Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8505–8506
Tetrahedron Letters

A simple route to β-aminomethylketones

Stefan Zawadzki* and Andrzej Zwierzak

Institute of Organic Chemistry, Technical University (Politechnika), Żeromskiego 116, 90-924 Łódź, Poland

Received 28 July 2004; revised 8 September 2004; accepted 16 September 2004
Available online 5 October 2004

Abstract—A simple procedure leading to β-aminomethylketones has been developed. The procedure involves base-catalyzed Michael-type addition of sodium *t*-butyl acetoacetate to *N*-Boc imines generated in situ followed by hydrolysis and decarboxylation of the adducts.

β-Aminoketones are of interest in view of their biological activity and application as building blocks in the preparation of many nitrogen-containing heterocyclic compounds.[1] While β-aminoketones substituted at nitrogen are easily accessible by Mannich reactions,[1a] for compounds with a free amino function only a few methods are available. The hitherto reported procedures include: synthesis via phthalimido derivatives,[2] addition of ammonia to α,β-unsaturated ketones,[3] addition of alkylmagnesium reagents to benzoylacetonitrile,[4] reduction of diimines with $LiAlH_4$ followed by hydrolysis,[5] hydrolysis of tetrahydropyrimidines,[6] reduction of isoxazoles,[7] and decomposition of β-isothiocyanatoketones by heating with concd HCl.[8] In the last few years substantial progress has been made with the enantioselective versions of Mannich-type reactions leading to various *N*-substituted β-aminoketones.[9,10]

In the course of our studies on potential applications of α-amidoalkyl-*p*-tolyl sulfones **1** as *N*-Boc imine equivalents **3**, we found that sodium hydride can be used for base-induced elimination of *p*-toluenesulfonic acid from **1**. Michael-type addition of sodium *t*-butyl acetoacetate to *N*-Boc imines **3** thus generated affords (after quenching with aq NH_4Cl) the corresponding adducts **4** in almost quantitative yields and spectroscopic purity. The crude adducts **4** on reflux with 10% aq HCl undergo easy deprotection followed by decarboxylation to give analytically pure β-aminomethylketone hydrochlorides **5** in high yields.[11]

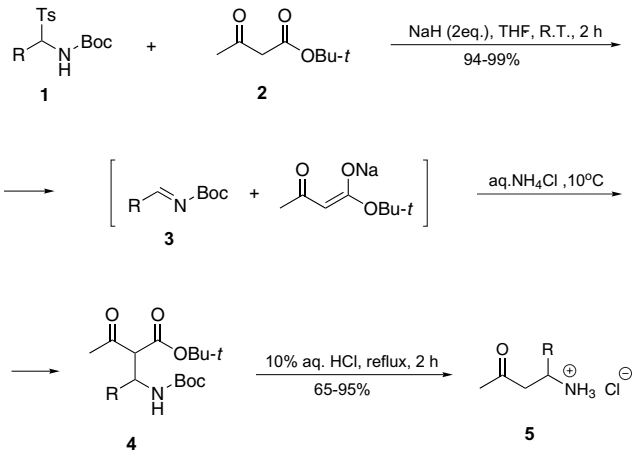
Similar addition/decarboxylation of methyl acetoacetate to *N*-benzoyl glyoxylic imines, leading to protected β-aminoketones has been reported previously.[12]

The following typical experimental procedure was used. Sodium hydride (0.24 g, 10 mmol) was added with stirring to a solution of α-amidoalkyl-*p*-tolyl sulfone **1**[13] (5 mmol) in THF (30 mL) for ca. 10 min. Then, *t*-butyl acetoacetate **2** (0.79 g, 5 mmol) dissolved in THF (10 mL) was slowly added dropwise. The resulting mixture was stirred at room temperature for 2 h, cooled to 10 °C, and quenched with satd aq NH_4Cl (25 mL). The organic layer was separated and the aqueous phase extracted with ether (10 mL). The combined organics were dried over $MgSO_4$ and evaporated to give pure (^1H NMR) adducts **4** as colourless, syrupy oils. The crude adducts **4** were treated with 10% aq HCl (15 mL) and refluxed with efficient stirring for 2 h (Scheme 1). Water and an excess of HCl were then evaporated, the residue dissolved in water (20 mL), heated over ca. 10 min with a small amount of powdered activated charcoal (Fluka), filtered and evaporated to dryness to give β-aminomethylketone hydrochlorides **5a**–**g** as oily liquids. Compound **5a**–**g** thus prepared were analytically pure. Some of them crystallized slowly and could then be recrystallized from EtOH–ether. Yields and mps of **5a**–**g** are compiled in the Table 1.

The outlined procedure for the synthesis of β-aminomethylketones represents a simple and economic approach to these compounds from easily available starting materials.

Keywords: α-Amidoalkyl-*p*-tolyl sulfones; *N*-Boc imines; *t*-Butyl acetoacetate; Decarboxylation.
* Corresponding author. Tel.: +48 42 6313143; fax: +48 42 6365530; e-mail: zawadzsp@mail.p.lodz.pl

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.122



Scheme 1.

Table 1. β-Aminomethylketone hydrochlorides **5**[a]

Entry	R	Yield (%)[b]	Mp (°C)
a	H	86	Oil
b	Me	95	131–133 (129–130)[c]
c	Et	75	73–75[c]
d	Pr	77	Oil
e	*i*-Pr	82	Oil
f	Ph	66	Oil
g	*p*-MeO–C_6H_4	65	140–143[c]

[a] All compounds were fully characterized by analytical and spectroscopic methods.
[b] Yields of crude, analytically pure products.
[c] Crystallized from EtOH–Et_2O. Literature[8] mp is given in parentheses.

References and notes

1. (a) Mayer, D. In *Houben-Weyl Methoden der Organischen Chemie*, 4th ed.; Müller, E., Ed.; Georg Thieme: Stuttgart, 1977; Vol. VII/2c, pp 2251–2307; (b) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 893; (c) Arend, M.; Wastermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1044–1070; (d) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–1837.
2. For example: (a) Gabriel, S.; Colman, J. *Ber.* **1909**, *42*, 1243–1249; (b) Hale, W. J.; Britton, E. C. *J. Am. Chem. Soc.* **1919**, *41*, 841–847; (c) McKenzie, A.; Barrow, F. *J. Am. Chem. Soc.* **1921**, *119*, 69–76; (d) Davies, R. E.; Powell, G. *J. Am. Chem. Soc.* **1945**, *67*, 1466–1468; (e) Lutz, R. E.; Wilson, J. W.; Deinet, H. J.; Harnest, G. H.; Martin, T. A.; Freek, J. K. *J. Org. Chem.* **1947**, *12*, 96–107.
3. For example: (a) Everest, A. E. *J. Chem. Soc.* **1919**, *115*, 588–592; (b) Smith, M. E.; Adkins, H. *J. Am. Chem. Soc.* **1938**, *60*, 407–409; (c) Barry, J. E.; Finkelstein, M.; Ross, S. D.; Uebel, J. J. *Tetrahedron* **1978**, *34*, 3401–3404.
4. Rehberg, C. E.; Henze, H. R. *J. Am. Chem. Soc.* **1941**, *63*, 2785–2789.
5. Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1983**, *48*, 2255–2259.
6. Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A. L. *J. Org. Chem.* **1992**, *57*, 1219–1223.
7. Büchi, G.; Vederas, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 9128–9132.
8. Ignatova, L. A.; Kazantsev, Yu. E.; Unkovskii, B. V. *Zh. Org. Khim.* **1969**, *5*, 1792–1794.
9. Enders, D.; Oberbörsch, S. *Synlett* **2002**, 471–473, and references cited therein.
10. Enders, D.; Oberbörsch, S.; Adam, J. *Synlett* **2000**, 644–646.
11. Selected spectroscopic data for compounds **5a**–**g**. Compound **5a**: ^{1}H NMR (250 MHz, D_2O): 2.25 (3H, s, CH_3), 3.02 (2H, t, J = 6.1 Hz, CH_2), 3.22 (2H, br t, J = 6.1 Hz, CH_2). ^{13}C NMR (63 MHz, D_2O): 28.2, 32.9, 37.7, 209.5. MS/CI: 88 (M_K), 71 (M_K-NH_3). Compound **5b**: ^{1}H NMR (250 MHz, D_2O): 1.31 (3H, d, J = 6.7 Hz, CH_3), 2.23 (3H, s, CH_3), 2.93 (1H, dd, J = 8.2, 19.0 Hz, CH_2), 3.01 (1H, dd, J = 4.7, 19.0 Hz, CH_2), 3.60–3.81 (1H, m, CH). ^{13}C NMR (63 MHz, D_2O): 20.3, 32.2, 46.2, 48.7, 214.1. MS/CI: 102 (M_K), 85 (M_K-NH_3). Compound **5c**: ^{1}H NMR (250 MHz, D_2O): 0.96 (3H, t, J = 7.5 Hz, CH_3–CH$_2$), 1.68 (2H, dq, J = 7.5 Hz, CH$_3$–CH_2), 2.25 (3H, s, CH_3), 2.90 (1H, dd, J = 8.6, 19.2 Hz, CH_2), 3.09 (1H, dd, J = 4.0, 19.2 Hz, CH_2), 3.50–3.65 (1H, m, CH). ^{13}C NMR (63 MHz, D_2O): 7.4, 23.4, 28.3, 41.9, 47.1, 209.7. MS/CI: 116 (M_K), 99 (M_K-NH_3). Compound **5d**: ^{1}H NMR (250 MHz, D_2O): 0.92 (3H, t, J = 7.2 Hz, CH_3–CH$_2$–CH$_2$), 1.37 (2H, 6 hex, J = 7.2 Hz, CH$_3$–CH_2CH$_2$), 1.53–1.70 (2H, m, CH$_3$–CH$_2$–CH_2), 2.24 (3H, s, CH_3), 2.90 (1H, dd, J = 8.4, 19.2 Hz, COCH_2), 3.08 (1H, dd, J = 4.0, 19.2 Hz, COCH_2), 3.55–3.70 (1H, m, CH). ^{13}C NMR (63 MHz, D_2O): 11.7, 16.3, 28.5, 32.3, 42.7, 45.6, 209.3. MS/CI: 130 (M_K), 113 (M_K-NH_3). Compound **5e**: ^{1}H NMR (250 MHz, D_2O): 0.96, 0.98 (6H, 2d, J = 6.6 Hz, (CH_3)$_2$CH), 1.98 (1H, 8 lines, J = 6.6 Hz, (CH$_3$)$_2$CH), 2.25 (3H, s, CH_3), 2.87 (1H, dd, J = 9.4, 19.3 Hz, CH_2), 3.09 (1H, dd, J = 3.1, 19.3 Hz, CH_2), 3.45–3.56 (1H, m, CH). ^{13}C NMR (63 MHz, D_2O): 15.5, 16.0, 28.0, 28.3, 39.9, 50.7, 209.7. MS/CI: 130 (M_K), 113 (M_K-NH_3). Compound **5f**: ^{1}H NMR (250 MHz, D_2O): 2.24 (3H, s, CH_3), 3.39 (2H, d, J = 6.9 Hz, CH_2), 7.46 (5H, br s, C_6H_5), CH signal hidden under D_2O. ^{13}C NMR (63 MHz, D_2O): 28.0, 44.1, 49.0, 125.4, 127.7, 127.8, 133,7, 208.5. MS/CI: 164 (M_K), 147 (M_K-NH_3). Compound **5g**: ^{1}H NMR (250 MHz, D_2O): 2.24 (3H, s, CH_3CO), 3.37 (2H, d, J = 7.0 Hz, CH_2), 3.85 (3H, s, OCH_3), 4.77 (1H, t, J = 7.0 Hz, CH), 7.00–7.48 (4H, m, C_6H_4). ^{13}C NMR (63 MHz, D_2O): 27.9, 44.0, 48.5, 53.7, 112.9, 113.2, 126.2, 127.1, 127.5, 208.6. MS/CI: 194 (M_K), 177 (M_K-NH_3).
12. Ben-Ishai, D.; Altman, J.; Bernstein, Z.; Peled, N. *Tetrahedron* **1978**, *34*, 467–473, and references cited therein.
13. Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, *43*, 1079–1080.