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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1819–1821

A new synthesis of β-amino acids by use of ketene diethyl acetal as enolate equivalent

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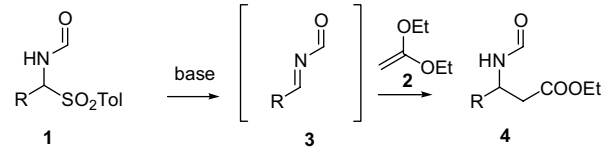
Received 17 November 2004; revised 20 January 2005; accepted 24 January 2005

Abstract—Reaction of phenylsulfonyl formamides, readily available in a single step from an aromatic aldehyde and sodium phenylsulfinate, with ketene diethyl acetal under basic conditions gives *N*-formyl β-amino acid esters in good yield, which can be kinetically resolved with a lipase.

While some β-amino acids are found in nature, it is primarily the more recent work of Seebach and Gellmann that pointed out to the organic community their importance.[1] The ability of even small β-amino acid peptides to form stable secondary structures is remarkable. Recently, a significant number of drug candidates in clinical development incorporate β-amino acids, highlighting the need for an efficient synthetic access.[2] Just as the classical Strecker α-amino acid synthesis consists of the addition of a carboxylate anion equivalent (cyanide) to an imine, β-amino acids are frequently prepared by adding an ester enolate equivalent to an imine. The classical example is the Rodionov reaction, whereby simply heating a mixture of an aromatic aldehyde, ammonium acetate and malonic acid leads directly to β-amino acid, typically in less than 60% yield. Mechanistically, the key step of this reaction is the addition of malonate to the in situ formed imine.[3] Recently, asymmetric versions of this reaction are reported, some with impressive ee values. In these reactions TMS enolethers are added to aniline derived imines or Boc imines using Lewis acid catalysis.[4] Unfortunately, the need to remove the aniline oxidatively with CAN and the expense in preparing the TMS-enolether impose a limit on the practical applicability of this approach.

While TMS-ketene acetals and TMS-ketenethio acetals are generally used as acetate anion equivalents, we are unaware of similar uses of the readily available and stable ketene diethyl acetal **2**. We now report on the successful addition of ketene diethyl acetal **2** into an in situ prepared acyl imine **3** for the synthesis of β-amino acid derivates **4** (Scheme 1, Table 1).[5] Indeed, *N*-formyl imines **3** are easily generated in situ from phenylsulfonyl formamides **1** using the chemistry described originally by Dutch workers and recently elegantly applied by the Merck and the Braese groups.[6]

Gratifyingly, combining **1** with 2 equiv of **2** led to the clean formation of **4** using 6 equiv of Et_3N in CH_2Cl_2 (Scheme 1). Optimization of reaction conditions showed that the reaction performs well in toluene and CH_3CN, but gave complex reaction mixtures in THF, MeOH and AcOEt. For R = Ph, optimization of bases by replacing Et_3N with the more basic DBU led to an increase of the rate of the reaction, albeit at the expense of reduced yields (Table 1). The optimum base for this reaction is Cs_2CO_3, which resulted in a very clean conversion in 24 h to give **4** in a gratifying 90% yield. More



Scheme 1. Synthesis of β-aminoesters using ketene diethyl acetal as enolate equivalent.

Keywords: β-Amino acid; Ketene diethylacetal; Acyl imine; Acetate enolate; Enzymic kinetic resolution.
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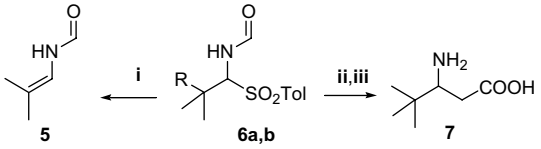
doi:10.1016/j.tetlet.2005.01.114

Table 1.

Entry	R	Base	Yield (%)	Conditions
4a	Ph	Et_3N	80	[a]
4a	Ph	DBU	48	[b]
4a	Ph	Cs_2CO_3	90	[a]
4d	4-NO_2Ph	Et_3N	77	[a]
4e	4-MeOPh	Et_3N	67	[a]
4f	4-OHPh	Et_3N	62	[a]
4g	3-Thiophenyl	Cs_2CO_3	55	[a]

[a] 6 equiv of base, 24 h, reflux.
[b] 2 equiv of base, 24 h, rt.

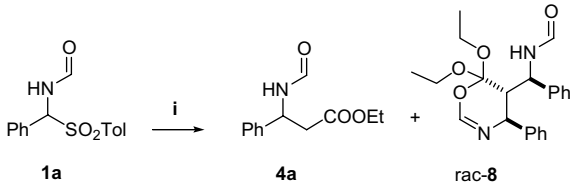


Scheme 2. Reagents and conditions: (i) Et_3N, DCHM, 24 h, 60%; (ii) Et_3N, ketene diethyl acetal, DCHM; (iii) concd. HCl, 50 °C, 5 h, 35% after two steps.

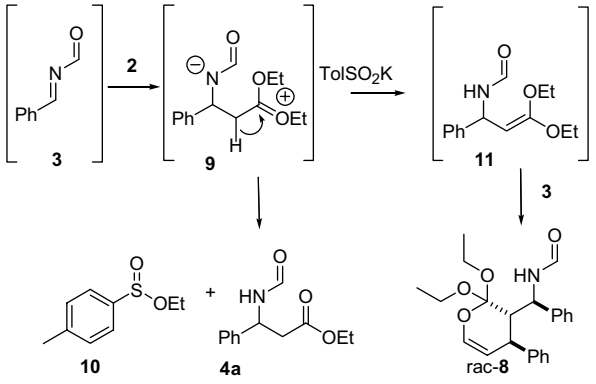
importantly, the classical Rodionov reaction is poor for both nitro- and hydroxy-substituted benzaldehydes (15–25% yield for 4-NO_2, no reaction for 4-OH). In contrast, our new reaction system works well for these substrates (Table 1). As expected, phenylsulfonyl imines derived from aliphatic aldehydes **6a** (R = H, Scheme 2) undergo elimination of phenylsulfinate to give formyl enamines **5** in about 60% yield. An exception is the pivaldehyde derived **6b** (R = Me), which gives rise to the β-amino acid analogue of *tert*-leucine **7**, albeit only in an unoptimized 35%.

An interesting insight into the mechanism of the reaction was obtained when K_2CO_3 was used as a base (Scheme 3).[7] In addition to the expected β-amino ester **4a** (10%), the major product of the reaction was **8**, isolated in 38% yield. The novel structure was elucidated by a combination of NMR methods and MS and is surprisingly present as a single diastereomer. The large coupling constant of 9.14 Hz between both ring methines is indicative of the expected diequatorial arrangement of the side chains. The conformation in the side chain is determined by a transformation to a simpler system (vide infra).

Unexpected as it may be, the formation of **8** is nevertheless mechanistically quite reasonable (Scheme 4). When the reaction is performed with a soluble base such as



Scheme 3. Reagents and conditions: (i) ketene diethyl acetal, K_2CO_3, DCHM, 24 h, reflux, 10% **4a**, 38% **8**.

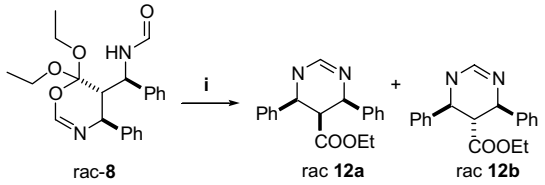


Scheme 4. Proposal mechanism of formation of *rac*-**8**.

Et_3N, the initial addition product **9** will react with a nucleophile to lead directly to the the β-amino ester **4a**. It is likely that triethylammonium phenylsulfinate acts as the nucleophile, as we have managed to isolate **10** from a reaction mixture. With K_2CO_3 as base, it is expected that the potassium phenylsulfinate is less soluble and an alternative stabilization of the intermediate **9** by the elimination of H^+ can become competitive. The resulting ketene acetal **11** can undergo a subsequent reaction with formyl imine **3** to give **8**. This condensation is novel in that this complex, and to the best of our knowledge unprecedented, heterocyclic structure is prepared in a 2 + 1 multicomponent condensation.

In order to explore the chemistry further and elucidate the relative stereochemistry of the three adjacent chiral centers, the molecule was heated with ethanolic HCl (Scheme 5). After neutralization the cyclic aminidine **12** was obtained in as a 6:4 mixture of diastereomers **12a** and **12b** in 93% yield, apparently resulting from the epimerization of the chiral center adjacent to the ethyl carboxylate group. Together with the coupling constant measured in **8**, it is possible to assign the relative stereochemistry to **8** as given. Clearly, the ease of formation of **8** and **12** and the multitude of reactions possible with these highly functionalized novel scaffold make them a promising starting material for further studies. While the chemistry constitutes an alternative to both the classical Rodionov reaction and newer methods for the preparation of β-amino acids, an enantioselective approach into this class of compounds would clearly be highly desirable.

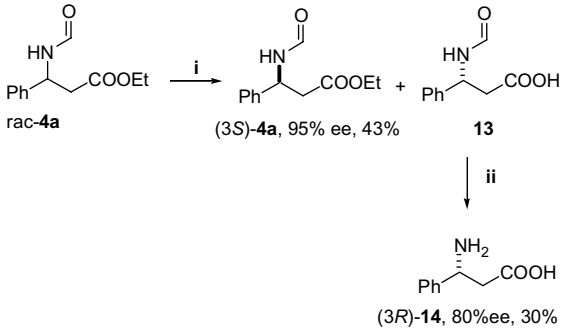
While initial attempts to induce chirality have met with very limited success, an enzymatic resolution of the for-



Scheme 5. Reagents and conditions: (i) EtOH, concd. HCl, 1.5 h, 100 °C, 93%, dr **12a**:**12b** 60:40.

Table 2. Resolution of β-aminoester **4a** with different enzymes

Enzyme	Ee (%)	Conversion (%)	*s*-Value
Esterase from hog liver	18	30	3
Chiro CLEC-CAB	16	48	2
NOVOZYM 525 L	40	30	74
SP 525	58	41	20



Scheme 6. Reagents and conditions: (i) NOVOZYM 525L, 78 h, phosphate buffer, 27 °C, pH = 7; (ii) concd. HCl, 2.5 h, 75 °C.

myl β-amino esters should be feasible. As expected, **4a** is no substrate for the acylase, but a screen of various lipases revealed partial conversion.[8] Measurement of the ee value obtained at partial conversion allowed the calculation of the *s*-values, thus giving a quick and objective comparison of the enantio-differentiating ability of the different enzymes (Table 2). The results showed that NOVOZYM 525 L, a *Candida antarctica* lipase B, is the best one found with *s*-values of about 70. A subsequent preparative run at 27 °C went to 54% conversion giving an isolated yield of 43% of (3*S*)-**4a** with 95% ee and (3*R*)-**14** with 30% unoptimized isolated yield of 80% ee (Scheme 6).

In summary, we have shown that ketene diethyl acetal can serve as an acetate enolate equivalent in a novel and apparently quite versatile formyl β-amino ester synthesis. We have demonstrated that a kinetic enzymatic resolution of this substrate is possible, thus extending this approach to the synthesis of valuable enantiomerically pure β-amino acid derivatives. Additionally, a complex 2 + 1 multicomponent reaction product is obtained in a highly diastereoselective manner by simply changing the reaction conditions.

Acknowledgements

We thank S. Merget for developing and performing the chiral assays.

Supplementary data

The supplementary data is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version, at 10.1016/j.tetlet.2005.01.114.

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5. To a solution of **1a** (0.0150 mol) in dichloromethane (70 mL) was added triethylamine (0.0900 mol, 12.5 mL) followed by diethyl ketene acetal (0.0300 mol, 3.9 mL). The resulting suspension was refluxed for 24 h. After cooling to room temperature the solution was extracted with water (two times 20 mL). The organic layer was dried over $MgSO_4$, concentrated under vacuum and the residue was purified by SiO_2 column chromatography (hexane/AcOEt 1:1) to afford **4a** as a yellowish oil, 80%. ^{1}H NMR (500 MHz, $CDCl_3$, major rotamer) δ 8.22 (s, 1H, formyl), 7.28 (m, 5H, phenyl), 6.77 (br, 1H, amide), 5.52 (m, 1H, H3),4.08 (q, J = 7.1 Hz, OCH_2), 2.89 (m, 2H, H2), 1.17 (t, J 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.1 (C1), 160.3 (formyl), 140.0 (C1′), 128.8 (C3′), 127.8 (C4′), 126.3 (C2′), 60.9 (OCH_2), 48.3 (C3), 40.0 (C2), 14.1 (CH_3).
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