Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2769–2772

TETRAHEDRON:
ASYMMETRY

Asymmetric synthesis of (*S*)-α-methyl α-amino acids by alkylation of chiral 3,6-dihydro-2*H*-1,4-oxazin-2-ones using unactivated alkyl halides and organic bases

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Received 22 June 1998; accepted 20 July 1998

Abstract

3,6-Dihydro-2*H*-1,4-oxazin-2-ones **1** have been diastereoselectively (>96% de) alkylated using unactivated alkyl halides and organic bases such as 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature in the presence of LiI. Hydrolysis of the resulting alkylated systems afforded enantiomerically enriched (*S*)-α-methyl α-amino acids. When 1,3-diiodopropane was used, spontaneous *N*-alkylation also took place giving bicyclic oxazinone **6** which was hydrolyzed to (*S*)-α-methylproline. © 1998 Elsevier Science Ltd. All rights reserved.

Among non-proteinogenic α-amino acids, α,α′-dialkyl derivatives, and in particular α-methyl α-amino acids (AMAAs), have assumed an important role in bioorganic chemistry in recent years. Many have been used as enzyme substrates or inhibitors and also as components of biologically active peptides, increasing resistance to hydrolysis by peptidases or locking peptide conformations.[1] All these applications make the development of new methods for the preparation of enantiomerically pure AMAAs desirable. The most direct asymmetric synthetic approach to AMAAs is the α-alkylation of chiral alanine anion equivalents, which usually requires strong anhydrous bases (Bu^nLi, LDA, LHMDS) and low temperatures in order to achieve high diastereoselectivities.[2]

Recently we have found that new chiral 3,6-dihydro-2*H*-1,4-oxazin-2-ones **1**[3] and 1,2,3,6-tetrahydro-2-pyrazinones **2**[4] from alanine are useful reagents for the asymmetric synthesis of (*S*)-α-methyl α-amino acids **5** after highly diastereoselective alkylation under solid–liquid phase-transfer and/or palladium catalysis at room temperature and further hydrolysis (Scheme 1). However, in spite of the synthetic interest of phase-transfer-catalysis (PTC) conditions due to their simplicity and mildness, PTC proved to be ineffective with **1** or **2** when using unactivated electrophiles.[5] In this communication we report the use of organic bases for the asymmetric alkylation of oxazinones **1** with representative unactivated alkyl halides at room temperature.

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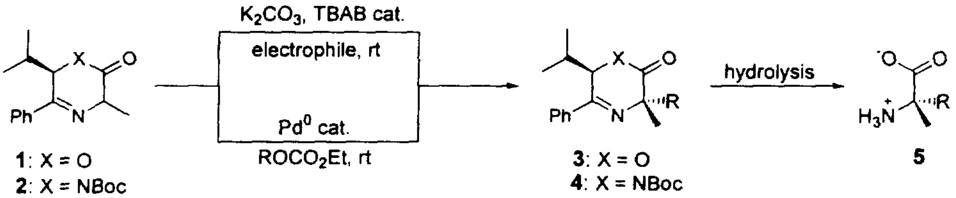
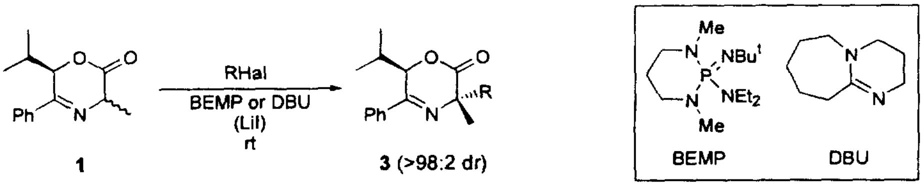
PII: S0957-4166(98)00288-2



Scheme 1.

Oxazinones **1**, prepared from alanine and (*S*)-2-hydroxyisovalerophenone and isolated as a 1:20 *cis*:*trans* diastereomeric mixture,[3] were deprotonated using organic bases such as Schwesinger's[6] 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)[7] or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and reacted with representative unactivated alkyl halides at room temperature in considerably shorter reaction times and also generally with higher diastereoselectivities (>96% de, 300 MHz ^{1}H NMR, GLC) than when using PTC conditions,[3] to afford oxazinones **3**[8] (Scheme 2 and Table 1). Compounds **3** were obtained in diastereomerically pure form in moderate yields after chromatographic purification (Table 1). In all cases, variable amounts of the corresponding *O*-alkylated product were also detected in the reaction crude. The best yields were achieved using the diazaphosphazine BEMP (1.1 equiv.) as base, whereas a large excess (5 equiv.) of DBU was necessary in order to obtain full conversion of the starting material although in general with lower yields (Table 1, entries 12–16). Polymer-bound BEMP was also investigated as the base, but the reaction was sluggish and needed much longer reaction times. 1-Methyl-2-pyrrolidinone (NMP) was the preferred solvent giving the best yield and *C*/*O*-alkylation ratio (Table 1, entries 4–7). When LiI was added, a significant improvement of the *C*/*O*-alkylation ratio was observed (compare entries 1 and 2, 7 and 8, or 13 and 14 in Table 1). The strong coordination of the lithium cation with the oxygen (hard–hard interaction) could explain the increasing *C*/*O*-alkylation ratio.[9] Moreover, the addition of LiI allowed the alkylation of **1** using an alkyl bromide such as *n*-butyl bromide as electrophile, although with lower yield than when the corresponding alkyl iodide was employed (compare entries 8 and 9 in Table 1).[10]



Scheme 2.

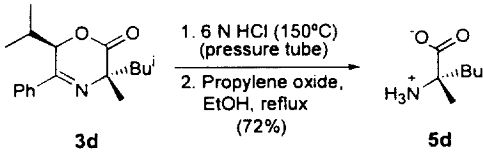
Hydrolysis of representative alkylated oxazinone **3d** was carried out by treatment with 6 N HCl, followed by reaction of the corresponding hydrochloride with propylene oxide affording (*S*)-α-methylleucine **5d** in 72% yield and >99% ee (Scheme 3),[11] thus confirming the absolute configuration of **3d**.

When the alkylation reaction was carried out with an unactivated alkyl diiodide such as 1,3-diiodopropane using BEMP as base and at room temperature, not only the *C*-alkylation took place, but also further *N*-alkylation and isomerization of the iminic double bond affording bicyclic oxazinone **6**[12] in 55% isolated yield after flash chromatography (Scheme 4). This spontaneous cyclization reaction should allow the preparation of precursors of interesting cyclic AMAAs[13] following a more simple and direct experimental procedure than when using other chiral templates.[14] The use of DBU as base afforded lower yields of bicyclic compound **6** due to a competing dehydrohalogenation process to a terminal olefin after the first *C*-alkylation step, also giving compound **3f** (R=$CH_2CH=CH_2$).[3] Subsequent acid hydrolysis of

Table 1
Alkylation of oxazinone **1** with unactivated alkyl halides

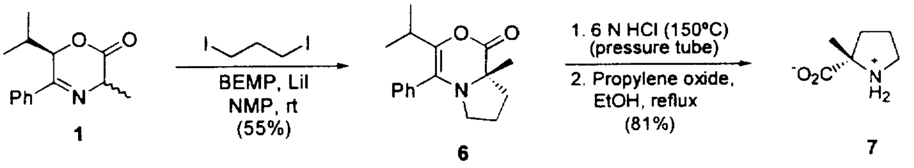
entry	RHal	no.[a]	Base (eq) + LiI (eq)	solvent	reaction time (h)[b]	*C*/*O*-alkylation ratio[c]	yield (%)[d]
1	EtI	**3a**	BEMP (1.1)	NMP	1	12/1	50
2	EtI	**3a**	BEMP (1.1) + LiI (1.2)	NMP	1	25/1	55
3	Pr^iI	**3b**	BEMP (1.1) + LiI (1.2)	NMP	1	24/1	48
4	Bu^nI	**3c**	BEMP (1.1)	THF	12	5/3	38
5	Bu^nI	**3c**	BEMP (1.1)	DMF	1	9/1	56
6	Bu^nI	**3c**	BEMP (1.1)	MeCN	1	10/1	58
7	Bu^nI	**3c**	BEMP (1.1)	NMP	1	17/1	64
8	Bu^nI	**3c**	BEMP (1.1) + LiI (1.1)	NMP	1	50/1	65
9	Bu^nBr	**3c**	BEMP (1.1) + LiI (2)	NMP	1	1/0	38
10	Bu^iI	**3d**	BEMP (1.1) + LiI (1.5)	NMP	1	1/0	45
11	$Ph(CH_2)_2I$	**3e**	BEMP (1.1) + LiI (1.5)	NMP	1	1/0	52
12	EtI	**3a**	DBU (5)	NMP	1	50/1	53
13	Pr^iI	**3b**	DBU (5)	NMP	1.75	5/1	46
14	Pr^iI	**3b**	DBU (5) + LiI (1.2)	NMP	1.25	100/1	33
15	Bu^nI	**3c**	DBU (5)	NMP	1	25/1	53
16	Bu^iI	**3d**	DBU (5)	NMP	2.5	10/1	28

[a] All compounds were >95% pure (300 MHz ^1H NMR, GLC) and showed satisfactory spectroscopical data (IR, ^1H and ^{13}C NMR, MS). [b] Monitorized by GLC. [c] Determined by ^1H NMR (300 MHz) and/or GLC. [d] Isolated yield of compound **3** after flash chromatography.



Scheme 3.

compound **6** and treatment with propylene oxide afforded enantiomerically enriched (*S*)-α-methylproline (**7**, 81%) in 99% ee[15] (Scheme 4). It is noteworthy that in this case a chromatographic enrichment in isomer **6** after purification is impossible, the final ee only arising from a highly diastereoselective initial *C*-alkylation step.



Scheme 4.

In conclusion, oxazinones **1** are proving to be versatile chiral templates which can now be highly diastereoselectively alkylated with unactivated alkyl mono- or dihalides using organic bases at room temperature for the asymmetric synthesis of acyclic and cyclic AMAAs under relatively mild and simple reaction conditions. Further work to exploit the synthetic uses of these heterocycles is underway.

Acknowledgements

We thank the Dirección General de Investigación Científica y Técnica (DGICYT) of the Spanish Ministerio de Educación y Cultura (MEC) (PB94-1515) for financial support. N.G. thanks MEC for a grant.

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5. Attempted alkylation of **1** with alkyl iodides using strong anhydrous bases (LDA, LHMDS, $KOBu^t$, NaH) under different reaction conditions failed.
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8. Specific rotations: **3a**: $[\alpha]_D^{25}$ +26.5 (*c* 1.6, CH_2Cl_2). **3b**: $[\alpha]_D^{25}$ +42.8 (*c* 2, CH_2Cl_2). **3c**: $[\alpha]_D^{25}$ +28.5 (*c* 1.1, CH_2Cl_2). **3d**: $[\alpha]_D^{25}$ +72.7 (*c* 1.4, CH_2Cl_2). **3e**: $[\alpha]_D^{25}$ +20.7 (*c* 1.3, CH_2Cl_2).
9. For a recent discussion on lithium salt effects in organic synthesis, see: Seebach, D.; Beck, A. K.; Studer, A. In *Modern Synthetic Methods 1995*, VCH Publishers: Basel, 1995; Vol. 7, pp. 1–178.
10. Typical procedure: To a solution of the oxazinone **1** (0.5 mmol, 116 mg) and LiI (see Table 1) in the appropriate solvent (1 mL) was added the corresponding base (BEMP: 0.55 mmol, 159 μL; DBU: 2.5 mmol, 374 μL) at 0°C. The alkyl halide (1 mmol) was added at once and the temperature was allowed to rise to rt until total consumption of the starting material (GLC, Table 1). The mixture was diluted with EtOAc (25 mL), 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 **3**.
11. Specific rotation: $[\alpha]_D^{25}$ +38.2 (*c* 2, H_2O). Lit. $[\alpha]_D^{25}$ +34.2 (*c* 3, H_2O): Kruizinga, W. H.; Bolster, J.; Kellog, R. M.; Kamphuis, J.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826–1827.
12. Selected data for **6**: $[\alpha]_D^{25}$ −317.8 (*c* 1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.01 (d, *J*=6.7 Hz, 3H), 1.30 (d, *J*=7.0 Hz, 3H), 1.31 (s, 3H), 1.66–1.86 (m, 2H), 1.94 (m, 1H), 2.67–2.84 (m, 3H), 3.16 (m, 1H), 7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.8, 21.1, 21.8, 22.9, 27.8, 35.5, 50.8, 61.2, 122.4, 128.1, 128.3, 129.2, 134.8, 139.3, 169.1.
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15. Specific rotation: $[\alpha]_D^{25}$ −71.9 (*c* 1, MeOH). Lit.[14b] $[\alpha]_D^{25}$ −72.1 (*c* 1, MeOH).