Pergamon

Tetrahedron Letters 40 (1999) 6221–6224

TETRAHEDRON
LETTERS

Solvent-free microwave-assisted Beckmann rearrangement of benzaldehyde and 2-hydroxyacetophenone oximes

André Loupy * and Serge Régnier

Laboratoire des Réactions Sélectives sur Supports, CNRS et Université Paris-Sud, Bâtiment 410, 91405 Orsay Cédex, France

Received 14 April 1999; accepted 15 June 1999

Abstract

Beckmann rearrangements of benzaldehyde and 2-hydroxyacetophenone were largely improved by performing solvent-free reactions in the presence of one equivalent of anhydrous zinc chloride. When compared to conventional heating under the same conditions, yields are significantly enhanced under microwave activation. © 1999 Elsevier Science Ltd. All rights reserved.

Although other conditions have been used for the Beckmann rearrangement of oximes,[1] it traditionally requires conc. sulfuric or polyphosphoric acids, methods which suffer from serious drawbacks. More recently, clays (solid recyclable non-polluting and non-corrosive acids) such as montmorillonites K-10 and KSF have been used with advantages.[2] For example, KSF clay has been used in toluene under reflux with, however, rather long reaction times (e.g. 8 h for acetophenone oxime to afford 71% of acetanilide).[3] A reduction in reaction time was possible with the use of $FeCl_3$ impregnated on K-10 (56% after 5 min in refluxing toluene).[4] Further improvements were developed using solid acidic supports coupled with microwave irradiation as an efficient, clean, safe and economic technology.[5] These supports were shown to be very useful in the microwave-assisted Beckmann rearrangement of ketoximes using K-10[6] or alumina[7] in dry media. However, these conditions could not to be adapted to aldoximes which are dehydrated into nitriles when irradiated in dry media on alumina[7] or giving a mixture of products on montmorillonite (Table 1, Entries 3 and 4). In this case, hydrogen very seldom migrates to give unsubstituted amides $RCONH_2$. This conversion can be accomplished by treatment of the aldoxime with nickel acetate under neutral conditions[8] or by heating the aldoxime for a long time in xylene after it has been adsorbed onto silica gel[9] (benzaldehyde oxime is thus isomerized into benzamide in 92% yield after 69 h in refluxing xylene).

In order to explore the scope of conditions for the Beckmann rearrangement to more difficult cases needing rather harsh conditions under classical procedures, two significant cases were selected: the rearrangements of benzaldehyde and of *o*-acylphenol oximes. We investigated improvements which would include the absence of solvents and microwave irradiation.[10]

---

* Corresponding author.

PII: S0040-4039(99)01159-4

Table 1
Reaction of benzaldehyde oxime **1** in the presence of different acidic catalysts supports under microwave irradiation[12]

Entry	Catalyst or Support	Ratio **1** to Catalyst	Time (min)	Temperature (°C)	**1** (%)	**2**[a] (%)	**3**[a] (%)	**4**[a] (%)
1	SiO_2	1:8	60	140	100	0	0	0
2	Al_2O_3	1:8	30	134	57	2	19	10
3	K-10	1:8	10	134	14	34	50	2
4	KSF	1:8	15	134	59	21	4	9
5	TsOH	3:1	60	140	0	0	**100**	0
6	$ZnCl_2$/K-10	1:1	20	140	3	57	6	20
7	$ZnCl_2$	1:1	20	140	0	**94** (92)	6	0
8	$SnCl_2$	1:1	20	140	0	30	57	0

a) g.c. yields with internal standard and in isolated product in brackets

Benzaldehyde oxime **1** (*syn* or *E*) was first examined as a typical substrate which in acidic medium is prone to proceed via three competitive pathways: (a) Beckmann rearrangement to benzamide (**2**); (b) dehydration into benzonitrile (**3**); and (c) hydrolysis to regenerate benzaldehyde (**4**).

$$\underset{\mathbf{1}}{PhCH{=}NOH} \xrightarrow{H^+} \underset{\mathbf{2}}{PhCONH_2} + \underset{\mathbf{3}}{PhC{\equiv}N} + \underset{\mathbf{4}}{PhCHO}$$

Several acidic conditions were tested under focused microwave irradiation in dry media, including mineral oxides as supports and some Lewis or Brönsted acids as catalysts. The most significant results are given in Table 1. It is obvious that the best result is by far the one using zinc chloride as the acidic agent whereby a 92% yield of Beckmann rearranged product was obtained within 20 min (Entry 7). Very recently, we have also shown $ZnCl_2$ to be the best reagent to promote glycosylation of some carbohydrates under microwave in a solvent-free procedure.[11] This result constitutes a spectacular improvement (91% yield) when compared to reaction using silica gel in anhydrous xylene (140°C, 69 h).

We have also to note the selective dehydration to the nitrile observed quantitatively, using *p*-toluenesulfonic acid as a catalyst under microwave irradiation (Entry 5). This reaction could be favorably compared with recent results using KSF clay under reflux of toluene (yield 70% within 15 h),[13] Envirocat EPZG support in a solvent-free procedure (yield 75% within 12 h).[14] Under microwaves, two cases were published using H_2SO_4/SiO_2 in dry medium (yield 76% in a domestic oven within 4 min)[15] and DBU on alumina (yield 92% within 2 min).[16]

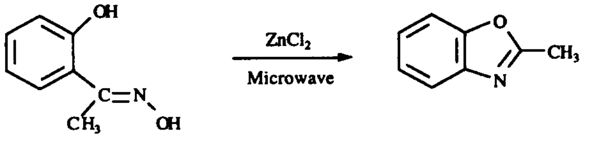
In our case, oxime hydrolysis to benzaldehyde is an insignificant side-product (Entry 6). Under microwaves several supported systems were advocated, in order to optimize this reaction (regeneration of carbonyl compounds), such as silica supported bismuth trichloride in THF,[17] supported sodium periodate on wet silica gel,[18] ammonium persulfate on silicagel[19] or finally silica supported chromium trioxide.[20]

To show the interest of both solvent-free method and microwave activation, we compared the results obtained by classical heating (in an oil bath thermostated at 140°C) and under microwave irradiation (Table 2), every condition being the same otherwise (time, pressure, profiles of raising in temperature). It is clear that both specific effects of microwaves and solvent absence are operating to induce enhancements in yields as yet evidenced in several other cases in our laboratory.[21]

Table 2
Comparison between classical heating (Δ) and microwave irradiation (MW) in the absence or presence of xylene: **1**+$ZnCl_2$ (1:1) 20 min at 140°C

Mode of activation	Solvent	**1** (%)	**2** (%)	**3** (%)	**4** (%)
MW	none	0	**94**	6	0
Δ	none	3	59	7	3
MW	xylene	18	78	1	1
Δ	xylene	50	50	0	0

We extended this process to the synthesis of benzoxazoles, due to their importance as intermediates for the preparation of polyether antibiotics, of fluorescent whitening agents and of dye releases in instant color photography.[22] One of the most efficient synthesis of these compounds involves the Beckmann rearrangement of *o*-acylphenol oximes **5**, followed by an intramolecular ring closure to **6**. This reaction has been reported using a combination of phosphoryl chloride and *N,N*-dimethylacetamide[22] and, more recently using zeolite catalysts but unfortunately after long time (7 h) in benzene at 160°C in a Parr reactor in excellent yields (95%).[23] We thus checked as above the behavior of anhydrous $ZnCl_2$ towards the 2-hydroxyacetophenone oxime **5** (molar ratio 1:1) (Table 3). The best result was obtained for solvent-free assisted procedure as previously observed with benzaldehyde oxime. It constitutes a major improvement when compared to the previous method advocating zeolite in benzene for 7 h at 160°C.



5 **6**

Table 3
Comparison between classical heating (Δ) and microwave irradiation (MW) in the absence or presence of xylene: **5**+$ZnCl_2$ (1:1) 20 min at 140°C

Mode of activation	Solvent	Conversion (%)	**6** (%)
MW	none	100	**86**
Δ	none	82	68
MW	xylene	78	68
Δ	xylene	30	18

The method herein[24,25] described constitutes an attractive alternative and improvement (when compared to classical ones) which avoids the use of toxic and expensive reactants and solvents.

References

1. Gawley, R. E. *Org. React.* **1988**, *35*, 1.
2. Balogh, M.; Laszlo, P. In *Organic Chemistry using Clays*; Springer Verlag Ed.; Berlin, 1993.
3. Meshram, H. M. *Synth. Commun.* **1990**, *20*, 3253.

4. Pai, S. G.; Bajpai, A. R.; Deshpande, A.B.; Samant, S.D. *ibid.* **1997**, *27*, 370.
5. Bram, G.; Loupy, A.; Villemin, D. In *Solid Supports and Catalysts in Organic Synthesis*; Smith K., Ed.; Ellis Horwood & Prentice Hall, Chichester, 1992; Chapter 12, p. 302.
6. Bosch, A. I.; De la Cruz, P.; Diez-Barra, E.; Loupy, A.; Langa, F. *Synlett* **1995**, 1259.
7. Touaux, B.; Texier-Boullet, F.; Hamelin, J. *Heteroatom Chem.* **1998**, *9*, 351.
8. Leusink, A. J.; Meerbeek, T. G.; Noltes, J. G. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 142.
9. Chattopadhyaya, J. B.; Rama Rao, A. V. *Tetrahedron* **1974**, *30*, 2899.
10. (a) Loupy, A.; Bram, G.; Sansoulet, J. *New J. Chem.* **1992**, *16*, 233; (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213.
11. Limousin, C.; Cléophax, J.; Petit, A.; Loupy, A.; Lukacs, G. *J. Carbohydrate Chem.* **1997**, *16*, 327.
12. Focused microwave irradiations were carried out with a Synthewave™ S402 Prolabo microwave reactor (monomode system, 2450 MHz, 300 W) which has a variable speed rotation, visual control, irradiation monitored by PC computer, infra-red measurement and continuous feedback temperature control.
13. Meshram, H. M. *Synthesis* **1992**, 943.
14. Bandgar, B. P.; Jagtap, S. R.; Ghodeshwar S. B.; Wadgaonkar, P. P. *Synth. Commun.* **1995**, *25*, 2993.
15. Sampath Kumar, H. M.; Mohanty, P. K.; Suresh Kumar, M.; Yadav, J. S. *ibid.* **1997**, *27*, 1327.
16. Sabitha, G.; Syamala, M. *Synth. Commun.* **1998**, *28*, 4577.
17. Boruah, A.; Baruah, B.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1997**, *38*, 4267.
18. Varma, R. S.; Dahiya, R.; Saini, R. K. *ibid.* **1997**, *38*, 8819.
19. Varma, R. S.; Meshram, H. M. *ibid.* **1997**, *38*, 5427.
20. Bendale, P. M.; Khadilkar, B. M. *ibid.* **1998**, *39*, 5867.
21. See, for instance: (a) Loupy, A.; Petit, A.; Bonnet-Delpon, D. *J. Fluorine Chem.* **1995**, *75*, 215; (b) Oussaid, A.; Loupy, A. *J. Chem. Res.* (S) **1997**, 342; (c) Bortolussi, M.; Bloch, R.; Loupy, A. *ibid.* **1998**, 34.
22. Fujita, S.; Koyama, K.; Inagaki, Y. *Synthesis* **1982**, 68.
23. Bhawal, B. M.; Mayabhate, S. P.; Likhite, A. P.; Deshmukh, A. R. A. S. *Synth. Commun.* **1995**, *25*, 3315.
24. Typical procedure. A mixture of *syn*-benzaldoxime (10 mmoles, 1.21 g) or 2-hydroxyacetophenone oxime[25] (10 mmoles, 1.52 g) and one equivalent of 98% anhydrous zinc chloride (10 mmoles, 1.36 g) was introduced in a Pyrex tube and submitted to microwave irradiation for 20 min in the Synthewave S402 monomode reactor[10b] at 140°C. The mixture was cooled to room temperature and dissolved in methanol and then filtered through silica gel. Products were analyzed by capillary gas chromatography (column OV1 12 m, temperature programmation from 80 to 200°C with 10°C/min, retention times **1**: 3.7, **2**: 5.6, **3**: 2.0, **4**: 3.9, **5**: 4.5, **6**: 3.0 min) using methyl benzoate (2.7 min) as an internal standard and compared by ^{1}H NMR (250 MHz, DMSO d_6) with authentic samples. Occasionally (see Table 2 and Table 3), the reactions were performed in the presence of 2.5 mL xylene or in a thermostated oil bath at 140°C.
25. Prepared from *o*-hydroxyacetophenone and hydroxylamine hydrochloride in aqueous ethanol according to: A. Lachman, *Org. Synth.* **1943**, *Coll. Vol. 2*, 70.