Pergamon

Tetrahedron Letters 40 (1999) 4107–4110

TETRAHEDRON LETTERS

Amino Acid derived Morpholine Amides for Nucleophilic α-Amino Acylation Reactions: A New Synthetic Route to Enantiopure α-Amino Ketones

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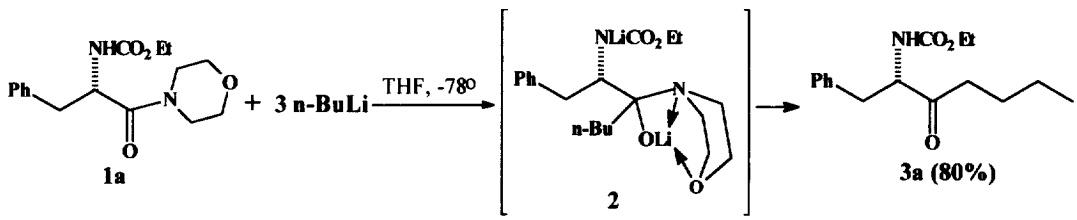
Received 5 February 1999; accepted 6 April 1999

Abstract: Nucleophilic acylation reactions of amino acid derived morpholine amides with organolithium reagents provide a new, cost-effective synthesis of enantiopure α-amino ketones.

In recent years, enantiopure α-amino ketones have received considerable attention in asymmetric synthesis. Stereoselective reductions of such ketones are finding increasing utility in the synthesis of enantiomerically pure 1,2-amino alcohols.[1,2] Thus, by starting with NH-monoprotected α-amino ketones, hydride reductions usually lead to *anti*-1,2-amino alcohols, whereas N,N-diprotected α-amino ketones, upon reduction, produce the *syn*-isomers (Felkin product), both in high de's.[2] It is important to note that, although, organometallic additions to α-amino aldehydes[3] is the prevalent synthetic route to enantiomerically pure 1,2-amino alcohols, of late, their synthesis *via* hydride reductions of α-amino ketones is getting increasing prominance, not only because it offers a stereocomplementary strategy but also because it avoids handling chemically sensitive and racemization-prone α-amino aldehydes. Enantiopure α-amino ketones also serve as key synthetic precursors to a number of biologically active heterocycles, amino sugars and deoxyazasugars.[4-6] Moreover, several peptidyl α-amino ketones show significant biological activities: inhibitors of thrombin, human heart chymase (serine protease), ICE, matrix metalloproteinase, aspartyl as well as HIV-1 proteases.[7] In view of such varied importance in synthesis and biology, there is a growing need for an efficient and broad synthetic repertoire for enantiopure α-amino ketones.

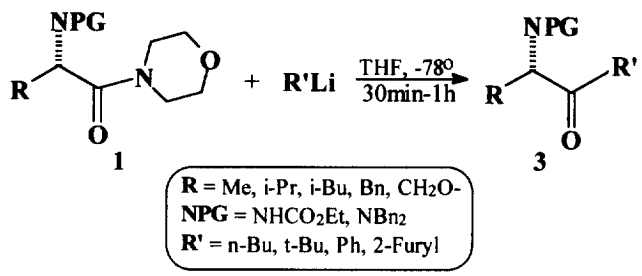
In a program directed towards stereoselective synthesis of enantiomerically pure 1,2-amino alcohols *via* hydride reductions of α-amino ketones, we were in need of a large-scale procedure for the synthesis of enantiopure α-amino ketones. The most common synthetic routes to α-amino ketones is the nucleophilic α-amino acylation reaction, where an excess of an organometallic reagent (RLi or RMgX) is reacted either with NHTos amino acids (Rapoport protocol) or better, with carboxyl-activated α-amino acid derivatives *viz.* acid chlorides, mixed anhydrides, Weinreb-amides, etc.[8] Amino acid derived Weinreb amides are the most efficient in this regard and their reactions with organometallic reagents lead to the corresponding α-amino ketones in good yields with no competition whatsoever from overadditions leading to tertiary alcohol formation.[8c] However, the high cost of MeONHMe.HCl that is required to make the Weinreb-amides and the occasional difficulties in preparing them from α-amino acids have remained severe drawbacks[9] in their application towards large-scale synthesis of α-amino ketones. For our present purpose, we therefore looked for new carboxyl-activated amino acid derivatives[10] which would be as effective as the Weinreb-amides but could be easily prepared at low cost. Towards this end, we have developed the amino acid derived morpholine amides[11] as a new class of cost-effective α-amino acylating agents and in this Letter, report on their reactions with organolithium reagents that have led to a facile new synthesis of enantiopure α-amino ketones.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00693-0



Scheme 1

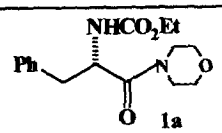
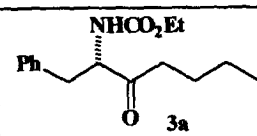
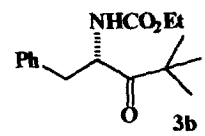
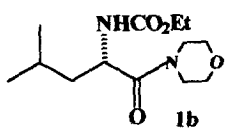
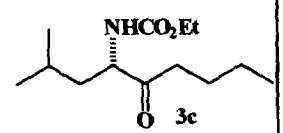
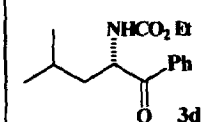
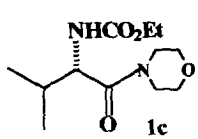
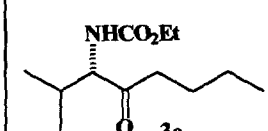
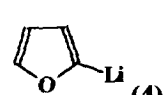
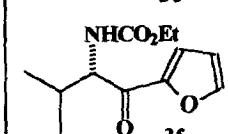
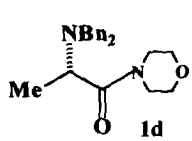
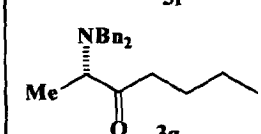
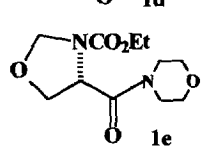
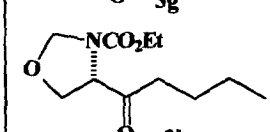
The morpholine amide **1a**[12] derived from NH-CO_2Et phenylalanine was used as the test substrate and its reaction with n-BuLi was screened under a variety of conditions. Best results were obtained with three equivalents of n-BuLi in THF at –78° which produced the α-amino butyl ketone **3a** in 80% yield within 30 mins (**Scheme 1**). Reactions carried out at higher temperatures (–40° to 0°) led to reduced yields of **3a** (*ca.* 15-25%) together with the formation of the corresponding α-amino dibutyl tertiary alcohol. Presumably, at temperatures higher than –78°, the tetrahedral intermediate **2** is not stable and liberates some of the product ketone in the medium which further reacts with n-BuLi to give the tertiary alcohol. Interestingly, the corresponding pyrrolidine amide was ineffective in this reaction, producing **3a** in only 7% yield together with 75% recovery of the starting amide. This points to the pivotal role played by the morpholine oxygen, which through electron withdrawal makes the morpholine amide more reactive towards BuLi and at the same time stabilizes the tetrahedral intermediate **2** through an extra co-ordination site for lithium.



Scheme 2

The synthetic efficacy of this reaction was then tested with a number of α-amino acid derived morpholine amides **1a-e**[12] (**Scheme 2**) and their results are collected in **Table 1**.[13] Morpholine amides derived from a wide range of α-amino acids successfully reacted with a variety of organolithium reagents to produce moderate to good yields of the corresponding α-amino ketones. Carbamate protected amides as well as those having N,N-Bn_2 protection can be used in these reactions with equally high efficacy. The reactions however were susceptible to steric hindrance, both on the part of the organolithium reagents as well as the starting amides. Similar trends have also been observed in α-amino ketone synthesis using other α-amino acylating agents.[8,10] Thus, n-BuLi reacts with the phenylalanine and leucine derived amides **1a** and **1b**, respectively, in high yields (entries 1 & 3, **Table 1**), whereas reactions of the same amides with the bulky t-BuLi or PhLi require greater than three equivalents of the organolithium reagents and gave lower yields (entries 2 & 4). The valine-amide **1c**, a particularly hindered system, also gave reduced yields of the α-amino ketones (entries 5 & 6) as did the orthogonally protected serine-amide **1e** (entry 8). It may however be noted that serinyl ketones such as **3h** are versatile synthetic intermediates for the stereoselective preparation of sphingosine, sphinganine and α-amino-β-hydroxy acids. Hence, a direct access to such ketones, as shown here, is of much synthetic value.

Table 1. Synthesis of Enantiopure α-Amino Ketones **(Scheme 2).**

Entry	α-Amino Morpholine Amides 1	Organolithium (equivs.)	α-Amino Ketones 3	Yield %
1	 1a	n-BuLi (3)	 3a	80
2	1a	t-BuLi (4)	 3b	51
3	 1b	n-BuLi (3)	 3c	75
4	1b	PhLi (4)	 3d	60
5	 1c	n-BuLi (4)	 3e	60
6	1c	 (4)	 3f	35
7	 1d	n-BuLi (2.2)	 3g	78
8	 1e	n-BuLi (1.2)	 3h	65[a]

[a]based on recovered 1e

In summary, amino acid derived morpholine amides have been developed as a new class of low-cost α-amino acylating agents. These amides react with organolithium reagents with high efficacy to provide a facile new synthetic route to enantiopure α-amino ketones.

Acknowledgements: Financial supports from DST (SP/S1/G-14/97) and JU (research fellowships to SM and DD) are gratefully acknowledged.

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12. The morpholine amides **1a-c,e** were easily prepared from N-CO_2Et α-amino acids *via* the mixed anhydride method. The amide **1d** was prepared *via* reaction of morpholine with N,N-Bn_2 alanine methyl ester.
13. Typical procedure: n-BuLi (1.5 mmol) was added dropwise to a solution of **1a** (0.5 mmol) in THF at −78°. After 30 mins, the reaction was quenched at −78° with satd. NH_4Cl soln. It was then extracted with CH_2Cl_2 and the organic layer washed with brine and dried. Removal of solvent under reduced pressure followed by silica-gel chromatography (15% EtOAc in pet. ether) gave the α-amino butyl ketone **3a** (80%) as a white crystalline solid; mp 36-38°; $[\alpha]_D^{25}$ +81.6 (*c* 1.6, $CHCl_3$); IR (nujol) : 3300, 2900, 1710, 1680, 1525, 1450, 1370 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) : 0.86 (t, 3H, J = 7.2 Hz), 1.19-1.28 (m, 5H), 1.43-1.58 (m, 2H), 2.27-2.47 (m, 2H), 2.94-3.09 (m, 2H), 4.08 (q, 2H, J = 7.2 Hz), 4.56-4.62 (m, 1H), 5.29 (br d, 1H), 7.12-7.32 (m, 5H).