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Tetrahedron Letters 45 (2004) 5175–5177
Tetrahedron Letters

Self-reproduction of chirality on α-aminophosphonates: asymmetric synthesis of α-alkylated diethyl pyrrolidin-2-yl-phosphonate

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Received 20 January 2004; revised 24 March 2004; accepted 2 April 2004

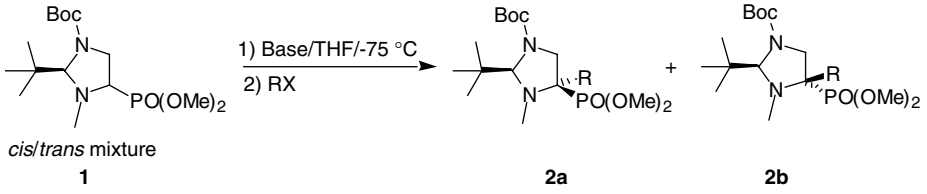
Abstract—A simple method for the asymmetric synthesis of α-substituted diethyl pyrrolidin-2-yl-phosphonate is described. The chiral oxazolopyrrolidine phosphonate was alkylated diastereospecifically with an alkyl halide. The key intermediate is an α-phosphonate-stabilized carbanion that can be alkylated without loss of optical activity and a single enantiomer of product was formed exclusively in 10–80% yield. The configurational assignment of the products relied on ^{1}H–^{1}H NOESY analysis of the alkylated oxazolopyrrolidine phosphonates. This represents an unprecedented case of self-regeneration of stereocenters (SRS) of cyclic aminophosphonates. The enantiomerically pure α-aminophosphonate diethyl-(2*S*)-(2-methylpyrrolidin-2-yl)-phosphonate, a surrogate of 2-methyl proline, was obtained upon hydrogenolysis of the chiral auxiliary in 83% yield.

α-Aminophosphonates and their derivatives are important compounds possessing diverse and useful biological activities.[1] Owing to their analogy to amino acids, they have found applications ranging from medicine to agriculture, for example, as antibiotics,[2] enzyme inhibitors,[3] anti-cancer agents,[4] and herbicides.[5] These biological properties are mostly associated with the tetrahedral structure of the phosphonyl group acting as a 'transition-state analogue'.[6]

Recently, cyclic α-aminophosphonates have found promising applications as surrogates of proline, increasing the need for their syntheses in enantiomerically pure form.[7]

In the present paper, we report a general method for the preparation of cyclic α-branched aminophosphonates. We also demonstrate that chiral cyclic α-aminophosphonates with a phosphonate carbanion functionality can be alkylated at the α-position to phosphorus and nitrogen by applying the Self-Regeneration of Stereocenters (SRS) principle.[8] To our knowledge little attention has been paid to such compounds, although in previous work, the asymmetric preparation of 1,2-diaminoalkane-2-phosphonic acid derivatives was reported, however, the authors started from a mixture of diastereoisomers of **1** to obtain compounds **2** (Scheme 1).[9]

We considered that oxazolopyrrolidine phosphonate **4** would be an interesting candidate-substrate to prepare cyclic aminophosphonates alkylated at the α-position. The deprotonation would involve formation of a resonance stabilized phosphonate carbanion and subsequent



Scheme 1.

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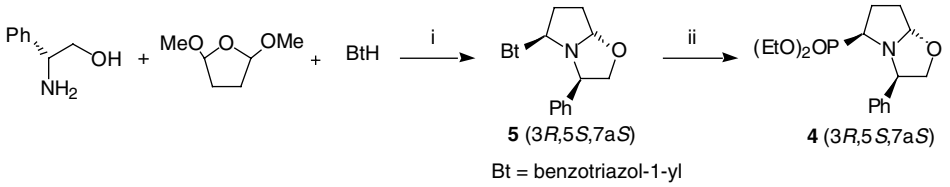
doi:10.1016/j.tetlet.2004.04.009



Scheme 2. Reagents and conditions: i, (a) 0.1 M HCl, 50 °C, 1 h (b) CH_2Cl_2, rt, 20 h; ii, $P(OEt)_3$ (2 equiv), $ZnCl_2$ (0.3 equiv), CH_2Cl_2, 0 °C, overnight.

reaction with an electrophile would be expected to proceed diastereoselectively under the directing effect of the remaining stereogenic center in the bicyclic system (Scheme 2).

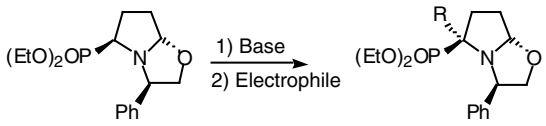
Oxazolopyrrolidine **5** was obtained according to the method described by Katritzky et al.[10] Thus, benzotriazole, (*R*)-phenylglycinol, and 2,5-dimethoxytetrahydrofuran (as an equivalent of succinaldehyde) reacted at room temperature via a double Robinson–Schopf condensation to yield compound **5** as a single diastereoisomer as shown by NMR analysis and confirmed by comparison with literature data.[10] Subsequent Arbuzov reaction in the presence of the mild Lewis acid $ZnCl_2$ (30 mol%), converted **5** into the desired oxazolopyrrolidine phosphonate **4** as the only diasteroisomer. Attempts to obtain **4** directly by replacing benzotriazole with triethyl phosphite in the initial reaction mixture resulted in a mixture of two diastereoisomers.

We first investigated the methylation of the oxazolopyrrolidine phosphonate **4** using LDA and LHMDS. However, with 1 equiv of such a base, we observed no product formation. When deprotonation of **4** was carried out with LDA/BuLi the desired product **6a** was obtained with 90% conversion. This trend in reactivity has been observed previously with such substrates. The use of an equivalent of BuLi, in excess, was explained by the necessity to break the hydrogen bond between the amine and the Li-nucleophile.[11] However better results in the alkylation reaction were obtained when using BuLi as base, and 95% conversion into **6a** was observed (entry 5, Table 1).[12]

Following this method, we next evaluated various other electrophiles for alkylation of **4** as shown in Table 1. While iodomethane and higher iodoalkanes were employed successfully in the alkylation reaction to provide **6a**–**d** in yields ranging from 10% to 80%, the very reactive allyl bromide did not give rise to the desired product. It is not yet clear whether BuLi in excess reacts with allyl bromide.

Interestingly, only one diastereoisomer was formed with all alkylating reagents, with the newly introduced alkyl group on the *endo*-face. This was proved by ^1H and ^{31}P NMR analysis and by gas chromatography. In the case of **6a**, the ^1H NMR spectrum had well resolved signals at room temperature and its stereochemical assignment was based on careful ^1H–^1H NOESY analysis. It was found that a NOE existed between the protons of the methyl in the α-position and H^3 and H^2 but not with H^{7a} (Fig. 1).

Table 1



4 (3*R*,5*S*,7a*S*)

6a (3*R*,5*S*,7a*S*): R = Me
6b (3*R*,5*S*,7a*S*): R = Et
6c (3*R*,5*S*,7a*S*): R = n-Pr
6d (3*R*,5*S*,7a*S*): R = Bn

Entry	Base	Product	Time	Conversion (%)[a,b]
1	LDA/BuLi (1:1)	**6a**	Overnight	90
2	LDA/BuLi (2:1)	**6a**	90 min	60
3	LDA/BuLi (2:2)	**6a**	Overnight	95
4	BuLi (1 equiv)	**6a**	Overnight	86
5	BuLi (2 equiv)	**6a**	90 min	95 (80)
6	BuLi (2 equiv)	**6b**	Overnight	52 (35)
7	BuLi (2 equiv)	**6c**	90 min	62 (41)
8	BuLi (2 equiv)	**6d**	60 min	10

[a] Determined by GC/MS analysis.
[b] Isolated yields after column chromatography separation in parentheses.

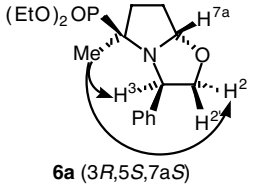


Figure 1.

The high diastereoselectivity and the retention of configuration observed in the alkylation reaction may be associated with the carbanion structure itself.

Solution state studies have shown that P(V) phosphonate-stabilized carbanions have a tendency for coordination of the metal center via the oxygen atom.[13] With closely related complexes such as Li^+**6a** there is no coordination to the carbanion itself. It was found that the carbanion was stabilized in either rotational conformation, that is parallel or perpendicular, with a low barrier to rotation about the P–C bond. It is reasonable to suggest that Li^+**6a** exists in a conformation where the carbanion lone pair will lie in parallel to the acceptor orbital σ^* P=O (hyperconjugation), with the additional coordination of the nitrogen donor group to lithium. Thus, the introduction of the alkyl group occurs with retention of configuration. It is also likely that the reaction is a kinetically controlled *endo* alkylation (Fig. 2).[14]

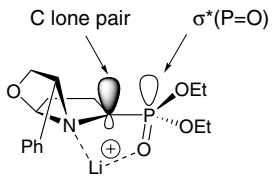
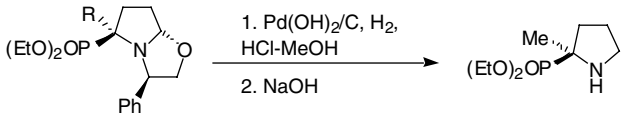


Figure 2.



Scheme 3.

The chiral auxiliary in phosphonate **6a** was readily removed by hydrogenolysis with $Pd(OH)_2/C$ in HCl/MeOH. Purification by flash chromatography eluting with CH_2Cl_2/MeOH (98/2) afforded diethyl (2*S*)-(2-methylpyrrolidin-2-yl)phosphonate **7a** in 83% yield as a yellow oil.[15] α-Aminophosphonate (2*S*)-**7a** could be a valuable precursor of a chiral version of the nitrone spin trap (5*S*)-5-(diethoxyphosphoryl)-5-methyl-1-pyrroline *N*-oxide (DEPMPO).[16] This study is currently underway in our group (Scheme 3).

In summary, α-alkylated pyrrolidine phosphonate precursors have been prepared. To this the end Self Regeneration of Stereocenter strategy was successfully applied to phosphonate stabilized carbanions. Further studies are in progress in our group on the scope of this methodology.

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12. Diethyl (3*R*,5*S*,7*aS*)-5-methyl-3-phenylhexahydropyrrolo[2,1-*b*]-[1,3]oxazol-5-yl-phosphonate **6a**. At −78 °C, *n*-BuLi (1.8 mmol, 2.26 M) was added to a solution of **4** (250 mg, 0.8 mmol) and the reaction mixture was allowed to warm to room temperature. MeI (186 μL, 3.0 mmol) was added and the resulting mixture was stirred at room temperature for 90 min. The reaction was quenched by addition of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by column chromatography using hexane/EtOAc (2/1) as eluent system giving **6a** (218 mg, 80%) as a yellow oil.
6a $[\alpha]_D^{20}$ −50.66 (*c* 2.60, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, $J = 7.2$ Hz, 3H), 1.15 (t, $J = 6.9$ Hz, 3H), 1.42 (d, $J_{H-P} = 16$ Hz, 3H), 1.87–2.04 (m, 2H), 2.26–2.32 (m, 1H), 2.38–2.46 (m, 1H), 3.63 (t, $J = 8.4$ Hz, 1H), 3.92–4.01 (m, 4H), 4.26 (m, 1H), 4.60 (m, 1H), 5.03 (m, 1H), 7.20–7.22 (m, 1H), 7.26–7.31 (m, 2H), 7.40–7.42 (m, 2H); ^{13}C NMR δ 16.6, 16.7, 18.9, 28.9, 34.9, 61.8, 62.6, 62.7, 64.3, 74.5, 99.6, 126.9, 128.4, 130.3, 143.6; MS (EI): *m*/*z* 339, 202, 138.
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15. Diethyl (2*S*)-(2-methylpyrrolidin-2-yl)phosphonate **7a**.
Compound **6a** (0.76 g, 2.24 mmol) was dissolved in methanolic HCl (30 mL). Palladium hydroxide on carbon (20% by weight, 120 mg) was added and the mixture was hydrogenated at a pressure of 4 atm at room temperature for 24 h. The catalyst was removed by filtration and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed with aqueous 1 M NaOH. The organic layer was dried over Na_2SO_4 and concentrated. The product was purified by column chromatography using CH_2Cl_2/methanol (98/2) as eluent giving **7a** (0.42 g, 83%) as a yellow oil: $[\alpha]_D^{20}$ +1.52 (*c* 2.60, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, $J = 6.9$ Hz, 6H), 1.36 (d, $J_{H-P} = 15.2$ Hz, 3H), 1.60–1.90 (m, 3H), 2.16–2.25 (m, 1H), 2.96–3.07 (m, 2H), 4.26 (q, $J = 6.9$ Hz, 4H); ^{13}C NMR 16.8, 24.3, 25.9, 34.8, 47.3, 58.9, 60.5, 62.4, 62.7; MS (EI): *m*/*z* 221, 205, 162, 138, 111, 83.
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