Tetrahedron Letters No. 1, pp 13 - 16, 1978. Pergamon Press. Printed in Great Britain.

NEW ANNULATION PROCESSES FOR FUSED AND SPIRO RINGS BASED ON THE CHEMISTRY OF BENZOTHIAZOLES

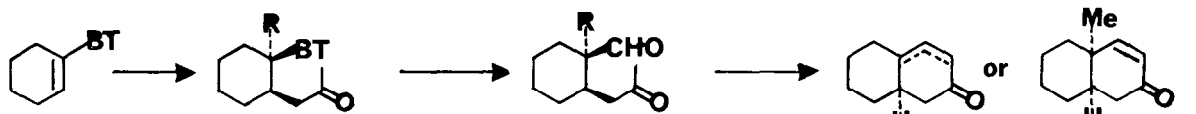
E. J. Corey and Dale L. Boger

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

(Received in USA 13 September 1977; received in UK for publication 8 November 1977)

The successful development of synthetic routes to complex cyclic molecules usually depends more heavily on the availability of processes for ring formation than on any other class of synthetic operation. Accordingly the discovery of versatile and especially stereoselective methodology in this area is of particular importance.[1,2] The studies reported in the two preceding papers[3] and those described herein all had as the paramount objective the generation of new synthetic methods for the formation of fused or spiro 5- and 6-membered rings. In our new approach the carbonyl group serves as the origin of reactivity in the precursor substrate and the 2-benzothiazole (BT) unit is introduced to direct or provide a basis for all subsequent operations. A variety of specific annulation sequences are now presented to illustrate the power and potentialities of such uses of the BT unit. It should be noted that the types of structures which result from these sequences often are not available as directly or with the same stereochemical control using preexisting annulation procedures.

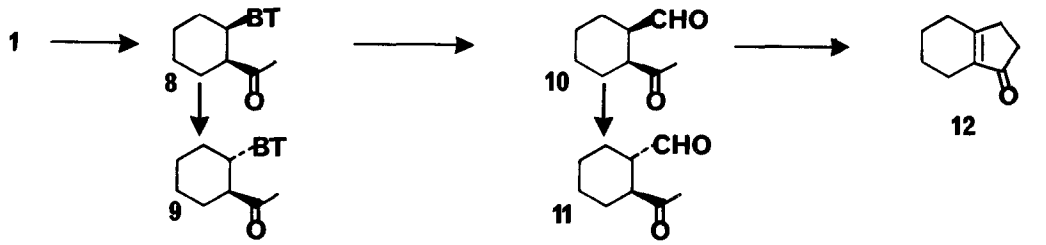
I. ANNULATION INVOLVING CONJUGATE ADDITION TO VINYL BT'S. (A) 6/6 FUSED RINGS. The α-lithio derivative of acetone dimethylhydrazone[4] (acetone DMH, 1.75 equiv) underwent clean conjugate addition to the vinyl BT 1 (-78°, 20 min, 0.12 M in THF containing 3.5 equiv HMPA) and upon quenching of the resulting α-lithio BT (MeOH, -78°) or (3.0 equiv MeI, -78°, 60 min) afforded the crude



1 (from cyclohexanone)[3] 2 R=H 3 R=Me 4 R=H 5 R=Me 6 R=H 7

DMH-BT's which were hydrolyzed to the corresponding ketones 2 (93%[5] overall, 86/14 cis/trans) and 3 (94% overall, 95/5 cis/trans) using pH 7 buffered $CuCl_2$[6] in aq. THF (1.2 equiv, 16 and 21 hr respectively). The pure cis-keto BT's 2 and 3 (which were obtained by routine column chromatography on SiO_2) were converted to the corresponding cis-keto-aldehydes 4 and 5 (91%, 62%, Table I). Cyclization of 4 and 5 (40-50 mg TsOH in 10 ml PhH per mmol, reflux, $-H_2O$) afforded the Δ^1-3-octalones 6[7] (81-90%) and cis-7[8] (60 min, 91%). In the case of enone 6 the cis/trans ratio varied with reaction time; 68/32 (30 min), 9/91 (3-4 hr), and ca. 3/97 (at equilibrium), and all products contained ca. 5% of the non-conjugated isomer.

(B) 6/5 FUSED RINGS. 1-Methoxyvinyllithium[9] (7.0 equiv) added readily to the vinyl BT 1 (-78°, 2 hr, 0.12 M THF; MeOH, -78°) to give after mild hydrolysis of the vinyl ether (7 ml of 0.020 N HCl in 4:1 THF:H_2O per mmol, 25°, 8 hr) the cis-keto BT 8 (93%, >95% cis). Prolonged treatment of 8 with 1-2 N HCl (aq THF) afforded the corresponding trans-keto BT 9. The cis-keto BT 8 was converted to the cis-keto aldehyde 10 (88%, Table I) which upon treatment with mild acid afforded the trans-keto aldehyde 11. Exposure of either 10 or 11 to 0.5 N NaOH in EtOH (55°, 15-20 min) afforded the cyclopentenone 12 (86%) identical in all respects to an authentic sample.[10]



(C) 6/5 SPIRO RINGS WITH VICINAL APPENDAGE INTRODUCTION (2 STEREOCENTERS). Treatment of the vinyl BT 1 with MeLi (1.75 equiv, -78°, 165 min, 0.12 M THF containing 4.5 equiv HMPA) followed by propargyl bromide (3.5 equiv, -78, 50 min, -78° to 25°, 10 min) afforded the BT 13 (96%, ≥ 98% isomerically pure). Conversion of the BT 13 to the aldehyde 14 (74%, ≥ 98% isomerically pure,

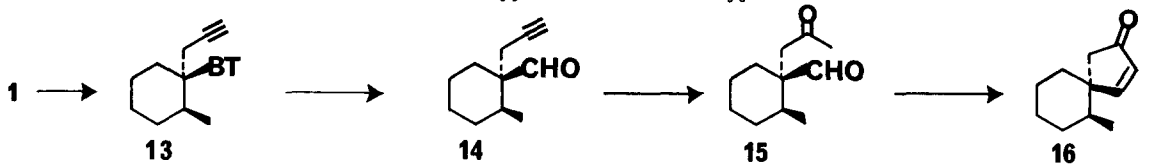
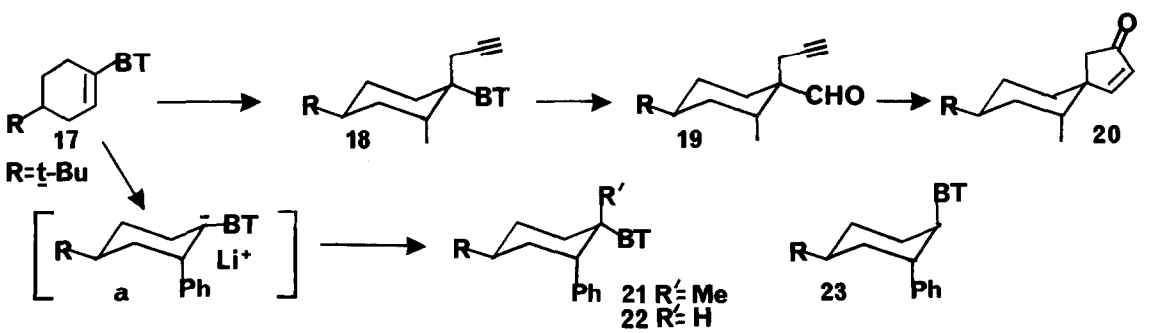


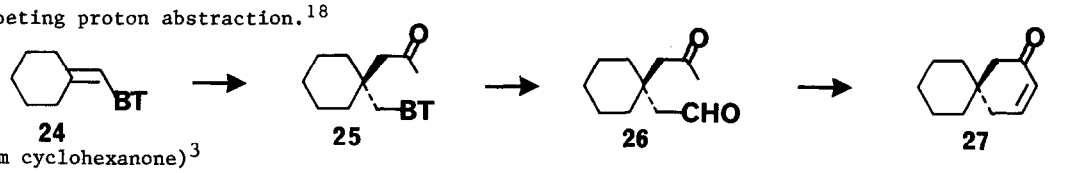
Table I) followed by Hg(II) catalyzed[11] hydration of the terminal triple bond (0.1 equiv $HgSO_4$; THF/H_2O/conc. H_2SO_4, 5 ml/2ml/0.2 ml per mmol of substrate; 60 min, 25°) afforded the crude keto-aldehyde 15 with no trace of dialdehyde. Treatment of 15 with 0.5 N NaOH/EtOH (8.0 ml per mmol, 25°, 60 min) gave the spiro-enone 16[12] in 78% overall yield from the aldehyde 14.

(D) SPIRO 6/5 RINGS WITH APPENDAGE INTRODUCTION (3 STEREOCENTERS). Treatment of the vinyl BT 17[3] with MeLi (2.0 equiv, -78°, 135 min, 0.12 M THF containing 4.5 equiv HMPA) followed by propargyl bromide (3.0 equiv, -78°, 2 hr, 0°, 2 hr) yielded the BT 18 (81%, mp 114-115°) as only one detectable isomer. The stereochemical assignment although not proved, seems reasonable on the basis of following observations. (1) The adduct derived from PhLi addition (1.75 equiv, 60 min, -78°, THF) to the vinyl BT 17 followed by quenching with MeI (3.0 equiv, -78°, 1 hr) affords a product 21 (94%, mp 129.5-130.5°) containing an axial phenyl group (equatorial benzylic methine)[13], indicating that axial attacks on the vinyl BT 17 is highly favored. Methylation of the intermediate anion (a) by axial attack can then be confidently expected. (2) In agreement, quenching of the intermediate anion (a) with MeOH (-78°) affords a product 22 (92%, mp 147-148°) which displays one axial and one equatorial methine proton as revealed by downfield peaks in the pmr spectrum[13] along with only a minor amount (3%) of a by-product 23 containing two downfield equatorial methines[13]. (3) The assigned stereochemistry also accords with previous observations on conjugate addition and alkylation of other cyclic unsaturated BT's reported in the preceding paper.[3,14]



Conversion of the BT 18 to the aldehyde 19 (75%, >99% isomerically pure, Table I) followed by Hg(II) catalyzed hydration of the terminal acetylene to a methyl ketone as described previously (25°, 45 min) and cyclization of the resulting keto-aldehyde (8.0 ml of 0.5 N NaOH in EtOH per mmol, 25°, 60 min) yielded the spiro enone 20[15] (75%).

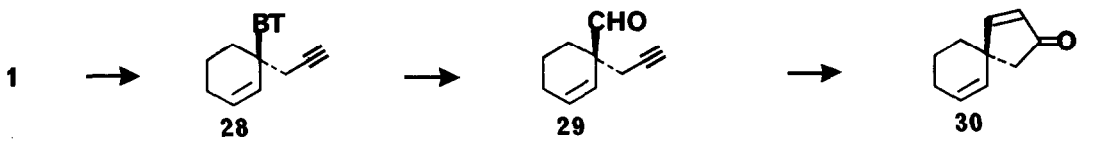
(E) SPIRO 6/6 RINGS. Treatment of the vinyl BT 24[3] with the orange-colored homo-cuprate derivative of acetone DMH[4,16] (3.0 equiv, 0.10 M in THF, -78°, 45 min, -30 to -20°, 45 min, 0°, 4 hr; MeOH quench) followed by pH 7 buffered $CuCl_2$ hydrolysis[6] (1.5 equiv, 14hr) of the crude DMH-BT afforded the keto-BT 25 (89%). Conversion of 25 to the keto-aldehyde 26 (85%, Table I) and cyclization (15 mg TsOH, 10 ml PhH per mmol, reflux, $-H_2O$, 55 min) afforded spiro-[5.5]-undec-2-ene-4-one 27[17] (90%). Noteworthy here is the fact that an organo-cuprate reagent adds in a conjugate fashion (≥ 90%) to a β,β-disubstituted vinyl BT (a β,β-disubstituted enal equivalent) with no trace of competing proton abstraction.[18]



24 25 26 27

(from cyclohexanone)[3]

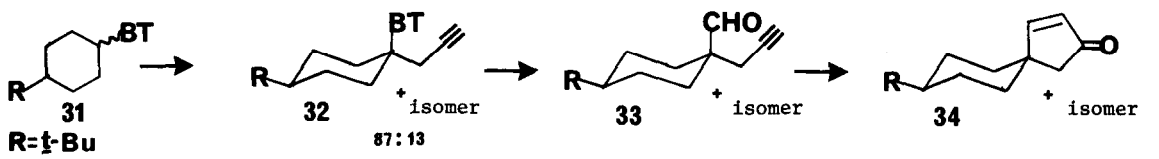
II. ANNULATION INVOLVING ALKYLATION OF VINYL BT's (F) 6/5 SPIRO RINGS. Reaction of the vinyl BT 1 with lithium diisopropylamide (1.1 equiv, -78°, 3 hr, 0.12 M in THF)[3] followed by propargyl bromide (3.0 equiv, 2.0 equiv HMPA, -78°, 2 hr, 0° to 25°, 4.5 hr) produced the BT 28 (96%). Conversion of 28 to the aldehyde 29 (82%, Table I) followed by Hg(II) catalyzed hydration of the terminal



28 29 30

acetylene to a methyl ketone as described previously (25°, 45 min) and aldolization of the resulting keto-aldehyde (8.0 ml 0.5 N NaOH/EtOH per mmol, 25°, 45 min) gave spiro-[4.5]-deca-1,6-diene-3-one 30[19] (78%).

III. ANNULATION INVOLVING ALKYLATION OF SATURATED BT'S (G) SPIRO 6/5 RINGS (2 STEREOCENTERS). Treatment of the saturated BT 31[3] with n-BuLi (1.2 equiv, -78°, 2 hr, 0.16 M in THF) followed by propargyl bromide (3.0 equiv, -78°, 2 hr, 0° to 25°, 3 hr) yielded the BT 32 (97%, 87:13 axial: equatorial BT), the major product being the result of equatorial alkylation.[3] Conversion of 32 to the aldehyde 33 (78%, Table I) followed by Hg(II) catalyzed hydration of the terminal acetylene to



31 R=t-Bu 32 87:13 33 34

to a methyl ketone as described (25°, 45 min) and cyclization of the resulting keto-aldehyde (8.0 ml of 0.5 N NaOH/EtOH per mmol, 25° 1 hr) afforded the known spiro-enone 34[20] (81%, 87:13 mixture of isomers); 2,4-DNP, mp 201-202° (red needles, from EtOH).

A plethora of ramifications and extensions of the approach entailed in this study can be envisaged, as well as applications to interesting synthetic problems.[21]

Table I. Conditions for Conversion of Substituted BT's to Aldehydes[3]

BT	Methylation[a] conditions	Reduction[b] conditions	Aldehyde method[c], % yield[d]	pmr (ppm)
2	1.2 (2.5 hr)	3.0, A., 1 hr	4, C., 91%	9.66 (s)
3	2.0 (313 hr)	3.0, A., 1 hr	5, C., 61%	9.47 (s)
8	1.2 (2.5 hr)	3.0, A., 0.5 hr	10, C., 88%	9.36 (s)
13	2.0 (99 hr)	4.4, B.	14, D., 74%[f]	9.81 (s)
18	2.0 (106 hr)	5.0, B.	19, D., 75%[g]	9.53 (s)
25	1.2 (3 hr)	3.0, A., 1 hr	26, C., 85%	9.81 (t, J = 2.5 Hz)
28	2.0 (48 hr)	5.0, B.	29, D., 82%[h]	9.52 (s)
32	2.0 (89 hr)	5.0, B.	33, D., 78%	9.58 (s)[i], 9.48 (s)

(a) No. of equiv $MeOSO_2F$ (time), run in 4.0 ml CH_2Cl_2 per mmol substrate, 25° (b) No. equiv $NaBH_4$; 5.0 ml EtOH per mmole substrate; A. = -78° in the presence of 10.0 equiv acetone; B. = -20°, 20 min. (c) C. = Ag(I) promoted hydrolysis[3]; D. = methylation followed by aq base/THF hydrolysis[3]. (d) After purification, distillation (e) Spectra recorded in $CDCl_3$, formyl pmr chemical shift reported. (f) 2,4-DNP, mp 131-132° (g) 2,4-DNP, mp 167-169° (h) 2,4-DNP mp 136.5-137.5° (i) Major isomer

References

1. For recent reviews see (a) M. E. Jung, Tetrahedron, 32, 3 (1976); (b) J. A. Marshall, S. F. Brady, and N. H. Andersen, Fortschr. Chem. Org. Naturst., 31, 283 (1974).
2. Often the key to devising a simple and logical synthetic sequence emerges from the strategy of taking as a goal the application of an appropriate ring transform(retroreaction) to the antithetic simplification of the target structure. Repetition of this strategy with effective look-ahead or search techniques (e.g. to remove obstacles, generate local symmetry, etc.) can assist in the solution of even very complicated problems. See, (a) E. J. Corey, Quart. Rev. Chem. Soc., 25, 455 (1971); (b) E. J. Corey, W. J. Howe, and D. A. Pensak, J. Am. Chem. Soc., 96 7724 (1974).
3. E. J. Corey and D. L. Boger, Tetrahedron Lett., preceding papers.
4. E. J. Corey and D. Enders, Tetrahedron Lett., 3, 11 (1976).
5. All yields reported herein refer to samples isolated by evaporative distillation or chromatography; all compounds reported were fully characterized by pmr, ir, and mass spectral analysis. THF and HMPA refer to tetrahydrofuran and hexamethylphosphoric triamide.
6. E. J. Corey and S. Knapp, Tetrahedron Lett., 3667 (1976).
7. M. P. Mertes, P. E. Hanna, and A. A. Ramsey, J. Med. Chem., 13, 125 (1970).
8. Stereochemical proof of the cis ring junction is presented in the following paper.
9. J. E. Baldwin, G. A. Hofle and O. W. Lever Jr., J. Amer. Chem. Soc., 96, 7125 (1974).
10. R. Bishop and W. Parker, Tetrahedron Lett., 2375 (1973).
11. G. Stork and R. Borch, J. Amer. Chem. Soc., 86, 935, 937 (1964); D. A. McCrae and L. Dolby, J. Org. Chem., 42, 1607 (1977); A.M. Islam and R. A. Raphael, J. Chem. Soc., 4068 (1952).
12. Pmr ($CDCl_3$, ppm): 7.73 (1H, d, J=6 Hz), 6.13 (1H, d, J=6 Hz), 0.78 (3H, d, J=6Hz); ir film: 1710, 1590; ms: 164 (M^+), 94 (base); 2,4-DNP mp 141-143°, ms: 344 (M^+, base).
13. Pmr ($CDCl_3$, ppm); 21: 3.4 (1H, rough t, J=4 Hz, $w_{1/2}$ = 9-10 Hz, equatorial benzylic methine); 22: 3.8 (1H, m, $w_{1/2}$ = 12-13 Hz, equatorial benzylic methine), 3.56 (1H, m, $w_{1/2}$ = 24-30 Hz, axial α-BT methine); 23: 3.79 (2H, one thin m, $w_{1/2}$ = 9-10 Hz, overlapping equatorial benzylic and α-BT methine).
14. See also H. O. House, C. Y. Chu, J. M. Wilkins, and M. J. Umen, J. Org. Chem., 40, 1460 (1975).
15. Pmr ($CDCl_3$, ppm): 7.58 (1H, d, J=6 Hz), 6.03 (1H, d, J=6 Hz), 1.08 (3H, d, J=7 Hz), 0.86 (9H, s); ir (film): 1720, 1590; ms: 220 (M^+), 57 (base); 2,4-DNP mp 175-177°, ms: 400 (M^+, base).
16. The homo-cuprate derivative of acetone DMH was formed as follows: the α-lithio derivative of acetone DMH[4] (0.25 M in THF, -78°) was treated with 0.5 equiv of CuI (solubilized using CuI/diisopropyl sulfide 1:4 ratio, precooled to -78° in THF, and added dropwise) and stirred at -78° (5-10 min), -30 to -20° (25 min) and 0° (5-10 min).
17. Pmr ($CDCl_3$, ppm): 6.80 (1H, t split d, J=4 and 10 Hz), 5.96 (1H, t split d, J=2 and 10 Hz); ir (film):1676; ms: 164 (M^+), 68 (base).
18. The reaction of the α-lithio derivative of acetone DMH (1.75 equiv, -78°, 1.5 hr, 0.12 M in THF containing 3.5 equiv of HMPA; MeOH, -78°) with the vinyl BT 24 gave 50% of conjugate addition product and 50% of the deconjugated isomer of 24.
19. Pmr ($CDCl_3$, ppm): 7.43 (1H, d, J=5.5 Hz), 6.04 (1H, d, J=5.5 Hz), 5.81 (1H, t split d, J=3.5 and 10 Hz), 5.33 (1H, rough d, J=10 Hz), 2.29 (2H, s); ir (film): 1715, 1588; ms: 148 (M^+), 91 (base); 2,4-DNP mp 140.5-141.5, ms: 328 (M^+).
20. S. F. Martin, T. Shue, and C. W. Payne, J. Org. Chem., 42, 2520 (1977).
21. This work was assisted financially by a grant from the National Science Foundation.