SYNTHESIS OF 5-ARYL-5,6,7,8-TETRAHYDROTHIAZOLO[3,4-a]PYRIDINIUM BROMIDES

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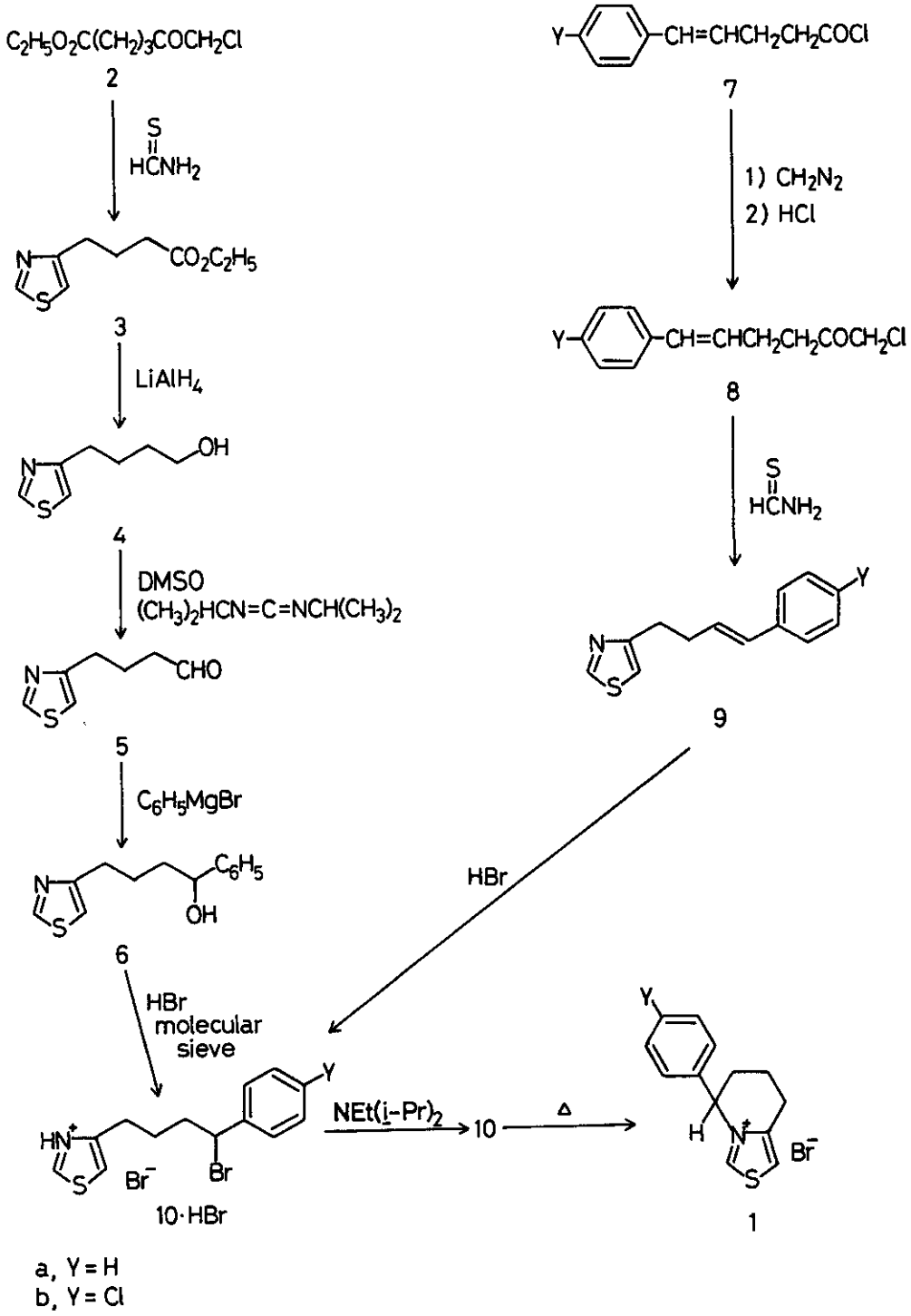
5,6,7,8-Tetrahydro-5-phenylthiazolo[3,4-a]pyridinium bromide (1a) and 5-(p-chlorophenyl)-5,6,7,8-tetrahydrothiazolo[3,4-a]pyridinium bromide (1b) have been synthesized with 4-(3-carboethoxypropyl)-thiazole (3) and/or 4-(4-phenyl-3-butenyl)thiazole (9a) or 4-[4-(p-chlorophenyl)-3-butenyl]thiazole (9b) as an intermediate.

In our continued study on the asymmetric benzoin condensation with optically active thiazolium salts,[2,3] it became necessary to synthesize 5-aryl-5,6,7,8-tetrahydrothiazolo[3,4-a]pyridinium salts (1). In this paper, we wish to report the synthesis of 1 by two different approaches (Scheme 1).

In the first approach, the α-chloroketone 2[4] was allowed to condense with thioformamide[5] to give the thiazole 3, bp 94.5–97.0°/0.15 mmHg, in 79% yield by stirring a solution of the two in ethanol–benzene (1:10) at room temperature for 16 h and then at 75° for 30 min. The spectral data of 3 were as follows: ir (neat) 1511 and 1411 cm^{-1} (thiazole ring); nmr ($CDCl_3$) δ 1.24 (3H, t, J=7 Hz, CH_3), 1.9–2.5 (4H, m, CH_2CH_2CO), 2.89 (2H, t, J=7 Hz, thiazole-CH_2), 4.14 (2H, q, J=7 Hz, OCH_2), 7.02 (1H, C=CH-S), 8.82 (1H, d, J=2 Hz, S-CH=N). Elemental analysis corresponded to $C_9H_{13}NO_2S$ (Calcd.: C, 54.24; H, 6.57; N, 7.03; S, 16.09. Found: C, 54.03; H, 6.65; N, 7.11; S, 16.34).

The reduction of 3 with lithium aluminum hydride gave 4 (59% yield): bp 97–99°/0.19 mmHg; ir (neat) 3320 (OH), 1060 cm^{-1} (C-O). Elemental analysis corresponded to $C_7H_{11}NOS$ (Calcd.: C, 53.49; H, 7.05; N, 8.91; S, 20.39. Found: C, 53.37; H, 7.14; N, 8.81; S, 20.29).

The dimethyl sulfoxide (DMSO)–carbodiimide oxidation[6] of alcohols was successfully applied to the conversion of 4 to the aldehyde 5. Compound 5 (oil) isolated in 44% yield by silica gel chromatography had the following spectral data: ir (neat) 2822 and 2722 (aldehyde -CH=), 1718 cm^{-1} (C=O); nmr ($CDCl_3$)


C2H5O2C(CH2)3COCH2Cl
2
S
HCNH2
CO2C2H5
3
LiAlH4
OH
4
DMSO
(CH3)2HCN=C=NCH(CH3)2
CHO
5
C6H5MgBr
C6H5
OH
6
HBr
molecular
sieve
Y
HN+
Br−
Br
10·HBr
NEt(i-Pr)2
10
Δ
Y
H
N+
Br−
1
Y-CH=CHCH2CH2COCl
7
1) CH2N2
2) HCl
Y-CH=CHCH2CH2COCH2Cl
8
S
HCNH2
Y
9
HBr
a, Y = H
b, Y = Cl

Scheme 1

2.06 (2H, quintet, J=7 Hz, $CH_2CH_2CH_2$), 2.52 (2H, distorted t, J=7 Hz, CH_2CO), 2.89 (2H, t, J=7 Hz, thiazole-CH_2), 7.02 (1H, C=CH-S), 8.81 (1H, d, J=2 Hz, S-CH=N), 9.81 (1H, t, J=1.4 Hz, CHO).

A Grignard reaction upon 5 using phenylmagnesium bromide gave the α-substituted benzyl alcohol 6 after silica gel chromatography (57% yield): oil; ir (neat) 3320 cm^{-1} (OH); nmr (DMSO-d_6) δ 1.66 (4H, m, CH_2CH_2CH-O), 2.74 (2H, m, thiazole-CH_2), 4.55 (1H, m, CH-O), 5.15 (1H, d, J=4 Hz, OH), 7.31 (6H, C_6H_5 and C=CH-S), 9.03 (1H, d, J=2 Hz, S-CH=N).

In the second approach, the acid chlorides 7 were converted to the chloroketones 8 (yields of crude products: 8a, 96%; 8b, 100%) by treating 7 with diazomethane and then hydrochloric acid. The following spectral data were obtained: (a) 8a, ir (KBr) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 2.21–2.84 (4H, m, CH_2CH_2), 3.89 (2H, s, CH_2Cl), 6.01 (dt, J=16 and 5 Hz, $C_6H_5CH=CH$), 6.38 (d, J=16 Hz, C_6H_5CH), 7.17 (5H, C_6H_5), (b) 8b, ir (KBr) 1726 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.3–2.9 (4H, m, CH_2CH_2), 4.08 (2H, s, CH_2Cl), 6.10 (dt, J=16 and 6 Hz, $C_6H_4CH=CH$), 6.45 (d, J=16 Hz, C_6H_4CH), 7.28 (4H, C_6H_4). Elemental analysis of 8a (crude, mp 56–58°) corresponded to $C_{12}H_{13}ClO$ (Calcd.: C, 69.08; H, 6.27; Cl, 16.98. Found: C, 69.13; H, 6.45; Cl, 17.06).

The chloroketons 8 were allowed to react with thioformamide[5] to give the thiazoles 9 (9a, 73% yield): (a) 9a, bp 130°/0.34 mmHg; ir (neat) 1512 and 1412 cm^{-1} (thiazole ring); nmr (CCl_4) δ 2.3–3.1 (4H, m, CH_2CH_2), 6.04 (dt, J=15.5 and 5 Hz, $C_6H_5CH=CH$), 6.36 (d, J=15.5 Hz, $C_6H_5CH=$), 6.77 (1H, C=CH-S), 7.13 (5H, C_6H_5), 8.55 (1H, d, J=2 Hz, S-CH=N) (Anal. Calcd. for $C_{13}H_{13}NS$: C, 72.50; H, 6.08; N, 6.50; S, 14.89. Found: C, 72.28: H, 6.04; N, 6.29; S, 14.66), (b) 9b, mp 60–62° (purified by distillation, bp 156–167°/0.1 mmHg, followed by recrystallization from hexane): ir (KBr) 1510 and 1406 cm^{-1} (thiazole ring); nmr ($CDCl_3$) δ 2.4–3.2 (4H, m, CH_2CH_2), 6.40 (dt, J=16 and 4 Hz, $C_6H_4CH=CH$), 6.43 (d, J=16 Hz, C_6H_4CH), 6.95 (1H, C=CH-S), 7.26 (4H, C_6H_4), 8.76 (1H, d, J=2 Hz, S-CH=N) (Anal. Calcd. for $C_{13}H_{12}ClNS$: C, 62.49; H, 4.84; Cl, 14.19; N, 5.61; S, 12.83. Found: C, 62.43; H, 4.84; Cl, 14.28; N, 5.40; S, 13.03).

The tetrahydrothiazolo[3,4-a]pyridinium bromides 1a,b were prepared from 6 and/or 9 via 4-(4-aryl-4-bromobutyl)thiazoles 10. Introducing of hydrogen bromide to an ice-cold solution of 6 or 9 in methylene chloride[7] followed by evaporation of excess hydrogen bromide and the solvent gave the corresponding 10·HBr,[8] from which the free bases 10 were generated by treating 10·HBr with N,N-diisopropyl-

ethylamine in methylene chloride. The solvent was displaced by dry benzene, insoluble N,N-diisopropylethylamine hydrobromide was removed by filtration, and the mixture was evaporated to remove any moisture present. The residue was taken up in dry benzene and heated at reflux to give 1 as precipitates (1a from 6, 71% yield; 1a from 9a, 78% yield; 1b from 9b; 84% yield). For the successful cyclization of 10 to 1, it was essential that the benzene solution of 10 was dry. When the solution was wet, dehydrobromination took place to give 9·HBr.

Both 1a and 1b were nicely crystalline compounds characterized by elemental analysis and ir and nmr spectroscopy: (a) 1a, mp 184.5–185.5° (recrystallized from CH_2Cl_2–CCl_4); ir (KBr) 1556 cm^{-1} (thiazolium ring); nmr ($CDCl_3$) δ 1.8–2.6 (4H, m, $C_6H_5CHCH_2CH_2$), 3.22 (2H, t, J=3 Hz, CH_2-thiazole), 6.34 (1H, t, C_6H_5CH), 7.29 (5H, C_6H_5), 8.31 (1H, C=CH-S), 9.75 (1H, d, J=2.5 Hz, S-CH=N^+) (Anal. Calcd. for $C_{13}H_{14}BrNS$: C, 52.70; H, 4.76; Br, 26.98; N, 4.73; S, 10.82. Found: C, 52.91; H, 4.85; Br, 26.81; N, 4.57; S, 10.96), (b) 1b, mp 236.5° (reprecipitated from CH_2Cl_2–CCl_4); ir (KBr) 1560 cm^{-1} (thiazolium ring); nmr (DMSO-d_6) δ 1.6–2.6 (4H, m, $C_6H_4CHCH_2CH_2$), 3.19 (2H, t, J=6 Hz, CH_2-thiazole), 6.11 (1H, t, J=7 Hz, C_6H_4CH), 7.35–7.71 (4H, m, C_6H_4), 8.23 (1H, C=CH-S), 9.77 (1H, d, J=2 Hz, S-CH=N^+) (Anal. Calcd. for $C_{13}H_{13}BrClNS$: C, 47.20; H, 3.96; Br, 24.16; N, 4.24; S, 9.69. Found: C, 47.56; H, 3.94; Br, 24.29; N, 4.10; S, 9.89). The observance of ir absorption at 1556 (1a) or 1560 cm^{-1} (1b) together with the lack of resonances around 2500 cm^{-1} supported the N-substituted thiazolium structure. The nmr spectra were featured by large downfield shifts observed for the C-1, C-3, and C-5 proton signals supporting the bonding of C-5 to the positively charged thiazolium ring.

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7) When 6 was used, molecular sieve (Linde 3A) was added to the solution to remove water to be generated by the reaction.

8) The conversion of 6 to 10 was also effected with thionyl bromide. However, the reaction was not a clean one, and the yield of 1a obtained via 10 was 26% based on 6.

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