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A Convenient Synthesis of Enaminones Using Tandem Acetonitrile Condensation, Grignard Addition

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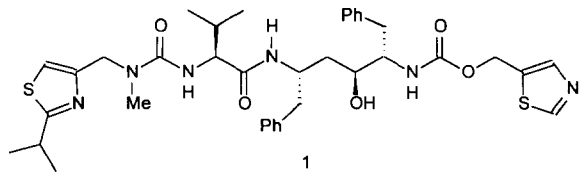
Summary: *Condensations of N,N-dibenzyl α-amino esters with the anion of acetonitrile followed by the addition of a Grignard reagent proceed in excellent yields. This affords rapid access to the peptidomimetic precursor α-amino enaminones in one pot from the esters.*

Ritonavir (Norvir®), **1**, is an HIV-1 protease inhibitor that recently received FDA regulatory approval for the treatment of HIV infection.[1] Retrosynthetically, Ritonavir requires the pseudosymmetric diaminoalcohol core unit **2**.[2] We recently reported an efficient route for the large scale synthesis of **2**.[3] This approach involves the synthesis of enaminone **5** with an asymmetric center adjacent to the carbonyl (Scheme 1). Formation of the enaminone **5a**, was accomplished by condensation of the aminoester, **3a**, with the anion of acetonitrile. The keto-nitrile, **4**, was isolated as a crystalline solid following workup. Treatment of **4** with greater than two equivalents of benzylmagnesium chloride yielded **5a**. In this communication, we report on a tandem condensation-addition to the enaminone **5a** directly from the aminoester **3a**. In addition we report on the synthetic utility and limitations of this approach to other substituted enaminones.



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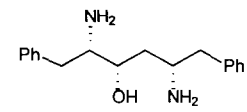
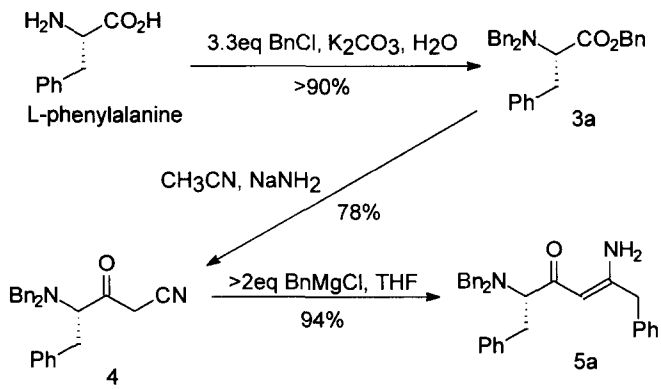


2

In our initial work, we found that temperatures of less than -50°C were necessary for the acetonitrile condensation to avoid epimerization. Presumably racemization is the result of enolization of the amino ester.[4] Attempts to perform

SCHEME 1:



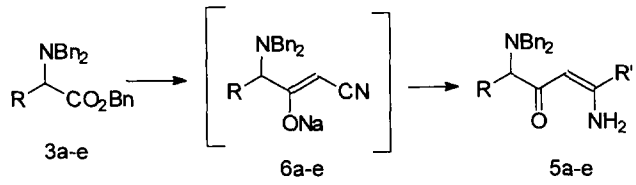
the reaction with other bases gave inferior results in our hands.[5] Returning to the sodium amide work, it was determined that a change in the solvent polarity could be used to decrease the racemization. Use of either THF/heptane solvent mixtures, or methyl-t-butyl ether (MTBE) was shown to be effective in preventing racemization at higher temperatures. Thus by adding a solution of the amino ester and 1.1 equivalents of acetonitrile in heptane/THF (2/1) to a slurry of the sodium amide in heptane/THF (2/1), the condensation could be performed at -10 to 0°C with less than 5% racemization[6] in 65-69% overall yield.[7] Replacement of the sodium amide with potassium tert-butoxide in heptane/THF (2/1) between -10 and 0°C was also shown to yield **4** without racemization, although in lower yields.

In the enaminone formation, we reasoned that the enolate-nitrile, **6a**, resulting from condensation, should react directly with the Grignard reagent (Scheme 2). In practice, addition of benzylmagnesium chloride to the condensation mixture gave erratic conversions to the desired **5a**. Reproducibility was obtained by first removing part of the THF/heptane solvent mixture from the condensation reaction mixture by vacuum distillation. This presumably removes residual ammonia (resulting from the use of sodamide). After partial distillation of the solvent, benzylmagnesium chloride was added followed by stirring for 12 hours at room temperature. Aqueous quench, workup, and crystallization gave **5a** in 65-69% isolated yield from L-phenylalanine. By performing the reaction sequence in MTBE, the overall yield was increased to 78-80%. The enantiomeric purity of **5a** was shown to be greater than 99.5% in the isolated product.[6]

Use of methyl and phenyl Grignard reagents in this procedure gave enaminones **5b** and **5c** (Table 1, entries 3 and 4).[7] Typically, the Grignard reactions were complete in under 12 hours at room temperature. The enantiomeric purities for the isolated enaminones were excellent, and the yields were also good.

The starting aminoester was varied to view the effect on the reaction. Replacing the L-phenylalanine with glycine as the starting amino acid, gave the enaminone **5d** in 46% yield from the amino ester **3d** (entry 5).[7] In the case of the ester of L-phenylglycine (**3e**), the enaminone was obtained in 89% yield.[7] The enantiomeric purity could not be determined by chiral HPLC,[6] however it appeared to have racemized based on the optical rotation.[8]

SCHEME 2:



3a-e 6a-e 5a-e

3a R=$C_6H_5CH_2$-
3d R=H-
3e R=C_6H_5-

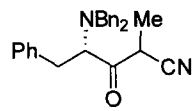
5a R=$C_6H_5CH_2$-, R'=$C_6H_5CH_2$
5b R=$C_6H_5CH_2$-, R'=CH_3-
5c R=$C_6H_5CH_2$-, R'=C_6H_5-
5d R=H, R'=$C_6H_5CH_2$-
5e R=C_6H_5-, R'=$C_6H_5CH_2$-

TABLE 1:

Entry	Ester (3)	Grignard	e.e.,% Isolated[a]	Yield %
1	L-Phe (**3a**)	BnMgCl	n.d.	65-69 (**5a**)[b,c]
2	**3a**	BnMgCl	>99.5	88 (**5a**)[c,d]
3	**3a**	MeMgCl	>99.5	65 (**5b**)
4	**3a**	PhMgCl	97.0	92 (**5c**)[c]
5	Gly (**3d**)	BnMgCl	--	46 (**5d**)
6	L-PhGly (**3e**)	BnMgCl	n.d.	89 (**5e**)

[a] Determined by chiral HPLC (Chiracel OD) relative to racemate. [b] Reaction Solvent: THF/heptane. [c] Yield based from L-phenylalanine. [d] Yield from a multikilo scale run.

Several attempts were made to use propionitrile in the initial condensation. While we were able to isolate the ketonitrile, 7, from the reaction (74%),[9] we were not able to effect the subsequent Grignard coupling either in tandem or independently. Presumably this is due to steric congestion. Treatment of the ketonitrile 7 with an alkyl lithium reagent (BuLi),[10] led only to complex reaction mixtures.



7

A typical procedure for the tandem condensation is as follows: A solution of benzylester **3a** (0.24mol) in 85ml MTBE with 27.5ml acetonitrile was slowly added to a slurry of 90% sodium amide (22.9g, 0.53mol) in 185ml MTBE

while keeping the temperature below 0°C. This was stirred 90 minutes at -5 to 0°C. Approximately 25% of the reaction volume was then removed by vacuum distillation. To the slurry was added 360ml of a benzylmagnesium chloride (1M in THF) solution.[11] This was stirred for 24 hours. The reaction was slowly quenched with 630ml water containing 120g citric acid. The aqueous was separated and the organics concentrated. The resulting enaminone was crystallized from 600ml ethanol to yield 90g (80%) of **5a**.

References and Notes:

[1] Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavanonda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Kong, X-P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W., *Proc. Natl. Acad. Sci. USA*, **1995**, *92*, 2484.

[2] For routes to **2** see: (a) Kempf, D. J.; Norbeck, D. W.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. F.; Wideburg, N. E.; Saldivar, A.; Craig-Kennard, A.; Vasavanonda, S.; Clement, J. J.; Erikson, J. In *Recent Advances in the Chemistry of Anti-infective Agents*, Cambridge Press, Cambridge, 1993, 297. (b) Baker, W. R.; Pratt, J. K., *Tetrahedron*, **1993**, *49*, 8739. (c) Rao, A. V. R.; Gurjar, M. K.; Pal, S.; Pariza, R. J.; Chorghade, M. S., *Tetrahedron Lett*, **1995**, *36*, 2505. (d) Nishikawa, M.; Murai, Y.; Onomura, O.; Ueda, Y., *Abstracts of the 15th International Congress of Heterocyclic Chemistry*, Taipei, **1995**, PO2-134. (e) Yamasaki, T.; Kumobayashi, H.; Sayo, N.; Murayama, T.; Sano, N.; Ishizaki, T., US Patent 5,523,458, 1996.

[3] (a) Stuk, T. L.; Haight, A. R.; Scarpetti, D.; Allen, M. S.; Menzia, J. A.; Robbins, T. A.; Parekh, S. I.; Langridge, D. C.; Tien, J-H. J.; Pariza, R. J.; Kerdesky, F. A. J., *J. Org. Chem.*, **1994**, *59*, 4040. (b) Stuk, T. L.; Allen, M. S.; Haight, A. R.; Reno, D. S.; Sham, H. L.; Sowin, T. J., US Patent 5,508,409, 1996. (c) Stuk, T. L.; ,Allen, M. S.; Haight, A. R.; Lijewski, L. M.; Morton, H. E.; Reno, D. S.; Sham, H. L.; Sowin, T. J., US Patent 5,565,604, 1996.

[4] The chiral purity of **3a** was >99% prior to the acetonitrile condensation. Exposure of **4** to stressed reaction conditions (room temperature/24hrs) did not cause racemization.

[5] Use of bases such as KOH, KOtBu, NaH, KHMDS, LiHMDS, led to incomplete reactions, slow conversions, or racemization.

[6] HPLC determination of enantiomeric ratios: Diacel Chiracel OD (250mmx4.6mm) column, hexane/isopropyl alcohol, 98/2 to 85/15.

[7] All synthetic materials were purified by either flash chromatography or crystallization. The structure assigned to each new compound is in accord with its infrared, 300-MHz ^{1}H NMR and 75-MHz ^{13}C NMR spectra.

[8] The optical rotation of the oil **5e** is $[\alpha]^{25}_{D}$ -0.5° (*c*=1.0, DMF). By comparison, the optical rotation of **5a** is $[\alpha]^{25}_{D}$ -147° (*c*=0.5, DMF).

[9] Isolated as a 1:1 ratio of diastereomers.

[10] Compare Hrubiec, R. T.; Smith, M. B., *J. Org. Chem.*, **1984**, *49*, 431 to Ihara, M.; Tokunaga, Y.; Fukumoto, K., *J. Org. Chem.*, **1990**, *55*, 4497

[11] Additional benzylmagnesium chloride can be added if the reaction is incomplete.

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