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BENZOTHIAZOLES AS CARBONYL EQUIVALENTS

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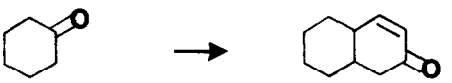
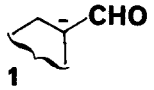
The objective of the investigation described in this and the following papers was to develop methodology for the conversion of cyclic ketones to spiro and fused annulation products not readily accessible by conventional methods[1] (e.g., cyclohexanone → Δ^1-3-octalone).



Our approach centered on two key synthetic operations: (1) the conversion of cyclic ketones to synthetic equivalents of formyl stabilized anions, illustrated by 1 and 2, and (2) the conversion of cyclic ketones to synthetic equivalents of formyl substituted Michael acceptors (3). Special properties are required for the formyl equivalent in each case; for example, it should be noted that α,β-unsaturated aldehydes tend to react with carbon nucleophiles (even cuprates) as carbonyl rather than Michael acceptors.[2]



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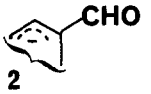

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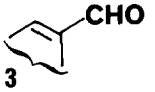

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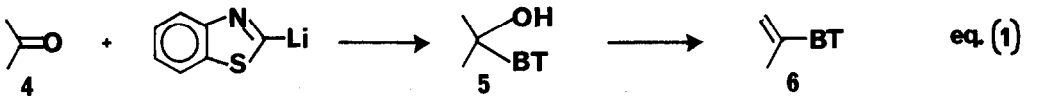
The benzothiazole nucleus (hereafter denoted as BT) appeared deserving of study since its chemical properties seemed appropriate, and 2-lithiobenzothiazole is available simply and in high yield and readily adds to carbonyl groups.[3] We now describe a number of key reactions of BT carbonyl adducts which form a basis for a broad range of synthetic applications.

The BT carbinols 5a-f were obtained in good yields (74-89%, Table I) by a procedure similar to that previously described.[3] Despite much work in the BT field including the preparation of α-hydroxy-BT's, little attention had been given to the dehydration of these carbinols. We have found three general methods that are effective for this conversion. The reagent composed of P_2O_5/CH_3SO_3H (1/10, w/w)[4,5] cleanly converts the tertiary carbinols 5 into the vinyl BT's 6 as indicated in Table I. The procedure, which is applicable to large scale preparations, involves dissolution of the carbinol 5 in the reagent (2.0 mmol/5.0 g, 1 hr, 25°) followed by gentle warming (60°) for 5-12 hr before basic aq. workup. In addition, the standard acid-catalyzed dehydration with azeotropic removal of H_2O (50-65 mg TsOH in 30 ml of benzene per mmol of substrate at reflux for 5 days) is effective. Thirdly, we have found that the reagent $MeOOCN^-SO_2N^+Et_3$[6] efficiently and rapidly dehydrates the carbinol 5a to the vinyl BT 6a in benzene employing conditions that should be generally applicable to acid sensitive compounds.[7]

The preparation of vinyl BT's involving the one carbon homologation is complemented by a two-carbon homologation based on the Peterson olefination.[8] Metallation [9] of 2-methyl BT was easily accomplished (1.0 equiv of n-BuLi, 10 min, -78°, 3.1 ml Et_2O/ mmol) and the resulting α-lithio

Table I. Conversion of Carbonyl Compounds to Vinyl Benzothiazoles



4 5 6 eq. (1)

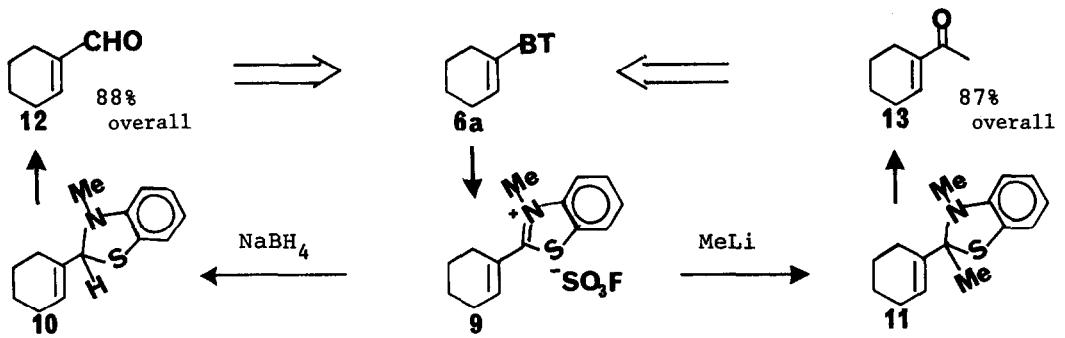
	Carbonyl Compound	% yield, mp of 5[a,b]	Conditions for 5→6 reagent[c], time (temp)	% yield, mp of 6[a,d]
a.	cyclohexanone	83-85%, 100-101°	A., 9-12 hr (60°)	98%, 63.5-64.5°
			B., 5 days (reflux)	96%
			C., 2 hr (25°)	99%
			3 hr (45-50°)	
b.	4-t-butyl-cyclohexanone	83%,[e]	A., 12 hr (60°)	98%, 96.5-97.5°
c.	cyclopentanone	79%, 83.5-84.5°	A., 5 hr (60-65°)	99%, 90-91°
d.	6-methoxy-α-tetralone	89%[f], 65-66°	A., 4 hr (25°)	86%, 70-72°
e.	cyclooctanone	80%, 65-66.5°	A., 9.5 hr (60-65°)	85%, 70-71°
f.	acetone	74%, 93-95°	A., 10 hr (60°)	93%[g]

(a) All products exhibited the expected pmr, ir, and mass spectral properties. Preparation of the carbinols 5 were all performed on 5.0-50.0 mmol scales. Preparation of the vinyl BT's 6 were all performed on 1.0-30.0 mmol scales. (b) After recryst. from ligroin. (c) A. P_2O_5/CH_3SO_3H (1/10, w/w); 2.0 mmol substrate/5.0 g reagent. Reaction mixtures were first stirred for 1 hr (25°) before warming. B. 50-65 mg TsOH in 30 ml benzene per mmole substrate at reflux with azeotropic removal of H_2O. C. 1.5-1.7 equiv. $MeOOCN^-SO_2N^+Et_3$, 10.0 ml benzene/mmole substrate. (d) Yield after column chrom. (SiO_2). (e) White solid, ca. 1:1 mixture of isomers. (f) 5.0 mmol of ketone in 7.5 ml of toluene was added to 5.0 mmol of 2-lithio BT in 15 ml of ether (g) Low melting solid.

derivative quantitatively silylated with trimethylsilyl chloride (1.0 equiv, -78°, 45 min, -23°, 45 min) to produce the reagent 7. Further metallation of 7 (without isolation using 0.93 equiv of n-BuLi, -78°, 20 min) and condensation of the resulting α-lithio derivative with carbonyl compounds (0.91 equiv, -78°, 45 min) followed by elimination of Me_3SiOLi (25°, 2-10 hr) affords the vinyl BT's 8 generally in > 90% yield (after column chromatography) in a variety of cases.[10] This mild one-flask preparation of vinyl BT's with in situ generation of $BTCH_2TMS$ 7 and the corresponding anion constitutes a superior alternative to the Horner-Emmons reagent[11], $BTCH_2P(O)(OEt)_2$, and offers special advantages over a two step procedure involving isolation of a β-hydroxy-BT.[12]

7 8 eq. (2)

The conversion of C-2 of the BT nucleus into a carbonyl group by the mildest possible method is imperative to the integration of BT chemistry into general synthetic methodology. To this end two general schemes have been devised for the preparation of α,β-unsaturated aldehydes and ketones, as illustrated and detailed below. Methylation of 2-substituted BT's utilizing methyl fluorosulfonate ($MeOSO_2F$) in CH_2Cl_2 (4.0 ml/mmole substrate) followed by hydride reduction of the crude salts (3-5.0 equiv $NaBH_4$, -20°, 5.0 ml EtOH/mmol substrate, 20 min) affords the crude N-methyl



benzothiazolines (e.g., 10) in near quantitative yields. For the reduction of these salts containing other reducible functionality (e.g., a keto) the reaction may be carried out similarly at -78° in the presence of 10.0 equiv of acetone requiring ca. 1 hr for completion. Alternatively, the crude salts (e.g., 9) react with organometallic reagents[13] (e.g., MeLi, MeMgBr) to afford 2,2-disubstituted N-methyl benzothiazolines (e.g., 11) in near quantitative yields.

Hydrolysis of the crude N-methyl benzothiazolines (e.g., 10 or 11) to the respective carbonyl compounds may be accomplished two ways; (a) treatment with $AgNO_3$ in aq. CH_3CN buffered to a pH of 7 followed by neutralization of the acid (HNO_3) released (1.0 equiv Et_3N) or (B) methylation utilizing $MeOSO_2F$ (1.2 equiv, 4.0 ml CH_2Cl_2/mmol substrate, 25°, < 19 hr) followed by treatment of the product with base (2 ml 5% aq K_2CO_3/2.5 ml THF per mmol substrate, 25°, 4 hr). Summarizing typical results, [aldehyde[15] produced, no. of equiv $MeOSO_2F$ (time) required for methylation, no. of equiv $NaBH_4$ (temp., time) used for reduction, method of hydrolysis (% yield overall after purification)]: cyclohexane carboxaldehyde, 1.2 (2.5 hr), 4.4 (-20°, 20 min), A. (81%); cis-2-acetonyl-cyclohexane carboxaldehyde, 1.2 (2.5 hr), 3.0 (-78°, 60 min) in the presence of 10.0 equiv of acetone, A. (91%); α-isopropenyl-hydrocinnamaldehyde, 1.2 (2.5 hr), 4.4 (-20°, 20 min), A. (92%); cyclohexene carboxaldehyde, 1.1 (9 hr), 4.4 (-20°, 20 min), A. (88%); 1-propargyl-cyclohex-2-ene carboxaldehyde, 2.0 (48 hr), 5.0 (-20°, 20 min), B. (82%); cis-2-methyl-1-propargyl cyclohexane carboxaldehyde, 2.0 (99 hr), 4.4 (-20°, 20 min), B. (74%). Noteable in the case of method (A) is the fact that such mild conditions are employed for the hydrolysis that epimerizable centers are unaffected (e.g., pure cis-2-acetonyl-cyclohexane carboxaldehyde is obtained from the corresponding pure cis-BT with no trace of the corresponding more stable trans-aldehyde).[16,17]

Hydrolysis of N-methyl benzothiazolines: Method A: The crude 2-substituted N-methyl benzothiazoline (1.0 mmol) in 15 ml of CH_3CN and 3 ml of pH 7, 0.05 M phosphate buffer is treated with $AgNO_3$ (1.5 mmol, 255 mg) in 2.5 ml of H_2O. After 15 min at 25° an additional 1.5 equiv of $AgNO_3$ in 2.5 ml H_2O is added (generally an easily filterable yellow ppt[14] appears after 5-10 min). After ca. 20 min at 25°, Et_3N (1.0 mmol, 139 µl) is added, the reaction mixture is stirred for 5-10 min and filtered through Celite (etheral wash). Addition of sat'd NaCl ppt's AgCl which is filtered (through Celite), and the crude aldehyde (free of 2-N-methyl-amino thiophenol) is isolated from the filtrate by standard methods.

The hydrolysis of 2,2-disubstituted N-methyl benzothiazolines requires more vigorous conditions (e.g., 11 → 13 requires 1 hr at 45-50° after the addition of Et_3N for complete hydrolysis).

Method B: A soln of the crude N-methyl benzothiazoline (1.0 mmol) in 4.0 ml of CH_2Cl_2 is treated with $MeOSO_2F$ (1.2 mmol, 97 µl) and stirred at 25° until no starting material remains (tlc, < 19 hr). The excess reagent is quenched with Et_2O (1.0 ml, 30 min) and the solvent removed under vacuum. The residue is taken up in 2.0 ml 5% aq. K_2CO_3, 2.5 ml THF and the soln stirred

for 4 hr at 25° before being extractively worked up with ether. The etheral extract was washed with 5% aq. HCl (4-8x, 5 ml), 5% aq. $NaHCO_3$ (1x, 5 ml) and brine, then dried ($MgSO_4$) and concentrated under reduced pressure affording the carbonyl compounds (> 90% pure).

References

1. M. E. Jung, Tetrahedron, 32, 3 (1976).
2. G. H. Posner, Org. React., 19, 1-113 (1972); unpublished observations made in these laboratories.
3. H. Gilman and J. A. Beel, J. Amer. Chem. Soc., 71, 2328 (1949). 2-Lithio BT was generated as follows: benzothiazole (5.0 mmol) was added dropwise (10 min) to a stirred soln of n-BuLi (5.0 mmol, -78°) in 15 ml of dry Et_2O under argon and further stirred at -78° for 10 min before the addition of carbonyl compounds.
4. P. E. Eaton, G. A. Carlson, and J. T. Lee, J. Org. Chem., 38, 4071 (1973). The reagent was prepared as described with the exception that CH_3SO_3H (Aldrich) was not distilled prior to reagent formation.
5. A. G. Schultz and J. D. Godfrey, J. Org. Chem., 41, 3494 (1976).
6. E. M. Burgess, H. R. Renton, and E. A. Taylor, J. Org. Chem., 38, 26 (1973).
7. Standard basic conditions ($SOCl_2$ or $POCl_3$/base) under a variety of conditions (base = Et_3N, pyridine; solvent = Et_2O, CH_2Cl_2, CH_3CN, pyridine; temp = -20° to 25°) all afforded the vinyl BT's in yields of ca. 70-80%.
8. For similar work see K. Sachdev, Tetrahedron Lett., 4041 (1976) and references cited therein.
9. Metallation of 2-MeBT using EtMgBr, $NaNH_2$, $LiNH_2$, or PhLi has been reported; C. Courtot and S. Tchelitcheff, Compt. rend., 217, 201 and 231 (1943); V. Dryanska and C. Ivanov, Dakl. Bolg. Akad. Nauk., 23, 1227 (1970).
10. Carbonyl compound, col. chrom. % yield of 8, reaction time at 25°, mp etc.; benzaldehyde, 95%, 6 hr, 108.5-109.5°; acetaldehyde, 96%, 5.5 hr, 82:18 trans:cis; acetone, 92%, 10 hr, 77.5-78.5°; cyclohexanone, 96%, 2 hr, low melting solid; 4-t-butylcyclohexanone, 90%, 3.5 hr; phenylacetone, 76%, 3.5 hr, ca. 1:1 E:Z.
11. E. B. Knott, J. Chem. Soc., 3793 (1965).
12. Condensation of α-lithio-2-MeBT with benzaldehyde (91%), acetone (95%), and cyclohexanone (85%) followed by P_2O_5/CH_3SO_3H (1/10, w/w) dehydration as described afforded the vinyl BT's 8 in 95%, 95% and 0% yields respectively.
13. E. D. Pretelli, M. Guiliano, G. Mille, J. Chouteau, R. Guglielmetti, and C. Gelebart, Helv. Chim. Acta, 60, 215 (1977); 9 → 11, 1.1 equiv MeLi, Et_2O, -78° to 10°, 45 min.
14. Vicinal amino-thiols are known to form insoluble Ag(I) salts; cf. M. Aresta, F. Ciminale and G. Bartoli, Chem. Comm., 1203 (1976); R. Luhowy and F. Meneghini, J. Org. Chem., 38, 2405 (1973).
15. The preparation of the substituted benzothiazoles that serve as precursors for these aldehydes is described in the following papers.
16. Structures of all compounds reported herein were confirmed by pmr, ir, and mass spectral analysis of distilled or chromatographically purified samples.
17. This research was assisted financially by a grant from the National Science Foundation.