Selective Reduction of α,β-Unsaturated Esters, Nitriles, and Nitro Compounds with Sodium Cyanoborohydride

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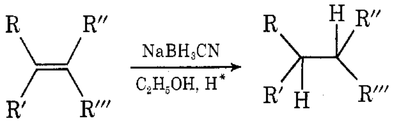
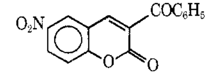
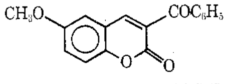
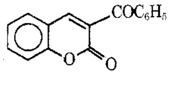
Our interest in the selective reducing properties of cyanoborohydride coupled with the recent attention accorded the reduction of α,β-unsaturated systems[1] prompts this report of the capability of cyanoborohydride for the facile and selective reduction of certain conjugated double bonds to the corresponding saturated derivatives.

The reduction of alkenes conjugated with strong electron-withdrawing groups such as esters,[5] nitriles,[5] sulfonate esters,[6] or nitro groups[7] has been observed with borohydrides or lithium aluminum hydride.[8] Thus, α,β-unsaturated esters are reduced by borohydride to the saturated derivatives if an additional cyano or ester is located at the α position.[5] Furthermore, conjugated cyano esters are often reduced to the saturated cyano alcohols.[5d,e] The highly electronegative cyano group evidently renders the normally resistant carbethoxy substituent electrophilic enough to suffer attack by borohydride. Recently, lithium tri-*sec*-butylborohydride (L-Selectride) at low temperatures has been found to effectively reduce conjugated carbonyl compounds, including esters, to the saturated derivatives,[9] Finally, Dittmer[6a] has reported reduction of the double bond in the strained ring thiete 1,1-dioxide with borohydride; acetylenic sulfones, however, apparently are reduced clearly to trans α,β-unsaturated sulfones.[6b]

Sodium cyanoborohydride is such an extremely nonaggressive reducing agent that even normally sensitive groups such as aldehydes and ketones are effectively reduced only when the electrophilicity of the carbonyl is increased by protonation.[4,10] Even under acidic conditions, however, other carbonyl derivatives, including esters, acids, and amides, remain unmolested. We envisioned that the reactivity of carbon–carbon double bonds of α,β-unsaturated carbonyl systems might be susceptible to activation by protonation and consequently enable the selective conversion of such systems to the saturated derivatives without affecting other functional groups. This note describes the successful realization of this conception using $NaBH_3CN$ in acidic ethanol at ambient temperature. The general procedure utilized was mild and convenient. The substrate, a 10% mole excess of $NaBH_3CN$, and a small quantity of bromocresol green were stirred in ethanol and concentrated HCl added dropwise until the solution was acidic as indicated by a color change to yellow.

Table I. Selective Reduction of Conjugated Alkenes with Sodium Cyanoborohydride[a]



Registry no. (alkene)	Entry	R	R'	R''	R'''	Time, h	% yield[b] (GLC)	Registry no. (product)
5292-53-5	1	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	(90)	607-81-8
	2	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	4.0	85	
	3	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	2.0[c]	(69)	
17422-56-9	4	*o*-$NO_2C_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	78	59803-35-9
22399-00-4	5	*p*-$NO_2C_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	0.75	98	7598-70-1
6331-45-9	6	*m*-$NO_2C_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	84	59803-36-0
22511-22-4	7	*p*-$CH_3CONHC_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	2.5	80	59803-37-1
59803-31-5	8	*m*-CNC_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	84	59803-38-2
2025-40-3		C_6H_5	H	$CO_2C_2H_5$	CN	1.0	67	6731-58-4
18925-00-3	9	*m*-$NO_2C_6H_5$	H	$CO_2C_2H_5$	CN	1.0	82	59803-39-3
6629-53-4	10	*p*-$CH_3CONHC_6H_5$	H	$CO_2C_2H_5$	CN	1.0	80	59803-40-6
59803-32-6	11	*o*-BrC_6H_5	H	$CO_2C_2H_5$	CN	1.0	88	59803-41-7
7324-89-2	12	2,4-di-ClC_6H_5	H	$CO_2C_2H_5$	CN	1.0	99[d]	59803-42-8
709-79-5	13	C_6H_5	H	$CONH_2$	CN	1.5	72	7216-46-8
705-60-2	14	C_6H_5	H	NO_2	CH_3	1.0	67	17322-34-8
6802-75-1	15	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	5.0	31[e]	759-36-4
103-36-6	16	C_6H_5	H	H	$CO_2C_2H_5$	1.0	0[f]	2021-28-5
59803-33-7	17					1.5	86	59803-43-9
59803-34-8	18					1.5	81	59803-44-0
1846-74-8	19					4.0	57	7216-47-9

[a] The reductions were conducted at ambient temperature as 0.4 M solutions of the compound in ethanol using a 10% mole excess of $NaBH_3CN$. Bromocresol green was employed as an indicator and the solutions were acidified with concentrated HCl. [b] Isolated yields, purified by distillation or recrystallization. GLC yields are corrected for detector response and utilized an internal standard. All known compounds corresponded to literature descriptions. New compounds gave satisfactory elemental analyses copies of which have been provided to the Editor (exception, entry 10). [c] No acid used. [d] Reaction was conducted in methanol; yield of crude product. [e] 69% recovery of starting material. [f] 93% recovery of starting material.

Additional HCl was added as required to maintain the solution acidity. After an appropriate time period, usually 1 h, the products were isolated by dilution with water followed by filtration or extraction with ether. Table I presents results for a variety of structural types. As evident, the method appears suitable for conjugated derivatives which are activated by a nitro group (entry 14) or by two α-positioned electron-withdrawing substituents including ester, cyano, lactone, ketone, or amide in varying combinations. Singly substituted double bonds as in ethyl cinnamate (entry 16) are resistant and aryl substitution enhances the reduction rate (entry 15). The method is quite selective in that other functional groups are unaffected including amido (entries 7, 10, 13), aromatic and aliphatic nitro (entries 4–6, 9, 14, 17) or cyano (entries 8–13) moieties, esters (entries 1–12, 15, 16), lactones (entries 17–19), or aryl ketones (entries 17–19). Furthermore, in contrast to analogous reductions with $NaBH_4$,[5d,e] cyano esters are not further reduced to the corresponding cyano alcohols. The use of acid, although not essential, results in higher yields (compare entries 1 and 3), ostensibly by rapid protonation of initially produced stable α carbanions before side reactions can intervene. This is evidenced by the relatively high yield of 1-methyl-2-phenylnitroethane obtained (entry 14) compared to previous investigations[7a,b] coupled with the absence of dimeric Michael products which are concomitantly produced with other hydride reagents.[7a,11]

Experimental Section

Materials. $NaBH_3CN$ was obtained from Aldrich Chemical Co. and used without purification. Starting materials were either obtained commercially or prepared by standard procedures.[12] All new compounds gave satisfactory elemental analysis and showed spectral (ir and NMR) data consistant with the structures. Elemental analyses were provided by Chemalytics, Inc., Tempe, Ariz., copies of which have been provided the Editor.

General Reduction Procedure. The general procedure utilized is presented in the text and is described below for the reduction of 6-nitro-3-benzoylcoumarin.

6-Nitro-3-benzoyl-3,4-dihydrocoumarin. A slurry of 6-nitro-3-benzoylcoumarin (2.95 g, 10 mmol), $NaBH_3CN$ (0.69 g, 11 mmol), and a small amount of bromocresol green indicator in 25 ml of ethanol was magnetically stirred while concentrated HCl was added dropwise until the color changed to yellow. Periodically, additional HCl was added in order to maintain the yellow color. After 1.5 h the reaction mixture was diluted with ca. 150 ml of water and cooled and the resulting while needles were filtered and dried under vacuum (2.54 g, 86%). The ir and NMR indicated complete reduction of the double bond.

Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73. Found: C, 64.70; H, 3.55.

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Registry No.—$NaBH_3CN$, 25895-60-7.

References and Notes

(1) Recent studies include the successful reduction of conjugated ketones to the corresponding saturated derivatives with potassium tri-*sec*-butylborohydride,[2a] various Cu(I) H complexes,[2b–e] hydrosilanerhodium(I) complexes,[2f] and ferrocene–HCl.[2g] Tetrahydroaluminate,[2h] borohydride,[3] and cyanoborohydride[4] are less discriminate and carbonyl reduction competes favorably in most cases.

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(11) The results further suggest the intriguing possibility of generating enolate ions in aprotic solvents with cyanoborohydrides which can subsequently be exploited for condensation or alkylation reactions.[9] This tactic is being actively pursued.

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Oxidation of Sterically Hindered Alcohols to Carbonyls with Dimethyl Sulfoxide–Trifluoroacetic Anhydride

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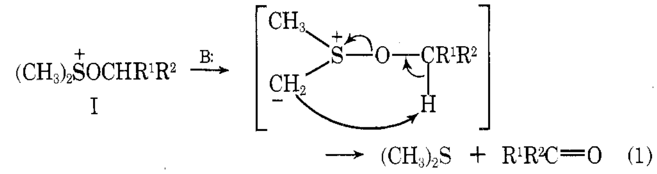
As an outgrowth of our earlier study of a new synthesis of iminosulfuranes,[1] we have investigated a new reagent for the oxidation of alcohols to aldehydes or ketones which appears to be generally useful, operationally simple, highly selective, and efficient.[2] This new reagent, dimethyl sulfoxide–trifluoroacetic anhydride (Me_2SO–TFAA), complements previous reagents[3–13] for the conversion of alcohols to dimethylalkoxysulfonium salt intermediates (I) which, on treatment with base under mild conditions, are rapidly converted to carbonyls in high yields (eq 1):



R^1, R^2 = alkyl, aryl, aralkyl, H, alicyclic, etc.

None of the previous methods gives satisfactory results with all classes of primary and secondary alcohols. The new reagent, dimethyl sulfoxide–trifluoroacetic anhydride, now appears to be a most generally useful reagent for the facile conversion of primary and secondary alcohols to carbonyls in high to quantitative yields. In assessing the scope and limitations of this new reagent, the oxidation of some model sterically hindered alcohols was studied. In this note we are reporting the results obtained thus far.

Yields of carbonyls from hindered alcohols (>80–100%) are higher than those from previously studied unhindered alcohols and by-product formation is reduced (usually to <5%) (Table I). We find that (a) the more hindered the alcohol, the higher the yield and alcohols (**5, 6**) with bulky groups on both sides of the carbinol carbon give quantitative yields; (b) no difficulty is experienced in oxidizing primary and secondary