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Communications

Dichloroisopropoxytitanium Nitronates as Reagents for Stereoselective Henry Reactions

Summary: Alkyl nitronates were reacted with aldehydes in the presence of isopropoxytitanium trichloride to give erythro β-nitro alcohols.

Sir: The Henry or nitro aldol reaction is one of the classical bond-forming processes in organic chemistry. However, until recently the problem of stereocontrol in this process had been largely neglected. Seebach[1,2] reported that α,α-doubly deprotonated nitroalkanes **1** reacted with aldehydes to give the intermediate nitronate alkoxides **2** (Chart I). Kinetic reprotonation at −100 °C in polar solvents (THF with HMPA or DMPU) gave the nitro alcohols enriched in the threo diastereoisomer **3** (18:7–47:3). In contrast, reprotonation of the *tert*-butyldimethylsilyl-protected nitronate anions **4** at −100 °C in THF solution gave β-[(*tert*-butyldimethylsilyl)oxy]nitroalkanes **5** enriched in the erythro diastereoisomer (41:9–19:1). High erythro selectivity (4:1–>19:1) was also observed[2] in the fluoride-catalyzed reaction of silyl nitronates **6** with aldehydes, although the experimental conditions were critically precise for success. In addition to Seebach's studies, Hanessian[3] has observed some variation in selectivity in the reaction of (*S*)-(benzyloxy)propionaldehyde with methyl 3-nitropropionate using zinc or magnesium salts and potassium *tert*-butoxide in THF. Since nitro alcohols can be hydrogenated over Raney nickel with retention of configuration,[4] they are useful intermediates in the elaboration of pharmacologically important β-amino alcohol[5] derivatives including chloramphenicol (**7**), ephedrine (**8a**) and norephedrine (**8b**).

As part of our studies on the chemistry of nitroalkanes and nitroalkenes,[6] we have discovered an experimentally simple procedure for stereoselectively preparing erythro β-nitro alcohols. Thus the alkyl nitronates **9**, formed by the action of *n*-butyllithium on nitroalkanes in THF solution, reacted with aldehydes in the presence of $TiCl_3(OPr^i)$ at room temperature to give the β-nitro alcohols enriched in the erythro diastereoisomer **10** (Tables I and II). It is clear from these results that the method is

Chart I. All Structures except 7 and 8 Refer to Racemic Modifications

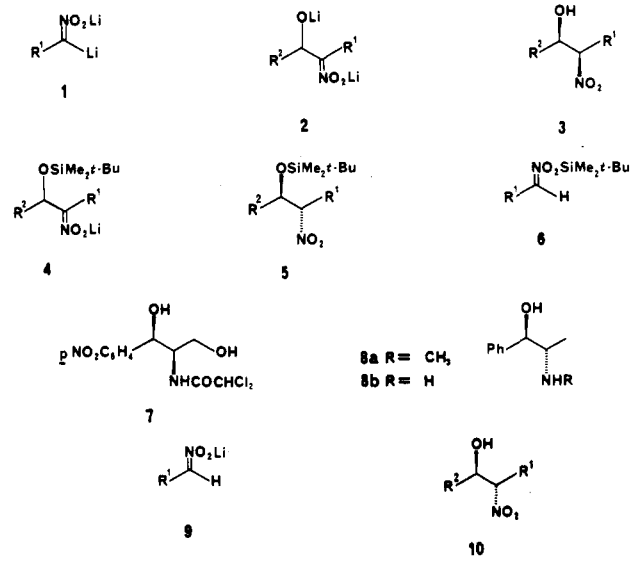

Table I. Reaction of Alkyl Nitronates with *p*-Nitrobenzaldehyde

nitroalkane	yield, % (isolated erythro isomer, %)	erythro:threo ratio[a,b]
a $CH_3(CH_2)_4CH_2NO_2$	81	3.9:1
b $EtO_2C(CH_2)_2CH_2NO_2$	72	7:1
c $THPOCH_2CH_2NO_2$	83	4:1
d $CH_3CH_2CH_2NO_2$	72 (60)	7:1

[a] Determined from the ^1H NMR spectrum of the crude product.[1] [b] All new compounds were fully authenticated by spectroscopic data and microanalyses or high resolution mass spectra.

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(6) Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1986**, *51*, 1012. Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *Ibid.* **1985**, *50*, 2603.

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Table II. Reaction of the Nitropropane Anion with Aldehydes

aldehyde	no. of equiv of nitronate	yield, % (isolated erythro isomer, %)	erythro:threo ratio[a,b]
a p-$NO_2C_6H_4CHO$	1	50	5.6:1[c]
	2	72 (60)	7:1[c]
b PhCHO	1	41	4.6:1
	2	61	6:1
c p-$MeOC_6H_4CHO$	1	21	1.7:1
	2	47	3.4:1
d o-$NO_2C_6H_4CHO$	1	46	9.4:1[c]
	2	65 (46)	6:1[c]
e o-$CF_3C_6H_4CHO$	1	38	7.3:1
	2	57 (42)	6.7:1[d]
f p-$MeO_2CC_6H_4CHO$	1	45	11.2:1[c]
	2	71 (41)	5.7:1[c]
g β-naphthaldehyde	2	61 (29)	4.9:1[d]
h (E)-cinnamaldehyde	2	43	8:1[d]
i $CH_3(CH_2)_5CHO$	1	13	3.8:1[e]
	2	28	3.8:1[e]
j $CH_3(CH_2)_3CHO$	2	27	2.9:1[e]
k t-BuCHO	2	0	
l MeO_2CCHO	2	36	1:1[e]

[a] Determined from the ^1H NMR spectrum of crude product.[1] [b] All new compounds were fully authenticated by spectroscopic data and microanalyses or high resolution mass spectra. [c] Recrystallization gave a single diastereoisomer. [d] Chromatography gave a single diastereoisomer. The ratio was determined by the ^{13}C NMR spectrum of the crude product.[1] [e] Determined by the ^{13}C NMR spectrum of the isolated β-nitro alcohol fraction.

particularly useful for electron-deficient aromatic aldehydes.[7] In contrast, the method is not efficient with aliphatic aldehydes, probably a consequence of competitive aldol chemistry.[8] There is a bizarre twist to this titanium-mediated Henry reaction. The nitronate **9** (R^1 = $THPOCH_2$) was found to react with isopropoxytitanium trichloride and benzaldehyde at −78 °C for 1 h to produce predominantely (9:1) the threo diastereoisomer **3** (R^1 = $THPOCH_2$, R_2 = Ph), although the conversion was low (~5%). It is reasonable to speculate that both the lower temperature threo-selective and higher temperature (≥−30 °C) erythro-selective processes are both kinetically controlled reactions via different titanium nitronate oligomers.[9] The higher temperature selectivity is not merely the result of threo–erythro equilibration.[10] Variation in quench conditions showed no observable changes in the product selectivity. The nitro alcohols are, however, stable to the reaction conditions.[11] Early results with $(^nBuO)_3ZrCl$, $EtAlCl_2$, and $TiCl_2(OPr^i)_2$ showed similar selectivities.

A typical procedure is as follows: n-BuLi (1.6M in hexane, 6.24 mL) was added dropwise with stirring to a solution of the nitroalkane (10 mmol) in THF (12 mL) at −78 °C. After 15 min a solution of $TiCl_3(OPr^i)$ (5 mmol) in THF (2 mL) and CH_2Cl_2 (3 mL) solution was added. After an additional 15 min, the aldehyde (5 mmol) was added and the mixture allowed to warm up to room temperature (~30 min). Stirring was continued for a further 3.5 h at room temperature and the mixture was quenched with an aqueous slurry of disodium EDTA (1.86 g, 5 mmol) and extracted with Et_2O (3 × 75 mL). The combined Et_2O fractions were washed with dilute hydrochloric acid (2 M, 75 mL), aqueous sodium bicarbonate (75 mL), and water (75 mL), dried, and evaporated in vacuo. Flash column chromatography using Et_2O/hexanes gave the pure nitro alcohols.

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(7) The yields reflect the conversion; remaining starting materials may be recovered by chromatography. Increasing the reaction time leads to better conversions.

(8) Titanium tetrachloride and derived alkoxides have been used in controlling the diastereoselectivities of many carbonyl addition reactions including the aldol reaction. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 149.

(9) Erythro selectivity was observed at temperatures as low as −30 °C, although conversions are superior at 25 °C.

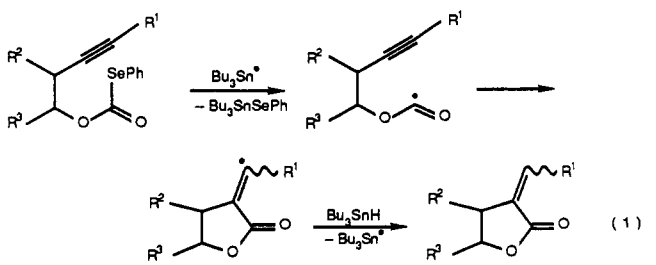
(10) The product ratio is clearly not that observed for isolated nitro alcohols under equilibrating conditions, see ref 1.

(11) Pure *erythro*-2-nitro-1-(2-nitrophenyl)-1-butanol (10 mol %) was recovered unchanged when added to a reacting mixture of 1-nitropropane and 2-(trifluoromethyl)benzaldehyde. In the same way, pure *threo*-2-nitro-1-phenyl-3-(tetrahydro-2-pyranyloxy)-1-propanol (10 mol %) was recovered unchanged when added to a reacting mixture of 2-nitrobenzaldehyde and 1-nitropropane.

Free Radical Cyclization of Thionocarbonic Acid Derivatives of 4-Phenyl-3-butenol. A New Route to Thionolactones

Summary: Treatment of various thionocarbonic acid derivatives of 4-phenyl-3-butenol with tri-n-butyltin hydride and AIBN in boiling benzene provides thionolactones and lactones in good yields via a free radical chain reaction.

Sir: The use of free radical reactions in the synthesis of complex functionalized molecules has recently become widespread.[1] In 1986 we reported a novel method for the preparation of α-alkylidene γ-lactones.[2] This method involves the intramolecular addition of alkoxycarbonyl radicals onto a carbon–carbon triple bond (eq 1). This cyclization reaction is readily extended to the synthesis of other lactones; for example *Se*-phenyl selenocarbonates of alk-3-enols and alk-4-enols yield γ- and δ-lactones, re-



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