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Catalyzing the Erlenmeyer Plöchl reaction: organic bases versus sodium acetate

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ABSTRACT

An evaluation of organic base versus sodium acetate as the base in the Erlenmeyer Plöchl reaction was performed. Aldehyde substituents play an important role in these reactions. Organic bases afford fast reactions, but other side reactions were observed. Alternatively, in the presence of solvent, sodium acetate could be used in catalytic amounts rather than the typical stoichiometric quantities. This Letter reports the comparative results for the use of organic bases versus sodium acetate in Erlenmeyer Plöchl reactions.

4-Arylidene-2-phenyl-5(4)-oxazolones are important intermediates for the synthesis of fine chemicals and precursors of several biologically active molecules such as amino acids and peptides.[1] The most common route to oxazolones involves the condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate in the presence of acetic anhydride as the dehydrating agent,[2] such methodology is known as the Erlenmeyer Plöchl reaction.[3,4] Interest in manufacturing compound **1** led to the evaluation of the Erlenmeyer reaction (See Fig. 1). A comparison of organic bases versus sodium acetate for the Erlenmeyer reaction using a variety of aldehydes is reported herein.

There have been a number of recent publications regarding the Erlenmeyer reaction.[1,5–15] The conditions reported in several of them[8,14,15] have been tested for the synthesis of compound **1**; however, these produced incomplete reactions and/or an unacceptable amount of transacylation by-products.[16] Although sodium acetate provided satisfactory conversion to compound **1**, long reaction time (24 h) and other scale up factors such as agitation and large a excess of sodium acetate led us to evaluate alternative organic bases.

It has been reported that the use of pyridine[17,18] as the base in the Erlenmeyer reaction resulted in high yields for specific substrates. The main purpose of evaluating other stronger organic bases other than pyridine such as Hunig's base (DIPEA), triethylamine (TEA), and 4-(dimethylamino) pyridine (DMAP) was to compare their basicity on the hippuric acid **2** and benzaldehyde **3** reaction (Scheme 1). The results are reported in Table 1. Although all the bases evaluated showed good results, DIPEA provided oxazolone **4** in the highest isolated yield and was therefore selected for further study.

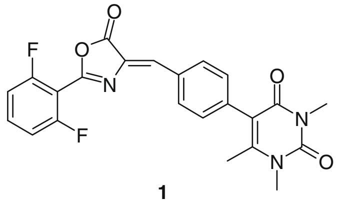

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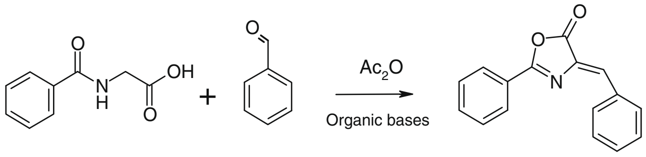
Figure 1. Intermediate from the Erlenmeyer reaction.

Several aldehydes were tested under DIPEA reaction conditions, and the results are shown in Table 2. The initial procedure investigated for these reactions involved the addition of DIPEA to a mixture of hippuric acid, aldehyde, and acetic anhydride (method **A**, entries 1–11). Better conversions and therefore higher isolated



2 **3** **4**

Scheme 1. General Erlenmeyer reaction.

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Table 1
Evaluation of organic base in the Erlenmeyer reaction and comparison with sodium acetate

Entry	Base	Reaction time (min)	Isolated yield (%)
1	DIPEA	60	82[a]
2	TEA	60	79[a]
3	Pyridine	60	76[a]
4	DMAP	60	67[a]
5	AcONa	60	80[b]

[a] Reaction of hippuric acid and benzaldehyde using method.
[b] AcONa 20 mol %.

yields were observed when electron-withdrawing groups (EWG-) were present in the aromatic aldehyde (Table 2; entries 2–8). On the contrary, benzaldehyde **3** and aromatic aldehydes with electron-donating groups (EDG-) resulted in lower conversion (Table 2; entries 1, 9–11). Similar structure–activity behavior has been observed in other condensation reactions, such as the Knoevenagel reaction.[19–21]

A careful examination of the by-products from these reactions provided insight into the lower yields for entries 1, 9–11 in Table 2. Most of the by-products came from either the Dakin–West reaction by-product **8** or the observed condensation of the oxazolone **6** and hippuric acid intermediates **5** (Scheme 2). The intermediates **5**, **6**, and the by-products **7** and **8** were tentatively confirmed by HPLC/MS analysis. It was hypothesized that the lower reactivity of the EDG-aldehydes caused the hippuric acid intermediates **5** and **6** to build up in the presence of excess acetic anhydride at the beginning of the reaction which resulted in the by-product formation. Therefore, to accommodate lower reactivity of EDG-aldehydes the concentration of acetic anhydride should be minimized during initial the reaction in order to improve the reaction conversion. To prove this hypothesis, alternative reaction conditions were explored. If acetic anhydride was added slowly to the system, the concentration of intermediates **5** and **6** would remain low relative to the large concentration of EDG-aldehyde. Therefore, the probability of generating the desired product could be greater. Hence, method **B** was developed utilizing a drop-wise addition of acetic anhydride to a mixture of hippuric acid, aldehyde, and DIPEA. When method **B** was applied to EDG-aldehydes **3** and **3h–j**, the reaction conversion improved as expected (Table 2; entries 12–15).

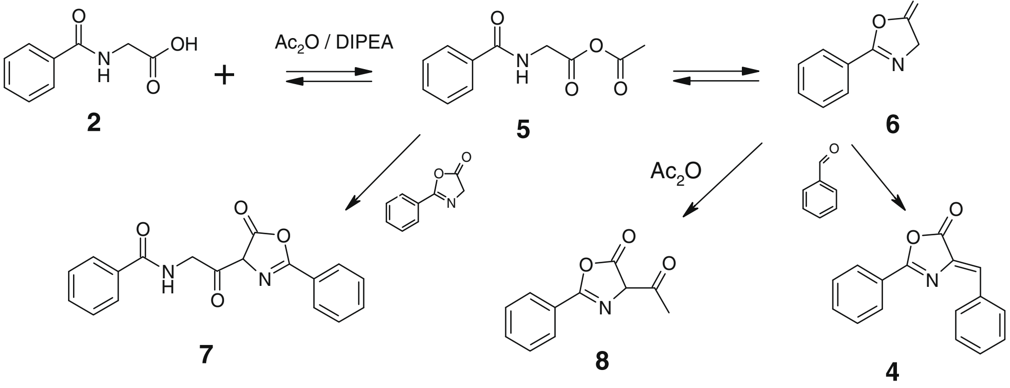
The DIPEA reaction conditions provided a fast reaction conversion and a simple work up to afford excellent product quality and acceptable isolated yields. However, when this methodology was applied to the synthesis of compound **1**, poor conversion was observed. This could be explained by the presence of substituents on the hippuric acid aromatic ring, as reported previously by our group.[22]

Re-evaluation of sodium acetate as base: The original Erlenmeyer reaction conditions involve the reaction of an appropriate hippuric acid with an aromatic aldehyde, sodium acetate as the base, and acetic anhydride as the dehydrating agent. Typically, this reaction is performed at a high temperature. These reaction conditions were

Table 2
DIPEA-mediated oxazolone reaction

Entry	Aldehyde **3**, Ar =		Method	Oxazolone	Reaction time (min)	Isolated yield (%)
1	Ph–	**3**	A[a]	**4**	30	74
2	2-$NO_2C_6H_4$–	**3a**	A	**4a**	20	92
3	2-ClC_6H_4–	**3b**	A	**4b**	20	86
4	3-$NO_2C_6H_4$–	**3c**	A	**4c**	20	84
5	4-$NO_2C_6H_4$–	**3d**	A	**4d**	20	92
6	4-FC_6H_4–	**3e**	A	**4e**	30	81
7	4-ClC_6H_4–	**3f**	A	**4f**	20	88
8	4-BrC_6H_4–	**3g**	A	**4g**	15	89
9	4-MeC_6H_4–	**3h**	A	**4h**	30	68
10	4-$MeOC_6H_4$–	**3i**	A	**4i**	30	61
11	2-Naphtyl–	**3j**	A	**4j**	30	70
12	Ph–	**3**	B[b]	**4**	60	82
13	4-MeC_6H_4–	**3h**	B	**4h**	60	84
14	4-$MeOC_6H_4$–	**3i**	B	**4i**	60	81
15	2-Naphtyl–	**3j**	B	**4j**	60	81

[a] To a mixture of hippuric acid, appropriate aldehyde, acetic anhydride at 45 °C was added DIPEA.
[b] To a mixture of hippuric acid, appropriate aldehyde, and DIPEA at 55 °C was added drop-wise acetic anhydride.



Scheme 2. Observed by-products in the Erlenmeyer reaction catalyzed with DIPEA.

Table 3
Erlenmeyer reaction using 20 mol % sodium acetate without a solvent[a]

Entry	Aldehyde **3**, Ar =	Oxazolone	Reaction time (h)	Reaction temperature (°C)	Isolated yield (%)
1	Ph–	**4**	1	95	80
2	2-$NO_2C_6H_4$–	**4a**	0.5	60	94
3	2-ClC_6H_4–	**4b**	0.5	60	89
4	3-$NO_2C_6H_4$–	**4c**	0.5	60	95
5	4-$NO_2C_6H_4$–	**4d**	0.5	60	95
6	4-FC_6H_4–	**4e**	2	95	85
7	4-ClC_6H_4–	**4f**	0.5	60	88
8	4-BrC_6H_4–	**4g**	0.5	60	92
9	4-MeC_6H_4–	**4h**	3	95	79
10	4-$MeOC_6H_4$–	**4i**	5	95	71
11	2-Naphtyl–	**4j**	1	95	63

[a] A mixture of hippuric acid, appropriate aldehyde, acetic anhydride, and sodium acetate was heated to the respective temperature and held to the reported reaction time.

Table 4
Solvent/amount of AcONa evaluation under Erlenmeyer reaction conditions. Results for oxazolones **1** and **4**

Entry	Solvent	Sodium acetate equivalents	Oxazolone **4**[a]		Oxazolone **1**[b]	
			Reaction time (h)	Reaction conversion (HPLC area %)	Reaction time (h)	Reaction conversion (HPLC area %)
1	Acetonitrile	1	1	78	24	47
2	1,2-Dichloroethane	1	24	89	24	64
3	Ethyl acetate	1	3	88	24	82
4	Me–THF	1	3	91	24	83
5	THF	1	3	92	24	84
6	Toluene	1	24	71	24	61
7	Me–THF	0.5	3	91	24	82
8	Me–THF	0.2	3	90	24	83
9	Me–THF	0.1	3	89	24	80

[a] Reaction of hippuric acid and benzaldehyde.
[b] Reaction of 2,6-difluoro-hippuric acid and 1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbaldehyde.

re-evaluated using 20 mol % sodium acetate instead of the typical one equivalent. As shown in Table 3, aldehydes with EWG resulted in faster reactions and good isolated yield and for those with EDG lower conversion and extended reaction time were observed even at higher temperature. A similar aldehyde substituent effect was observed as compared with those results from the DIPEA reaction conditions (Table 2).

As in the DIPEA process, these forcing reaction conditions lead to unfavorable results, especially with substituted hippuric acids.[22] To attenuate the concentration effect, the use of a solvent was introduced. Various solvents were screened for the formation of oxazolones **1** and **4** under various amounts of sodium acetate (Table 4).

In the formation of oxazolones **1** and **4**, the best conversion was observed with THF and Me–THF (Table 4). Further, the amount of sodium acetate was varied in the presence of Me–THF. Me–THF was a solvent of choice because of its immiscibility with water and labeled as a *Green solvent*. As indicated in Table 4, acceptable reaction conversion was achieved with as little as the 10 mol %, however, further reaction optimization afforded more reproducible results by using 15 mol % of sodium acetate.

In a direct comparison of the optimized sodium acetate/Me–THF (method C) with DIPEA conditions (method B) with aromatic aldehydes (**3**, **3a–j**) and hippuric acid **2** were evaluated. Similar aldehyde substituent effects were observed in both processes; EWG's facilitated the reaction conversion whereas EDG's demonstrated the opposite effect. However, unlike the DIPEA cases, in the presence of method C conditions all the screened examples afforded excellent isolated yields due to minimization of condensation and/or transacylation by-products. As for the reaction time, highly activated aldehydes showed an expected short reaction time and deactivated aldehydes required longer reaction times to reach their maximum conversion (Table 5, entries 9 and 10).

Finally the method C reaction conditions were applied to compound **1** at gram scale with acceptable results.[22]

Table 5
Erlenmeyer reaction using 15 mol % sodium acetate and methyl–THF. Effect of aldehyde substituents on reaction conversion

Entry	Aldehyde **3**, Ar =		Method[a]	Oxazolone	Reaction time (Hrs)	Isolated yield (%)
1	Ph–	**3**	C	**4**	3	83
2	2-$NO_2C_6H_4$–	**3a**	C	**4a**	0.5	88
3	2-ClC_6H_4–	**3b**	C	**4b**	0.2	75
4	3-$NO_2C_6H_4$–	**3c**	C	**4c**	0.5	89
5	4-$NO_2C_6H_4$–	**3d**	C	**4d**	1	94
6	4-FC_6H_4–	**3e**	C	**4e**	3	84
7	4-ClC_6H_4–	**3f**	C	**4f**	1	91
8	4-BrC_6H_4–	**3g**	C	**4g**	2	91
9	4-MeC_6H_4–	**3h**	C	**4h**	24	81
10	4-$MeOC_6H_4$–	**3i**	C	**4i**	24	80
11	2-Naphtyl–	**3j**	C	**4j**	0.2	85

[a] Hippuric acid, aldehyde, acetic anhydride, sodium acetate in Me–THF were kept at reflux for the appropriate reaction time.

In conclusion, we were able to demonstrate that DIPEA could be used as an alternative base in a solvent free process. Yields were good to excellent, and the product quality was high enough that further purification was not required. Alternatively, sodium acetate could be used in catalytic amounts; the reaction could be carried out without a solvent at moderate to extreme reaction conditions depending on the aldehyde substituents; and isolated yield varied from good to excellent. On the other hand, cleaner reactions with fewer by-products were observed if the reaction was carried out in Me–THF (method C). Therefore, method C reaction conditions would result in a more robust process,[22] especially for gram/kilogram scale up. Independent to the reaction conditions, EWG-aldehydes observed faster reaction and good isolated yield as compared with those having EDG.

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Supplementary data

Supplementary data (^{1}H NMR data of oxazolones **4** products and general methods A, B, and C) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.125.

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