

Dienediolates of α,β -Unsaturated Carboxylic Acids in Synthesis: A New Synthetic Method to 2-Pyridones

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Abstract: We report a simple procedure for the preparation of 4,6-disubstituted and 3,4,6-trisubstituted-2-pyridones and 3-substituted-1-isoquinolones, in good yields, from lithium dienediolates of α,β -unsaturated carboxylic acids and nitriles.

Key words: pyridones, isoquinolones, lithium enolates, carboxylic acids

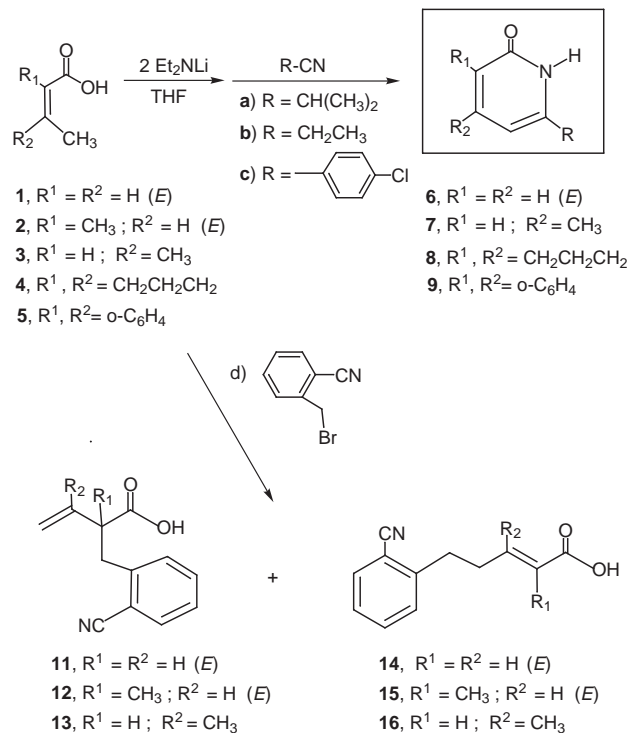
Versatile methods of preparation of functionalized 2-pyridones is an important area of interest due to the high number of biologically active compounds containing this structure¹ and to the easy conversion of pyridones to the corresponding pyridines.² Thus, despite the large number of methods developed for the synthesis of functionalized 2-pyridones,³ new procedures are being developed continuously.⁴

Here we wish to report a new, convenient synthesis of 4,6-disubstituted and 3,4,6-trisubstituted 2-pyridones from α,β -unsaturated carboxylic acids and nitriles.

It is well known that unsaturated carboxylic acids are synthetically useful building blocks. Double deprotonation by lithium dialkylamides generate their lithium dienediolates that behave as ambident nucleophiles, through either their α or γ carbon atoms, leading to single or predominant compounds when allowed to react with electrophiles under adequate conditions.⁵ Thus, α attack is favoured for irreversible reactions,⁶ whereas γ -adducts are obtained when reversible additions to carbonyl compounds are carried out under equilibrium conditions.^{7,8}

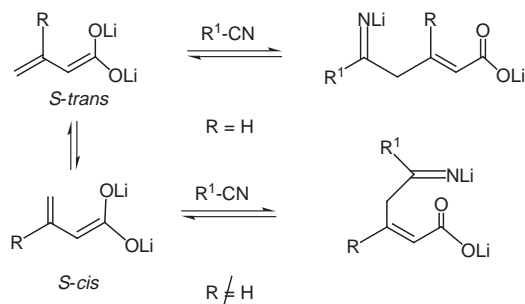
Reactions of these dienediolates with aryl or alkyl nitriles has however remained unexplored. In this particular case reversible addition leading to γ -adducts might be expected to prevail. Buten-2-oic acids with an alkyl or aryl substituent at C-3 usually afford *Z*- γ -adducts. This aspect has led to cyclized products upon Michael-Dieckmann addition to unsaturated carboxylic acid lithium salts.⁹ It is reasonable therefore that the primary γ -adducts resulting from these C-3 substituted acids or *o*-toluic acid and nitriles would afford pyridine rings (Scheme 1).

The present, preliminary results, summarised in table 1, show the wide applicability of the method as several α,β -unsaturated carboxylic acids (**1-5**) and both alkyl (**a, b**) or aryl nitriles (**c**) can be used leading, in a versatile way, to substituted 2-pyridones (**6-8**) and 1-isoquinolones (**9**), easily isolated as pure compounds in most cases.¹⁰



Scheme 1

For the acids **1** and **2**, which usually afford *E*- γ -adducts,⁹ (Scheme 2) mainly starting material was recovered (entries 1, 2, 4, 5) which was consistent with no addition or with a low equilibrium constant in the reversible addition process.



Scheme 2

Table 1 Nucleophilic Addition of Dienediolates of Carboxylic Acids to Nitriles

Entry	Acid	Nitrile	Yield (%)	
			Recovered acid	Alkylation Products (α,γ)
1	1	a	75	13 (6a)
2	1	c	25	
3	1	d		70 (11:14; 67:33)
4	2	a	80	
5	2	c	56	
6	2	d		68 (12:15; 56:44)
7	3	a		78* (7a)
8	3	b		65* (7b)
9	3	c		85* (7c)
10	3	d		85 (13:16; 74:26)
11	4	a		72* (8a)
12	4	b		60 (8b)
13	4	c		82 (8c)
14	5	a		84* (9a)
15	5	b		55* (9b)
16	5	c		52* (9c)

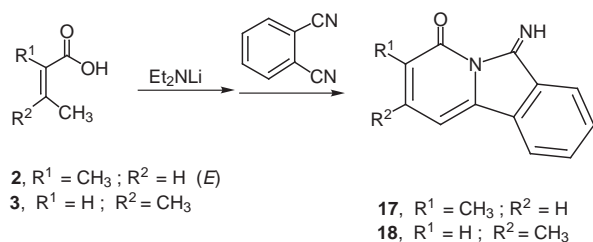
All new compounds have been completely characterized by Hrms and spectroscopic analysis (Ir, ^1H and ^{13}C nmr).

* purified product by recrystallization

We expected the addition of dienediolates to nitriles to be a slow process as it has been described that cyano aldehydes led, with good yield, to the corresponding cyano hydroxy acids.⁸ However being reversible additions it is not clear if it is a kintically preferred attack to the carbonyl moiety. Taking into account that the alkylation of a benzylic substrate is an irreversible reaction, we examined a competition reaction using 2-cyanobenzylbromide (entries 3, 6 and 10). Only 2-cyano alkylation products (**11** to **16**) were obtained (Scheme1), showing that alkylation is faster than addition to the nitrile.⁶ The isoindole corresponding to an addition to the nitrile and intramolecular substitution of the bromide by the nitrogen atom has not been detected in the reaction products.

Additions to acetonitrile have not been included because a polymeric material was formed, and the corresponding pyridones cannot be the obtained reliably.

We have extended this method to include 1,2-dicyanobenzene (Scheme 3) and here surprisingly products **17** and **18** were isolated upon addition to lithium dienediolates of acids **2** and **3**, in 9% and 39% yield, respectively.

**Scheme 3**

Despite the poor yields found for the latter addition it is of interest as it shows that both *s-cis* and *s-trans* dienediolates add to the cyano group. In addition, the highly substituted polycyclic 2-pyridones which may be easily obtained from carboxylic acids and 1,2-dicyano compounds and could be of interest in evaluating new reaction conditions in order to obtain better yields and selectivity of formation.

In summary, we have found a simple procedure for preparation of 4,6-disubstituted and 3,4,6-trisubstituted-2-pyridones from lithium dienediolates, derived from α,β -unsaturated carboxylic acids and nitriles as starting materials, which are either commercially available or conveniently prepared by conventional or well stabilised procedures. The method may also be extended to 2-alkylbenzoic acids leading to the 1-isoquinolone moieties. In addition, both 2-pyridones and 1-isoquinolones are easily isolated from the reaction mixture, as they precipitate on work-up with water and can be easily purified by a simple crystallisation.

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- (10) *Typical Reaction procedure:* Diethyl amine (1 mmol) in THF (2 mL) was added dropwise at -78°C to butyllithium 1.6 M 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 nitrile (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 24h and then poured into water (50 mL). In most cases the 2-pyridone crystallize from this mixture and can be directly isolated, otherwise it was extracted with ethyl acetate. When the reaction fails to go to completion, the acidic products are extracted, from the aqueous layer, by acidification 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.

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