Chemistry of Heterocyclic Compounds, Vol. 31, No. 8, 1995

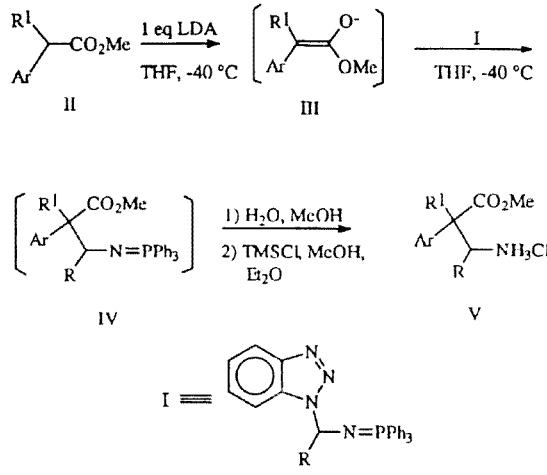
A CONVENIENT ONE-POT PREPARATION OF METHYL α-ARYL-β-PRIMARYLAMINO ALKANOATES*

A. R. Katritzky, O. Lingibe, and B. Yang

Six examples of α-aryl-β-primarylamino esters (V) were synthesized by a convenient one-pot methodology, i.e., reaction of lithiated methyl α-aryl-acetates with 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (BETMIP) followed by hydrolysis.

β-Aminoesters are an important class of organic compounds with diverse biological activity [1-3]. Methods for the preparation of β-aminoesters include (i) Michael addition of nitrogen nucleophiles to α,β-unsaturated esters, acids, or nitriles [4-6]; (ii) nucleophilic addition of a carbanion or enolate anion to C=N- and cyano groups [7-11]; (iii) Arndt-Eistert homologation of N-protected α-amino acids [12]; (iv) ring-opening of β-lactams [13]. Recently, Mitani *et al.* reported that β-aminoesters could be prepared from ethyl azidoformate and 1-alkoxy-1-siloxycyclopropanes [14]. Treatment of N-(acetyl)thioamide with methyl (triphenylphosphoranyliden)acetate followed by hydrogenation then hydrolysis afforded β-aminoesters [15]. Recent reports from our group detailing the synthesis of β-aminoesters involved the reaction of organozinc reagents [16] or ketene silyl acetals [17] with N-(alkylamino)benzotriazoles giving various tertiary or secondary β-aminoesters in good yields.

1-(Triphenylphosphoroylideneaminomethyl)benzotriazole, BETMIP, with the good benzotriazole leaving group and a protected amino group, has been shown to be a convenient $+CH_2NH_2$ synthon equivalent for introducing primary-aminomethyl groups [18-21]. We now report our recent results on the synthesis of β-aminoesters using BETMIP.



*Submitted in honor of the 60th anniversary of Professor Nikolai S. Zefirov, an outstanding Russian chemist and a good friend, by Alan R. Katritzky.

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, USA. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1023-1025, August, 1995. Original article submitted July 3, 1995.

 0009-3122/95/3108-0890$12.50

TABLE 1. Preparation of β-Aminoester Hydrochlorides V

Compound	Ar	R^1	R	Yield, %	mp, °C
Va	Ph	H	H	78	198-201 [23]
Vb	Ph	Ph	H	75	226-227
Vc	3-MePh	H	H	80	154-155
Vd	2-Naph	H	H	87	242-243
Ve	3,4-DiMeOPh	H	H	82	200-201
Vf	Ph	H	Me	76	205-207

α-Arylacetate II was lithiated with one equivalent of LDA under argon at −40°C to form the enolate III, which was reacted with BETMIP eliminating benzotriazole to generate the intermediate IV, which after hydrolysis afforded the β-aminoester hydrochloride salts V in good yields.

However, when analogous α-alkylacetates were used in this reaction, no products were obtained even after adding HMPA to coordinate with the lithium and enhance the nucleophilic ability, or zinc bromide to assist benzotriazolyl displacement. Presumably, the enolates III of α-alkylacetates are not as stable as those of α-arylacetates. When dimethyl malonate and methyl α-cyanoacetate were used as starting materials, no reaction was observed. This may be due to the weak nucleophilicity of the corresponding α-carbanion.

In conclusion, a new method for the preparation of α-aryl-β-primarylamino esters from α-arylesters in good yields has been developed, based on the facile replacement of the benzotriazole group in BETMIP with an α-arylenolate anion.

EXPERIMENTAL

Melting points were measured with a Kofler Hot Stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a VXR-300 spectrometer at 300 MHz and 75 MHz, respectively, in D_2O and D_2O-DMSO-d_6. D_2O [δ = 4.80] was used as an internal reference for ^1H NMR spectra, and the central line of DMSO [δ = 39.5] as the reference for ^{13}C NMR spectra. Elemental analyses were performed on a Carlo Erba-1106 instrument at our university. THF was freshly distilled from a sodium benzophenone ketyl immediately prior to use. BETMIP (I) is readily available in our lab [19]. 1-[α-(Triphenylphosphoranylideneamino)ethyl]benzotriazole was prepared *in situ* [22].

One-pot Preparation of Methyl α-Aryl-β-primarylamino Alkanoates (V); General Procedure. To a solution of a methyl α-aryl ester II (5 mmole) in dry THF (30 ml), LDA (5 mmole, 1.5 M in hexane, 3.4 ml) was added at −40°C under argon. The resulting clear yellow solution was stirred at this temperature for 1 h, before a solution of BETMIP I (2.01 g, 5 mmol) in THF (20 ml) was added in one portion. The reaction mixture was stirred overnight and the temperature was allowed to rise slowly to room temperature. The organic solution was washed with KOH aq. solution (1 M, 60 ml), and water (60 ml) and then dried over $MgSO_4$. After removal of the solvent, the yellow oil was diluted with methanol (20 ml) and hydrolyzed with water (15 mmol, 0.27 g) for 15 h at room temperature. The solvent was then removed and the orange residue was dissolved in Et_2O (40 ml), and treated with methanol (10 mmol, 0.32 g) followed by trimethylsilyl chloride (10 mmol, 1.05 g) under argon. The solution was stirred for 10 min during which time a white solid formed which was filtered, washed with Et_2O and dried under vacuum. This white salt was purified by recrystallization from ethyl acetate and methanol.

Methyl 3-Amino-2-phenylpropionate Hydrochloride (Va) [23]. ^1H NMR (D_2O): 3.43 (1H, dd, J = 7.5, 13.2 Hz), 3.68 (1H, dd, J = 7.5, 13.2 Hz), 3.74 (3H, s), 4.16 (1H, overlapping dd, J = 7.5, 7.5 Hz), 7.35-7.40 (2H, m), 7,44-7.55 (3H, m). ^{13}C NMR (D_2O-DMSO-d_6): 42.3, 49.9, 54.5, 129.6, 130.3, 131.0, 135.7, 174.4. Found, %: C 55.37; H 6.49; N 6.34. $C_{10}H_{13}NO_2 \cdot HCl$. Calculated, %: C 55.69; H 6.54; N 6.49.

Methyl 3-Amino-2-diphenylpropionate Hydrochloride (Vb). ^1H NMR (D_2O): 3.84 (3H, s), 4.08 (2H, s), 7.20-7.30 (4H, m), 7.32-7.44 (6H, m). ^{13}C NMR (DMSO-d_6): 44.5, 53.1, 58.7, 127.8, 128.4, 128.5, 139.1, 172.2. Found, %: C 65.95; H 6.26; N 4.72. $C_{16}H_{17}NO_2 \cdot HCl$. Calculated, %: C 65.86; H 6.22; N 4.80.

Methyl 3-Amino-2-(3-methylphenyl)propionate Hydrochloride (Vc). ^{1}H NMR (D_2O): 2.37 (3H, s), 3.43 (1H, dd, J = 7.5, 13.1 Hz), 3.68 (1H, dd, J = 7.6, 13.1 Hz), 3.76 (3H, s), 4.11-4.16 (1H, m), 7.15-7.25 (2H, m), 7.28-7.33 (1H, m), 7.37-7.43 (1H, m). ^{13}C NMR (D_2O-DMSO-d_6): 22.1, 42.2, 49.7, 54.3, 126.4, 130.0, 130.8, 135.7, 140.8, 174.2. Found, %: C 57.31; H 7.02; N 6.00. $C_{11}H_{15}NO_2 \cdot HCl$. Calculated, %: C 57.52; H 7.02; N 6.10.

Methyl 3-Amino-2-(1-naphthyl)propionate Hydrochloride (Vd). ^{1}H NMR (D_2O): 3.57 (1H, dd, J = 6.5, 13.2 Hz), 3.73 (3H, s), 3.87 (1H, dd, J = 7.8, 13.2 Hz), 4.92-4.96 (1H, m), 7.55-7.75 (4H, m), 7.95-8.10 (3H, m). ^{13}C NMR (D_2O-DMSO-d_6): 42.0, 46.0, 54.6, 123.9, 127.3, 127.8, 128.1, 129.0, 130.8, 130.9, 132.0, 132.2, 135.4, 174.9. Found, %: C 62.99; H 6.03; N 5.12. $C_{14}H_{15}NO_2 \cdot HCl$. Calculated, %: C 63.28; H 6.07; N 5.27.

Methyl 3-Amino-2-(3,4-dimethoxyphenyl)propionate Hydrochloride (Ve). ^{1}H NMR (D_2O): 3.45 (1H, dd, J = 7.8, 13.1 Hz), 3.67 (1H, dd, J = 7.4, 13.2 Hz), 3.76 (3H, s), 3.88 (6H, s), 4.08-4.14 (1H, m), 6.95-7.02 (2H, m), 7.07-7.12 (1H, m). ^{13}C NMR (D_2O-DMSO-d_6): 42.4, 49.5, 54.5, 57.1, 112.9, 113.7, 122.5, 128.5, 149.9, 150.1, 174.5. Found, %: C 51.91; H 6.52; N 4.89. $C_{12}H_{17}NO_4 \cdot HCl$. Calculated, %: C 52.27; H 6.58; N 5.08.

Methyl 3-Amino-2-phenylbutanoate Hydrochloride (Vf). ^{1}H NMR (D_2O): 1.45 (3H, d, J = 6.3 Hz) [1.19 (3H, d, J = 6.3 Hz) (ratio of diastereoisomers, 2:1)], 3.77 (3H, s), 3.98-4.15 (2H, m), 7.35-7.54 (5H, m). ^{13}C NMR (D_2O-DMSO-d_6): 18.1 (17.5), 50.3 (50.1), 54.5 (54.4), 55.9 (55.7), 130.2 (129.8), 130.7, 131.1 (130.9), 135.6 (134.2), 174.3 (174.0). Found, %: C 56.98; H 6.93; N 5.77. $C_{11}H_{15}NO_2 \cdot HCl$. Calculated, %: C 57.52; H 7.02; N 6.10.

REFERENCES

1. H. R. Crumpler, C. E. Dent, H. Harris, and R. G. Westall, Nature, **167**, 307 (1951).
2. T. P. Hettinger, Z. Kurylo-Borowska, and L. C. Craig, Biochemistry, **7**, 4153 (1968).
3. H. Yoshioka, T. Aoki, H. Goko, K. Nakatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, and T. Kaneko, Tetrahedron Lett., No. 23, 2043 (1971).
4. V. Rachina and I. Blagoeva, Synthesis, No. 11, 967 (1982).
5. L. Wessjohann, G. McGaffin, and A. de Meijere, Synthesis, No. 5, 359 (1989).
6. W. R. Jackson, P. Perlmutter, and A. J. Smallridge, Tetrahedron Lett., **29**, 1983 (1988).
7. T. Shono, N. Kise, F. Sanda, S. Ohi, and K. Tsubata, Tetrahedron Lett., **29**, 231 (1988).
8. F. Scavo and P. Helquist, Tetrahedron Lett., **26**, 2603 (1985).
9. D. H. Hua, S. W. Miao, J. S. Chen, and S. Iguchi, J. Org. Chem., **56**, 4 (1991).
10. S. Laschat and H. Kunz, J. Org. Chem., **56**, 5883 (1991).
11. T. Mukaiyama, H. Akamatsu, and J. S. Han, Chem. Lett., No. 6, 889 (1990).
12. K. Balenovic, N. Bregant, D. Cerar, and M. Tkalcic, J. Org. Chem., **16**, 1308 (1951).
13. J. H. Jones, in: Comprehensive Organic Chemistry, I. O. Sutherland (ed.), Vol. 2, Pergamon Press, Oxford (1979), p. 834.
14. M. Mitani, O. Tachizawa, H. Takeuchi, and K. Koyama, J. Org. Chem., **54**, 5397 (1989).
15. M. Slopianka and A. Gossauer, Liebigs Ann. Chem., No. 12, 2258 (1981).
16. A. R. Katritzky and K. Yannakopoulou, Synthesis, No. 10, 747 (1989).
17. A. R. Katritzky, N. Shobana, and P. A. Harris, Tetrahedron Lett., **31**, 3999 (1990).
18. A. R. Katritzky, J. Jiang, and L. Urogdi, Tetrahedron Lett., **30**, 3303 (1989).
19. A. R. Katritzky, J. Jiang, and L. Urogdi, Synthesis, No. 7, 565 (1990).
20. A. R. Katritzky, S. Rachwal, and G. J. Hitchings, Tetrahedron, **47**, 2683 (1991).
21. A. R. Katritzky, J. Wang, and B. Yang, Synth. Commun. (1995), in press.
22. A. R. Katritzky, R. Mazurkiewicz, C. V. Stevens, and M. F. Gordeev, J. Org. Chem., **59**, 2740 (1994).
23. R. J. Cox and D. O'Hagan, J. Chem. Soc. Perkin Trans. 1, No. 10, 2537 (1991).