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Erlenmeyer azlactone synthesis with aliphatic aldehydes under solvent-free microwave conditions

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Abstract—2-Phenyl-5(4*H*)-oxazolone (azlactone) reacts with aliphatic aldehydes upon adsorption on neutral alumina and irradiation with microwaves (<2 min). The corresponding condensation products are obtained in good yields (62–78%), indicating the satisfactory resolution of a long-standing problem plaguing the classical Erlenmeyer synthesis (poor results with aliphatic aldehydes). Plausible mechanistic reasons for the success of the procedure are discussed.

We have recently reported interesting mechanistic findings on the classical Erlenmeyer azlactone synthesis,[1,2] essentially suggesting that the aromaticity of the intermediate azlactone anion (cf. **II**, Scheme 1) is the key to the success of the reaction. The azlactone anion functions as a glycine enolate equivalent, and is condensed with aldehydes in a process related to the Knoevenagel[3] and Perkin reactions.[4] However, a serious limitation to the original Erlenmeyer procedure is that it generally fails in the case of aliphatic aldehydes,[2,5–7] as these are unstable under the reaction conditions (this possibly applies to the products also, vide infra). We report herein a resolution of this long-standing problem.

When a mixture of 2-phenyloxazol-5-one (azlactone, **1**) and an aliphatic aldehyde **2** was adsorbed on neutral alumina and irradiated in a commercial microwave oven, Erlenmeyer products **3** were obtained in good yields (Scheme 1 and Table 1, which includes previously reported results). The reaction residue was directly purified chromatographically, without work-up. The reaction was successful in the case of several aliphatic aldehydes, being complete within 2 min (at 300 W). Irradiation beyond this time led to a drastic fall in yields, presumably because of destruction of the product.

Microwave-assisted reactions are increasingly employed in synthesis,[8–10] and this method is an important addition as the Erlenmeyer reaction is a general method for the synthesis of amino acids.[1,2] (A previously reported microwave procedure for the Erlenmeyer synthesis is apparently valid only for aromatic aldehydes.[11]) The success of the microwave procedure has been attributed to the high temperatures that are rapidly attained upon absorption of the radiation. In the present case, the reasons noted below are also likely to be important.

The success of the procedure is possibly due to (i) absence of both a strong base and a solvent that would facilitate the self-condensation of the aldehyde; (ii) alumina acting as a mild base to generate the azlactone anion **II**; and (iii) the high temperatures attained during irradiation that possibly facilitate diffusion of the reactants on the surface of alumina, and the ensuing condensation step in which water is eliminated from the intermediate adduct **I**. (The pK_a of azlactones is likely to be much lower than aldehydes,[1] so the selective deprotonation of **1** is feasible.)

It is also noteworthy that the Erlenmeyer synthesis with aromatic aldehydes is possibly driven by the resonance stabilization of the products, via conjugation of the aromatic ring with the newly formed double bond (cf. **3**). As this is absent in the aliphatic case, elimination of water during the condensation possibly needs to be driven to completion and is presumably achieved under microwave conditions. (In fact, our attempts to effect the above reaction between **1** and **2** with mild bases, e.g. Et_3N or DBU in CH_2Cl_2, led to only poor yields of **3** despite using molecular sieves to remove the water formed.)

Keywords: Aliphatic aldehydes; Alumina; Azlactones; Erlenmeyer synthesis; Microwave; Oxazolone; Solvent-free.
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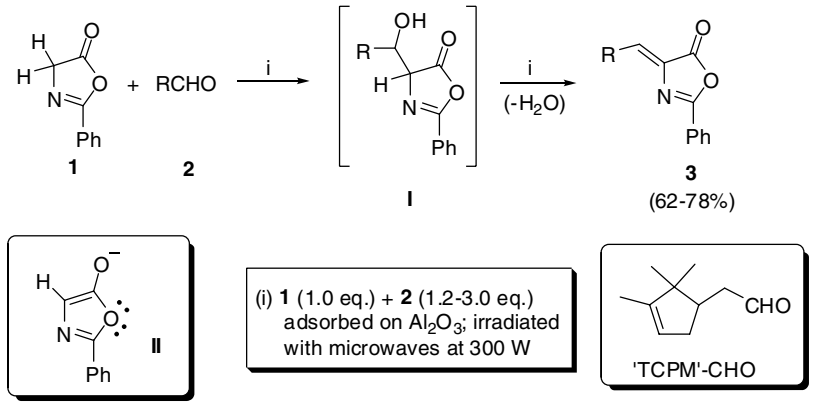

Scheme 1. The Erlenmeyer azlactone synthesis effected with azlactone **1** and aliphatic aldehydes **2** in the presence of alumina and microwave irradiation.

Table 1. Percentage yields of products **3** in the Erlenmeyer synthesis between azlactone **1** and aliphatic aldehydes **2** (cf. Scheme 1)[a]

Entry	'R' in **2**/**3**[b]	Yield of **3** (%)	
		This study	Reported
1	Et (3)	62	45[7]
2	Pr^n (3)	65	20[5]
3	Pr^i (3)	71	31[7]
4	Bu^i (2)	74	—
5	n-C_6H_{13} (1.5)	78	0[5]
6	TCPM (1.2)[c]	69	—

[a] Products **3** were identified by mp (if crystalline) and spectral data (vide infra), including HRMS.
[b] Number of molar equivalents of **2** employed is parenthesized, excess being needed to offset evaporation during irradiation.
[c] TCPM = (1,5,5-trimethylcyclopent-1-en-4-yl)methyl (cf. Scheme 1).

In conclusion, we have described a successful extension of the Erlenmeyer azlactone synthesis to aliphatic aldehydes, in a novel microwave-induced, solvent-free process that is also remarkably rapid. This not only removes a serious limitation of the classical Erlenmeyer synthesis, but also adds to the growing list of microwave-induced organic reactions.

Typical procedure: (Azlactone **1** was prepared as reported[2] and aldehydes **2** were procured commercially; microwave irradiation was performed on a BPL-800T apparatus manufactured by BPL-Sanyo India Ltd.) *Caution*: Occasionally, sparks were observed during irradiation. An intimate mixture of azlactone **1** (1.0 mmol), aldehyde **2** (1.2–3.0 mmol, cf. Table 1) and neutral Al_2O_3 was prepared in a 10 ml round-bottomed flask, by trituration in CH_2Cl_2 followed by the removal of volatiles in vacuo. The flask (with residue) was fitted with a septum that had been punctured (to release pressure), and irradiated in a microwave oven at 300 W for 2 min. After cooling, the residue was chromatographed directly on a silica gel column eluting with hexane–EtOAc (9:1) to afford pure condensation product **3**. These were crystalline solids in three cases, but waxy in the other; R (mp/°C): Et (81), Pr^n (57), Pr^i (84). Typical spectral characteristics (R=Et): ν_{max} (film)/cm^{-1} 2961, 2930, 1800, 1673; δ_H (300 MHz, $CDCl_3$) 8.15–7.90 (2H, m, Ar*H*), 7.70–7.30 (3H, m, Ar*H*), 6.96 (1H, t, *J* 8.8 Hz, C=C*H*), 2.75–2.64 (2H, 'quintet', *J* 8.7 Hz, $MeCH_2CH$=C), 1.18 (3H, t, *J* 8.8 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 162.6 (*C*=O), 141.0 (*C*=N), 135.7 (Ar_C), 133.0 (Ar_C), 132.9 (Ar_C), 128.8 (Ar_C), 128.1 (CH=$C_{azlactone}$), 125.6 (*C*H=C), 22.2 (C=C–*C*), 12.9 (Me_C); HRMS found 202.0868 (calcd for M+H $C_{12}H_{12}NO_2$ 202.0865).[12]

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References and notes

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