



## Towards the Rehabilitation of the Leuckart Reductive Amination Reaction using Microwave Technology.

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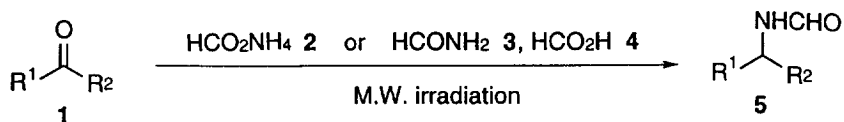
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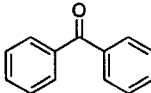
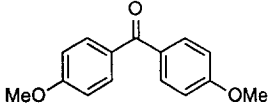
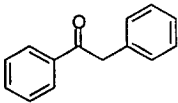
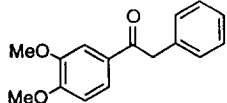
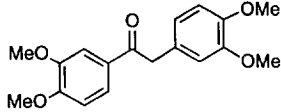
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**Abstract:** Leuckart reductive amination of carbonyl compounds was dramatically enhanced with respect to conventional heating by a specific microwave effect when the reaction was performed, under solvent-free conditions, in a monomode microwave reactor. Excellent isolated yields (up to 97%) were attained within short reaction times (typically, 30 minutes)  
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The Leuckart reaction, a reductive amination procedure of carbonyl compounds, is roughly one century old<sup>1</sup> and during this period, the harsh experimental conditions required to carry out the reaction have remained essentially unchanged. Particularly, the need for high reaction temperatures ( $\approx 240^\circ\text{C}$ ), sealed containers and long reaction periods to obtain often only low to moderate yields<sup>2</sup> have overshadowed some of its main potential advantages say, simplicity, high chemical productivity and the use of inexpensive reagents. In the recent years, microwave technology has been used in combination with solvent-free techniques to improve many organic syntheses, leading to shorter reaction times, higher yields, cleaner reaction products and easier work-up than classical heating.<sup>3</sup>

We now have found that using microwave irradiation<sup>4</sup> under solvent-free conditions, the Leuckart reaction takes place in excellent yields and short reaction times. In a first approach, we checked the behaviour of ammonium formate (10 equivalents) as a reagent previously recommended by Leuckart et al.<sup>1</sup> and used by several other authors.<sup>5</sup> However, on the mechanistic basis<sup>6</sup> suggesting formamide as the actual reactive species and formic acid as a reducing agent, we also studied the behaviour of different  $\text{HCONH}_2 + \text{HCOOH}$  mixtures (see Table).

Table. Microwave-mediated reductive Leuckart amination of carbonyl compounds <sup>a</sup>

| Substrate  | Entry | Reagents <sup>b</sup> |                 |                 | Conditions |          |                    | Yield <sup>d</sup> (%) |    |
|--|-------|-----------------------|-----------------|-----------------|------------|----------|--------------------|------------------------|----|
|  |       | 2                     | 3               | 4               | Power      | time(mn) | T(°C) <sup>c</sup> | 5                      | 1  |
| <br><b>1a</b>   | 1     | 10                    | ---             | ---             | 120W       | 20       | 187                | 80                     | 10 |
|  | 2     | 10                    | ---             | ---             | 200W       | 5        | 223                | 63                     | 7  |
|  | 3     | 10                    | ---             | ---             | ---        | 20       | 187                | 2                      | 80 |
|  | 4     | 10                    | ---             | ---             | ---        | 600      | 187                | 30                     | 70 |
|  | 5     | ---                   | 3               | 3               | 120W       | 30       | 200                | 88                     | 3  |
|  | 6     | ---                   | 3               | 3               | 60W        | 30       | 202                | 99(97)                 | 1  |
| <br><b>1b</b>   | 7     | ---                   | 3               | 3               | 60W        | 30       | 182                | 50                     | 40 |
|  | 8     | ---                   | 6 <sup>f</sup>  | 6 <sup>f</sup>  | 60W        | 30       | 193                | 95(93)                 | 5  |
|  | 9     | ---                   | 6               | 6               | ---        | 30       | 193                | 2                      | 93 |
| <br><b>1c</b>   | 10    | ---                   | 3               | 3               | 60W        | 30       | 210                | 95(92)                 | 2  |
|  | 11    | ---                   | 3               | 3               | ---        | 30       | 210                | 12                     | 78 |
| <br><b>1d</b> | 12    | ---                   | 30 <sup>f</sup> | 30 <sup>f</sup> | 60W        | 30       | 180                | 95(86)                 | 2  |
| <br><b>1e</b> | 13    | ---                   | 30 <sup>f</sup> | 30 <sup>f</sup> | 60W        | 30       | 180                | 91(75)                 | 2  |

<sup>a</sup>Typical procedure: a mixture of formamide **3** (0.6ml, 15 mmol), formic acid **4** (0.56ml, 15 mmol) and the corresponding carbonyl compound (5 mmol) was introduced in a pyrex cylindrical tube placed in the Synthwave 402 system and irradiated until completion (GLC, internal standard). The recovery of organic products was performed by extraction with CH<sub>2</sub>Cl<sub>2</sub>, filtration on Florisil and solvent evaporation. <sup>b</sup> Equivalents referred to the carbonyl compound. <sup>c</sup> Maximal temperature during irradiation. <sup>d</sup> GLC yields (isolated yields in brackets). <sup>e</sup> Heating by conventional thermo-regulated sand bath. <sup>f</sup> To attain optimum results, three portions (2 equivalents each for entry 8 and 10 equivalents each for entries 12 and 13) of formamide and formic acid were added and irradiated at 10 min. intervals.

Analysis of selected reaction data (see Table) obtained from model compounds **1a-e**<sup>7</sup> shows the following outstanding facts:

a) The formamide-formic acid system was slightly superior to the ammonium formate in terms of both conversion and yield of the expected formamides **5**.

b) The optimal power range was estimated to be around 60W, since an excessive power (see entries 1 and 2) caused a faster consumption of carbonyl compound without concomitant transformation into the expected formamide.

c) Comparison between classical heating and microwave irradiation (everything equal elsewhere, see entries 1 vs. 3; 8 vs. 9; 10 vs. 11) revealed a strong specific effect (non thermal) of microwaves evidenced because under classical heating the reaction occurred in a very limited extension and starting materials were recovered.<sup>8</sup>

d) In some cases, the reaction seemed to "re-start" when fresh formamide-formic acid was added (see entries 8, 12 and 13), probably due to the thermal decomposition of the reagent system.

e) In general, the reductive amination worked well either for non-enolizable or enolizable substrates.

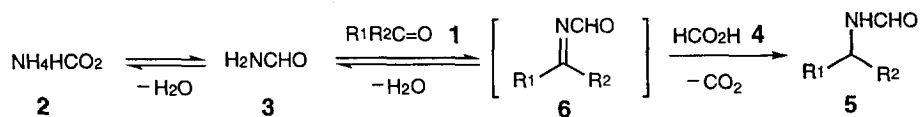
In spite of the research underway in our laboratories to establish the scope of this new version of the Leuckart's reductive amination, the preliminary results presented here constitute a considerable improvement with regard to the current conditions used for this reaction and may set the basis for its rehabilitation in a near future. They are presently extended to the more difficult case of ketone groups linked to  $\beta$ -lactams.

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 For recent improvements, see: (d) Carlson, R.; Lejon, T.; Lundstedt, T.; Le Clouerec, E. *Acta Chem. Scand.*, **1993**, *47*, 1046-1049.
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4. Experiments were performed in a focused monomode microwave reactor (Synthewave 402 from Prolabo; Commarmot, R.; Didenot, R.; Gardais, J.F. **1986**, Rhône-Poulenc/Prolabo Patent N°84/03496 ) due to the great efficiency of the system needing low powers and consequently high energetic yield when compared to multimode microwave domestic ovens, see: (a) Loupy, A.; Pigeon, P.; Ramdani, M.; Jacquault, P. *J. Chem. Res. (S)*, **1993**, 36-37. (b) Loupy, A.; Le Ngoc, T. *Synthetic Commun.*, **1993**, *23*, 2571-2577. The temperature was continuously measured and controlled by infrared detection (Jacquault, P.; **1992**, Patent n° 549 495 AI).
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6. The more generally accepted mechanism for the Leuckart reaction <sup>5(d)</sup> involves the intermediacy of *N*-formyl imine species **6** generated from carbonyl compounds and formamide **3**:



7. Formamide **5b** is a useful precursor of di(*p*-anysyl)methylamine (DAM) (see: (a) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron*, **1989**, *45*, 5767-5790). Formamides **5d** and **5e** are precursors of the aporphinic alkaloid Muciferin and the widespread protoberberines, respectively ( see: (b) Ahmad, R.; Saá, J.M.; Cava, M.P. *J. Org. Chem.*, **1977**, *42*, 1228-1230. (c) Philipson, J.D.; Roberts, M.F.; Zenk, M.H. in "The Chemistry and Biology of Isoquinoline Alkaloids", Springer-Verlag: Berlin, 1985, pp 90-146).
8. The origin of such an intrinsic effect can arise from different phenomena including a better homogeneity in temperature distribution, an increased rate in heating and/or modifications of activation parameters  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ . See, for instance: (a) Stuerge, D.; Gaillard, P. *Tetrahedron*, **1996**, *52*, 5505-5510. (b) Stuerge, D.; Gonon, K.; Lallemand, M. *Tetrahedron*, **1993**, *49*, 6229-6234. (c) Lewis, D.A.; Summers, J.D.; Ward, T.C.; Mc Grath, E.J. *J. Polym. Sci.*, **1992**, part A, *30*, 1647-1653.

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