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A SYNTHESIS OF 3-(α,β-EPOXY)-2-AZETIDINONES DERIVATIVES

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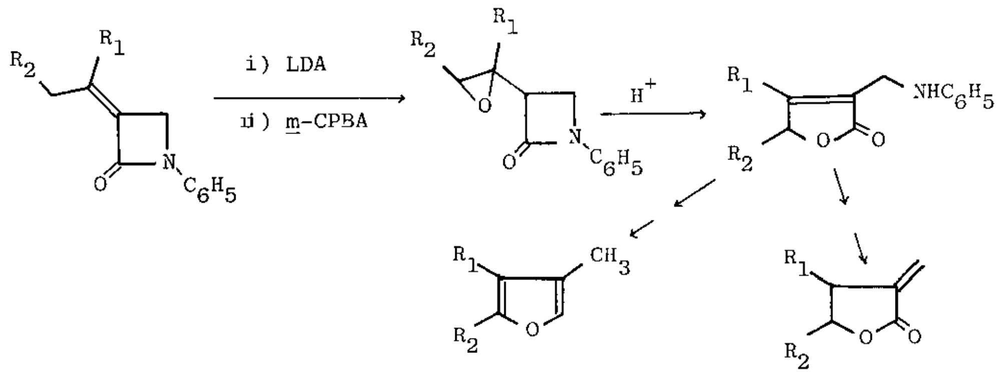
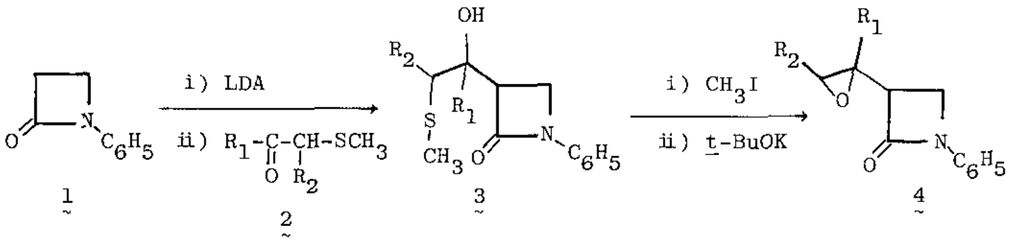
Abstract   Condensation of 1-phenyl-2-azetidinone with α-methylthio ketones yielded the corresponding β-hydroxy sulfides, which were converted to 3-(α,β-epoxy)-1-phenyl-2-azetidinones through two steps involving desulfurization of the sulfonium iodides. In a similar fashion, condensation of 1-phenyl-2-azetidinone with ethyl α-methylthioacetates gave the corresponding sulfenyl ketones, which were also converted to the 3-(α,β-epoxy)-2-azetidinone derivatives. These 2-azetidinones were further lead to α-anilinomethyl-1,2-butenolides by treatment with methanesulfonic acid.

In our continuing efforts aimed at the synthetic utility of 2-azetidinones as a source of heterocyclic compounds[1,2], we found that the epoxides of 1-phenyl-3-vinyl-2-azetidinones were easily converted to α-anilinomethyl-1,2-butenolides by treatment with methanesulfonic acid in benzene[3]. (See Scheme 1).



Scheme 1

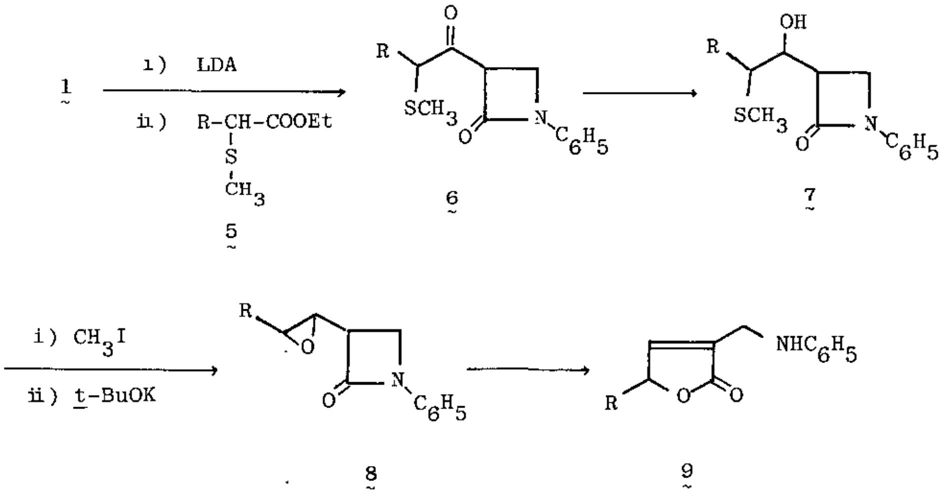
Since those 1,2-butenolides were found to be useful intermediates leading to α-methylene-γ-butyrolactones[3,4] and 3-methylfuran derivatives[5], we have further investigated the alternative facile approach to the 3-(α,β-epoxy)-2-azetidinone derivatives by an application of desulfurization of β-hydroxy sulfonium iodides in the formation of oxirane moiety[6]. These results were described in this paper. Condensation[7] of lithium salt of 1-phenyl-2-azetidinone (**1**)[8] with α-methylthioacetone (**2a**) at -78 °C afforded the β-hydroxy sulfide (**3a**) as a mixture of stereoisomers in 70 % yield, mp 68-79 °C, *m/e* 251 (M^+), 233 (M^+-18). Methylation of **3a** with methyl iodide in methanol for 2 hr under reflux, followed by treatment of the resulting methylsulfonium iodide, without purification, with one equivalent of potassium *t*-butoxide in ethanol at room temperature for 0.5 hr gave the desired 3-(α,β-epoxy)-2-azetidinone (**4a**)[3] as a mixture of stereoisomers in 53 % yield. In a similar fashion, **1** was condensed with α-methylthioacetophenone (**2b**)[9] and α-methylthiopropionophenone (**2c**)[9], to give the corresponding alcohols (**3b**; 68 %, oil) and (**3c**, 70 %, mp 76-83 °C), respectively. **3b** and **3c** were converted to the corresponding epoxides (**4b**[3], 48 %) and (**4c**[3], 50 %) through the same manner as above as outlined in the Scheme 2. These 2-azetidinones (**3b**), (**3c**), (**4b**) and (**4c**) should be considered to be a mixture of diastereomers according to their ^{1}HNMR spectra ($CDCl_3$). Although the over all yields of the epoxides (**4**) were not improved comparing with those in the previous method[3], this approach might be useful when one wishes to prepare **4** and related compounds without using oxidative conditions.



a: R_1=CH_3, R_2=H; **b**: R_1=C_6H_5, R_2=H; **c**: R_1=C_6H_5, R_2=CH_3

Scheme 2

Successively, we examined the condensation of **1** with ethyl methylthioacetate (**5a**) at -78 °C to give 3-methylthioacetyl-1-phenyl-2-azetidinone (6a), reduction of which with sodium borohydride in methanol at -78 °C afforded the diastereoisomeric mixture of the β-hydroxy sulfide (7a) in nearly quantitative yield. Methylation of 7a with methyl iodide in methanol under reflux for 2 hr, followed by treatment of the resulting sulfonium iodide, without purification, with potassium *t*-butoxide yielded the corresponding epoxide (8a) as a mixture of diastereomers in 30 % yield accompanied by the formation of 1 (20 %) and 7a (25 %). These were separated by column chromatography on silica gel. Elution with benzene-chloroform (1:1) gave 1 and elution with benzene-chloroform (2:3) afforded 8a. 7a was obtained from the benzene-chloroform (1:2) fraction. In a similar fashion, the reaction of lithium salt of 1 with the ester (5b) and (5c) yielded the corresponding 3-acyl-1-phenyl-2-azetidinones (6b) and (6c) as diastereoisomeric mixtures. These were smoothly converted to the diastereoisomeric mixtures of the epoxides (8b) and (8c), respectively, *via* β-hydroxy sulfides (7b) and (7c) as shown in the Scheme 3. Treatment of 8a-8c with methanesulfonic acid in benzene under reflux[3] gave the α-anilinomethyl-1,2-butenolides (9a) and (9c), respectively, in 70-75 % yield.



a: R=H; b: R=CH_3; c: R=CH_3CH_2

Scheme 3

Table 1. Physical Data of 6, 7, 8 and 9[10]

Compd	Yield (%)	mp °C	m/e (M$^+$)	^{1}HNMR (CDCl$_3$) δ
6a	75	80-83	235	2.11 (s, 3H), 3.30 (d, J=14 Hz, 1H), 3.63 (d, J=14 Hz, 1H), 3.68 (t, J=6.0 Hz, 1H), 4.08 (d,d, J=3 and 6 Hz, 1H), 4.79 (d,d, J=3 and 6 Hz, 1H), 6.93-7.47 (m, 5H)
6b	72	98-100	249	1.42 (d, J=6.5 Hz, 3H), 1.96 (s, 3H), 3.56-4.17 (m, 3H), 4.96 (d,d, J=3 and 5 Hz, 1H), 6.93-7.40 (m, 5H)
6c	73	80-82	363	0.80-1.18 (m, 3H), 1.48-2.03 (m,2H), 1.92 (s, 3H), 3.53 (t, J=7 Hz, 1H), 3.66 (t, J=5.5 Hz, 1H), 4.10 (d,d, J=3 and 5.5 Hz, 1H), 4.95 (d,d, J=3 and 5.5 Hz, 1H), 6.95-7.43 (m, 5H)
7a	96	106-108	237	2.13 (s, 3H), 2.60-4.34 (m, 6H), 6.88-7.48 (m, 5H)
7b	95	104-106	251	1.36 (d, J=6 Hz, 3H), 2.13 (s, 3H), 2.63-4.18 (m, 5H), 6.93-7.45 (m, 5H)
7c	95	102-106	265	1.09 (t, J=7.5 Hz, 3H), 1.34-1.94 (m, 2H), 2.14 (s, 3H), 2.58 (d,t, J=9.5 and 5.5 Hz, 1H), 3.52-3.82 (m, 2H), 3.96-4.14 (m, 1H), 6.91-7.36 (m, 5H)
8a	30	oil	189	2.58-3.81 (m, 6H), 6.92-7.43 (m, 5H)
8b	68	109-120	203	1.41 (broad d, J=5 Hz, 3H), 2.98-3.90 (m, 5H), 6.90-7.47 (m, 5H)
8c	70	69-79	217	1.16 (t, J=7 Hz, 3H), 1.65 (d,t, J=7 and 14 Hz, 2H), 2.93-3.85 m, 5H), 6.85-7.39 (m, 5H)
9a	83	73-75	189	4.03 (d, J=2 Hz, 1H), 4.10 (d, J=2 Hz, 1H), 4.73 (d, 2 Hz, 1H), 4.80 (d, J=2 Hz, 1H), 6.48-7.35 (m, 6H)
9b	75	oil	203	1.38 (J=7 Hz, 3H), 4.04 (broad s, 2H), 4.78-5.23 (m, 1H), 6.43-7.37 (m, 6H)
9c	75	oil	217	0.94 (t, J=7 Hz, 3H), 1.23-2.35 (m, 2H), 4.07 (broad s, 2H), 4.73-5.07 (m, 1H), 6.44-7.42 (m, 6H)

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