A Practical Synthesis of α-Amino Ketones via Aryllithium Addition to *N*-Boc-α-Amino Acids

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Received 7 May 2003

To the memory of Professor Henry Rapoport for his insight and advice while conducting this research.

Abstract: The reaction of *N*-Boc-α-amino acids with aryllithium reagents followed by removal of the nitrogen protecting group provides enantiomerically pure α-amino aryl ketones as their corresponding HCl salts. This practical two-step sequence gives rapid access to a pharmaceutically interesting class of compounds from commercially available starting materials.

Key words: arylations, amino acids, lithiation, ketones, nucleophilic additions

In drug discovery research, practicality and ease of synthesis are often important factors in the initial chemical design and SAR development of a project. With increased pressure to produce larger numbers of unique analogues in a shorter time-frame, finding chemistry amenable to rapid diversification and scalability can be crucial to the success of a medicinal chemistry project. It was during the course of investigation of a series of matrix metalloprotienase inhibitors, that we discovered that the terminal *N*-methyl amide of L-phenylalanine could effectively be replaced by the corresponding phenyl ketone (Figure 1).[1]

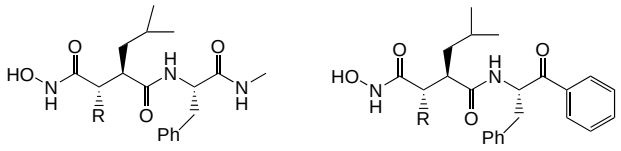
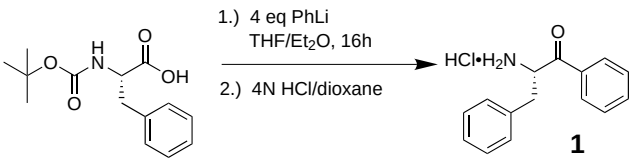


Figure 1 Structures showing terminal *N*-methyl amide group and its replacement with aryl ketone

Since α-amino ketones serve as useful precursors to a wide variety of natural products and pharmaceutically relevant compounds, a fairly large body of work exists detailing their synthesis.[2,3] N-Protected α-amino acids and their derivatives have been used as starting materials in the synthesis of α-amino ketones by addition of alkyl- and aryllithium anions, Grignard reagents, and via Friedel–Crafts chemistry.[2] All of these approaches require protection of the amine by a variety of groups (benzyloxy and methoxycarbonyl,[2b,d,4] phenylfluorenyl,[5] phenylsulfonyl,[2a] etc.), and most require fuctionalization of the carboxylate prior to the aryl addition reaction (acid chloride,[2c,d,5] morpholine amide,[6] imidazolide,[7] hemi-acetal,[8] isoxazolidide,[9] Weinreb amide,[10] etc.). Due to the instability of *tert*-butyl carbamates in the presence of highly nucleophilic bases,[11] very little has been described utilizing the large number of commercially available *N*-Boc-α-amino acids as precursors to α-amino ketones. Work done by Rapoport[2d] in the early 80's and Pace and Kabalka,[12] in the mid-90's did show that this transformation was feasible, but still largely unexplored. Taking the precedent from these early examples, we sought a way to develop the chemistry into a rapid and efficient way of obtaining a unique set of pharmaceutically interesting precursors.

Initial experiments began with the slow addition of 4 equivalents of cold (–78 °C) phenyllithium in diethyl ether to a solution of *N*-Boc-L-phenylalanine at –78 °C in THF, and warming to room temperature overnight (Equation 1). The purified *N*-Boc-amine of **1** was then deprotected to give an initial 7% yield of **1**. It was observed that when using THF as solvent or co-solvent, yields were consistently lower. Incorporating a combination of anhydrous diethyl ether as the lone solvent, carefully controlling the reaction times (1–2 h) and temperatures (–78 °C, then warming to 0 °C) a greatly improved 57% yield of **1** could be obtained, after deprotection, with minimal racemization.[1] Presumably, the presence of the adjacent negative charge on the carbamate nitrogen under the reaction conditions blocks potential enolization of the α-center, protecting the stereochemical integrity of the amino ketone.[2d]



Equation 1

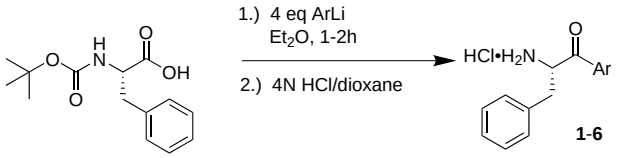
From a practical standpoint, this chemistry requires no special precautions, and can be run on multi-gram scale. The isolation of the intermediate *N*-Boc-amino ketone is accomplished via silica plug or quick column chromatography, and treating the resulting material with 4 N HCl/dioxane for several hours. The amino ketone **1**, as its

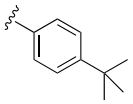
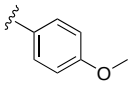
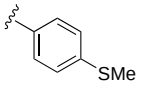
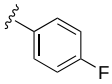
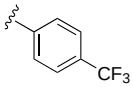
Synthesis 2003, No. 11, Print: 05 08 2003.
Art Id.1437-210X,E;2003,0,11,1653,1656,ftx,en;C02603SS.pdf.

corresponding HCl salt, was precipitated out of solution with diethyl ether, filtered and dried as a white solid.

With the reaction conditions made more efficient and higher yielding, we sought to explore the scope of the reaction with regard to substitution on aryllithium as well as the generality of the amino acid partner. A survey of a variety of substitutions on the aryllithium showed that both electron-releasing and -withdrawing groups in the *para* position are well tolerated and seem to have only a minor effect on the overall yield of the reaction with *N*-Boc-L-phenylalanine (Table 1).

Table 1 Formation of Aryl Ketones from *N*-Boc-L-phenylalanine



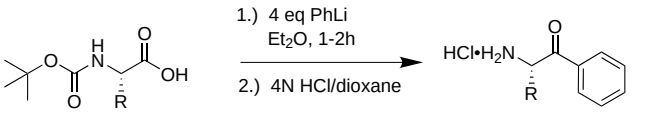
Product	Ar	Yield (%)	ee (%)
1		57	>99
2		55	>99
3		54	>99
4		50	>99
5		42	>99
6		47	>99

To further explore the scope of the chemistry, a variety of *N*-Boc-amino acids were reacted with phenyllithium under the standard reaction conditions. Not surprisingly, it was found that with increasing size at the α-position, especially with respect to β-branching (products **11**–**13**), a dramatic drop in yield of the corresponding phenyl ketone was observed (Table 2).

All reactions were run on a 500 mg to one gram scale, and in the case of **7**, the reaction was scaled up to provide 30 g in 55% yield.[13]

During the course of our medicinal chemistry research, most of the amino ketones were coupled directly to a variety of enantiopure succinic acids (Figure 2). NMR analysis of the corresponding amide products did not provide evidence of diastereomer formation. The stereochemical integrity of the amino ketones was also verified by chiral

Table 2 Preparation of Phenyl Ketones from *N*-Boc-Amino Acids



Product	R	Yield (%)	ee (%)
1	CH_2Ph	57	>99
7	CH_2PhOBu-*t*[a]	60	>99
8	Me	63	>99
9	Et	63	>99
10	$CH_2C_6H_{11}$	58	>99
11	CH_2CHMe_2	39	>99
12	$CH(Me)CH_2Me$	30	>99
13	*t*-Bu	12	>99

[a] Isolated as the free phenol.

HPLC analysis,[14] and all were found to be in excellent enantiomeric excess.

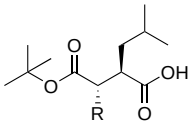


Figure 2 Structure of an enantiopure succinic acid

We feel that we have demonstrated that a series of pharmaceutically useful precursors can be quickly and efficiently synthesized, from commercially available materials, in multi-gram quantity, with excellent enantiomeric purity.

Aryl Ketones from *N*-Boc-Amino Acids; General Procedure

To a 0 °C solution of *n*-BuLi (4 equiv, 20 mmol, 2.5 M/hexanes) in Et_2O (15 mL), was added neat aryl bromide (4.1equiv, 20.5 mmol) over 2–3 min. The solution was allowed to stir at 0 °C for 25 min and added, via cannula, to a cold –78 °C solution of *N*-Boc-amino acid (5 mmol) in Et_2O (100 mL). The resulting solution was held at –78 °C for 25 min, then warmed to 0 °C over 1–2 h, then quenched with H_2O. The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organic layers were washed with brine (25mL), dried ($MgSO_4$) and concentrated in vacuo. The *N*-Boc-amino ketone was isolated by flash chromatography or silica plug (typically 9:1 hexane–EtOAc), which was immediately treated with 4 N HCl/dioxane for 2–8h, then diluted with Et_2O. The corresponding HCl salt was collected via filtration and dried in high vacuum for 16 h.

(*S*)-2-Amino-1,3-diphenylpropan-1-one Hydrochloride (1)

Yield: 2.55 g (57%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.58 (br s, 2 H), 7.99–7.95 (d, 1 H, *J* = 8.7 Hz), 7.73–7.66 (t, 1 H, *J* = 8.6 Hz), 7.55–7.47 (t, 1 H, *J* = 8.7 Hz),

7.30–7.09 (m, 5 H), 5.44–5.37 (t, 1 H, *J* = 7.5 Hz), 3.20–3.15 (d, 2 H, *J* = 7.5 Hz).

MS (ESI): *m*/*z* = 226 (M + H).

Anal. Calcd for $C_{15}H_{16}ClNO$: C, 68.84; H, 6.01; N, 5.37. Found C, 68.83; H, 6.16; N, 5.35.

(*S*)-2-Amino-1-(4-*tert*-butylphenyl)-3-phenylpropan-1-one Hydrochloride (2)
Yield: 0.98 g (55%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.43 (s, 2 H), 7.94–7.91 (d, 2 H, *J* = 8.5 Hz), 7.57–7.54 (d, 2 H, *J* = 8.5 Hz), 7.32–7.12 (m, 5 H), 5.40–5.32 (t, 1 H, *J* = 7.4 Hz), 3.20–3.11 (m, 2 H), 1.32 (s, 9 H).

MS (ESI): *m*/*z* = 282 (M + H).

Anal. Calcd for $C_{18}H_{24}ClNO$: C, 70.68; H, 7.90; N, 4.57. Found: C, 70.60; H, 7.79; N, 4.50.

(*S*)-2-Amino-1-(4-methoxyphenyl)-3-phenylpropan-1-one Hydrochloride (3)
Yield: 0.76 g (54%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.56 (s, 2 H), 7.97–7.94 (d, 2 H, *J* = 9.2 Hz), 7.26–7.19 (m, 3 H), 7.14–7.12 (m, 2 H), 7.05–7.02 (d, 2 H, *J* = 8.1 Hz), 5.36–5.31 (t, 1 H, *J* = 6.1 Hz), 3.85 (s, 3 H), 3.19–3.16 (d, 2 H, *J* = 6.4 Hz).

MS (ESI): *m*/*z* = 256 (M + H).

Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.21; N, 4.80. Found: C, 65.62; H, 6.19; N, 4.67.

(*S*)-2-Amino-1-(4-methylsulfanylphenyl)-3-phenylpropan-1-one Hydrochloride (4)
Yield: 0.52 g (50%); off-white solid.

^{1}H NMR (DMSO-d_6): δ = 8.35 (s, 2 H), 7.91–7.81 (m, 2 H), 7.41–7.35 (m, 2 H), 7.30–7.19 (m, 3 H), 7.18–7.06 (m, 2 H), 5.42–5.35 (m, 1 H), 3.21–3.05 (m, 2 H), 2.60–2.42 (m, 3 H).

MS (ESI): *m*/*z* = 272 (M + H).

Anal. Calcd for $C_{16}H_{18}ClNO$: C, 62.43; H, 5.89; N, 4.55. Found: C, 62.21; H, 5.89; N, 4.37.

(*S*)-2-Amino-1-(4-fluorophenyl)-3-phenylpropan-1-one Hydrochloride (5)
Yield: 0.66 g (42%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.47 (s, 2 H), 8.06–8.01 (m, 2 H), 7.37–7.31 (t, 2 H, *J* = 7 Hz), 7.23–7.11 (m, 5 H), 5.41–5.35 (t, 1 H, *J* = 7.4 Hz), 3.15–3.12 (m, 2 H).

MS (ESI): *m*/*z* = 244 (M + H).

Anal. Calcd for $C_{15}H_{15}ClFNO$: C, 64.40; H, 5.40, N, 5.00. Found: C, 64.33; H, 5.33; N, 5.02.

(*S*)-2-Amino-3-phenyl-1-(4-trifluoromethylphenyl)propan-1-one Hydrochloride (6)
Yield: 0.94 g (47%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.71 (s, 2 H), 8.13–8.10 (d, 2 H, *J* = 8.4 Hz), 7.87–7.84 (d, 2 H, *J* = 8.5 Hz), 7.23–7.10 (m, 5 H), 5.50–5.46 (t, 1 H, *J* = 7.6 Hz), 3.27–3.11 (m, 2 H).

MS (ESI): *m*/*z* = 294 (M + H).

Anal. Calcd for $C_{16}H_{15}ClF_3NO$: C, 58.27; H, 4.58; N, 4.24. Found: C, 58.14; H, 4.60; N, 4.02.

(*S*)-2-Amino-3-(4-hydroxyphenyl)-1-phenylpropan-1-one Hydrochloride (7)
Yield: 1.5 g (60%); white solid.

^{1}H NMR (DMSO-d_6): δ = 9.4 (s, 1 H), 8.42 (s, 2 H), 7.99–7.97 (d, 2 H, *J* = 8.5 Hz), 7.72–7.68 (t, 1 H, *J* = 7.5 Hz), 7.57–7.52 9 (t, 2 H, *J* = 7.8 Hz), 6.91–6.89 (d, 2 H, *J* = 8.4 Hz), 6.63–6.60 (d, 2 H, *J* = 8.5 Hz), 5.33–5.50 (t, 1 H, *J* = 7.4 Hz) 3.07–3.02 (m, 2 H).

MS (ESI): *m*/*z* = 242 (M + H), 240 (M – H).

Anal. Calcd for $C_{15}H_{16}ClNO_2$: C, 64.86; H, 5.80; N, 5.04. Found: C, 64.75; H, 5.74; N, 4.99.

(*S*)-2-Amino-1-phenylpropan-1-one Hydrochloride (8)
Yield: 0.62 g (63%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.43 (s, 2 H), 8.08–8.04 (d, 2 H, *J* = 7.4 Hz), 7.77–7.72 (t, 1 H, *J* = 7.8 Hz), 7.63–7.58 (t, 2 H, *J* = 7.6 Hz), 5.20–5.10 (q, 1 H, *J* = 7.5, 7.6 Hz), 1.43–1.41 (d, 3 H, *J* = 7.1 Hz).

MS (ESI): *m*/*z* = 150 (M + H).

Anal. Calcd for $C_9H_{12}ClNO$: C, 58.22; H, 6.51; N, 7.54. Found: C, 58.12; H, 6.50; N, 7.48.

(*S*)-2-Amino-1-phenylbutan-1-one Hydrochloride (9)
Yield: 0.93 g (63%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.56 (s, 2 H), 8.08–8.05 (d, 2 H, *J* = 7.1 Hz), 7.77–7.71 (t, 1 H, *J* = 7.5 Hz), 7.62–7.57 (t, 2 H, *J* = 7.0 Hz), 5.13–5.10 (m, 1 H), 2.10–1.78 (m, 2 H), 0.88–0.83 (t, 3 H, *J* = 7.4, 7.5 Hz).

MS (ESI): *m*/*z* = 164 (M + H).

Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.06; N, 7.01. Found: C, 60.11; H, 7.12; N, 6.88.

(*S*)-2-Amino-3-cyclohexyl-1-phenylpropan-1-one Hydrochloride (10)
Yield: 0.83 g (58%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.44 (s, 2 H), 7.99–7.97 (d, 2 H, *J* = 7.6 Hz), 7.77–7.72 (t, 1 H, *J* = 7.4 Hz), 7.64–7.59 (t, 2 H, *J* = 7.7 Hz), 5.16 (m, 1 H), 2.00–1.96 (m, 1 H), 1.65–1.50 (m, 7 H), 1.20–0.84 (m, 5 H).

MS (ESI): *m*/*z* = 232 (M + H).

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.24; H, 8.20; N, 5.20.

(*S*)-2-Amino-4-methyl-1-phenylpentan-1-one Hydrochloride (11)
Yield: 0.57 g (39%); white solid.

^{1}H NMR (DMSO-d_6): δ = 8.49 (s, 2 H), 8.01–7.92 (d, 2 H, *J* = 7.6 Hz), 7.77–7.73 (t, 1 H, 7.6 Hz), 7.64& ndash;7.59 (t, 2 H, *J* = 7.5 Hz), 5.13–5.08 (m, 1 H), 1.82–1.54 (m, 3 H), 1.00–0.98 (d, 3 H, *J* = 6.4 Hz), 0.83–0.81 (d, 3 H, *J* = 6.6Hz)

MS (ESI): *m*/*z* = 192 (M + H).

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.28; H, 7.96; N, 6.15. Found: C, 63.10; H, 7.85; N, 5.99.

(*S*)-2-Amino-3-methyl-1-phenylpentan-1-one Hydrochloride (12)
Yield: 0.3 g (30%); off-white solid.

^{1}H NMR (DMSO-d_6): δ = 8.32 (s, 2 H), 8.06–8.03 (d, 2 H, *J* = 7.3 Hz), 7.75–7.71 (t, 1 H, *J* = 7.4 Hz), 7.63–7.58 (t, 2 H, *J* = 7.5 Hz), 5.12–5.10 (m, 1 H), 1.99–1.85 (m, 1 H), 2.3–2.05 (m, 1 H), 0.98–0.96 (d, 3 H, *J* = 6.7 Hz), 0.78–0.73 (t, 2 H, *J* = 7.5 Hz).

MS (ESI): *m*/*z* = 192 (M + H).

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.28; H, 7.96; N, 6.15. Found: C, 63.21; H, 7.90; N, 6.12.

(*S*)-2-Amino-3,3-dimethyl-1-phenylbutan-1-one Hydrochloride (13)

Yield: 0.1 g (12%); off-white solid.

^{1}H NMR (DMSO-d_6): δ = 8.32 (s, 2 H), 8.10–8.08 (d, 2 H, *J* = 7.7 Hz), 7.81–7.74 (t, 1 H, *J* = 7.6 Hz), 7.61–7.59 (t, 2 H, *J* = 7.5 Hz), 5.04 (s, 1 H), 0.93 (s, 9 H).

MS (ESI): *m*/*z* = 192 (M + H).

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.28; H, 7.96; N, 6.15. Found: C, 63.27; H, 7.91; N, 6.09.

Acknowledgment

Thanks to Professor Peter Beak, Dr. Michael Curtin and the late Professor Henry Rapoport for helpful discussions regarding this research, and Mark Mullaly of the High-Throughput Purification group for most of our chiral HPLC analysis.

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