^t (1.0)	CH_2=$CHCH_2I$	0.75	99:1	**6a**	50	93:7
5	NaOEt (3.0)	CH_2=$CHCH_2I$	3	90:10	**6a**	64	88:12
6	NaOEt (3.0)[f]	CH_2=$CHCH_2I$	0.75	99:1	**6a**	72	95:5
7	LiOBu^t (1.0)	$PhCH_2Br$	0.5	99:1	**6b**	60	95:5
8	NaOEt (3.0)[f]	$PhCH_2Br$	3.5	92:8	**6b**	62	91:9
9	LiOBu^t (1.0)	CH_3I	5	99:1	**6c**	57	97:3
10	NaOEt (3.0)[f]	CH_3I	2	90:10	**6c**	38	90:10
11	LiOBu^t (1.0)	CH_3CH_2I	3	99:1	**6d**	49	98:2
12	NaOEt (3.0)[f]	CH_3CH_2I	3	80:20	**6d**	16	90:10
13	LiOBu^t (1.0)	EtO_2CCH_2I	15	75:25	**6e**	40	82:18

[a] The reactions were carried out in THF at rt.
[b] Determined by GLC.
[c] Yield of isolated product after column chromatography, based on compound **5**.
[d] At 0°C.
[e] LiCl (6 equiv.) was added.
[f] TBAB (10 mol%) was added.

Myers' group. Glycinamides **7** were hydrolyzed to (*R*)-α-amino acids **8a** (R = allyl) and **8b** (R = benzyl) in 70–89% yield, respectively, by simple heating under reflux in water.[2a] (+)-Pseudoephedrine was recovered from this process in ca. 75% yield. The diastereoselectivity of the alkylation process was determined by transformation of glycinamides **7** into their acylated derivatives **9** by treatment with acetic anhydride in pyridine and 4-(dimethylamino)pyridine (DMAP) and analyzing the products by chiral GLC (Chirasil-Val). As in the case of reagent **1**, the alkylation of compound **5** took place at the same face as the methyl group of the (+)-pseudoephedrine.

The corresponding benzophenone derivative could be also prepared from the reaction between the chlorohydrate of Myers' reagent **2** and benzophenone imine. However, this product was very sensitive during the alkylation process, during purification and even on standing at 0°C. As such, it could only be isolated in less than 20% yield. Pseudoephedrine was exclusively isolated in all these attempts.

In conclusion, the pseudoephedrine–glycinamide derived imine **5** is a good derivative of Myers' reagent **1** because it can be prepared in one step from (+)-pseudoephedrine and can be alkylated diastereoselectively at rt and under less basic conditions than **1**.

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6. Typical procedure: To a solution of glycinamide **5** (0.3 mmol, 100 mg) and LiO-*tert*-Bu (0.3 mmol, 24 mg) or NaOEt (0.9 mmol, 61 mg) and TBAB (0.09 mmol, 31 mg) in THF (3 mL) was added the corresponding alkyl halide (1.5 mmol). After the reaction was completed (TLC monitoring) water was added and the reaction was extracted with CH_2Cl_2 (10 mL). The organic layer was washed with water (3×10 mL), dried (Na_2SO_4), evaporated in vacuo (15 torr) and the residue purified by flash chromatography on silica gel (Hex/EtOAc mixtures) affording compounds **6**.