A New Method for the Synthesis of 3-Methylene-2-azetidinones

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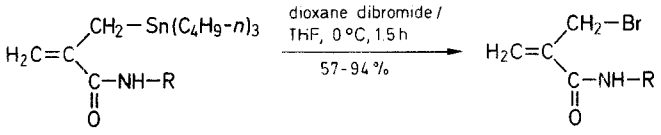
The reaction of *N*-monosubstituted 2-[(tributylstannyl)-methyl]propenamides with dioxane dibromide affords *N*-monosubstituted 2-(bromomethyl)-propenamides which upon treatment with sodium hydride or potassium *t*-butoxide are converted to 3-methylene-2-azetidinones in good yields.

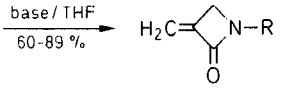
α-Methylene carbonyl compounds have recently attracted much attention because of the importance of these substances as biologically active species and as useful synthetic intermediates[1,2,3]. For this reason, a great deal of effort has been devoted to the development of methods for the construction of α-methylene-γ-butyrolactones[4,5] and α-methylenecyclopentanones[6–10]. However, only a few methods are reported for the preparation of their nitrogen analogues, the α-methylene lactams[11–16].

We have recently reported that chiral *N*-monosubstituted 2-[(tributylstannyl)-methyl]propenamides[17a] **(1)** can serve as efficient reagents for the asymmetric synthesis of α-methylene-γ-butyrolactones from carbonyl compounds[17b].

We now report that the amides **1** can also act as useful intermediates for 3-methylene-2-azetidinones[18-26] under very mild conditions. Thus, the reaction of the chiral amides **1** with dioxane dibromide[27] in dry tetrahydrofuran afforded the corresponding 2-(bromomethyl)-propenamides **2** in high yields. The use of molecular bromine led to a substantial reduction in yield as a result of contamination with byproducts. Compounds **2** were treated with sodium hydride or potassium *t*-butoxide in dry tetrahydrofuran at −78 °C to afford 3-methylene-2-azetidinones **3** in good yields.



1 a-h **2 a-h**



3 a-h

1-3	R	1-3	R
a	(*S*)-C_6H_5–CH(CH$_3$)–	e	(*S*)-*i*-C_3H_7–CH_2–CH(H_3C–O–CH_2)–
b	(*R*)-C_6H_5–CH(CH$_3$)–	f	(*R*)-*i*-C_3H_7–CH_2–CH(H_3C–O–CH_2)–
c	(*S*)-C_6H_5–CH_2–CH(H_3C–O–CH_2)–	g	(*S*)-*i*-C_3H_7–CH(H_3C–O–CH_2)–
d	(*R*)-C_6H_5–CH_2–CH(H_3C–O–CH_2)–	h	(*R*)-*i*-C_3H_7–CH(H_3C–O–CH_2)–

I.R. (Nujol): ν = 3295, 1650, 1610, 1230, 960 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.51 (d, 3H, J = 7 Hz); 4.19 (s, 2H); 4.96–5.33 (m, 1H); 5.60 (s, 1H); 5.73 (s, 1H); 6.39 (br. s, 1H); 7.29 ppm (s, 5H).

We have also found that *n*-Butyllithium and lithium diisopropylamide were also effective bases, but the reactions were less clean and yields were lower. A one-pot synthesis was accomplished by reaction of *N*-α-methylbenzyl-2-[(tributylstannyl)-methyl]propenamide with dioxane dibromide and subsequent addition of potassium *t*-butoxide to give 1-α-methylbenzyl-3-methylene-2-azetidinone in 78% yield.

This methodology should be useful in the preparations of a wide variety of 3-methylene-2-azetidinones from the readily available starting materials **1**[17a] and dioxane dibromide[27].

N-[(*S*)-α-Methylbenzyl]-2-(bromomethyl)propenamide (2a); Typical Procedure:

To a solution of *N*-[(*S*)-α-methylbenzyl]-2-[(tributylstannyl)-methyl]propenamide[17a] (**1a**; 2.39 g, 5 mmol) in dry tetrahydrofuran (30 ml) cooled to 0 °C, dioxane dibromide[27] (1.24 g, 5 mmol) is added. The solution is stirred at 0 °C for 1.5 h. The mixture is diluted with water (50 ml) and extracted with ether (3 × 40 ml). The combined extracts are washed successively with saturated sodium thiosulfate solution (50 ml), brine (50 ml), and dried with sodium sulfate. The residue obtained after removal of the solvent is chromatographed on a silica gel column using *n*-hexane/ethyl acetate (4:1) as eluent to give **2a**; yield 1.15 g (85%); m.p. 83 °C; $[\alpha]_D^{25}$: −54.8° (*c* 1.52, ethanol).

$C_{12}H_{14}BrNO$ (268.2) calc. C 53.75 H 5.26 N 5.22
found 53.72 5.25 5.22

I.R. (Nujol): ν = 3295, 1650, 1610, 1230, 960 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.51 (d, 3H, J = 7 Hz); 4.19 (s, 2H); 4.96–5.33 (m, 1H); 5.60 (s, 1H); 5.73 (s, 1H); 6.39 (br. s, 1H); 7.29 ppm (s, 5H).

Table 1. *N*-Monosubstituted 2-(Bromomethyl)-propenamides **2** prepared

Product	Yield [%][a]	m.p. [°C]	$[\alpha]_D^{25}$ (*c*, ethanol)	Molecular Formula[b]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
2a	85	83°	−54.8° (1.52)	$C_{12}H_{14}BrNO$ (268.2)	see experimental section	
2b	87	83°	+54.8° (1.69)	$C_{12}H_{14}BrNO$	3300, 1650, 1610, 1230, 960	1.51 (d, 3H, J = 7 Hz); 4.21 (s, 2H); 5.01–5.35 (m, 1H); 5.63 (s, 1H); 5.73 (s, 1H); 6.23 (br. s, 1H); 7.29 (s, 5H)
2c	94	46°	−27.4° (1.47)	$C_{14}H_{18}BrNO_2$ (312.2)	3300, 1650, 1610, 1220, 960	2.89 (d, 2H, J = 6 Hz); 3.32 (m, 5H); 4.00–4.52 (m, 3H); 5.60 (s, 1H); 5.68 (s, 1H); 6.28 (br. s, 1H); 7.25 (s, 5H)
2d	64	43°	+26.8° (1.39)	$C_{14}H_{18}BrNO_2$ (312.2)	3270, 1650, 1225, 970	2.96 (d, 2H, J = 6 Hz); 3.37 (m, 5H); 3.93–4.56 (m, 3H); 5.60 (s, 1H); 5.68 (s, 1H); 6.25 (br. s, 1H); 7.24 (s, 1H)
2e	69	oil[c]	−33.1° (1.76)	$C_{11}H_{20}BrNO_2$ (278.2)	3250, 1650, 1620, 1210, 950	0.52–2.21 (m, 9H); 2.93–3.53 (m, 5H); 3.85–4.41 (m, 3H); 5.61 (s, 1H); 5.70 (s, 1H); 6.16 (m, 1H)
2f	78	oil[c]	+27.5° (1.65)	$C_{11}H_{20}BrNO_2$ (278.2)	3280, 1650, 1620, 1220, 960	0.52–2.12 (m, 9H); 2.92–3.52 (m, 5H); 3.64–4.36 (m, 3H); 5.60 (s, 1H); 5.72 (s, 1H); 6.00 (m, 1H)
2g	57	oil[c]	−23.3° (1.40)	$C_{10}H_{18}BrNO_2$ (264.2)	3275, 1650, 1620, 1220, 950	0.96 (m, 6H); 1.63–2.19 (m, 1H); 3.11–3.72 (m, 5H); 3.72–4.33 (m, 3H); 5.59 (s, 1H); 5.71 (s, 1H); 6.17 (m, 1H)
2h	58	oil[c]	+22.9° (1.82)	$C_{10}H_{18}BrNO_2$ (264.2)	3275, 1650, 1610, 1220, 950	0.95 (m, 6H); 1.65–2.85 (m, 1H); 2.96–3.65 (m, 5H); 3.65–4.28 (m, 3H); 5.51 (s, 1H); 5.62 (s, 1H); 6.11 (m, 1H)

[a] Yield of isolated pure product.
[b] The microanalyses were in good agreement with the calculated values (C ±0.36, H ±0.17, N ±0.38).
[c] I.R. spectra were recorded as films.

Table 2. 3-Methylene-2-azetidinones **3** prepared

Product[a]	Base	Reaction Conditions temperature/time	Yield [%][b]	$[\alpha]_D^{25}$ (*c*, ethanol)	Molecular Formula[c]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3a	NaH	−78 °C/2 h then 0 °C/1 h	87	−58.6° (1.77)	$C_{12}H_{13}NO$ (187.2)	see experimental section	
3b	t-C_4H_9OK	−78 °C/1 h then 0 °C/1 h	89	+60.1° (1.73)	$C_{12}H_{13}NO$ (187.2)	1740, 940	1.65 (d, 3H, J = 7 Hz); 3.45–3.80 (m, 2H); 5.00–5.25 (m, 1H); 5.21 (m, 1H); 5.79 (m, 1H); 7.43 (s, 5H)
3c	NaH	−78 °C/1 h then r.t./2.5 h	86	−87.5° (1.83)	$C_{14}H_{17}NO_2$ (231.3)	1735, 940	2.96 (d, J = 8 Hz, 2H); 3.37 (s, 3H); 3.52 (d, 2H, J = 5 Hz); 3.74 (s, 2H); 4.04–4.24 (m, 1H); 5.08 (s, 1H); 5.63 (m, 1H); 7.24 (s, 5H)
3d	NaH	−78 °C/1 h then r.t./2.5 h	80	+84.6° (1.53)	$C_{14}H_{17}NO_2$ (231.3)	1742, 940	2.92 (d, 2H, J = 8 Hz); 3.32 (s, 3H); 3.49 (d, 2H, J = 6 Hz); 3.73 (s, 2H); 4.16 (m, 1H); 5.09 (s, 1H); 5.64 (m, 1H); 7.25 (s, 5H)
3e	NaH	−78 °C/1 h then r.t./18 h	60	−33.1° (1.76)	$C_{11}H_{19}NO_2$ (197.3)	1735, 930	0.58–1.79 (m, 9H); 3.00–3.61 (m, 5H); 3.76 (s, 2H); 4.03 (m, 1H); 5.11 (s, 1H); 5.62 (s, 1H)
3f	NaH	−78 °C/1 h then r.t./18 h	63	+36.2 (1.64)	$C_{11}H_{19}NO_2$ (197.3)	1735, 930	0.58–1.82 (m, 9H); 3.20–3.62 (m, 5H); 3.78 (s, 2H); 4.08 (m, 1H); 5.10 (s, 1H); 5.65 (s, 1H)
3g	NaH	−78 °C/1 h then r.t./18 h	82	−47.1° (1.36)	$C_{10}H_{17}NO_2$ (183.3)	1745, 930	0.93 (dd, 6H, J = 2 Hz, 7 Hz); 1.49–2.21 (m, 1H); 3.19–3.91 (m, 8H); 5.08 (s, 1H); 5.60 (s, 1H)
3h	NaH	−78 °C/1 h then r.t./18 h	89	+48.3° (1.52)	$C_{10}H_{17}NO_2$ (183.3)	1743, 930	0.94 (dd, 6H, J = 2 Hz, 7 Hz); 1.64–2.14 (m, 1H); 3.16–3.93 (m, 8H); 5.04 (s, 1H); 5.61 (s, 1H)

[a] All products are viscous oils.
[b] Yield of isolated product.
[c] The microanalyses were in good agreement with the calculated values (C ±0.45, H ±0.17, N ±0.38).

1-[(*S*)-α-Methylbenzyl]-3-methylene-2-azetidinone (3a), Typical Procedure:

To a stirred solution of potassium *t*-butoxide (0.49 g, 4.4 mmol) in dry tetrahydrofuran (30 ml) at −78 °C under argon, *N*-[(*S*)-α-methylbenzyl]-2-(bromomethyl)propenamide (**2a**; 0.80 g, 3 mmol) in dry tetrahydrofuran (20 ml) is added dropwise. After stirring for the time given in Table 2, the mixture is quenched by the addition of water (10 ml), and extracted with ether (4 × 50 ml). The combined extracts are washed with brine (50 ml) and dried with sodium sulfate. The crude product obtained after removal of the solvent is chromatographed on a silica gel column using *n*-hexane/ethyl acetate (4:1) as eluent to give **3a**; yield 0.49 g (87%); $[\alpha]_D^{25}$: −58.6° (*c* 1.77, ethanol).

$C_{12}H_{13}NO$ (187.2) calc. C 76.98 H 7.00 N 7.48
found 77.15 7.09 7.66

I.R. (neat film): ν = 1730, 940 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.60 (d, 3H, J = 7 Hz); 3.45–3.80 (m, 2H); 4.83–5.35 (m, 1H); 5.08 (m, 1H); 5.63 (m, 1H); 7.28 ppm (s, 5H).

One-Pot Synthesis of 1-α-Methylbenzyl-3-methylene-2-azetidinone:

To a solution of *N*-α-methylbenzyl-2-[(tributylstannyl)-methyl]propenamide (2.41 g, 5.0 mmol) in dry tetrahydrofuran (30 ml) at 0 °C, is added dioxane dibromide (1.54 g, 6.2 mmol) under argron. After stirring for 1.5 h, the mixture is cooled to −78 °C and potassium *t*-butoxide (1.41 g, 13 mmol) is added. The mixture is stirred for 1 h at −78 °C and allowed to warm to 0 °C. After 1 h at 0 °C, the mixture is diluted with water (50 ml), and extracted with ether (3 × 40 ml). The combined extracts are washed with saturated sodium thiosulfate solution (50 ml), brine (50 ml), dried with sodium sulfate, filtered, and the solvent removed in vacuum. The crude product is purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (4:1) as eluent to give pure 1-α-methylbenzyl-3-methylene-2-azetidinone; yield: 0.73 g (78%).

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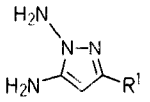
Errata and Addenda 1986

I. Ganboa, C. Palomo *Synthesis* **1986**, 52. The ^{1}H-NMR data for compounds **2d** and **2e** in the Table (p. 53) should be, respectively: 8.13 (d, $2H_{arom}$); 7.46 (d, $2H_{arom}$); 7.3 (s, $5H_{arom}$); 5.73 (m, 1 H, C–H); 5.26 (s, 2H, CH_2–$C_6H_4NO_2$); 4.9 (m, 1H, C–H); 3.7 (m, 2H, CH_2–CO–NH); 3.3 (m, 2H, S–CH_2); 2.13 (s, 3H, CH_3). 7.33 (s, $5H_{arom}$); 7.3 (s, $5H_{arom}$); 5.76 (m, 1 H, C–H); 5.2 (s, 2H, C_6H_5–CH_2); 4.9 (m, 1 H, C–H); 3.63 (s, 2 H, CH_2–CO–NH); 3.3 (m, 2H, S–CH_2); 2.13 (s, 3 H, CH_3).

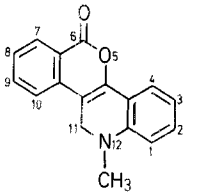
The ^{1}H-NMR data for compound **6** (p. 54) should be:
^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 8.03 (d, $2H_{arom}$); 7.43 (d, $2H_{arom}$); 5.65 (s, 1 H, CH); 5.23 (s, 2 H, CH_2); 4.5 (s, 1 H, NH); 1.53, 1.35 ppm (2 s, 6 H, 2 CH_3).

K. Tanaka, H. Yoda, K. Inoue, A. Kaji *Synthesis* **1986**, 66. The $[\alpha]_D^{25}$ value for compound **2e** in Table 1 (p. 67) should be:
$-28.2°$ (1.80).

D. R. Sliskovic, M. Siegel, Y. Lin *Synthesis* **1986**, 71. The structures for compounds **6a, b** (p. 73) should be:

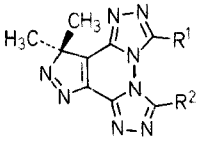


O. Meth-Cohn *Synthesis* **1986**, 76. The correct numbering for compounds **8** and **10** (p. 76) is as illustrated below for compound **10**:



10

B. Furlan, B. Stanovnik, M. Tišler *Synthesis* **1986**, 78. The double-bond arrangement of compounds **3, 6,** and **7** (pp. 78, 79) should be:

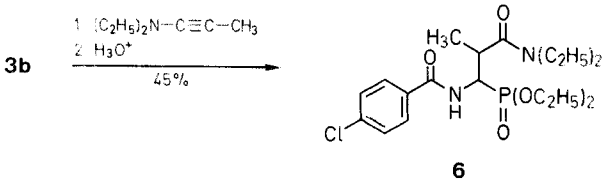


N. Petragnani, H. M. C. Ferraz, G. V. J. Silva *Synthesis* **1986**, 157. The authors wish to include the following pertinent references:
R. M. Adlington, A. G. M. Barret *Tetrahedron* **1981**, *37*, 3935.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Perkin Trans. I* **1981**, 2848.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Chem. Commun.* **1981**, 65.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Chem. Commun.* **1979**, 1122.

A. J. Fatiadi *Synthesis* **1986**, 249. The heading for the first experimental procedure on p. 268 should be:
2,6-Diphenyl-4-(2,3,3-tricyanoallylidene)pyran (201)[354]:

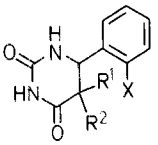
D. P. Matthews, J. P. Whitten, J. R. McCarthy *Synthesis* **1986**, 336. The headings for the first and last experimental procedures should be, respectively:
***N*^{1},*N*^{3}-Bis(2,2-dimethoxyethyl)oxaldiamidine Dihydrochloride (2):**
2-(2-Imidazolyl)-4-methoxy-4,5-dihydroimidazole (5):

T. Schrader, R. Kober, W. Steglich *Synthesis* **1986**, 372. The last equation in the formula scheme (p. 372) should be:

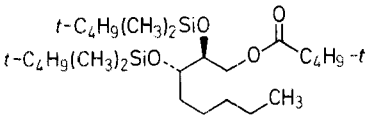


6

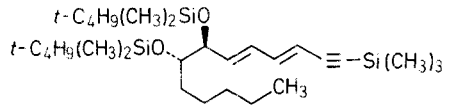
D. N. Dhar, K. S. K. Murthy *Synthesis* **1986**, 437. The heading for Table 2 (p. 440) should be:
4-Aryl-2(1*H*)-quinazolines **(13)** and 4-Aryl-1*H*-2,1,3-benzothiadiazine 2,2-Dioxides **(14)**
The names of compounds **13a** and **14a** in the experimental procedure on the same page should be corrected accordingly.
For compounds **60** and **61** (p. 445) R^3 = H, SO_2Cl.
The product in the lower, left reaction scheme on p. 446 should be:



K. C. Nicolaou, S. E. Webber *Synthesis* **1986**, 453. The structures of compounds **8** (p. 454) and **16** (p. 455) should be:



8

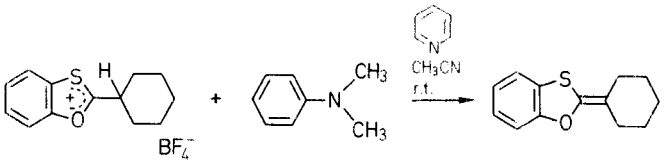


16

E. Dalcanale, M. Foà *Synthesis* **1986**, 492. In the reaction scheme, products **4** and **5** are obtained in 33 and 8%, respectively, a ratio of 80:20.

W. G. Dauben, J. M. Gerdes, G. C. Look *Synthesis* **1986**, 532. In the experimental procedure headings (p. 534), the names of compounds 3, 5, 7, and 9 should read:
(3,3-Ethylenedioxybutyl)triphenylphosphonium Bromide (3)
6-*t*-Butyldimethylsiloxy-3,7-dimethyl-1,6-octadiene (5)
5-[1,1-Bis(ethoxycarbonyl)ethyl]bicyclo[3.3.0]octan-2-one (7)
2,2-Ethylenedioxy-1,3,3-trimethylbicyclo[2.2.1]heptane (9).

S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi *Synthesis* **1986**, 544. Formula Scheme **B** should be:



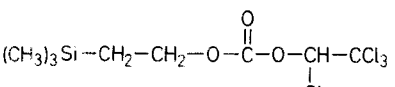
1c **2** **5**

H. M. R. Hoffmann, K. Giesel, R. Lies, Z. M. Ismail *Synthesis* **1986**, 548. The heading for the last experimental procedure (p. 551) should be:
Cycloadditions; 4-Oxatricyclo[7.2.1.0^{3,8}]dodeca-3,10-dien-2-one (11e):

Abstract 7330, *Synthesis* **1986**, 599. The structure of compound **7** should be: CH_2=C(R^6)R^7.

Abstract 7333, *Synthesis* **1986**, 600. Line 2 of the text should read: dimenthyl succinate **(1)** with lithium 2,2,6,6-tetramethylpiperidide reacts...

G. Barcelo, J. P. Senet, G. Sennyey, J. Bensoam, A. Loffet *Synthesis* **1986**, 627. The structure of compound **1k** (p. 630) should be:



D. Achet, D. Rocrelle, I. Murengezi, M. Delmas, A. Gaset *Synthesis* **1986**, 642. The last word of the title should be: **Sulfate**