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ENOLBORONATES : NEW PRACTICAL REAGENTS FOR REGIOSELECTIVE ALDOL CONDENSATIONS.

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SUMMARY : Enolboronates, new enolates directly accessible from carbonyl compounds and giving aldol products regioselectively and in good yield with aliphatic and aromatic aldehydes, are described.

The remarkable success already obtained, over the past few years, in the development of stereoregulated aldol condensations[1] makes one question the usefulness of searching for new reagents in this area. In order to be comparable or preferable to the known methods, a new one should answer to at least some of the following points. 1) Direct and regioselective enolate formation from carbonyl compounds by the combined use of simple and easy to handle Lewis acid and base. 2) Smooth cross-aldol reactions, under mild conditions and in good yields, even with enolizable aldehydes. 3) Internal stereochemical control (diastereoselection) and absolute stereochemical control (enantioselection) provided by the metal ligands. In this Letter, we report that enolboronates (3) fulfill the first two requirements, whereas the last one is under current careful investigation.[2]

Ethylene chloroboronate (1) was readily prepared from BCl_3 and ethylene glicol.[3] Treatment of the chloroboronate in CH_2Cl_2 at -78 deg C with iPr_2NEt and then with carbonyl compounds produces enolboronates (3). The enolboronate derived from t-butyl methyl ketone was fully characterized (3, R=tBu) by ^1H and ^{13}C NMR spectroscopy (Table 1,2).

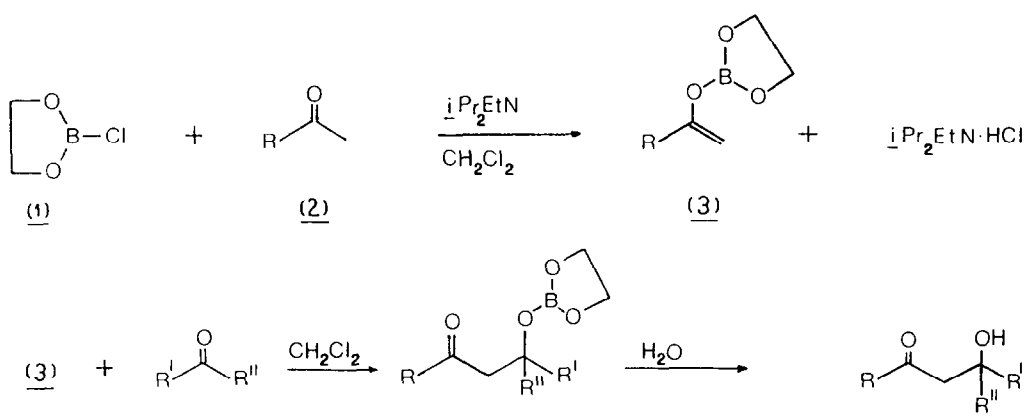


TABLE 1. ^{1}H NMR spectra ($CDCl_3$).

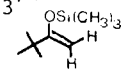
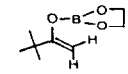
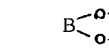
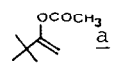
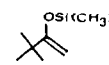
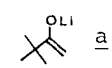
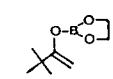
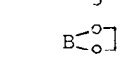
δ			
tBu	1.12 (s)	1.01 (s)	1.01 (s)
Me/CH_2	2.11 (s)	3.90 (d) J=1.3 Hz	4.30 (d) J= 1.7 Hz
		4.06 (d) J=1.3 Hz	4.35 (d) J= 1.7 Hz
	=	=	4.17 (s)

TABLE 2. ^{13}C NMR spectra ($CDCl_3$).

δ		 a	 a	 a	 b
C=O/C=	212.9	162.2	166.5	176.8	165.0 (s) c
CH_2/Me	24.4	98.4	85.5	73.5	91.1 (t)
C(tBu)	44.2	36.3	36.6	37.5	36.1 (s)
CH_3(tBu)	26.3	27.9	28.2	29.7	27.9 (q)
	=	=	=	=	65.1 (t)

a Solvent DME. H.O. House, A.V. Prabhu, and W.V. Phillips, J.Org.Chem.,41,1209 (1976). b Halflife ca. 2 hours at R.T. c Notations in brackets refer to the off-resonance spectrum.

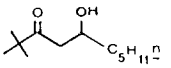
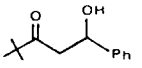
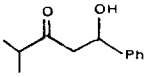
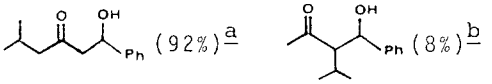
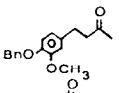
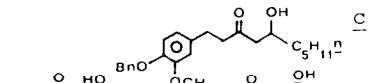
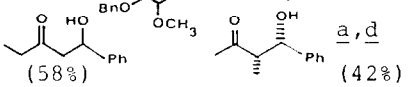
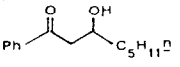
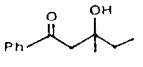
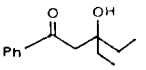
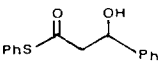
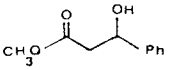
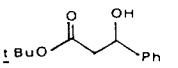
Enolboronates derived from ketones react smoothly with aldehydes in CH_2Cl_2 from -78 to -15 deg to give aldol products in good yields (Table 3).[4] Other bases including triethylamine, 2,6-lutidine were significantly less effective at promoting the aldol condensation. Kinetically controlled deprotonations are regioselective (Table 3, entries 3-5) except for the case of methyl ethyl ketone (entry 6) where an equal amount of the erythro compound was obtained.[5]

The selectivity of enolboronates was briefly examined using various other electrophiles such as benzyl bromide, acetic anhydride, chlorotrimethylsilane, and N-(trimethylsilyl)-imidazol. In all these cases no clean reaction occurred. Cross-coupling between ketones proceeded with moderate yields (entries 8,9).[6]

Esters and thioesters are harder to enolize than ketones, and require more vigorous conditions.[7] The enolate from the thioester (3, R=SPh) reacts with benzaldehyde at -78 deg to give the adduct in good yield (entry 10). The enolates from the esters (3, R=OMe, OtBu) tend to decompose or selfcondense under the enolization conditions, and therefore give lower yields (entries 11,12).

Finally, comparing our enolboronates to the Evans-Masamune-Mukaiyama vinyloxyboranes[1], we note that no oxidative work-up is here necessary.[4]

TABLE 3. Aldol condensations.

Entry	$R-\overset{O}{\overset{\|}{C}}-CH_3$	$R'-\overset{O}{\overset{\|}{C}}-R''$	Product(s)	Yield %[e]
1		$^nC_5H_{11}CHO$		67
2		PhCHO		68[f]
3		PhCHO		70[f]
4		PhCHO	 (92%)[a] (8%)[b]	76[f]
5		$^nC_5H_{11}CHO$	 [c]	60[g]
6		PhCHO	 (58%) (42%) [a,d]	85
7		$^nC_5H_{11}CHO$		70
8				48[h]
9				40[h]
10		PhCHO		62
11		PhCHO		30[i]
12		PhCHO		31[i]

a Isomer ratios were measured by integration of well-resolved signals in the ^1H NMR spectrum.
b Single stereoisomer : ^1H NMR ($CDCl_3$) δ 4.85 (CH-O), d, J= 6 Hz.
c O-benzylgingerol.(D. Enders, H. Eichenauer, Chem. Ber., 3703 (1979)).
d Erythro-threo > 99:1.
e Isolated yields.
f 1-5% cynnamic-type compound was isolated as byproduct.
g 95% yield considering the starting ketone recovery.
h 10-20% selfcondensed acetophenone was isolated as byproduct.
i Yields determined by ^1H NMR spectroscopy.

NOTES AND REFERENCES :

1. REVIEWS: D.A. Evans, J.V. Nelson, and T.R. Taber, Top. Stereochem., 13, 1 (1982); T. Mukaiyama, Org. React., 28, 203 (1982).

2. For preliminary results see the following communication in this issue.

3. PREPARATION OF (1): to a stirred solution of BCl_3 (35.2 gm, 0.3 mol) in CH_2Cl_2 (100 ml) at -78 deg C, ethylene glicol (15.2 ml, 0.27 mol) was added dropwise. Then the mixture was warmed up to R.T., evaporated under vacuum, and distilled (J.A. Blau, W. Gerrard, and M.F. Lappert, J. Chem. Soc., 4116 (1957)) to yield ca 24.4 gm (85%) ethylene chloroboronate. The viscous, air-sensitive chloroboronate was dissolved in CH_2Cl_2, and stored in the freezer as 1 M solution in CH_2Cl_2.
^{1}H NMR ($CDCl_3$) δ 4.38 (s). ^{13}C NMR ($CDCl_3$) δ 65.8 (t, off-resonance).

4. GENERAL PROCEDURE FOR THE ALDOL CONDENSATION : to a stirred solution of ethylene chloroboronate (1.1 mmol) and iPr_2EtN (1.15 mmol) in CH_2Cl_2 (2.5 ml), at -78 deg, under nitrogen, the ketone (1.0 mmol) was added dropwise. The mixture was stirred at -78 deg for 30 min, then the aldehyde (1.0 mmol non-enolizable; 1.2 mmol enolizable) was added. Then the reaction was stirred at -78 deg for 30 min, and at -15 deg for 1 h. The reaction was quenched by directly applying the mixture to the top of the silica gel bed of the flash-chromatography column (small scale), or by adding pH 7-phosphate buffer (large scale). In the last case the product was extracted into CH_2Cl_2, the extracts were dried (Na_2SO_4) and evaporated, and the compound was isolated by flash-chromatography (W.C. Still, M. Kahn, and A. Mitra, J.Org. Chem., 43, 2923 (1978)).

5. RATIOS: reaction performed at -78 deg (1 h), and quenched at -78 deg : linear-branched ca 58:42; erythro-threo > 99:1; yield 85% (as shown in Table 3). Reaction performed at -78 deg (5 min), 0 deg (1 h), using 2.2 eq. of (1) : branched- linear ca 80:20; threo-erythro ca 7.5:1; yield 65%. Erythro isomer: ^{1}H NMR ($CDCl_3$) δ 5.04 (CH-O), d, J= 4.07 Hz. Threo isomer: ^{1}H NMR ($CDCl_3$) δ 4.70 (CH-O), d, J= 8.0 Hz.

6. For condensations with ketones the above procedure was modified as follows: the reaction was warmed up from -78 deg to 0 deg during 1 h, and then stirred at 0 deg for 1 h , quenched and worked-up as usual.

7. After the addition of the substrate (2, R= SPh, OMe, OtBu), the mixture was warmed to 0 deg, and stirred at 0 deg for 1 h. Then the solution was cooled down to -78 deg, and the aldehyde was added. After 1 h at -78 deg, the reaction was quenched with pH 7-phosphate buffer, worked-up as usual, and flash-chromatographed, or directly analyzed by ^{1}H NMR spectroscopy.

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