Regiocontrol in Alkylation of Lithium Dienediolates of Unsaturated Carboxylic Acids

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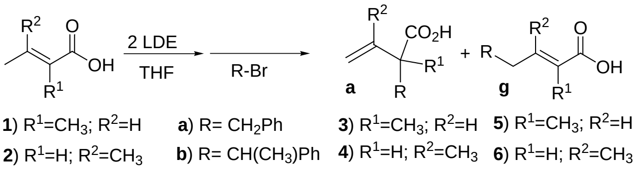
Abstract: Alkylation of dienediolates from unsaturated carboxylic acids with benzylic halides often results in mixtures of regioisomers. However it can be controlled by adequate modification of the reaction conditions. Thus, addition of DMI leads mainly to the α-regioisomer, whereas addition of 12-crown-4 allows to obtain the γ-regioisomer as the major product from the same reactants.

Key words: alkyl halides, carboxylic acids, chelates, regioselectivity, solvent effects

Unsaturated carboxylic acids are synthetically useful building blocks[1] because they afford dienediolates by deprotonation reaction with two equivalents of lithium dialkylamides. These intermediates react with electrophiles under adequate conditions.[2] The dienediolates act as ambident nucleophiles through their α or γ carbon atoms leading to a sole or clearly predominant compounds. Regioselectivity trends depend on both the electrophile compound and the reaction conditions. Thus α attack predominates in the irreversible reactions with primary alkyl halides.[3] Reversion of this selectivity has been described only for allylic halides by counter ion interchange with copper (I) salts.[4] On the other hand, we had found that selectivity of these alkylations strongly depended on the reactivity of the electrophile. The alkylation of the π-extended enolates of unsaturated carboxylic acids with secondary halides and benzylic or allylic primary halides showed significant deviations from α selectivity giving always both regioisomers (Scheme).[5] However α-isomers can be obtained using the corresponding tosyl-derivatives.[6]



Scheme

Here we describe that reaction conditions, namely solvent, temperature and additives, can be also used to control this regioselectivity. It is a well established feature that lithium enolates exist as complex ion pair aggregates, whose metal centre may be coordinated to solvent molecules or other chelating ligands. Available information confirms the complexity present in the aggregated reactive species along with the influence of several factors[7] on the reactivity. For that reason, we have now studied the influence of solvent and some additives on the alkylation

Table 1 Alkylation of Dienolates of Unsaturated Carboxylic Acids. Solvent Change.

Entry	Acid	R-Br	Solvent	Yield	Starting acid	α	γ
1	1	a	THF	84		70	30[6]
2	1	a	Toluene	58		75	25
3	1	b	THF	83		45	55[8]
4	1	b	THF[a]	83		45	55
5	1	b	THF[b]	80		47	53
6	1	b	THF[c]	44	56	33	67
7	1	b	C_6H_{12}	61	25	56	44
8	1	b	Toluene	55	10	50	50
9	1	b	DME	82		60	40
10	1	b	TMEDA	75	7	49	51
11	2	a	THF	70		85	15
12	2	b	THF	75		73	27[8]
13	2	b	Toluene[d]	46	32	76	24

a) at 0 °C, 6 h.
b) at −25 °C, 24h.
c) at −78 °C, 24 h.
d) at −40 °C, 24h.

Table 2 Alkylation of Dienediolate of Tiglic Acid (**1**). Introduction of Additives.

Entry	Bromide	Solvent	Additive (equiv.)	Yield (%)	Starting acid	α	γ
1	b	C_6H_{12}	DMI (2)	43	75	44	56
2	b	DME	DMI (2)	59		49	51
3	b	THF	DMI (2)	70	14	49	51
4	b	THF	DMI (5)	56	10	50	50
5	b	THF	DMI (10)	40	18	64	36
6	b	THF	DMI (2)[a]	71		73	27
7	b	THF	DMI (5)[a]	77		81	19
8	b	Toluene	LiBr (2)	67	6	73	27
9	b	THF	LiBr (2)	79	6	56	44
10	b	THF	LiBr (2)[a]	85		84	16
11	a	C_6H_{12}	12-crown-4 (0.5)	76		50	50
12	a	C_6H_{12}	12-crown-4 (1)	79		37	63
13	b	C_6H_{12}	12-crown-4 (0.1)	48	7	54	46
14	b	C_6H_{12}	12-crown-4 (1)	74	7	30	70
15	b	C_6H_{12}	12-crown-4 (2)	76		31	69
16	b	MeC_6H_{12}	12-crown-4 (0.5)	74		33	67
17	b	MeC_6H_{12}	12-crown-4 (1)	56	39	29	71
18	b	Toluene	12-crown-4 (2)	73	16	46	54
19	b	Toluene	DDOMG (1)	54	43	40	60
20	b	C_6H_{12}	DDOMG (1)	77	47	37	63
21	b	C_6H_{12}	DDOMG (2)	81	50	32	68
22	b	THF	DDOMG (2)	66	15	65	35
23	a	THF	DDOMG (1)	76		63	37
24	a	THF	DDOMG (2)	83		44	56
25	b	C_6H_{12}	DDOTG (1)	75		53	47

[a] at −10 °C, 15 h.

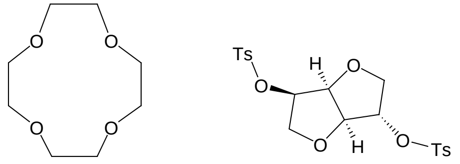
regioselectivity of lithium dienediolates of 2-methylbutenoic (**1**) and 3-methylbutenoic (**2**) acids with benzyl bromide (**a**) and 1-phenyl-1-bromoetane (**b**). These two halides have been chosen because both show strong deviations from α selectivity (Table 1, entries 1, 3, 11 and 12) under standard conditions.[2] The usually reported conditions are 2.25 mmol of both the dienediolate and the halide and a slight excess (4.8 mmol) of lithium diethylamide (LDE) as a base in THF. In the present study, after generation of the dienediolate in THF, this solvent was eliminated under an Ar stream and the dianion redissolved in the studied solvent. Additives were introduced at this step, when necessary. After work-up a clean mixture of acids was obtained in every case.[8]

The obtained results in the alkylation for each studied solvent are summarised in Table 1. Yield decreases in non-polar solvents which can be related to the lower solubility of the lithium aggregates. In any case α/γ ratios are quite similar both in non-polar (cyclohexane or toluene) and polar (TMEDA) solvents. Many factors can account for this: weak interaction or even no participation of the solvent in the mixed aggregates, or a statistically isotropic interaction which does not favour a reaction site over the other.

Alternatively, some additives are known that coordinate lithium ions leading to useful reagents to enhance alkylation rates for enolates.[9] 1,3-Dimethyl-2-imidazolidinone (DMI) had been developed as a safe substitute with similar properties in order to avoid use of the carcinogenic suspect agent HMPA[10] (Figure). On the other hand, it is generally accepted that 12-crown-4 ether cavity matches most closely the dimensions of a lithium ion, favouring formation of a 1:1 complex and thus, some crown ethers have been applied as catalysts in different processes.[11] In the same trend, we decided to test the influence of 1,4,3,6-tetrahydro-di-O-methyl-D-glucitol (DDOMG) and 1,4,3,6-tetrahydro-di-O-tosyl-D-glucitol (DDOTG) (a non expensive chiral auxiliary) because simple molecular mechanics (MNDO in MOPAC) showed that three of their four oxygen atoms are at adequate distance to coordinate with a lithium ion (O-Li 1.88 Å in $NaOCH_3$).

1,3-dimethyl-2-imidazolidinone (DMI)

1,4,3,6-tetrahydro-di-O-methyl-D-glucitol (DDOMG)



ether 12-crown-4

1,4,3,6-tetrahydro-di-O-tosyl-D-glucitol (DDOTG)

Figure Additives used

The obtained results with these additives are summarised in Table 2. Only tiglic acid (**1**) was used for dianion generation because it showed the least regioselectivity under standard conditions.[5] Considering only those cases where an acceptable yield was attained and no starting acid was recovered some conclusions can be extracted: DMI, that can act as a lithium ion ligands or as a co-solvent that increase the polarity, led to a higher α/γ ratio. However, the ratio did not improve with the amount of DMI, which indicated that only a fixed amount of DMI molecules were able to chelate lithium ions. These results allowed us to affirm that this compound had no effect as a co-solvent (Table 2, entries 6 and 7). This is in agreement with the hypothesis, stated above, that regioselectivity is a function of the ion-pair structure of the lithium reagent. Addition of DMI and the use of lower temperatures favoured the presence of solvent separated ion pairs (SIP) *versus* contact ion pairs with an intact C-Li association.[9a] A similar effect was observed with LiBr (Table 2, entries 8 to 10) a well known additive for changing aggregation states of lithium enolates.[12] Consequently, contact ion pairs would favour attack to the most accessible site whereas separate pairs would react on the α-position. Entries 3 to 6 (Table 1) clearly show that a temperature change, under standard conditions, has no effect on the regioselectivity. So, the combined effect of additives and temperature is which controls the α-regioselectivity.

An important change in the selectivity of this alkylation of unsaturated carboxylic acids dienediolates was experimented on addition of 12-crown-4 ether. In this case a non polar solvent was needed. γ-Regioisomer was obtained in 70% ratio when 1 equivalent of crown ether and a secondary halide was used (Table 2, entries 14 and 17) and even with primary halide a 63% yield was observed (entry 12: comparing Table 1, entry 1). This effect can be associated to a steric hindrance of the α position in close contact ion pairs. By contrast, in more polar solvents the effect is lost because the coordination between the crown-ether and the lithium aggregate decrease.

Unfortunately, results with DDOMG and DDOTG are not much better. Although α/γ ratios are similar to those obtained above, which confirms their capability to chelate lithium (Table 2, entry 21), yields decrease probably because of the lower solubility of the aggregated complexes (leaving 50% starting acid unreacted).

In conclusion, α/γ regioselectivity in alkylation of dienediolates from unsaturated carboxylic acids may be controlled on addition of specific lithium chelating compounds that can modify the aggregation system what direct the preferred position.

Acknowledgement

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(8) *General procedure for α-alkylation of carboxylic acids*: Diethylamine (5 mmol) in THF (1 mL) was added to a solution of BuLi (5 mmol) in THF (1 mL) and stirred under Ar atmosphere at −78 ºC (CO_2/acetone bath). After half an hour at 0 ºC, the corresponding carboxylic acid (2.25 mmol) in THF (2 mL) was slowly added at -78 ºC. The solution was stirred for 30 minutes at 0 ºC and cooled again at -78 ºC. DMI and the corresponding halide (2.25 mmol) in THF (2 ml) was added dropwise, and the solution stirred at −10 °C for 1 hour for the primary bromide and 5 hours for the secondary halides. *General procedure for γ-alkylation of carboxylic acids*: Diethylamine (5 mmol) in THF (1 mL) was added to a solution of BuLi (5 mmol) in THF (1 mL) and the mixture was stirred under Ar atmosphere at −78 ºC (CO_2/acetone bath). After half an hour at 0 ºC, the corresponding carboxylic acid (2.25 mmol) in THF (2 mL) was slowly added at -78 ºC. The solution was stirred for 30 minutes at 0 ºC. The amine and THF were eliminated by strong Ar stream. Then, the mixture was suspended in cyclohexane (2 mL) and cooled again at −78 ºC. 12-Crown-4 and the corresponding halide (2.25 mmol) in cyclohexane (2 mL) was added dropwise, and the solution stirred at room temperature for 1 hour for the primary bromide and 5 hours for the secondary halides. Water (15 mL) was added and the aqueous layer was extracted with (3 × 15 mL) diethyl ether that was dried ($MgSO_4$). Evaporation of solvent, gave the amine as a reusable material. The aqueous layer was acidified under ice-cooling by careful addition of concd HCl, and then extracted with (3 × 15 mL) ethyl acetate. The organic layer was washed with water, aqueous NaCl, and water, and dried ($MgSO_4$). Evaporation of solvent, gave the crude acid reaction mixture that was analysed by ^1H NMR to give the α/γ ratio. Both α- and γ-adducts could be easily isolated by column chromatography from the crude mixture. Compounds **3** to **6** are described in reference 5.

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