3-(Dialkylamino)-1-(benzotriazol-1-yl)-1-(carbazol-9-yl)propanes: Novel β-Aminoacyl Anion Equivalents

Alan R. Katritzky,* Zhijun Yang, and Jamshed N. Lam

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-2046

Received November 17, 1992

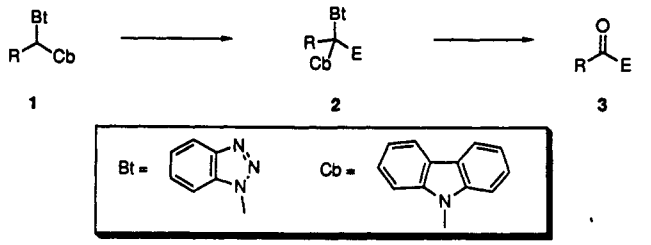
Work in our laboratory over the past several years has amply demonstrated the use of benzotriazole as a synthetic auxiliary in a variety of interesting transformations.[1] Several of these depend on the activation by the benzotriazole group of the adjacent CH toward deprotonation; thus, tris(benzotriazol-1-yl)methane has been employed as a carboxylic acid[2] anion synthon, and (benzotriazol-1-yl)(carbazol-9-yl)methanes have been used as formyl[3] and as acyl[4] anion synthons. In all these cases, removal of the heterocyclic moieties occurred under relatively mild conditions and afforded α-functionalized carboxylic acids, aldehydes, and ketones, respectively, in good yields. We now report our further exploration of the versatility of these systems leading to a novel β-aminoacyl anion equivalent and a new synthesis of β-aminoethyl ketones.

β-Aminoethyl ketones have been widely used as precursors for in situ generation of the relatively unstable and reactive vinyl ketones required for Robinson annulation type reactions, e.g., of cyclohexanones[5] or 1,3-diketones,[6] for constructing carbocyclic rings in natural product synthesis.[7] However, few α′-(functionalized alkyl) β-aminoethyl ketones are mentioned in the literature. Most of the reported β-aminoethyl ketones,[8] e.g., those used in the Robinson method, have been prepared by the treatment of simple ketones such as acetone or acetophenone with amines in the presence of formaldehyde and lack other functionality. Some α′-hydroxy β-aminoethyl ketones have been prepared by aminomethylation of tertiary acetylcarbinols,[9] but there has been no mention of the synthesis of any of the title ketones via acyl anion equivalents. We now describe a system to generate such ketones.

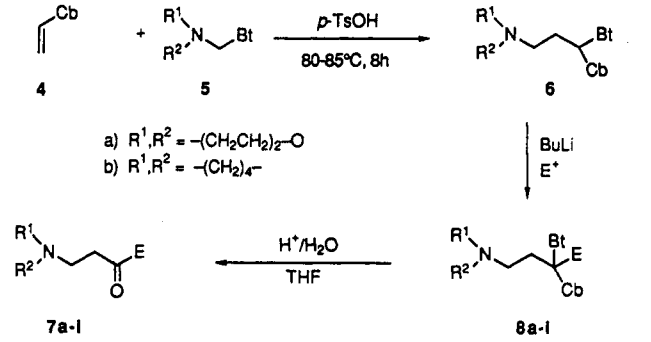
Results and Discussion

Our previous paper[4] demonstrated the use of substituted (carbazol-9-yl)(benzotriazol-1-yl)methanes **1** as acyl anion equivalents (Scheme I). The benzyl and the butyl derivatives readily underwent deprotonation by butyllithium, and the anion reacted readily with alkyl halides, aldehydes, and isocyanates to afford the expected intermediates. These were then hydrolyzed by dilute acid at ambient temperature to form the corresponding ketones

Scheme I



Scheme II



3. If a β-aminoethyl group were attached to **1**, then this system should act as a synthetic equivalent for the synthesis of β-amino ketones.

Recent work in our laboratory has demonstrated that α-(benzotriazol-1-yl)alkylamines of type **5** are in equilibrium with the corresponding immonium cation and undergo additions to enol ethers[10] and also to enamines including *N*-vinylcarbazole[11] to afford adducts **6**. Employing conditions similar to those described previously,[4] the morpholino derivative **6a** underwent smooth deprotonation with butyllithium at −78 °C to give the corresponding carbanion which reacted readily with alkyl and benzyl halides to afford the corresponding products **8a–d** in yields of 74–86% (Scheme II). As in our previous work[3,4] to obtain reasonable yields with aldehydes, we trapped the reaction intermediate with trimethylsilyl chloride (TMSCl) to give the corresponding stable silyl ether derivatives **8e–g** (57–68%) (see Table I). Similarly, the anion of the pyrrolidino derivative **6b** reacted with benzyl bromide and with octyl iodide to afford **8h** (69%) and **8i** (71%). The crude products **8a–i** were subjected to a preliminary purification on silica gel to remove unwanted impurities.

Hydrolyses of the products **8a–i** were readily achieved at ambient temperature in the presence of dilute hydrochloric acid. Careful control of pH during workup enabled easy removal of carbazole and benzotriazole and afforded essentially pure β-aminoethyl ketones **7a–i** in high yields (82–96%) (see Table I).

The ketones **7a–i** were characterized by their NMR and HRMS data (see Table II). The ^{1}H and ^{13}C NMR spectra displayed the expected patterns for the respective compounds. In general, the carbonyl signals were observed between 207.0 and 211.7 ppm in the ^{13}C NMR spectra. Absence of the heterocyclic signals indicated that the β-aminoethyl ketones obtained were essentially pure after workup.

(1) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.
(2) Katritzky, A. R.; Yang, Z.; Lam, J. N. *Synthesis* **1990**, 666.
(3) Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 2143.
(4) Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 6917.
(5) Yanagita, M.; Yamakawa, K. *J. Org. Chem.* **1957**, *22*, 291.
(6) Balasubramanian, K.; John, J. P.; Swaminathan, S. *Synthesis* **1974**, 51.
(7) Kametani, T.; Nemoto, H.; Fukumoto, K. *J. Synth. Org. Chem. Jpn.* **1977**, *35*, 1009.
(8) Tramontini, M. *Synthesis* **1973**, 703.
(9) Nazarev, I. N.; Matsoyan, S. G.; Vartanyan, S. A. *J. Gen. Chem. USSR* **1959**, *29*, 765.
(10) Katritzky, A. R.; Rachwal, S.; Rachwal, B.; Steel, P. J. *J. Org. Chem.* **1992**, *57*, 4932.
(11) Katritzky, A. R.; Rachwal, S.; Rachwal, B. Unpublished results.

0022-3263/93/1958-1970$04.00/0

Table I. Preparation of Adducts 8 and Ketones 7

compd index	R^1, R^2	electrophile (E)	compd 8 formula	compd 8 yield (%)	compd 8 mp	compd 7 formula	compd 7 yield (%)
a	$-(CH_2)_2O(CH_2)_2-$	$PhCH_2Br$ ($PhCH_2-$)	$C_{32}H_{31}N_5O$	78	101–104	$C_{14}H_{19}NO_2$	92
b	$-(CH_2)_2O(CH_2)_2-$	p-$MeC_6H_4CH_2Br$ (p-$MeC_6H_4CH_2-$)	$C_{33}H_{33}N_5O$	74	119–121	$C_{15}H_{21}NO_2$	87
c	$-(CH_2)_2O(CH_2)_2-$	n-$CH_3(CH_2)_5I$ (n-$CH_3(CH_2)_5-$)	$C_{31}H_{37}N_5O$	86	104–106	$C_{13}H_{25}NO_2$	96
d	$-(CH_2)_2O(CH_2)_2-$	n-$CH_3(CH_2)_7I$ (n-$CH_3(CH_2)_7-$)	$C_{33}H_{41}N_5O$	82	96–99	$C_{15}H_{29}NO_2$	94
e	$-(CH_2)_2O(CH_2)_2-$	PhCHO/TMSCl (PhCH(OTMS)-)	$C_{35}H_{43}N_5O_2Si$	61	92–96	$C_{14}H_{19}NO_3$	89
f	$-(CH_2)_2O(CH_2)_2-$	p-MeC_6H_4CHO/TMSCl (p-$MeC_6H_4CH(OTMS)-$)	$C_{36}H_{45}N_5O_2Si$	68	101–104	$C_{15}H_{21}NO_3$	88
g	$-(CH_2)_2O(CH_2)_2-$	c-$C_6H_{11}CHO$/TMSCl c-$C_6H_{11}CH(OTMS)-$)	$C_{35}H_{49}N_5O_2Si$	57	106–108	$C_{14}H_{25}NO_3$	82
h	$-(CH_2)_4-$	$PhCH_2Br$ ($PhCH_2-$)	$C_{32}H_{31}N_5$	69	96–98	$C_{14}H_{19}NO$	84
i	$-(CH_2)_4-$	n-$CH_3(CH_2)_7I$ (n-$CH_3(CH_2)_7-$)	$C_{33}H_{41}N_5$	71	86–89	$C_{15}H_{29}NO$	91

Table II. ^1H and ^{13}C NMR Data of Ketones 7

compd	^1H	^{13}C >C=O	^{13}C NR^1R^2	^{13}C $NC_\alpha C_\beta$	^{13}C E
7a	7.35–7.19 (m, 5 H), 3.71 (s, 2 H), 3.64 (t, 4 H, J = 4.6 Hz), 2.62 (s, 4 H), 2.41–2.34 (m, 4 H)	207.0	66.8, 73.4	73.0, 39.1	134.0, 129.3, 128.7, 127.0, 50.3
7b	7.18–7.06 (m, 4 H), 3.07–3.60 (m, 6 H), 2.61 (s, 4 H), 2.41–2.35 (m, 4 H), 2.32 (s, 3 H)	207.3	66.7, 73.4	73.0, 38.9	136.5, 130.9, 129.3, 129.1, 49.9, 20.9
7c	3.75–3.67 (m, 4 H), 2.70–2.55 (m, 4 H), 2.48–2.40 (m, 6 H), 1.64–1.53 (m, 2 H), 1.36–1.22 (m, 6 H), 0.92–0.85 (m, 3 H)	209.9	66.8, 73.5	73.1, 39.9	43.0, 31.5, 28.8, 23.6, 22.4, 13.9
7d	3.75–3.60 (m, 4 H), 2.70–2.55 (m, 4 H), 2.48–2.35 (m, 6 H), 1.65–1.50 (m, 2 H), 1.27 (s, 10 H), 0.91–0.80 (m, 3 H)	209.9	66.8, 53.5	53.1, 39.9	43.0, 31.7, 29.3, 29.0, 29.0, 23.6, 22.5, 14.0
7e	7.42–7.25 (m, 5 H), 5.10 (s, 1 H), 4.55 (s, br, 1 H), 3.65–3.59 (m, 4 H), 2.60–2.46 (m, 4 H), 2.38–2.29 (m, 4 H)	208.5	66.6, 53.3	53.1, 35.2	137.8, 128.9, 128.6, 127.2, 29.8
7f	7.25–7.16 (m, 4 H), 5.07 (s, 1 H), 4.50 (s, br, 1 H), 3.67–3.58 (m, 4 H), 2.61–2.50 (m, 4 H), 2.40–2.30 (m, 7 H)	208.7	66.6, 53.3	53.1, 35.2	138.4, 134.8, 129.5, 127.1, 79.6, 21.0
7g	3.99 (d, 1 H, J = 3.1 Hz), 3.69 (t, 4 H, J = 4.6 Hz), 2.77–2.60 (m, 4 H), 2.55–2.42 (m, 4 H), 1.85–1.60 (m, 5 H), 1.50–1.10 (m, 6 H)	211.7	66.7, 53.5	53.4, 35.9	80.9, 41.2, 29.8, 26.4, 25.9, 25.8, 25.5
7h	7.47–7.19 (m, 5 H), 3.70 (s, 2 H), 2.75–2.61 (m, 4 H), 2.49–2.40 (m, 4 H), 1.80–1.68 (m, 4 H)	207.2	54.0, 23.3	50.4, 41.4	134.1, 129.3, 128.6, 126.9, 50.2
7i	2.76–2.70 (m, 2 H), 2.68–2.60 (m, 2 H), 2.54–2.40 (m, 6 H), 1.81–1.75 (m, 6 H), 1.64–1.52 (m, 2 H), 1.27 (s, br, 10 H), 0.91–0.85 (m, 3 H)	209.9	53.9, 23.6	50.4, 42.1	42.8, 31.6, 29.2, 29.0, 28.9, 23.3, 13.9

Conclusions

The use of substituted (carbazol-9-yl)(benzotriazol-1-yl)methanes as acyl anion equivalents has been extended to the synthesis of β-aminoethyl ketones. The high yields and purity of the final products together with the lack of necessity for purification of the intermediates makes this route an attractive system for further exploration.

Experimental Section

The apparatus, instrumentation, and general techniques used here are identical to those used previously.[4]

The following compounds were prepared by known literature procedures: ***N*-[(benzotriazol-*N*-yl)methyl]morpholine (5a)**, mp 104–105 °C (lit.[12] mp 103–104 °C); ***N*-[(benzotriazol-*N*-yl)methyl]pyrrolidine (5b)**, mp 80–81 °C (lit.[12] mp 79–81 °C).

General Procedure for the Preparation of 1-(Benzotriazol-1-yl)-1-(carbazol-9-yl)-3-aminopropanes. A mixture of the corresponding amine (**5a** or **5b**) (25 mmol) and *N*-vinylcarbazole (**4**) (25 mmol) was heated to 80 °C, and then *p*-TsOH (0.1 g) was added. The mixture was stirred at 80–85 °C for 8 h, the mixture cooled, and the crude product purified by chromatography ($CHCl_3$) to afford the products as sticky oils. The following compounds were prepared in this manner:

1-(Benzotriazol-1-yl)-1-(carbazol-9-yl)-3-morpholinopropane (6a): colorless needles from EtOH (43%); mp 145–147 °C; ^1H NMR ($CDCl_3$) δ 8.1–7.95 (m, 3 H), 7.7–7.55 (m, 3 H), 7.45–7.35 (m, 2 H), 7.3–7.1 (m, 5 H), 3.7–3.6 (m, 4 H), 3.45–3.35 (m, 2 H), 2.5–2.4 (m, 3 H), and 2.15–2.05 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.3, 139.0, 133.1, 127.9, 126.2, 124.3, 123.7, 120.5, 120.3, 120.0, 110.1, 109.7, 67.0, 65.9, 53.5, 53.4, and 27.7. Anal. Calcd for $C_{25}H_{27}N_5O$: C, 72.61; H 6.58; N, 16.94. Found: C, 72.96; H, 6.27; N, 16.96.

1-(Benzotriazol-1-yl)-1-(carbazol-9-yl)-3-pyrrolidinopropane (6b): colorless plates from Et_2O/hexane (26%); mp 127–129 °C; ^1H NMR ($CDCl_3$) δ 8.08–7.94 (m, 3 H), 7.75–7.56 (m, 3 H), 7.48–7.34 (m, 2 H), 7.28–7.01 (m, 5 H), 3.50–3.30 (m, 2 H), 2.52–2.20 (m, 6 H), and 1.74 (s, br, 4 H); ^{13}C NMR ($CDCl_3$) δ 146.6, 139.9, 133.4, 128.0, 126.5, 124.5, 123.9, 120.7, 120.5, 120.2, 110.4, 110.1, 66.3, 54.1, 51.1, 30.6, and 24.1. Anal. Calcd for $C_{25}H_{25}N_5$: C, 75.92; H 6.37; N, 17.71. Found: C, 75.53; H, 6.40; N, 17.67.

General Procedure for the Lithiation of 6 and Subsequent Reaction with Electrophiles. The general procedure used here has previously been described in detail.[4] (Note: for **8e–g** a solution of TMSCl[4] was also added.) The crude products were subjected to a preliminary purification by column chromatography ($CHCl_3$) (see Table I).

General Procedure for the Hydrolysis of Adducts 8. To a solution of the corresponding **8** (5 mmol) in THF–H_2O (20 + 10 mL) was added aqueous HCl (5 M; 2 mL). The solution was stirred at room temperature for 3 h (TLC showed the complete

(12) Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Org. Prep. Proceed. Int.* **1989**, *21*, 135.

disappearence of the starting material **6**), and then aqueous HCl (1 M; 10 mL) was added. The whole reaction mixture was washed with Et_2O (3 × 10 mL) and the aqueous phase neutralized with Na_2CO_3 until pH = 9 and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the prue products **7a–i** as colorless oils which were fully characterized by their ^1H and ^{13}C NMR spectra and also by their high-resolution mass spectral data (see Table II and supplementary material).

Acknowledgment. The authors would like to thank Dr. S. Rachwal and Ms. B. Rachwal for providing us with a procedure for the preparation of compounds **6a,b**.

Supplementary Material Available: HRMS data and NMR spectra for **7a–i** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.