Notes

Cyclopropylidene Derivatives via Low-Valent Titanium-Induced Dehydroxylative Debenzotriazolylation of 1- and 2-(Cyclopropylbenzotriazolyl)carbinols

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Received April 3, 1998

Available general routes to cyclopropylidene compounds include phase transfer catalyzed Wittig reaction of cyclopropylidenetriphenylphosphorane,[1] Peterson olefination,[2] additions of carbenes to allenes,[3] and Petasis titanocene methodology.[4] While elegant, these methods often utilize unstable and/or not-readily accessible reagents and intermediates. The Wittig methodology is useful for the introduction of an unsubstituted cyclopropylidene moiety, due to the commercial availability of cyclopropyltriphenylphosphonium bromide, but other cyclopropylidene derivatives are more difficult to access.[5] Peterson olefination requires the synthesis of thioacetal/1-(phenylthio)trimethylsilylcyclopropane intermediates.[6] The titanocene methodology succeeds in the conversion of readily enolizable aldehydes/ketones, as well as esters and lactones, and the parent dicyclopropyltitanocene intermediate is easily synthesized. However, complications arise when substituted cyclopropyl derivatives are required.

Cyclopropylidene derivatives are increasingly important as building blocks for organic synthesis,[7] and new routes for their synthesis are relevant. We herein report an efficient synthesis of cyclopropylidene derivatives utilizing our recently introduced low-valent titanium (LVT) induced dehydroxylative-debenzotriazolylation which was demonstrated[8] to give alkenes in good to excellent yields and stereoselectivities. This new methodology exploits the synthetic advantages of benzotriazole[9] to both (i) stabilize α-carbanions[10] and (ii) act as a leaving group.[11] The starting cyclopropylbenzotriazole derivatives are readily available *via* the well-precedented[12] cyclopropane ring formation by 1,3-intramolecular nucleophilic substitution cyclopropane ring formation.

Results and Discussion

The reaction of 1-bromo-3-chloropropane (**1a**) with sodium benzotriazolate (from benzotriazole and sodium hydroxide) in DMSO gives 97% of a mixture of 1- and 2-(3-chloropropyl)benzotriazole (**2a** and **2b**) (see Scheme 1). 1-Bromo-3-chloro-2-methylpropane (**1b**) similarly yields 99% of a mixture of 1- and 2-(2-chloromethyl)-propylbenzotriazole (**2c** and **2d**). The 1- and 2-benzotriazolyl isomers are readily separated either by column chromatography or by acidic extractive workup (see Experimental Section). Upon treatment at −78 °C with *n*-butyllithium (*n*-BuLi) or lithium diisopropylamide (LDA), and warming to 20 °C, compounds **2** (whether as pure 1- or 2-benzotriazolyl isomers, or as a mixture) undergo quantitative conversion to 1- and/or 2-cyclopropylbenzotriazoles **5**. Compounds **5** can be isolated at this stage, and **5a** was characterized by ^{1}H and ^{13}C NMR, but **5** are generally treated with a second equivalent of *n*-BuLi/LDA at −78 °C, followed by addition of an aldehyde/ketone **4**, to give carbinols **3a**−**j** in good yields (as either the 1- or the 2-benzotriazolyl isomers, or as a mixture, depending upon the nature of the starting product **2**). Cyclopropylbenzotriazole[13] and derivatives[14] have been previously described and could be used in place of the *in situ* generated cyclopropylbenzotriazoles used herein, thus expanding the range of potentially accessible (cyclopropylbenzotriazolyl)carbinol intermediates.

In contrast to the facile rearrangements observed for phenylthio-derived cyclopropane carbinols,[15] the intermediate carbinols **3a**−**j** do not readily rearrange and hydrolyze to the cyclobutanone derivatives **6**. However, LVT methodology readily achieves the simultaneous loss of both the hydroxyl and benzotriazolyl moieties. Thus, treatment of 1- or 2-(1-cyclopropylbenzotriazolyl)carbinol

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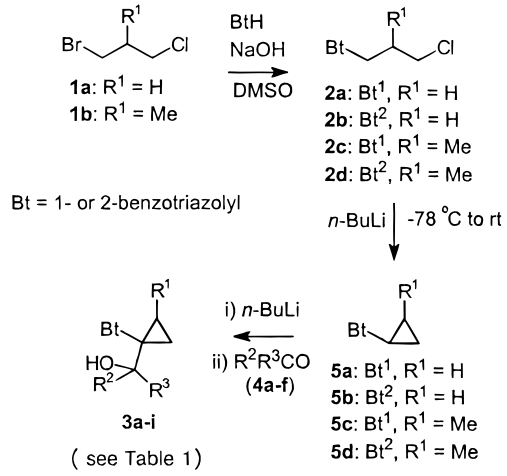
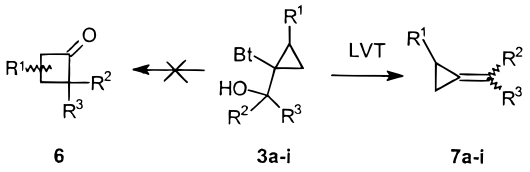
S0022-3263(98)00617-3 CCC: $15.00
Published on Web 09/02/1998

Scheme 1



Scheme 2



with Ti^0 (generated by method D or E from the preceding paper[8c]) gives the desired cyclopropylidene derivatives **7** in good yields, after workup and column chromatography (see Scheme 2). The synthesis was carried out on purified 1- or 2-benzotriazolyl isomers and on a mixture of both, and shown to be successful in all cases. Therefore, it is not necessary to purify at any step other than after final LVT alkenylation, even though the characterization by spectral analysis of the intermediates is much easier if pure 1- or 2-benzotriazolyl isomers are used. Thus, the overall procedure can be greatly simplified to allow access to cyclopropylidene derivatives directly from cheap and readily available starting materials.

In conclusion, we have introduced a new method for accessing cyclopropylidene derivatives, by utilizing low-valent titanium-activated dehydroxylative-debenzotriazolylation of 1-(1-cyclopropylbenzotriazolyl)carbinols. The overall procedure involves readily available and inexpensive starting materials, using standard experimental procedures, wherein all intermediates are stable and isolatable in good to excellent yields. The method is complementary to those already available and gives an alternative route to a variety of synthetically useful cyclopropylidene derivatives.

Experimental Section

General Comments. See the preceding paper.[8c]

General Procedure for the Synthesis of 1- and 2-(3-Chloropropyl)benzotriazole (2a,b) and 1- and 2-(2-Chloromethyl)propylbenzotriazole (2c,d). Benzotriazole (100 mmol) was dissolved in DMSO (200 mL), and finely powdered NaOH (100 mmol) was added. The resulting suspension was stirred at room temperature, with $CaCl_2$ drying tube, until a clear solution was obtained. 1-Bromo-3-chloropropane (**1a**) (100 mmol) or 1-bromo-3-chloro-2-methylpropane (**1b**) (100 mmol) was added dropwise at room temperature, the reaction mixture was stirred at this temperature overnight before being poured into water (500 mL), extracted into ethyl acetate (organic phase A), and dried ($MgSO_4$), and the solvent was removed. The residual oil was presorbed onto silica and flash columned on silica with 100 mL portions of ethyl acetate:hexanes = 10:100 until all the Bt^2 isomer (**2b** or **2d**) was removed. The polarity was increased, and 100 mL portions of ethyl acetate:hexanes = 20:100 were used to remove the Bt^1 isomer (**2a** or **2c**). The separation could be carried out by extracting organic phase A into 5 N HCl, washing with ether, neutralizing with saturated aqueous $NaHCO_3$, extracting into ether, drying, and concentrating to give >95% pure Bt^1 isomer (**2a** or **2c**). Residual, initially extracted, organic phase A could be washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give >95% pure Bt^2 isomer.

Table 1. (Cyclopropylbenzotriazolyl)carbinols 3 and Cyclopropylidene Derivatives 7

	substituents		Bt	compound **3**		compound **7**	
	R^1	R^2	isomer	yield, %	mp, °C	yield, %	mp, °C
a	H	*p*-BrC_6H_4	1	71	154−6	51[c]	48−50
b	H	*p*-MeC_6H_4	1	62	152−4	37[c]	oil[f]
c	H	*p*-ClC_6H_4	1	60	179−80	48[c]	oil
d	H	*p*-ClC_6H_4	2	72	106−7	46[c]	oil
e	H	*p*-ClC_6H_4	1 + 2	75[a]		55[b,c]	oil
f	H	3,4-$Cl_2C_6H_4$	2	65	111−3	35[c]	oil
g	H	1-naphthyl	1	44	131−3	40[c]	oil
h[g]	H	*p*-ClC_6H_4	1	64	217−9	15,[c] 30[d]	112−4
i	Me	*p*-ClC_6H_4	1	52[d,e]		42[d,e]	oil
j	Me	*p*-BrC_6H_4	1	53[d,e]		41[d,e]	oil

[a] Based on combined GC yield of Bt^1 and Bt^2 isomers. [b] Based on crude **3** being 75% yield. [c] Method D.[8c] [d] Method E.[8c] [e] Mixture of isomers. [f] Lit.[16] bp 58 °C/0.2 mmHg. [g] R^3 = *p*-ClC_6H_4, in other cases R^3 = H.

General Method for the Synthesis of (Benzotriazolylcyclopropyl)carbinols 3a−i. *n*-BuLi (10 mmol of 1.6 M in hexanes) was added dropwise to a solution of $BtCH_2CH_2CH_2Cl$ (**2a** or **2b** or mixture) (10 mmol) or $BtCH_2CH(Me)CH_2Cl$ (**2c** or **2d** or mixture) (10 mmol) dissolved in THF (200 mL) at −78 °C, under argon. The reaction mixture was left stirring at this temperature for 35 min, warmed to room temperature over 15 min, left for 5 min (sample taken and analyzed by GC to show complete conversion of the starting material), and recooled to −78 °C before adding *n*-BuLi (10 mmol of 1.6 M in hexanes). The reaction mixture was left at −78 °C for 50 min, and aldehyde/ketone (10.5 mmol) was added as a solution in THF (20 mL). The reaction was left at −78 °C for 30 min, warmed to room temperature, quenched with water (100 mL), extracted with ethyl acetate, dried ($MgSO_4$), and concentrated. The crude product was presorbed onto silica and dry flash columned on silica with ethyl acetate:hexanes, gradient dilution. The relevant fractions were combined and concentrated, and for pure Bt^1 or Bt^2 isomers the residual oil was triturated with ether/hexanes to give pure products as white crystals.

General Procedure A for the Synthesis of Cyclopropylidene Derivatives 7. To a solution of LVT[8c] were added Et_3N (15 mmol) and (benzotriazolylcyclopropyl)carbinol **3** (3 mmol) in dry DME (20 mL). The reaction mixture was heated at 60 °C for 12 h, cooled, diluted with diethyl ether (200 mL), and filtered. The filtrate was washed with 5% aqueous NaOH (3 H 100 mL) and brine (100 mL) and dried ($MgSO_4$). After concentration the residue was purified by column chromatography on silica gel, using hexanes or pentane as eluent, to afford pure **7** as either a colorless oil or colorless crystals.

General Procedure B for the Synthesis of Cyclopropylidene Derivatives 7. Exactly as procedure A above, except that $TiCl_4$ and Zn−Cu dust were used. Identical molar quantities of all reagents were employed.

Supporting Information Available: ^1H and ^{13}C NMR data for all isolated intermediates; combustion analyses, or HRMS and ^1H NMR (and ^{13}C NMR) spectra for all novel compounds (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980617N