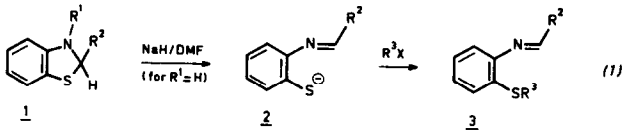
Tetrahedron Letters,Vol.26,No.11,pp 1457-1460,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A RING EXPANSION METHOD FOR THE PREPARATION OF 2,3-DIHYDRO-1,4-BENZOTHIAZINES FROM 2-ARYL-2,3-DIHYDROBENZOTHIAZOLES

Sabir H. Mashraqui and Richard M. Kellogg*
Department of Organic Chemistry, University of Groningen,
Nijenborgh 16, 9747 AG Groningen, The Netherlands

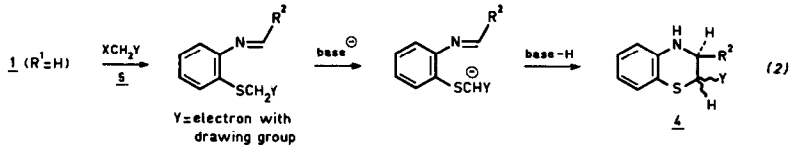
Summary: In the presence of KF in dimethylformamide (DMF) 2-aryl-2,3-dihydrobenzothiazoles react with α-haloketones to provide in good yield 2,3-dihydro-2,3-disubstituted-1,4-benzothiazines.

During the course of examination of the reducing properties of N-alkylated-2-substituted-2,3-dihydrobenzothiazoles,[1,2] we observed, in accord with literature precedent,[3] that attempts to alkylate 1a (excess NaH/DMF, alkyl halide) led in good yields to the ring-opened products 3 as shown in eq. 1.[4] The imine (2) must surely be an intermediate.[5]



(1)

We anticipated that the sequence detailed in eq. 2 would lead to the otherwise difficultly accessible 2,3-dihydro-1,4-benzothiazine derivatives 4 by means of a 6-endo trig carbon-carbon bond forming step.[6] This is indeed the case when KF in DMF[7] is allowed to react with 1 in the



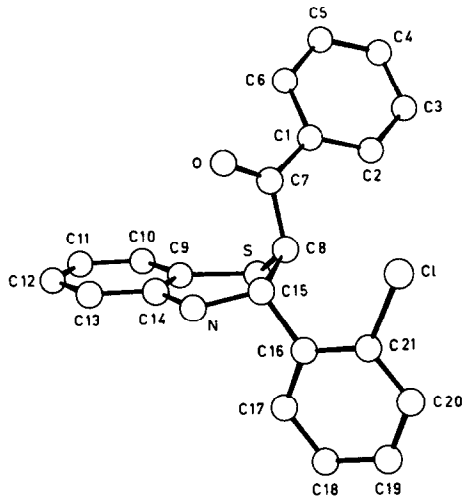
(2)

presence of suitable α-halo ketones 5 (Y = aryl). The results are given in the Table.

A representative example is the reaction of 1a (R^1 = H, R^2 = C_6H_5) with α-bromoacetophenone (5, X = Br, Y = COC_6H_5) carried out with a 10 molar excess of commercial KF in DMF for 15 hr at room temperature. The product 4, obtained in 90% isolated yield, consisted of two diastereomers in ca 4:1 ratio. The spectral data and the elemental analysis supported the assigned gross structures. The major diastereomer could be obtained pure in 55-60% yield by

crystallization from CH_3CN or C_2H_5OH. The ^1H NMR spectrum at 200 MHz in $CDCl_3$ reveals that H2 at δ 4.56 (d, J_{23} 5.6 Hz) and H3 at δ 4.98 (dd, J_{23} 5.6, J_{3NH} 2.9 Hz). The minor diastereomer has H_2 at δ 4.79 (J_{23} 2.9 Hz and H3 at δ 5.03 (dd, J_{23} 2.9, J_{3NH} 2.8 Hz). On the basis of the greater J_{23} coupling the major diastereomer is assigned the trans configuration.

The gross structural assignment to 4 was unambiguously confirmed by a X-ray crystallographic structural determination of the major diastereomer obtained from the ortho-chlorophenyl derivative of 1 with phenacyl bromide (entry 4, Table). An ORTEP projection is shown in the Figure. The compound clearly has the C2/C3 substituents arranged trans-diaxially. This is apparently also true in solution as judged from the anomalous J_{23} proton-proton coupling of 2.4 Hz. This is consistent, however, with an H-H angle of 85° as obtained from the crystal structure.[9,10]



ORTEP projection of 2-benzyl-3-(2-chlorophenyl)-2,3-dihydro-1,4-benzothiazine.[8] Hydrogen atoms omitted for clarity. The numbering is for crystallographic purposes.

The ortho-chloro group is apparently responsible for the diaxial conformation. Unfortunately crystals of the product of entry 1 were unsuitable for structural determination; attempts to dechlorinate the ortho-chlorophenyl derivative to this same product also failed.

With KF in DMF the reactions with bromoacetonitrile and ethyl α-bromoacetate (entries 2 and 3) stopped at the stage of S-alkylated 3. However, with NaH in DMF the subsequent ring closure proceeded smoothly. In contrast, α-chlorocyclopentanone (entry 9) reacted in the presence of KF/DMF to form the ring-expanded spiro derivative in a not optimized yield of 41%. A single diastereomer was isolated but the disposition of the carbonyl group relative to phenyl is not known.

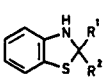
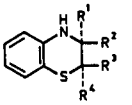
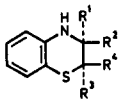
The stereoselectivity of the ring closure step reflects kinetic control arising from the steric bulk of the substituents at C2 and C3. For the benzoyl group trans/cis ratios of 4:1 to 14:1 (entries 1, 4, and 5) were obtained whereas with ethoxycarbonyl as the substituent on C2 the ratio drops to 3:1 and for the small nitrile group the trans/cis ratio is 1:1. When the dihydrobenzothiazine mixture of entry 8 (chosen to eliminate the possibility of reversible β-elimination of thiolate) was subjected to the enolizing conditions of 10% KOH in ethanol for 10 hr the trans/cis ratio changed from 2:1 to 10:1.

Ring expansions of N-acetylated benzothiazolines via oxidative pathways to N-acylated benzothiazolines have been described recently.[11] However, to the best of our knowledge, this is the first description of a ring expansion route that leads cleanly to the more elusive 2,3-dihydro derivatives. Extension to the synthesis of many substituted (2,3-dihydro)benzothiazine systems should be possible.

Acknowledgement. Partial support of this work was provided by the Netherlands Foundation for Scientific Research (Z.W.O.) administered by the Office for Chemical Research (S.O.N.) in the form of a fellowship to S.H.M. We are grateful to Mr. F. van Bolhuis of the Department of Chemical Physics for determination of the crystal structure.

TABLE

Ring Expansion of Dihydrobenzothiazoles[a] to 2,3-Dihydrobenzothiazines

Entry		Alkylating Agent	Yield[b,c]		
1	R^1=H; R^2=C_6H_5	$BrCH_2COC_6H_5$[d]	90	R^3=COC_6H_5; R^4=H (4)	R^3=H; R^4=$CO_2C_2H_5$ (1)
2	same	$BrCH_2CO_2C_2H_5$[e]	74	R^3=$CO_2C_2H_5$ R^4=H (3)	R^3=H; R^4=$CO_2C_2H_5$ (1)
3	same	$BrCH_2CN$[e]	76	R^3=CN; R^4=H (1)	R^3=H; R^4=CN (1)
4	R^1=H; R^2=2-ClC_6H_4	$BrCH_2COC_6H_5$[d]	93	R^3=COC_6H_5; R^4=H (14)	R^3=H; R^4=COC_6H_5 (1)
5	R^1=H; R^2=4-ClC_6H_4	same	91	R^3=COC_6H_5; R^4=H (4)	R^3=H; R^4=COC_6H_5 (1)
6	R^1=R^2=CH_3	same	72	R^3=H; R^4=COC_6H_5	
7	same	$BrCH_2CN$[e]	70	R^3=H; R^4=CN	
8	R^1=CH_3; R^2=C_6H_5	$BrCH_2COC_6H_5$[d]	81	R^3=COC_6H_5; R^4=H (2)[f]	R^3=COC_6H_5; R^4=H (1)[f]
9	R=H; R^2=C_6H_5	2-chlorocyclopentanone	41[g,h]	R^3, R^4=$CO(CH_2)_3$	

a) Prepared by condensation of o-aminothiophenol with appropriate carbonyl precursors; b) Combined yields cis/trans mixtures; c) Trans/cis ratios (given in parentheses) based on integration of ^{1}H NMR spectra; d) Reaction conditions: 10 molar excess KF in DMF for 15 hr at ambient temp; e) Reaction conditions: 1.25 equiv. NaH in DMF for 1-3 hr at 0° to ambient temp; f) On treatment with 10% KOH in C_2H_5OH ratio changed to 10:1 in favor of trans diastereomer; g) About 30% benzothiazoline was recovered; h) Single diastereomer by NMR spectroscopy; stereochemistry unknown.

Footnotes and References

1. See preceding paper in this issue.
2. Syntheses of 1 (R^1 = alkyl) are usually carried out by alkylating the nitrogen at an earlier stage. See, for example, preceding paper, ref. 2 and Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F.M.; J. Org. Chem., 1975, 40, 3453.
3. The tautomeric equilibrium for 2,3-dihydrobenzothiazoles lies entirely on the side of the ring-closed structure: see: (a) Goetz, F.J.; J. Heterocyclic Chem., 1968, 5, 509; 1967, 4, 80; (b) Hori, M.; Kataoka, T.; Schimizie, H.; Imai, H.; Heterocycles, 1978, 15, 1413.
4. For 1 (R^1 = H, R^2 = C_6H_5) reaction with NaH in DMF followed by treatment with CH_3I gave 3 (R^2=C_6H_5, R^3=CH_3) in 65% yield [mp 44-45°, lit. (Heterocycles, 1975, 12, 567) 46-47°].
5. The imine functionality in 2 should be trans. See: (a) Grellmann, K.H.; Tauer, E.; J. Am. Chem. Soc., 1973, 95, 3104; (b) Fischer, E.; Frei, Y.; J. Chem. Phys., 1957, 21, 808.
6. Baldwin, J.E.; J. Chem. Soc., Chem. Commun., 1976, 734.
7. For fluoride ion induced alkylations, enolizations, and other reactions, see: (a) Clark, J.H.; Miller, J.M.; J. Chem. Soc., Chem. Commun., 1976, 229; (b) Clark, J.H.; Miller, J.M.; J. Am. Chem. Soc., 1977, 99, 498; (c) Ishikawa, I.; Kitazume, T.; Nakabayashi, M.; Chem. Lett., 1980, 1089; (d) Mukaiyama, T.; Morito, N.; Wanatabe, Y.; Chem. Lett., 1976, 531.
8. (a) The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom. Any request should be accompanied by the full literature citation for this communication; (b) Supplementary data available include cell dimensions, standard deviations, space group, units per cell, refined coordinates, bond distances, and structure factors. See Announcement to Authors, Tetrahedron Letters, 1983, 47, 5154.
9. Some physical and spectral data for representative products follow: Entry 1, major: m.p. 146-147°; IR (KBr): 3405, 1670 cm^{-1}; NMR: δ 4.29 (NH), δ 4.56 (d, 1H, J 5.7 Hz), δ 4.96 (dd, 1H, J 5.7 and 2.5 Hz); minor (not isolated): NMR: δ 4.35 (NH), δ 4.79 (d, 1H, J 2.88 Hz), δ 5.03 (dd, 1H, J 2.9 and 2.8 Hz). Entry 2: major (oil); NMR: δ 3.88 (d, 1H, J 7 Hz), δ 4.26 (NH), δ 4.81 (d, 1H, J 7 Hz); minor (oil); NMR δ 3.97 (d, 1H, J 3.5 Hz), δ 4.26 (NH), δ 5.0 (d, J 3.5 Hz). Entry 3 (major): m.p. 135-130°; IR (KBr): 3410, 2235 cm^{-1}; NMR: δ 4.0 (d, 1H, J 5.7 Hz), δ 4.47 (NH), δ 4.97 (dd, 1H, J 5.7 and ~ 1 Hz); minor (not isolated): NMR: δ 3.95 (d, 1H, J 1-1.5 Hz), δ 4.30 (NH), δ 4.86 (1H, d, J 1-1.5 Hz). Entry 4 (major): m.p. 194-197°; IR (KBr): 3375, 1657 cm^{-1}; NMR: δ 4.58 (d, 1H, J 2.4 Hz), 4.64 (d, NH, J 5.5 Hz), δ 5.58 (dd, 1H, J 2.4 and 5.5 Hz); minor (not isolated): NMR: δ 4.88 (d, 1H, J 3.35 Hz), δ 5.49 (d, J 3.35 Hz), NH absorption not discernible. Entry 5 (major): m.p. 155-156°; IR (KBr): 3390, 1660 cm^{-1}; NMR: δ 4.29 (NH), δ 4.51 (d, 1H, J 5.36 Hz), δ 4.96 (dd, J 5.36 and ~ 1 Hz); minor (not isolated) NMR: δ 4.13 (NH), δ 4.79 (d, 1H, J 2.7 Hz), δ 5.03 (dd, J 2.7 and 1 Hz); Entry 6 (major): IR (neat) 3395, 1662 cm^{-1}; NMR: δ 1.36 (6H, s), δ 4.0 NH), δ 4.41 (s, 1H); Entry 7 (major): m.p. 62-63°; IR (KBr): 3370, 2240 cm^{-1}; NMR: δ 1.28 (s, 3H), δ 1.45 (s, 3H), δ 3.50 (s, 1H), δ 3.83 (NH); Entry 8 (major): m.p. 151-152°C, IR (KBr): 3392, 1662 cm^{-1}; NMR: δ 1.71 (s, 3H), δ 4.40 (NH), δ 4.71 (s, 1H); minor (not isolated): NMR: δ 1.74 (s, 3H), δ 4.51 (NH), δ 4.60 (s, 1H); Entry 9 (major): m.p. 127-128°; IR (KBr): 3370, 1705 cm^{-1}; NMR: δ1.35-2.42 (m, 6H), δ 4.48 (NH), δ 4.80 (s, 1H). All NMR spectra were taken in $CDCl_3$ at ambient temperature on a 200 MHz apparatus.
10. H-3 in both major and minor diastereomers appears downfield by about 0.5 ppm compared to H-3 of the phenyl and 4-chlorophenyl analogs. The proximity of the chloro substituent to H-3 in o-chlorophenyl substituted dihydrobenzothiazine (entry 5) is thus clearly evident.
11. See, for example: (a) Chiocara, F.; Nicolaus, R.A.; Movellino, E.; Prota, G.; Synthesis, 1977, 876; (b) Chioccara, F.; Oliva, L.; Prota, G.; Synthesis, 1978, 744; (c) Hori, M.; Kataoka, T.; Shimizu, H.; Yutaka, I.; Heterocycles, 1978, 1413; (d) Hori, M.; Kataoka, T.; Shimizu, H.; Ueda, N.; Tetrahedron Lett., 1981, 1701; (e) Liso, G.; Trapani, G.; Latrofa, A.; Marchini, P.; J. Heterocyclic Chem., 1981, 18, 279; (f) Hori, M.; Kataoka, T.; Shimizu, H.; Imai, Y.; Chem. Pharm. Bull., 1979, 29, 1982; for the condensation of ortho-aminothiophenol with phenacylbromide, see: (g) Wilhelm, M.; Schmidt, P.; J. Heterocyclic Chem., 1969, 6, 635; for some alternative syntheses, see ref. 2 and (h) Rai, M.; Kumar, S.; Krishan, K.; Singh, A.; Chem. Ind. (London), 1979, 26; (i) Knyazev, V.N.; Drozd, V.N.; Minov, V.M.; Akimova, N.P.; Zh. Org. Khim., 1977, 13, 1255; Chem. Abstr., 1977, 87, 152098x.

(Received in UK 18 January 1985)