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APPLICATION OF BENZOTHIAZOLES TO CARBON-CARBON BOND FORMATION IN ORGANIC SYNTHESIS

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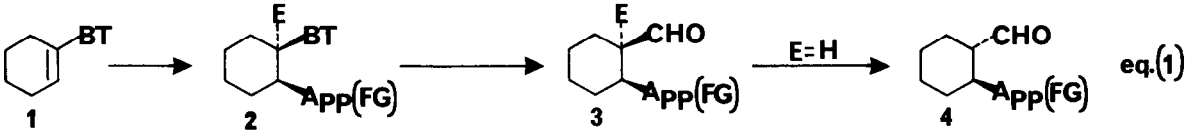
In the foregoing paper[1] we described efficient routes to a variety of 2-vinyl benzothiazoles (vinyl BT's) and also mild, effective modification of C-2 of the BT nucleus to form carbonyl compounds. This note is primarily concerned with new carbon-carbon bond forming reactions of BT's which are highly effective for the stereoselective attachment of one or two carbon appendages to a ring and which substantially broaden synthetic methodology.

I. VINYL BT's AS MICHAEL ACCEPTORS. An extensive and useful series of annulation processes could be developed if a reliable method were found for the conjugate addition of carbon nucleophiles to α,β-unsaturated aldehydes. However, direct 1,4-addition to conjugated aldehydes is usually thwarted by addition at the carbonyl carbon.[2,3] We now report that organo-lithium reagents undergo clean conjugate addition to the model vinyl BT 1a (an enal equivalent) with no trace of competing proton abstraction or further reaction[4] with excess lithium reagent.[5,6]



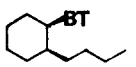
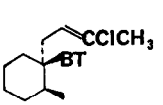
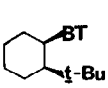
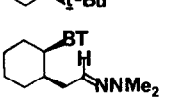
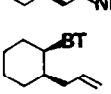
App(FG) = appendage, non-functionalized or functionalized
E = electrophile (H or carbon-derived)

Table I summarizes some of the results obtained with 1a using a wide variety of organo-lithium reagents. In each case, addition to the vinyl BT 1a is clean and rapid (0.5 - 3 hr, -78°, THF), and affords the cis-2-substituted cyclohexane BT's 2 with a high degree of stereoselectivity (generally 85-95%). The stereochemistry[7] of the various adducts 2 was confirmed not only by conversion to and isolation of the corresponding cis-aldehydes 3 (which upon mild acid treatment (H^+, THF) afford the corresponding trans-aldehydes 4 (Table II), but also by proton magnetic resonance (pmr) analysis.

Though in most instances the intermediate lithio-derivative which results from conjugate addition to 1a was quenched with H^+ (MeOH, -78°), this intermediate also undergoes facile reactions with other electrophiles (e.g., allyl bromide, -78°, 0.5 hr; methyl iodide, -78°, 1 hr). The latter process constitutes an efficient method for the introduction of two vicinal appendages at one time with a high degree of stereoselectivity (Table I).[6,9]

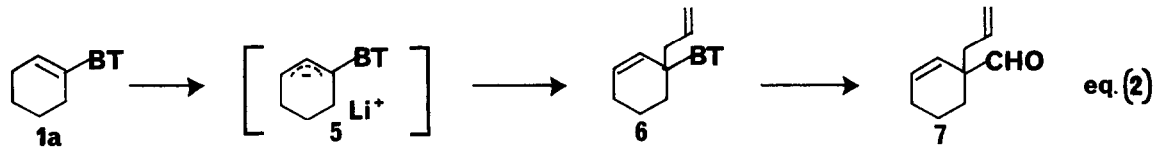
It is noteworthy that cis-2-substituted cyclohexane carboxaldehydes (e.g., 3a-d, Table II) suffer no detectable epimerization when formed by Ag(I) promoted hydrolysis of the corresponding N-methyl benzothiazolines.

Table I. Conjugate Addition of Organo-Lithium Reagents to the Vinyl BT 1a

RLi (equiv)	Conditions[a]	Electrophile	Product 2	% yield[b] (cis/trans)
a. n-BuLi (1.4)	-78°, 45 min	MeOH, -78°		99% (89/11)[c]
b. CH_2=CHLi (1.5)	-78°, 40 min	MeOH, -78°		97% (95/5)[d]
c. PhLi (1.75)	-78°, 50 min	MeOH, -78°		96% (>95/5)[d,e]
d. MeLi (1.75)	-78°, 160 min 4.5 equiv HMPA	MeOH, -78°		90% (89/11)[d]
e. MeLi (1.75)	-78°, 160 min 4.5 equiv HMPA	allyl bromide (-78°, 20 min) (-78° to 25°, 30 min)		90% (89/11)[d]
f. MeLi (1.85)	-78°, 165 min 4.5 equiv HMPA	$ClCH_2CH$=$CClCH_3$ (-78°, 80 min)		96%[f]
g. t-BuLi (1.75)	-78°, 75 min	MeOH, -78°		>95% (>80/20)[g,h]
h. $HC(NNMe_2)CH_2Li$[15] (1.75)	-78°, 20 min 3.5 equiv HMPA	MeOH, -78°		>95% (>85/15)[h,i]
i. CH_2=$CHCH_2Li$ (1.5)	-78°, 15 min	MeOH, -78°		78% (85/15)[h]

(a) THF as solvent; 8.2 ml/mmole 1a. (b) After column chrom. (SiO_2), all products displayed the expected pmr, ir and mass spectral characteristics. (c) Cis and trans isomers separated by column chrom. (d) Ratio of cis/trans aldehydes (gc) obtained upon reductive hydrolysis of the BT's. (e) Mp. 83.5-85°. (f) 70:30 Mixture of E/Z olefinic isomers. (g) Slowly isomerizes to the trans compound at 25°. (h) Cis/trans ratio by pmr. (i) Yield of unpurified product.

II. ALKYLATION OF VINYL BT'S. The direct alkylation of α,β-unsaturated aldehydes to afford α-alkylated β,γ-unsaturated aldehydes is plagued by O-alkylation, dialkylation, and self condensation.[10] We report here an attractive alternative which involves the generation and alkylation of BT-stabilized allyl anions (e.g., 5 and 8). Treatment of the vinyl BT's 1a and 1b with freshly



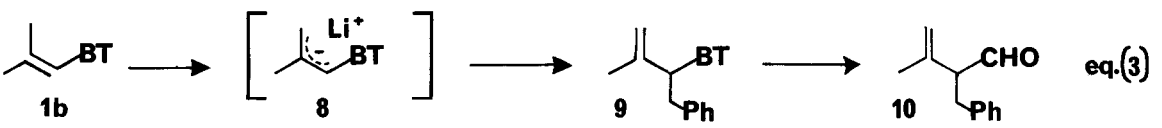
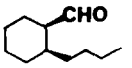
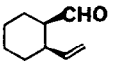
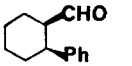
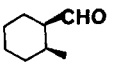
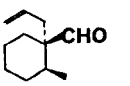
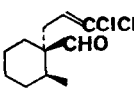
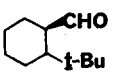


Table II. Conversion of BT Conjugate Adducts to Aldehydes

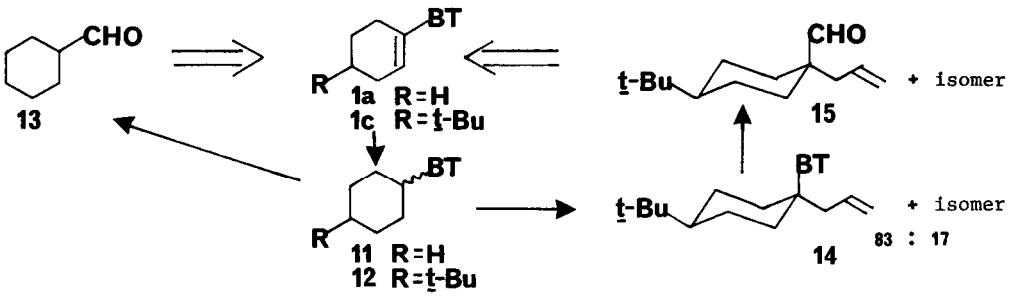
Benzothiazole	Methylation[a] conditions	Reduction[b] conditions	Aldehyde 3[c] % yield (cis/trans)[d]	Aldehyde 4[e] (cis/trans)
2a	1.2 (2.5 hr)	A.	 90% (84/16)	(5/95)
2b	1.1 (1.5 hr)	A.	 85% (95/5)	(12/88)
2c	1.2 (2.5 hr)	A.	 90% (> 95/5)	> 99% trans
2d	1.2 (2.5 hr)	A.	 86% (89/11)	(3/97)
2e	2.0 (94 hr)	A.	 90% (89/11)	
2f	2.0 (268 hr)	A.	 76%[f]	
2g[g]	1.2 (3 hr)	A.	 88%[g]	> 95% trans

(a) Equiv (time) of $MeOSO_2F$; 4.0 ml CH_2Cl_2 per mmol substrate. (b) A. = 4.4 equiv $NaBH_4$, -20°, 5 ml EtOH per mmol. (c) Ag(I) promoted hydrolysis[1] of the intermediate N-methyl benzothiazolines. (d) All aldehydes were purified by evap. bulb to bulb distillation and exhibited the expected pmr, ir, and mass spectral characteristics; cis/trans ratio determined by gc. (e) Isomerization (3→4) was carried out in THF containing a catalytic amount of HCl; cis/trans ratio determined by gc. (f) 70:30 Mixture of E/Z olefinic isomers. (g) Sample of BT 2g that was 60/40 trans/cis was used.

prepared lithium diisopropylamide (1.1 equiv, -78°, THF, 3 hr for 1a and 2 hr for 1b) led to the intermediate anions 5 and 8 (0.12 M in THF) which underwent clean α-alkylation[11] respectively with allyl bromide (3.0 equiv, -78°, 2 hr, 0°, 3 hr) and benzyl bromide (1.5 equiv, -78°, 130 min, 0°, 30 min) to afford the β,γ-unsaturated BT's 6 (95%) and 9 (99%) after chromatography (SiO_2). As described previously[1] methylation of 6 (2.0 equiv $MeOSO_2F$, 27 hr, CH_2Cl_2) and 9 (1.2 equiv of $MeOSO_2F$, 2.5 hr, CH_2Cl_2) followed by $NaBH_4$ reduction (4.4 equiv, -20°, 20 min, EtOH) and Ag(I) promoted hydrolysis affords the aldehydes 7 (93%) and 10 (92%). In the later case, no α,β-unsaturated (i.e. isomerized) aldehyde could be detected in the product.

III. REDUCTION OF VINYL BT'S, ALKYLATION OF SATURATED BT'S. The vinyl BT's 1a and 1c are readily hydrogenated (1 atm H_2, 25 mg 10% Pd-C per mmol substrate, EtOH, < 4 hr) to the corresponding saturated BT's 11 (99%) and 12 (98%, 3:2 cis:trans) without significant catalyst poisoning. Using the methodology previously developed[12] the saturated BT 11 was converted to cyclohexane carboxaldehyde 13 in an overall yield of 81% from 11 (80 % from 1a).

Metallation[13] of the saturated BT 12 (1.2 equiv n-BuLi, -78°, 2 hr, 6.0 ml THF per mmol substrate) followed by treatment of the resulting α-lithio derivative with allyl bromide (3.0 equiv, -78°, 2 hr, 0° to 25°, 3 hr) afforded the alkylated product 14 (98% chromatographed) as



an 83:17 mixture of axial:equatorial BT. Alkylation of similar systems[14] have been shown to proceed in the same stereochemical manner affording products primarily derived from equatorial alkylation. Conversion of 14 to the 83:17 axial:equatorial mixture of known[14] aldehydes 15 (83% from 14, 80% from 1c) was accomplished as follows; methylation (2.0 equiv $MeOSO_2F$, 89 hr, CH_2Cl_2), $NaBH_4$ reduction (5.0 equiv, -20°, 20 min, EtOH) and hydrolysis of the resulting N-methyl benzothiazoline (Method B[1], methylation - 1.2 equiv $MeOSO_2F$, 18 hr, CH_2Cl_2 followed by 5% aq K_2CO_3-THF treatment of the residue and purification of 15).[16]

Cis-1-(2-benzothiazolyl)-2-phenyl cyclohexane 2c: A soln of PhLi (8.75 mmol, 4.17 ml of 2.1 M in 70:30 PhH:Et_2O) in 31 ml of dry THF cooled to -78° under argon was treated dropwise (10 min) with the vinyl BT 1a (5.0 mmol, 1.08 g) in 10 ml of dry THF. The resulting yellow-orange soln was stirred at -78° for an additional 50 min before MeOH (5.0 ml) was added. The reaction mixture was poured onto sat'd NH_4Cl/NH_4OH (pH ∿8) and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the crude product (75 g SiO_2, 25.5 x 2.8 cm, hexane to CH_2Cl_2 gradient elution) afforded 1.41 g (96%) of pure 2c as a white solid, mp 83.5-85°, >95% cis; pmr ($CDCl_3$, ppm): 3.77 (1H, α-BT methine, $w_{1/2}$= 8-9 Hz), 3.16 (1H, benzylic methine, t split d, J=4 and 11 Hz, $w_{1/2}$=16 Hz); ms: 293 (M^+, strong), 162 (base).

References

1. E. J. Corey and D. L. Boger, Tetrahedron Lett., preceding paper.
2. G. H. Posner, Org. React., 19, 1-113 (1972); unpublished observations made in these laboratories.
3. For some relevant recent work see (a) S. Hashimoto, S. Yamada, and K. Koga, J. Amer. Chem. Soc., 98, 7450 (1976), (b) A. I. Meyers and A. C. Kovelsky, Tetrahedron Lett., 4809 (1969).
4. A. I. Meyers and A. C. Kovelsky, J. Amer. Chem. Soc., 91, 5887 (1969), (b) A. I. Meyers and C. W. Whitten, Tetrahedron Lett., 1947 (1976); see also reference 3b.
5. A. I. Kirprianov, A. Y. Il'chenko, and L. M. Syromolatova, Zh. Obsheh, Khim., 34, 1926 (1964).
6. Further illustrations are presented in the following paper.
7. Similar stereochemical results have been observed in the conjugate addition of organo-cuprates; H. O. House, C. Y. Chu, J. M. Wilkins, and M. J. Umen, J. Org. Chem., 40, 1460 (1975).
8. The α-BT methine appears at ∿ 3.5 ppm as a multiplet ($w_{1/2}$ ≃ 8-20 Hz, varying with the size of the 2-substituent) in the major cis isomers whereas it appears at ∿ 3.0 ppm as a doublet split triplet (J ≃ 10 and 4 Hz, $w_{1/2}$ ≃ 24 Hz, axial hydrogen) in the minor trans isomer.
9. Though here the stereochemical course of aklylation was presumed to be the same as protonation, we offer in the following papers definitive proof that this indeed is the case.
10. S. A. G. de Graaf, P. E. R. Oosterhoff, and A. van der Gen, Tetrahedron Lett., 1653 (1974); G. R. Kieczykowski, R. H. Schlessinger, and A. B. Sulsky, Tetrahedron Lett., 597 (1976).
11. No γ-alkylation was detected in accord with past observations that stabilized allylic anions undergo C-alkylation at the carbon α to an electron withdrawing substituent; H. O. House, "Modern Synthetic Reactions", 2nd Ed., Benjamin, Menlo Park, Calif., 1972, Chap. 9.
12. The experimental details for this particular conversion are recorded in the preceding paper.[1]
13. It is noteworthy that the related 2-oxazoline and dihydro-1,3-oxazine (but not 2-thiazoline) systems resist useful deprotonation on an α-tertiary center; see A. I. Meyers and J. L. Durandetta, J. Org. Chem., 40, 2021 (1975) and references cited therein.
14. H. O. House, J. Lubinkowski, and J. J. Good, J. Org. Chem., 40, 86 (1975).
15. E. J. Corey and D. Enders, Tetrahedron Lett., 3, 11 (1976).
16. This research was assisted financially by a grant from the National Science Foundation.