Direct Alkylation of α-Substituted Aldehydes

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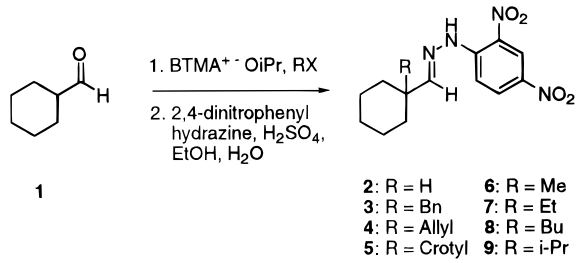
Received August 2, 1996

On the basis of extensive reported studies, alkylation of aldehydes[1] is not considered to be a generally useful synthetic transformation. Aldol condensations and Cannizzaro−Tishchenko reactions[1] typically reduce the yields of the desired alkylated aldehydes severely. Reactions of potassium enolates of aldehydes containing one α-H atom with reactive alkylating agents (benzyl and allyl bromide, methyl iodide), in which 75−95% yields of the desired C-alkylated products were obtained,[2,3] form an instructive exception. However, lower yields and unfavorable C/O alkylation ratios reported for less reactive electrophiles (BuI, iPrI)[2,3] limit the usefulness of this approach.

We have undertaken a study designed to probe whether the replacement of the normally used metal counterions by nonmetal cations would significantly slow down or completely suppress the undesired side reactions.[4] This was inspired by the report that, in contrast to the reactions of lithium (and other alkali metal) enolates,[1] no enolate−ketone H-exchange takes place in alkylations of the two possible benzyltrimethylammonium (BTMA) enolates of 2-methylcyclohexanone,[5] as well as the success by others[6−8] in similar reactions with nonmetal cations.

Scheme 1 and Table 1 summarize some of our results using the base BTMA 2-propoxide, prepared by vacuum evaporation of a solution of the commercially available BTMA methoxide (40% in methanol) in a large excess of 2-propanol. Products were isolated as their 2,4-dinitrophenylhydrazones.[9,10] Since these were prepared under acidic conditions, product enol ethers hydrolyzed and gave hydrazone **2**. The extent of O-alkylation was therefore determined in each case by a ^{1}H NMR spectrum of the crude product before hydrazone formation. The ratio of product hydrazone to starting material hydrazone

Scheme 1



1

2: R = H **6**: R = Me
3: R = Bn **7**: R = Et
4: R = Allyl **8**: R = Bu
5: R = Crotyl **9**: R = i-Pr

Table 1. Alkylation of Cyclohexanecarboxaldehyde 1 with Various Alkyl Halides[a]

RX	product (%)	starting material (%)	time
$PhCH_2Br$	**3** (100)		30 min
CH_2=$CHCH_2Br$	**4** (98)		30 min
CH_3CH=$CHCH_2Br$	**5** (98)		30 min
MeI	**6** (92)	**2** (8)	2 h
EtI	**7** (82)	**2** (17)	2 h
BuI	**8** (80)	**2** (18)	12 h
i-PrI	**9** (72)	**2** (22)	12 h

[a] All reactions were run at ambient temperature using a 0.033 M solution of cyclohexanecarboxaldehyde **1** in *tert*-butyl alcohol, 1.3−1.4 equiv of base, and 3 equiv of alkylating agent.

(columns 2 and 3 in Table 1) was then determined to be identical to the C- versus O-alkylation product ratio shown by ^{1}H NMR integration. No starting material (**1**) or any byproduct was detected in any crude products.

Benzyl, allyl, and crotyl bromides gave a near-quantitative yield of C-alkylated products, with the crotyl bromide alkylating exclusively by the S_N2 mechanism. With primary iodides, a not unexpected trend of decreasing C/O alkylation ratios with increasing chain length (methyl, ethyl, butyl) was observed. Nevertheless, even the "slow" butyl iodide gave a good (and unprecedented) yield of C-alkylation product. Equally encouraging was the reasonably efficient C-alkylation using the secondary halide, 2-iodopropane. A quick survey of the less reactive halides (bromides and chlorides) was undertaken; as anticipated, butyl bromide gave a higher proportion of O-alkylation (2:1 C/O ratio), while unfortunately, butyl chloride did not react.

In order to establish whether 3 equiv of alkylating agent are required, the reaction of cyclohexanecarboxaldehyde **1** with iodomethane was repeated using equal amounts of base and alkylating agent (1.4 equiv). The result (89% yield of 2,4-dinitrophenylhydrazone **6**) indicated that ∼1.4 equiv of both base and the alkylating agent are sufficient for a complete monoalkylation.

A solvent study using aldehyde **1** and iodomethane revealed that benzene and toluene could be used but gave yields slightly lower than those in *tert*-butyl alcohol, while THF (59% yield; low solubility of base) and 2-propanol (8% yield) were clearly inferior. The low yield in 2-propanol is presumably due to a shift in the equilibrium away from the enolate and toward 2-propoxide in the presence of a large excess of its conjugate acid.

The generality of this methodology was then tested by the alkylation of isobutyraldehyde (**10**) (a representative acyclic aldehyde), cyclopentanecarboxaldehyde (**11**), myrtenal (**12**) (an α,β-unsaturated aldehyde which could α-alkylate only once), and keto aldehyde **15** (suitable for a test of chemoselectivity). Each was separately treated with 1.3−1.4 equiv of BTMA 2-propoxide and 3 equiv of iodomethane in a 0.1 M solution of aldehyde in *tert*-butyl alcohol at ambient temperature for 30 min with the exception of aldehyde **12**, which required 12 h. Analysis

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(8) Dietl and Brannock reported 15−85% yields in C-alkylations of isobutyraldehyde and 2-ethylhexanal using a 50% aqueous NaOH−benzene two-phase system with tetrabutylammonium iodide as the transfer salt. See: Dietl, H. K.; Brannock, K. C. *Tetrahedron Lett.* **1973**, 15, 1273.

(9) All compounds gave satisfactory ^{1}H and ^{13}C NMR, IR, and HREIMS.

(10) These derivatives were prepared for a precise determination of yield, since it proved impossible to prevent product aldehyde losses, using small quantities, by partial or complete air oxidation on SiO_2 chromatography.

S0022-3263(96)01471-5 CCC: $12.00

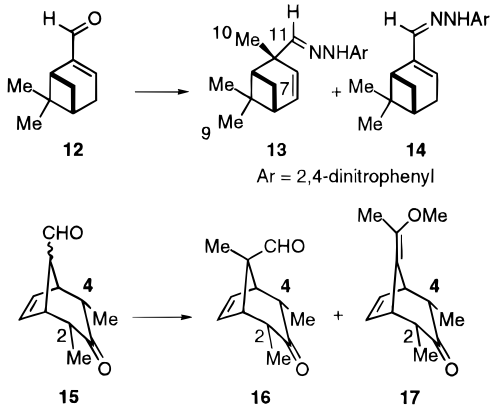
Table 2. Alkylation of Various Aldehydes with Iodomethane

entry	aldehydes	% C-alkylated	% O-alkylated
1	**10**	96	
2	**11**	92	3
3	**12**	60	40
4	**15**	71	5

(^{1}H NMR spectra of crude products, 2,4-dinitrophenylhydrazones) was performed as described above. The results are presented in Table 2.[9,11] In all cases examined, no starting material was recovered, and with one exception, C-alkylation was strongly predominant. The rigidity and steric hindrance imposed upon the enolate of myrtenal **12** by the four-membered ring clearly slowed down the reaction and changed the C/O alkylation ratio,[12] Scheme 2.

*Possibly the most significant result of this survey is the chemoselective (and stereoselective) alkylation of keto aldehyde **15**,*[11] Scheme 2. No C- or O-alkylation products of the possible ketone enolate were detected. Furthermore, there was no indication of any isomerization at the C2 or C4 centers, which are known to be prone to base-catalyzed isomerization.[13] In order to eliminate any possibility that the chemoselectivity observed in the alkylation of compound **15** was due to some of its special features, a competitive reaction was performed in which cyclohexanecarboxaldehyde **1** (1 equiv) and 2,6-dimethylcyclohexanone (1 equiv) were treated in *tert*-butyl

Scheme 2



alcohol with 1.4 equiv of BTMA 2-propoxide and 3 equiv of iodomethane. Methylated aldehyde was isolated as its 2,4-dinitrophenylhydrazone **6** in 90% yield, while none of the 2,6-dimethylcyclohexanone, isolated partly as free ketone and partly as its 2,4-dinitrophenylhydrazone, was methylated. Hydrogen atoms α to an aldehyde group are reported to be more acidic than those α to a keto group[14] and *our results indicate that the base used in this study possesses just the right strength for an efficient differentiation.*

A study using this methodology on aldehydes amenable to double alkylation and on unsymmetrically substituted ketones is in progress.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council of Canada, the University of New Brunswick, and CIDA-General Training Program (fellowship to S.S.) is gratefully acknowledged.

Supporting Information Available: Procedures and characterization data (8 pages).

JO9614710

(11) The structures of **13** and **16** were determined by NOE studies. For compound **13**, irradiation of the C10 methyl protons in the ^{1}H NMR spectrum produced a 2.7% enhancement of the syn C7 proton, while no enhancement was observed for the C9 methyl protons. Irradiation of the C9 methyl protons resulted in a 0.9% enhancement for the C11 proton and a 0.6% enhancement of the ortho proton on the aryl group. For compound **16** irradiation of the C2 and C4 protons yielded a 4.5% enhancement in the aldehyde proton, but no enhancement was observed for the C9 methyl protons.

(12) Evidence to support this was that alkylation of 2-methyl-2-butenal and 2-methyl-2-pentenal with benzyl bromide proceeded to give the expected C-alkylated products in 89% and 93% yields, respectively (isolated as their 2,4-dinitrophenylhydrazones).

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