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Dicyclohexyliodoborane/Triethylamine - a New Reagent Which Achieves the Facile Enolboration of Esters and Tertiary Amides

Herbert C. Brown* and Kumaraperumal Ganesan

H. C. Brown and R. B. Wetherill Laboratories of Chemistry
Purdue University, West Lafayette, Indiana 47907

Abstract: *A smooth, rapid, quantitative enolboration of esters and tertiary amides has been achieved for the first time with dicyclohexyliodoborane, Chx_2BI, a new reagent, in the presence of triethylamine.*

Enolborinates are highly promising intermediates in organic synthesis.[1] They are especially valuable for the aldol reaction because of their high stereoselectivity.[2-4] It has been well demonstrated that *Z* enolborinates form syn aldols and *E* enolborinates form anti aldols stereoselectively.[2,5,6]

In spite of considerable research effort in the past decade, the development of simple and efficient methodologies for the generation of enolborinates has provided an attractive challenge to organic chemists. A well studied methodology[3] involves the reaction of ketones with a suitable organoboron reagent having a good leaving group, R'_2BX, in the presence of a suitable tertiary amine, R''_3N (eq 1).

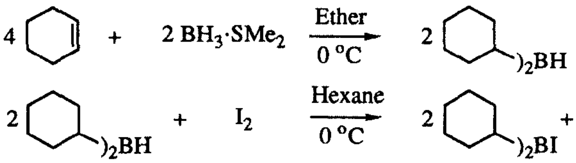
(1)

Many of the various reagents developed earlier for this methodology involve difficult procedures to achieve the synthesis of pure reagents or give only moderate yields of the desired enolborinates.[2-4] The lack of control of enolate geometry in achieving the selective generation of *E* enolborinates is another serious limitation of these earlier reagents. One of our research objectives is the exploration of new organoboron reagents for enolboration and the achievement of an understanding of the different factors controlling the geometry of enolate formation. Our first successful reagent, Chx_2BCl, overcomes many of these limitations.[7] It enolizes various classes of ketones[7b] and carbonyl compounds[7a] such as aldehydes, carboxylic acids, anhydrides, thioesters and β-keto esters. However, both esters and tertiary amides are not enolized by this reagent.

Despite the fact that a considerable number of organoboron reagents are available for the successful enolization of ketones,[2-7] very little is known of reagents which can achieve the successful enolboration of esters and tertiary amides. Evans has shown that the widely used R_2BOTf reagents are also ineffective for the enolization of esters and tertiary amides.[2b] A similar resistance to the formation of enolborinates has also been observed by the attempted 1,4-addition of catecholborane to α, β-unsaturated esters and tertiary amides.[8] However, thioesters are readily enolized by both R_2BOTf[2,4b,d] and R_2BCl[7a] reagents.

Only one organoboron reagent, $R^*{}_2BBr$, has been reported so far in the literature for the generation of enolborinates from esters.[9] Essentially no organoboron reagent is now available for the enolization of tertiary amides except for di-*n*-butylboron triflate, *n*-Bu_2BOTf, which has been shown to enolize a special class of reactive tertiary amides, the *N*, *N*-dialkyl-2,3,3,3-tetrafluoropropanamides.[10]

The lack of simple and efficient reagents in this field for the enolboration of esters and tertiary amides encouraged us to explore new organoboron reagents. Our studies revealed that Chx_2BI/Et_3N is a satisfactory reagent for these applications. Chx_2BI is readily prepared by hydroboration[6a] of cyclohexene (2 equiv) with borane-methyl sulfide (1 equiv) followed by treatment of the intermediate Chx_2BH with I_2 (1/2 equiv)[10b] as

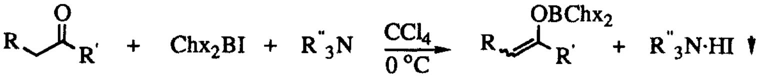


(2)

(3)

The enolboration was carried out in CCl_4 since in this solvent the ^1H NMR spectra can be directly recorded for the reaction mixtures.[12] Benzene, an internal standard, was added for quantification. The ^1H NMR spectrum (olefinic proton) was used to determine the extent of enolboration by comparing the integration of the olefinic protons of the enolborinates with those of the internal standard benzene. The ^{11}B NMR spectrum (borinate region) was also used to confirm the formation of enolborinates. This technique has been previously utilized in our studies of the quantitative formation of enolborinates.[7] Enolization was also successfully carried out in other solvents, such as CH_2Cl_2 and hexane. Ether solvents were avoided since R_2BI reagents are known to cleave ethers rapidly. However, it has been shown that the diastereoselection with the enolborinates is either the same or slightly enhanced in non-polar solvents as compared to polar solvents.[2a] Therefore the choice of a suitable solvent is not a significant problem.

Representative examples of both aliphatic and aromatic esters and tertiary amides were enolized to test the efficiency of our reagent (eq 4). The results are summarized in Table 1.



(4)

R = alkyl, phenyl ; R' = *O*-alkyl, *N*, *N*-dialkyl ; $R''_3N = Et_3N$, *i*-Pr_2EtN

From the results in Table 1, it is clear that the enolization of both esters and tertiary amides is rapid and quantitative even at 0 °C except for the sterically hindered *tert*-butyl propionate. However, an increase in temperature to 25 °C brought about the rapid enolization of this relatively hindered ester.

In the case of aliphatic esters and amides, the yields are slightly better with Et_3N when compared with bulky *i*-Pr_2EtN. But, in the case of aromatic compounds, the yields are essentially the same with both amines. In general, these results suggest that Chx_2BI/Et_3N is the preferred combination for both aliphatic and aromatic esters and tertiary amides.

Table 1. Enolboration of Esters and Tertiary Amides with Chx_2BI in the Presence of Different Amines[a]

Ester/Amide	Amine	^{1}H NMR (δ ppm)[b]	Yield[c,d]
$MeCH_2COOEt$	Et_3N	3.97 (q, J = 7.2 Hz)	96
	i-Pr_2EtN		70
$PhCH_2COOEt$	Et_3N	4.84 (s)	96
	i-Pr_2EtN		95
$EtCH_2COOEt$	Et_3N	3.96 (t, J = 7.1 Hz)	95
i-$PrCH_2COOEt$	Et_3N	3.60 (d, J = 8.7 Hz)	94
t-$BuCH_2COOEt$	Et_3N	3.59 (s)	84
$MeCH_2COOCMe_3$	Et_3N	4.11 (q, J = 6.7 Hz)	60
	Et_3N[e]		87
	i-Pr_2EtN		57
	i-Pr_2EtN[e]		74
$MeCH_2CONMe_2$	Et_3N	4.59 (q, J = 6.7 Hz)	96
	i-Pr_2EtN		86
$PhCH_2CONMe_2$	Et_3N	4.20 (s)	96
	i-Pr_2EtN		93
$MeCH_2CONEt_2$	Et_3N	3.45 (q, J = 7.1 Hz)	94
	i-Pr_2EtN		83

[a] Reactions were carried out in CCl_4 at 0 °C unless otherwise stated. [b] Corresponds to the olefinic protons of the enolborinates. [c] Based on the ^{1}H NMR by comparing the integration of the olefinic proton of the enolborinate with those of the internal standard benzene (the estimated error limit ± 3%). [d] In representative cases, the NMR yields were also confirmed by collecting and weighing the solid $Et_3N{\cdot}HI$. [e] Enolization at 25 °C.

Chx_2BI is easy to prepare, handle and very stable even at room temperature under an inert atmosphere. No cleavage of ester has been observed under our experimental conditions. The reaction is essentially instantaneous, even at 0 °C, in all cases except for the sterically hindered *tert*-butyl propionate. Visual observation of the formation of $Et_3N{\cdot}HI$ as a pale yellow precipitate as the enolization progresses is an added advantage for this reagent, providing a convenient guide to the course of the reaction. These advantages make Chx_2BI a valuable, practical reagent for the enolization of esters and tertiary amides.

Initial investigation of the stereochemistry of the enolborinates, based on the well established aldol method,[6] suggests that aliphatic esters give Z enolborinates essentially exclusively (for example, Z:E = 99:1 for CH_3CH_2COOEt), whereas the related tertiary amides give E enolborinates predominantly (for example, Z:E = 5:95 for $CH_3CH_2CONEt_2$). Interesting variation of the Z:E ratios can be achieved by variation in the enolboration conditions. These results will be presented and discussed in a full paper following completion of our study both of the enolboration process and of the stereochemistry of the enolboration process.

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11. To a suspended solution of Chx_2BH (22.3 g, 125.3 mmol) [ref. 7(a)] in hexane (100 mL) at 0 °C under a N_2 atmosphere, solid I_2 (15.95 g, 62.84 mmol) is added through a side arm in small instalments with constant stirring. Hydrogen is evolved and should be safely vented. After adding all the iodine, the reaction mixture is stirred at 0 °C for 2h and at 25 °C for 1h. A pale pink color (due to the small excess of I_2) persists which shows the completion of the reaction. Then the solvent is removed by a water aspirator (20 mm). Distillation of the concentrated mixture under vacuum yields pure, colorless Chx_2BI, bp 198-200 °C (1.25 mm), 80% yield, ^{11}B NMR (hexane) δ 84 ppm.

12. To a stirred solution of Chx_2BI (1.1 mL, 5.15 mmol) and the R''_3N (5.15 mmol) in CCl_4 (15 mL) kept at the required temperature under N_2 atmosphere, the ester or tertiary amide (5.0 mmol) is added dropwise. The enolborinate is generated instantaneously with concurrent formation and precipitation of $R''_3N{\cdot}HI$. An internal standard, benzene (0.50 mL, 1.00 M in CCl_4, 0.50 mmol), is added (except for the aromatic compounds) for quantification of the enolborinate. The reaction mixture is stirred for 2 h at the same temperature and transferred into a centrifuge vial through a double-ended needle (18 guage). Centrifugation results in the separation of the enolborinate solution from the solid $R''_3N{\cdot}HI$. In representative cases, we have collected and weighed the precipitated $R''_3N{\cdot}HI$. Essentially quantitative yields are obtained. The enolborinate solution is then transferred into an NMR tube by a double-ended needle. The ^1H NMR (olefinic proton) analysis gives the extent of enolization and the ^{11}B NMR spectrum (borinate region, usually broad, 50-56 ppm) confirms the formation of enolborinates. In representative cases, the enolborinates were treated with benzaldehyde and the enolates proved to be highly reactive even at -78 °C.

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