Alkylations of Alkynols with Organoaluminum Reagents Promoted by Bis(η^5-cyclopentadienyl)titanium Dichloride

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We have been interested in adapting the chemistry of titanium–aluminum based Ziegler–Natta catalyzed olefin polymerization to effect the alkylation of isolated unsaturated carbon–carbon bonds in a manner useful for ordinary (i.e., nonmacromolecular) organic synthesis.[1,2] Ziegler–Natta catalyst systems are potent alkylating agents toward olefinic and acetylenic linkages as evidenced from their widespread use in synthesizing linear stereospecific polyhydrocarbons.[3] However, single nonrepetitive alkylations of isolated carbon–carbon multiple bonds useful for extending the carbon framework in organic systems are not common. The paucity of research reported in this area is somewhat surprising if one accepts the idea that organic synthesis can be divided into the broad areas of (1) formation of carbon skeletons and (2) introduction, modification, and/or removal of functionality[4] and that within these areas the first is generally the more difficult.[5] Recently, we have had some success in utilizing organoaluminum–titanium systems capable of polymerizing ethylene to alkylate alkynols to give olefinic alcohols.[1,2] Specifically, an alkynol such as 3-butyn-1-ol was incorporated into the complex (3-butyn-1-oxy)chlorobis(2,4-pentanedionato)titanium(IV), $[Ti(OR)Cl(acac)_2]$, and allowed to react with diethylaluminum chloride at −78 °C. After hydrolysis a ~50% yield of the terminally alkylated cis-addition product *trans*-3-hexen-1-ol was obtained. Several additional alkynols were alkylated, and in all cases the alkyl group added to the carbon furthest from the hydroxyl functionality and gave the cis-addition product.

In this paper we wish to report a new alkylation system which gives significant improvements in yields and synthetic convenience and also demonstrates the potential for control of regiospecificity through variation of ligand environments. In previous work it was necessary to first synthesize and isolate a titanium–alkynoxy complex, $[Ti(OR)Cl(acac)_2]$, by the reaction of $[TiCl_2(acac)_2]$, alkynol, and pyridine. The pyridinium chloride was filtered from the reaction mixture, and the complex was then isolated from the filtrate. A much simpler procedure would be the addition of an alkynol to a solution of the organoaluminum reagent liberating an alkane and generating an $[Al_2(OR)R_xCl_{5-x}]$ species which subsequently could be added to a solution of $[TiCl_2(acac)_2]$. Through ligand exchange this system might become equivalent to the initial one and thus eliminate the inconvenience of preparing the titanium–alkynoxy complexes. Attempts to effect alkylation by this latter route were unsuccessful. However, upon replacing $[TiCl_2(acac)_2]$ with titanocene dichloride, Cp_2TiCl_2, in the 3-butyn-1-ol-diethylaluminum chloride system a 55% yield of the ethylated products *trans*-3-hexen-1-ol (I) and 3-ethyl-3-buten-1-ol (II) (ca. 50:50) was obtained as represented in reactions 1 and 2. On lowering the quantity of Cp_2TiCl_2 relative to 3-butyn-1-ol yields improved significantly (see Table I). Using 10 mol % of Cp_2TiCl_2, 80–90% yields of ethylated products were obtained with the ratio of terminal to internal addition products varying from ca. 50:50 to 60:40, respectively. Thus the titanium species in the cyclopentadienyl system functions catalytically with an average turnover number of 8–9. Cp_2TiCl_2 at 5 and 1 mol % gave decreasing yields again. Hydrolysis with D_2O gave greater than 95% deuterium incorporation at the olefinic carbon atoms. Additional alkylation data are presented in Table I.

$$2.5Al(C_2H_5)_2Cl + HC{\equiv}CCH_2CH_2OH \xrightarrow[CH_2Cl_2]{0\ ^\circ C} Al_{2.5}(OCH_2CH_2C{\equiv}CH)(C_2H_5)_4Cl_{2.5}] + C_2H_6 \quad (1)$$

(III)

$$Cp_2TiCl_2 + III \xrightarrow[(2)\ H_2O]{(1)\ CH_2Cl_2,\ 0\ ^\circ C,\ 6\ h} I + II \quad (2)$$

Reference to Table I shows that methyl-group substitution at the hydroxy end (4-pentyn-2-ol) and at the acetylenic position (3-pentyn-1-ol) reduces the yield of alkylated products somewhat. With 3-pentyn-1-ol addition was observed only at the 4-carbon whereas 4-pentyn-2-ol gave a mixture of terminally and internally ethylated products similar to 3-butyn-1-ol. 4-Pentyn-1-ol also gave a mixture of two products. In all alkylation reactions a significant portion of Cp_2TiCl_2 is recovered in the workup procedure.

In summary, the mild conditions, the catalytic possibilities

Table I. Alkynol Alkylations[a]

Alkynol	Registry no.	Temp, °C	Mol % Cp_2TiCl_2[b]	Products	Registry no.	Total % yield of Products	Reaction time, h
3-Butyn-1-ol	927-74-2	0	50	*trans*-3-Hexen-1-ol (I) and 3-ethyl-3-buten-1-ol (II)	928-97-2 1170-98 1	85[c]	6
		−22	50	I and II		80	6
		−78	50	None			6
	d	0	100	I and II		55	6
		0	25	I and II		78	6
		0	10	I and II		88	6
		0	10	I and II		80	6
3-Pentyn-1-ol	10229-10-4	0	50	4-Methyl-3-hexen-1-ol	63714-11-4	46[e]	4
4-Pentyn-2-ol	2117-11-5	0	50	4-Ethyl-4-penten-2-ol and *trans*-4-hepten-2-ol	63714-12-5 58927-81-4	66[f]	4
4-Pentyn-1-ol	5390-04-5	0	50	*trans*-4-Hepten-1-ol and 4-ethyl-4-penten-1-ol	24469-79-2 59518-08-0	72[g]	4

[a] All reactions are of the type $xCp_2TiCl_2 + [Al_{2.5}(OR)(C_2H_5)_4Cl_{2.5}]$, OR = alkynoxy. Solvent is methylene chloride. [b] Relative to OR in $[Al_{2.5}(OR)(C_2H_5)_4Cl_{2.5}]$. [c] For all 3-butyn-1-ol ethylations the ratio of I to II ranged between 50:50 and 60:40, respectively, with no systematic variation apparent. [d] Solvent is benzene. [e] The *E* configuration is suggested by the absence of observable methyl group splitting by the proton attached to the double bond. This configuration, which arises from cis addition of a metal–alkyl group, is also consistent with the fact that terminal ethylation of the terminal alkynols reported herein gives products arising from cis addition. [f] Product ratio ca. 55:45 internal to terminal addition. [g] Product ratio ca. 50:50.

with titanium, the availability of organoaluminum reagents, and the possible control of regioselectivity through a variety of available titanium compounds indicate that titanium–organoaluminum systems offer synthetic promise for the alkylation of γ and δ alkynols. Furthermore, the deuterium incorporation mentioned indicates the possibility of additional functional conversions of the reaction intermediates.

Experimental Section

Materials. All alkynols were purchased from Farchan Division, Story Chemical Corp., and were dried over 3-A Molecular Sieves. Methylene chloride was distilled from P_2O_5 under nitrogen. Liquid materials were transferred under N_2 or argon using syringe techniques. Cp_2TiCl_2 was purchased from Strem Chemicals, Inc., and used without further purification.

Alkylation Procedure. Reactions were carried out in glassware which had been dried at 110 °C, assembled while hot, and flushed with argon while cooling. In a typical reaction 50 mmol of 2 M $Al(C_2H_5)_2Cl$ solution in methylene chloride was transferred to a 250-mL three-necked round-bottom flask equipped with a gas inlet, magnetic stirrer, and 50-mL dropping funnel. Additional solvent was added to dilute the organoaluminum reagent to 0.75 M. The alkynol (20 mmol) was added to the dropping funnel with a syringe (weighed before and after) along with 25 mL of methylene chloride. The $Al(C_2H_5)_2Cl$ solution was cooled to 0 °C, and the alkynol was added dropwise to form the mixed ethylchloroalkynoxyaluminum system (solution I).

A second 250-mL flask equipped as described above was charged with the appropriate amount of Cp_2TiCl_2 followed by 50 mL of methylene chloride and cooled to the desired temperature. Solution I was transferred to the dropping funnel with a syringe and added dropwise. The reactions were terminated by addition of 8 mL of methanol followed by 50 mL of a 5% H_2SO_4 solution saturated with sodium chloride. The resulting mixture was stirred over an oxygen atmosphere for 1 h, filtered, and then extracted with 5 50-mL portions of diethyl ether. The ether extract was dried over $MgSO_4$ and filtered. The product solutions were then reduced in volume, filtered, and analyzed by GLC.

Gas Chromatographic Analyses. All yields were determined by GLC (Hewlett-Packard 5750) using an 8 ft × 1/8 in. XE-60 column and are corrected for response factors. Samples were isolated for spectral investigations by preparative GLC using 0.25 in. Carbowax 20M and SE-30 columns.

Spectra. NMR spectra were run on a Perkin-Elmer R-20 B spectrometer. IR spectra were taken with a Perkin-Elmer 457 spectrophotometer.

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Registry No.—Cp_2TiCl_2, 1271-19-8; $Al(C_2H_5)_2Cl$, 96-10-6.

References and Notes

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Selective Reduction of Some *N*-Formyl Dipeptide Esters with Borane–Tetrahydrofuran

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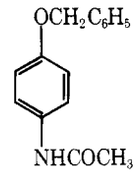
In recent years there have been reported a number of examples of selective reduction of carbonyl groups in polyfunctional molecules by borane–tetrahydrofuran (BH_3·THF).[1-4] We describe here some results that we obtained while investigating the reduction products of peptide derivatives as compounds of possible biological interest.

The *N*-formyl dipeptide esters **3a–c**, prepared by the EEDQ coupling method,[5] were reduced for 1.5 h at reflux temperature in tetrahydrofuran with limited amounts of borane. To avoid the drastic workup conditions (refluxing methanolic HCl) recommended by Kornet et al.[1] for borane reductions of acylamino esters, we tried HBr in acetic acid for this purpose. When reduction of the amide **1** was followed by addition of HBr–HOAc to the reaction mixture, a 90% yield of analytically pure *N*-ethyl-4-benzyloxyaniline (**2**·HBr) was



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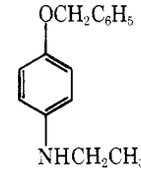

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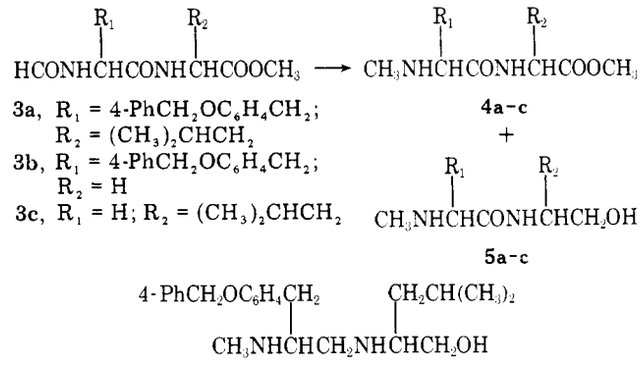
obtained directly. We therefore adopted this procedure for all of our reductions and have found it useful whenever a mild or nonaqueous workup is desirable.[6]

Reduction of *N*-formyl-*O*-benzyl-L-tyrosyl-L-leucine methyl ester (**3a**) with different amounts of BH_3·THF gave as principal isolated products (by crystallization) the *N*-methyl dipeptide ester **4a** and the (*N*-methylaminoacyl)amino alcohol **5a**; these and subsequent *N*-methylated products were easily recognized by the NMR singlet at δ 2.5–3.1. The results (Table I) show that the *N*-formyl group in **3a** is reduced more easily than the peptide or ester functions (runs 1 and 2). An increase in the hydride ion–substrate ratio leads to larger amounts of direduction product **5a** at the expense of mono-



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reduction product **4a** (run 3); however, with further increases in hydride, separation of products by crystallization becomes more difficult, and interpretation of the results is correspondingly less certain. Possibly under these conditions some

Table I. BH_3 Reduction of Formyl Dipeptide Ester 3a

Run	Mequiv of hydride ion mmol of substrate	Products,[a] % yield 4a·HBr[b]	5a·HBr[c,d]	6·2HBr[e]
1	4	40	6	
2	5	53	9	
3	6	20	27	
4	7	1	15	9
5	11			34

[a] Satisfactory analytical data (±0.3% for C, H, N, Br) were reported for all new compounds listed in the table. [b] Mp 166–176 °C (MeOH–Et_2O); $[\alpha]^{26}_D$ −30° (*c* 1, DMF). [c] Mp 218–222 °C (MeOH–Et_2O); $[\alpha]^{26}_D$ −27° (*c* 1, DMF). [d] Microanalysis obtained on free base: mp 128–129 °C (EtOAc); $[\alpha]^{23}_D$ −60° (*c* 0.8, $CHCl_3$). [e] Mp 166–170 °C (MeOH–Et_2O); $[\alpha]_D$ +29° (*c* 0.5, $CHCl_3$).