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New Conditions for the Generation of Dianions of Carboxylic Acids.

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Abstract: Lithium carboxylic acid enediolates are generated efficiently using lithium amides prepared from thienyllithium or butyllithium and either diethylamine, piperazine, N,N'-dibenzylethylenediamine, N-benzylpiperazine or 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane, even in catalytic amounts.

***Keywords**: Lithium Amides; Alkylation; Enolates; Enediolates; Carboxylic acids.*

Double deprotonation of carboxylic acids by lithium dialkylamides is the most common method of generation of their lithium enediolates due to the low nucleophilicity of these bases, and to the fact that they are soluble in non-polar solvents [1,2]. However, lithium dialkylamides are in fact intermediate bases, as they are usually generated by deprotonation of the corresponding amines by n-butyllithium. Complete avoidance of the amines would mean an obvious simplification of the synthetic method, whereas use of catalytic amounts could be expected to alter ion pair aggregation states of the enediolates [3,4], and hence the reactivity of the latter might be modified. Double deprotonation of saturated carboxylic acids with n-butyllithium is feasible [5] but addition and other side reactions compete with the acid base equilibrium for unsaturated carboxylic acids [6], due to the high nucleophilicity of the reagent. The lower basicity of thienyllithium (pK_a=38.2) relative to n-butyllithium (pK_a=46) [7,8], led us to attempt alkylation of tiglic and phenylacetic acids, **1a** and **1b** respectively, by benzylbromide **3a** after double deprotonation of the acids with commercially available thienyllithium. The starting acids were recovered in high yield in pure form thus showing absence of deprotonation and of side reactions.

When the deprotonations were performed by n-butyllithium or thienyllithium and equivalent amounts of diethylamine, the alkylations occurred normally, but when only 0.27 equivalents of the amine were employed, in the alkylation of tiglic acid **1a** with benzylbromide, a significant decrease of alkylation yield was obtained for n-butyllithium (Table 1, entry 2) whereas no change in yield was observed for thienyllithium. High yields were obtained for both acids **1a** and **1b** on alkylation with other bromides under the same deprotonation conditions.

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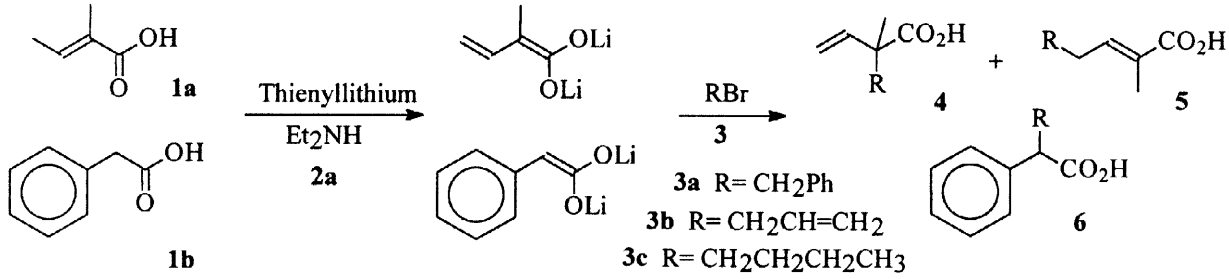
Similar results for alkylation of carboxylic acids have been now obtained (Table 1) to those resulting with equivalent amounts of LDE and saturated, benzylic and allylic bromides (Scheme 1)[1]. This observation shows that the amount of LDE does not contribute significantly to the regioselectivity of alkylation reactions of the enediolate of tiglic acid.

However, we expect that these results will be the starting point for further studies where the use of small amounts of amine, for carboxylic acid enediolate generation, may change the regioselectivity outcome of previously published reactions with other electrophiles [9-11].



Scheme 1

Next, we wanted to find whether the nature of the amine could alter the possibility of use of catalytic amounts as well as the reactivity of the enediolates of carboxylic acids. It has been shown by one of us that LDE is a better base than LDA [12], the use of other amides for enolate generation is widely described in the literature [13-16]. Therefore, we have assayed the diamines: piperazine **2b**, N,N'-dibenzylethylenediamine **2c**, N-benzylpiperazine **2d** and the strained 1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane **2e** (Figure 1) as source of the corresponding lithium amides, and preliminary results in the alkylation of tiglic acid **1a** with benzylbromide are shown in Table 2. Each amine was metallated with stoichiometric amounts of n-butyllithium and

Table 1
Alkylation of enediolates of carboxylic acids, generated from thienyllithium and diethylamine **2a** (1:0.27)

Entry	Acid	Bromide	Yield (%)	4 / 5[c]
1	1a[a]	3a	72	69/31
2	1a[b]	3a	43	43/57
3	1a	3a	72	65/35
4	1a	3b	70	62/38
5	1a	3c	68	86/14
6	1b	3a	69	
7	1b	3b	73	
8	1b	3c	67	

a: Enediolate generated from butyllithium and diethylamine (1:1)
b: Enediolate generated from butyllithium and diethylamine (1:0.27)
c: Ratio obtained from integration of the corresponding ^{1}H nmr signals.

[1] ***Standard procedure***: Amine **2** (1.35 mmol) in THF (2 mL) was added dropwise at -78°C to thienyllithium 1M in THF (5 mmol) and the solution was stirred for 1/2h at 0°C. The unsaturated carboxylic acid (2.25 mmol) in THF (2 mL) was then added dropwise at -78°C. After 1/2h at 0°C a solution of alkylbromide (2.25 mmol. in 2 mL of THF) was added at –78°C. The mixture was stirred and gradually warmed from –78 C to room temperature over 1h and then poured into water (30 mL) and extracted with diethyl ether. The aqueous layer was acidified with conc. hydrochloric acid at 0°C and extracted with ethyl acetate. The combined organic layers were washed with brine to neutral pH and dried ($MgSO_4$). Evaporation of solvent, gave the crude acidic fraction.

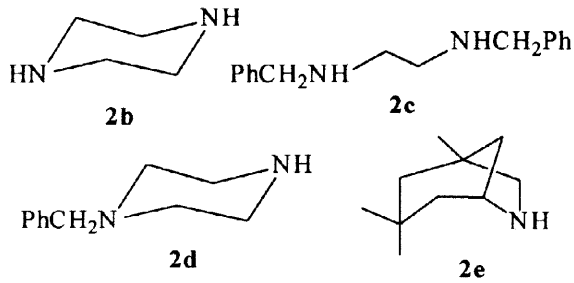


Figure 1

Table 2

Alkylation of enediolate of tiglic acid with benzylbromide, generated from 2-thienyl and butyllithium respectively and amines **2** in stoichiometric amount.

Entry	Amine	Yield (%)	4 / 5[b]
1	**2b**	62	60/40
2	**2b**	51	60/40
3	**2c**	67	62/38
4	**2c**	68	66/34
5	**2d**	61	74/26
6	**2d**	54	62/38
7	**2e**	77	74/26
8	**2e**	62	62/38
9	**2e**[a]	55	76/24
10	**2e**[a]	75	64/36

a: Enediolate generated from organolithium and this amine (1:0.27)

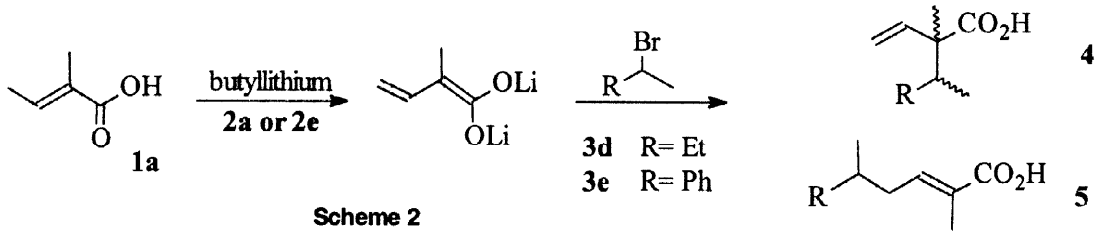
b: Ratio from integration of the corresponding ^{1}H nmr signals.

thienyllithium. Yields obtained under these conditions were slightly superior for thienyllithium than for butyllithium, except for the acyclic diamine **2c**, and regioselectivities were quite similar in all cases. Amine **2e** was employed as well in catalytic amounts for both organolithium reagents (entries 9 and 10), and surprisingly a better yield was attained using butyllithium as the primary base. No Michael products were observed in this case, probably because amine **2e** is deprotonated much faster than amine **2a.** In fact, in the alkylation of crotonic acid (2-butenoic acid) dienediolate, the use of reaction times optimized for amide **2a** led to some double alkylation, this problem can be avoided thanks to the shorter reaction periods required when amide **2e** is used. This faster enediolate generation led us to attempt its reaction with those electrophiles, as secondary halides, where elimination competes with the desirable substitution reaction.

Thus, when 2-bromobutane **3d** was allowed to react for 16 h with the enediolate, generated by butyllithium and diethylamine **2a,** a 16% yield of α-alkylated product **4d** is obtained. When the lithium amide of amine **2e** is employed, the same reaction conditions afford a 58% yield of α- and γ-alkylation acids **4d** and **5d** (60:40) and, under optimized conditions, in just 4 h, a 92% conversion though lower α/γ ratio (**4d/5d**, 50:50) is attained.

Use of chiral secondary halides opens the opportunity for diastereoselective recognition of the prochiral α-carbon atom of the enediolate, and the chiral nature of the amine **2e** should contribute to the actual d.e. resulting for α-alkylation.

No diastereoselectivity for the α-alkylation product **4d** of tiglic acid with 2-bromobutane **3d** was observed, probably due to the similar steric hindrance of methyl and ethyl groups. But, for 1-bromo-1-phenylethane **3e**, a significant difference in diastereoselectivity was found as a function of the amine (Scheme 2). Thus, with diethylamine **2a** a 77% yield was obtained of an α/γ mixture (**4e/5e**; 47:53) and a 69:31 R*S*/R*R* ratio for the α-alkylation acid **4e**, and with amine **2e** a 75% yield of a 42:58 **4e/5e** mixture, in which an 80:20 R*S*/R*R* ratio was established for the diastereoisomers of acid **4e**.



Scheme 2

R*,S* and R*,R* configurations have been tentatively identified by ^1H-^1H nOe experiments (Figure 2).

This increase in the d.e. from 38 to 60 confirms the influence of the amine in the stereoselectivity of the process.

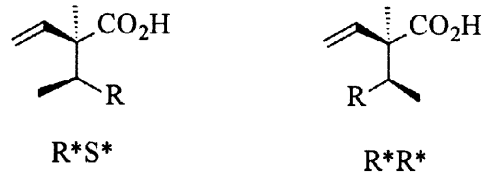


Figure 2

We claim that the present results, along with the low price of 1,3,3-trimethyl-6-azabicyclo[3.2.1]-octane **2e**, open the possibility of an extensive use of its lithium amide as deprotonating reagent for the generation of enediolates of carboxylic acids, and may foster the use of catalytic amounts of amine in the generation of enolates.

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