

A Convenient Generation of Acetic Acid Dianion

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The lithium enediolate of acetic acid can be generated efficiently, as a 0.5 M solution in THF, using lithium amides prepared from *n*-butyllithium in THF and either diethylamine or 1,3,3-trimethyl-6-azabicyclo-(3.2.1)-octane (AZA). Its reaction with carbonyl compounds leads to the corresponding β -

hydroxy acids in good to moderate yields. Better yields are usually obtained when these amines are added in sub-stoichiometric amounts.

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Introduction

Carboxylic acids are synthetically useful building blocks because, after double deprotonation, they afford enediolates that react with several electrophiles under appropriate conditions.^[1,2] Lithium dialkylamides are generally used as bases to generate lithium dienediolates^[1–3] due to their strength and low nucleophilicity — especially when they are derived from sterically hindered amines — and to their solubility in non-polar solvents.^[3,4] It is well known that, in these solvents, lithium enolates generally exist as complex ion-pair aggregate structures whose metal centre may be coordinated to solvent molecules or other chelating ligands, such as the amines resulting from deprotonation of the acid by the lithium amide. The available data confirm the complexity present in these aggregated reactive species, whose reactivity and selectivity products can be influenced by many different factors.^[2,4–9]

The reactivity of acetic acid dianion appears to be a special case as its generation in THF is slow and incomplete. It is prone to equilibrate with other species in solution as can be seen from its alkylation reaction, where the formation of the corresponding α -branched acids (secondary product) competes with the formation of the expected straight-chain homologues (primary product).^[10]

Related theoretical studies have been described and, not surprisingly, most of them concentrate on the enol, enolate and enediolate of acetic acid.^[11–14] Although, from a thermodynamic point of view, dianions of carboxylic acids are more basic ($pK_a \approx 33.5$) than the corresponding enolates from amides ($pK_a \approx 29$) and esters ($pK_a \approx 26$),^[11] from a kinetic point of view, double deprotonation of carboxylic acids is not as difficult as their pK_a value would suggest. Theoretical studies of proton abstraction from acetic

acid^[12] show that, despite the acetate anion stability (acetic acid $pK_a = 4.6$) when compared with enolate anion (carbon ionisation of acetic acid $pK_a^c \approx 26.5$), the intermediate minimum on the enolate pathway makes the kinetically controlled proton abstraction from carbon quite competitive with respect to oxygen. This is confirmed in flowing afterglow experiments,^[15] where hydroxide reacts with CD_3CO_2H ; 60% of the proton abstraction occurs from the carbon and 40% from the oxygen atom. Once acetic acid enolate is formed, it is quite acidic ($pK_a \approx 11.7$;^[11] 13.3^[13]) and its second deprotonation can be quicker than ketonisation. On the other hand, simulation data indicate that solvent effects have a much greater contribution to the keto-enol equilibrium of the acetate ion than acetic acid in water.^[14]

Despite this, to the best of our knowledge, synthetic procedures based on the simplest carboxylic acid dianion are rare^[16] and, according to the literature, this should be ascribed to the low solubility of acetic acid dianion in common organic solvents.^[17]

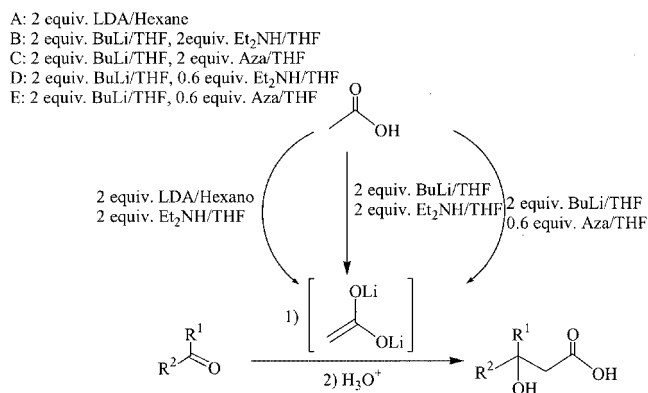
As an alternative route, Yus et al.^[18] start from chloroacetic acid, which, on deprotonation with LDA followed by treatment with an excess of lithium in the presence of a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 5%), yields an equivalent of acetic acid dianion that, on reaction with carbonyl compounds, leads, after hydrolysis and acidification, to the expected hydroxy acids in 46–65% yield.

Results and Discussion

In the last years we have developed new conditions for the generation of dianions of carboxylic acids,^[9,19] which, as we report here, can be applied to acetic acid in order to improve its reaction with carbonyl compounds (Scheme 1).

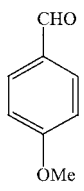
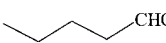
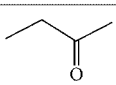
A variety of conditions have been tested on a ketone and both an aromatic and an aliphatic aldehyde. These results are summarized in Table 1.

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Scheme 1. Methods for generation of the acetic acid dianion

Table 1. Conditions optimisation for generation of acetic acid dianion

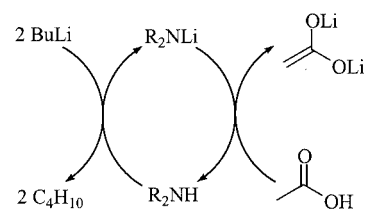
Carbonyl Compound	Entry	Equivalents of Carbonyl Compound	Amine	Equivalents of Amine	Yield (%)
	1	1	<i>i</i> Pr ₂ NH-Hexane	2	32
	2	1	Et ₂ NH	2	43
	3	1	Et ₂ NH	0.6	63
	4	1	AZA	2	39
	5	1	AZA	0.6	68
	6	3	AZA	0.6	47
	7	0.3	AZA	0.6	48
	8	1	AZA	0.6	32 ^[a]
	9	1	AZA	0.6	42 ^[b]
	10	1	<i>i</i> Pr ₂ NH-Hexane	2	41
	11	1	Et ₂ NH	2	49
	12	1	AZA	2	45
	13	1	AZA	0.6	45
	14	1	AZA	0.6	16
	15	3	AZA	0.6	31
	16	3	AZA	0.6	49 ^[b]
	17	3	Et ₂ NH	2	61
	18	3	Et ₂ NH	2	49 ^[a]

^[a] Two equiv. of DMI were added to the enediolate before addition of the carbonyl compound. ^[b] The amine was evaporated under vacuum (0.5 Torr) for half an hour before addition of the carbonyl compound

There are two main problems for acetic acid dianion generation. First of all, it is slow and incomplete, probably due to the low solubility of some of the species involved. Secondly, the deprotonation equilibrium by the lithium amide seems to be slightly displaced to the right, and many factors can move the equilibrium towards the acetate ion by reprotonation of the dianion by the amine.

The first problem can be easily solved by generating the dianion in THF as the only solvent. This means that hexane contained in the commercially available 1.6 M *n*BuLi solution must be evaporated and replaced by THF before the acetic acid dianion is generated. Under these conditions, a 0.5 M yellow solution of acetic acid dianion can be obtained (compare any entries in Table 1 with entries 1 and 10).

We have optimised a complete generation of dianions of carboxylic acids by using an equimolar amount of *n*BuLi combined with a sub-stoichiometric amount of amine^[19] (Scheme 2). The amount and nature of the amine can be changed, but 0.6 equivalents of 1,3,3-trimethyl-6-azabicyclo-(3.2.1)-octane (AZA) has evolved as a standard in our laboratory because it has proved to be of general use to generate dianions efficiently, avoiding addition of *n*BuLi to the acid or appearance of any self-condensation products. These conditions, when applied to the generation of acetic acid dianion, lead to a clear increase in the yield for the addition to *p*-methoxybenzaldehyde (entry 5). Alternatively, the amount of amine can be further reduced after generation of the dianion by total evaporation under vacuum and dissolving the resulting semisolid lithium dianion in THF, although lower yields are obtained (entries 9, 16).



Scheme 2. Generation of acetic acid dianion under catalytic conditions

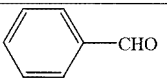
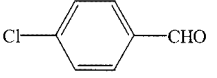
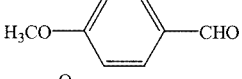
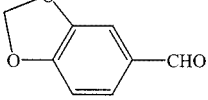
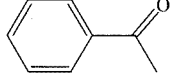
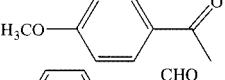
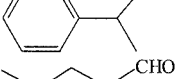
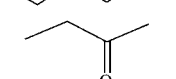
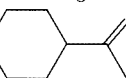
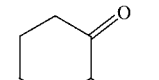
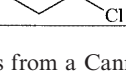
Highly aggregated states of the dianionic species could also be responsible for the low yields. Addition of LiCl, a disaggregating agent of enolates,^[20] to the acetic acid dianion results in clearly worse yields. LiCl also enhances the acidity of the amine and probably favours the protonation of the dianion to the acetate ion. 1,3-Dimethylimidazolidin-2-one (DMI) has also been described as a Li coordination agent that does not favour protonation of dianions.^[19,21] Lower yields were obtained when two equivalents were added to the acetic acid dianion (entries 8 and 18). Addition of up to 18 equivalents of DMI, which should increase the medium's polarity, has no further effect. The latter observation, in agreement with that previously described,^[8,15] shows that DMI only acts as a Li coordinating agent of dianions and has no effect as a co-solvent.

As can be deduced from Table 1, best results for aldehydes are obtained with a 1:1 ratio between acid and carbonyl compound, whereas for ketones an increase in yield is obtained until a 1:3 ratio is reached, a higher ratio does not increase the yield.

After the optimisation test, we decided to apply these conditions, namely **B** and **E**, to fix the scope and limitations of this method. The results are summarized in Table 2.

Surprisingly, carbonyl compounds prone to enolization give better results with an equimolar amount of amine (**B** conditions in Table 2). This can be explained by considering that, under conditions **D** or **E**, the addition is slower, allowing secondary aldol reactions to compete. In a similar manner, benzaldehyde leads to low yields under both reaction conditions due to its Cannizzaro disproportionation.

Table 2. Reaction of acetic acid dianion with aldehydes and ketones

Entry	Carbonyl Compound	Yield for B Conditions Et ₃ NH (2 equiv.)	Yield for E Conditions AZA (0.6 equiv.)
1		51 ^[a]	42
2		59	69
3		43	68
4		59	55
5		42	48
6		43	53
7		56	33
8		49	45
9		61	31
10		53	35
11		60	35

^[a] Mainly products from a Cannizzaro reaction

Conclusion

In conclusion, solutions of acetic acid dianion in pure THF can be generated easily. Its direct use in the addition to carbonyl compounds is possible, with the results depending on the mode of generation and reaction conditions. From those results it can be concluded that this methodology allows an easy access to β -hydroxy acids, which can be easily transformed into the corresponding β -lactones. These compounds, which are important units in many naturally occurring compounds, are thus easily obtained in yields similar to, or even better than, those described for more complicated methodologies.^[18,22]

Experimental Section

General Remarks: All reagents were of commercial quality and solvents were dried using standard procedures. All products obtained have been already described in the literature.

General Procedure: As standard conditions, acetic acid (2.25 mmol) and carbonyl compound (1 or 3 equivalents) were used. The base was generated from *n*-butyllithium (5.0 mmol) and amine (number of equivalents is stated in each case) in THF (2 mL). Acetic acid, in THF (2 mL), was slowly added at -78°C . The temperature was allowed to rise to 0°C and the mixture kept for half an hour to ensure the enediolate generation. After slow addition of the carbonyl compound, in THF (2 mL), to the enediolate at -78°C , the solution was stirred at room temperature for 1 h. In the work up, the acid layer was obtained by acidification to a pH of roughly 1, with hydrochloric acid, leading to the isolation of crude products with chromatographic purity.

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