ChemComm
www.rsc.org/chemcomm

Microwave-assisted free radical chemistry using the persistent radical effect†

Christian Wetter and Armido Studer*
Chemistry Department, Philipps University Marburg, 35032 Marburg, Germany.
E-mail: studer@mailer.uni-marburg.de; Fax: +49 6421 2825629; Tel: +49 6421 2825562

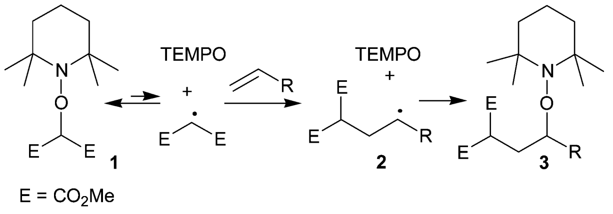
Received (in Cambridge, UK) 20th October 2003, Accepted 18th November 2003
First published as an Advance Article on the web 8th December 2003

Environmentally benign radical carboaminoxylations of various nonactivated olefins and difficult radical cyclization reactions are performed in good to excellent yields and with short reaction times under microwave irradiation.

Recently, we published the first results on tin-free radical carboaminoxylations[1] controlled by the so called persistent radical effect (PRE).[2] Thermal reversible homolysis of alkoxyamine **1** generates the persistent 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) and the stabilized transient malonyl radical, which subsequently reacts with an olefin CH_2CHR to afford the adduct **2**. Irreversible trapping of **2** with TEMPO eventually provides the carboaminoxylation product **3** (Scheme 1).[3]

However, it takes up to 3 days to complete these radical addition processes.[1] This is certainly a serious limitation of the published method. We therefore decided to use microwave (MW) irradiation to conduct these thermal processes.[4] To our knowledge, this is one of the first examples of MW-assisted free radical chemistry.[5]

We first examined the addition of malonate **1** onto 1-octene (5 eq.) to provide **3a** using DMF as a typical "MW-solvent". The carboaminoxylations were performed in sealed tubes using professional laboratory microwave equipment.‡ The experimental setup allowed precise temperature control inside the vessel. The best results were obtained at 180 °C (Table 1, run 1, 0.07 M). The reaction took only 10 min for completion. Addition product **3a** was isolated in 63% yield (Fig. 1) and no side products were detected. Obviously, decomposition of the starting alkoxyamine **1** to volatile compounds occurred under the applied conditions. Interestingly, no oligomerization was observed under the applied conditions (high pressure) which indicates highly efficient trapping of the adduct radical of type **2** by TEMPO. Lower temperatures and longer reaction times did not provide better results. Addition reactions at higher concentrations afforded lower yields. Under the optimized conditions good results were also obtained using acetophenone, 1,2-dichlorobenzene and DMSO, whereas in nitrobenzene only a moderate yield was obtained (runs 2–5). To document the power of MW-assisted heating for conducting these radical carboaminoxylations, the results are compared with those previously obtained using classical heating (dichloroethane (DCE), 135 °C, 3 d). A similar yield was obtained by this approach, however, the reaction took 3 days (run 6).[1] Thus, a 430-fold acceleration was achieved upon switching to MW-irradiation. In order to exclude any concentration and solvent effects, we also repeated the MW-experiment using

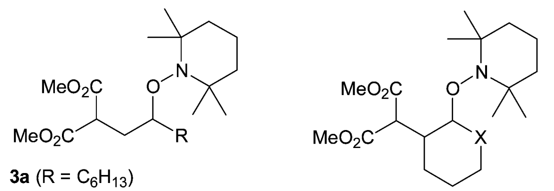


Scheme 1 The PRE in intermolecular addition reactions.

Table 1 Addition reactions of **1** onto various olefins under different conditions

Run	Compound	Solvent	Conditions	Yield (%)
1	**3a**	DMF	MW, 10 min, 180 °C	63
2	**3a**	PhCOMe	MW, 10 min, 180 °C	62
3	**3a**	$C_6H_4Cl_2$	MW, 10 min, 180 °C	58
4	**3a**	DMSO	MW, 10 min, 180 °C	53
5	**3a**	$PhNO_2$	MW, 10 min, 180 °C	27
6[a]	**3a**	DCE	3 d, 135 °C	66
7	**3a**	DMF	3 d, 135 °C	41
8	**3b**	DMF	MW, 10 min, 180 °C	84
9[a]	**3b**	DCE	3 d, 135 °C	78
10	**3b**	DMF	3 d, 135 °C	88
11	**3c**	DMF	MW, 10 min, 180 °C	71
12[a]	**3c**	DCE	3 d, 135 °C	49
13	**3c**	DMF	3 d, 135 °C	33
14	**3d**	DMF	MW, 10 min, 180 °C	78
15[a]	**3d**	DCE	3 d, 135 °C	70
16	**3d**	DMF	3 d, 135 °C	27
17	**3e**	DMF	MW, 10 min, 180 °C	70
18[a]	**3e**	DCE	3 d, 135 °C	42
19	**3e**	DMF	3 d, 135 °C	29
20	**3f**	DMF	MW, 10 min, 180 °C	72
21	**3f**	DCE	3 d, 135 °C	64
22	**3f**	DMF	3 d, 135 °C	49
23	**4**	DMF	MW, 10 min, 180 °C	42 (dr = 2.5 : 1)[b]
24[a]	**4**	DCE	3 d, 135 °C	58 (dr = 2.1 : 1)[b]
25	**4**	DMF	3 d, 135 °C	21 (dr = 2.0 : 1)[b]
26	**5**	DMF	MW, 10 min, 180 °C	46 (dr = 1.6 : 1)[c]
27[a]	**5**	DCE	3 d, 135 °C	80 (dr = 1.0 : 1)[c]
28	**5**	DMF	3 d, 135 °C	57 (dr = 1.2 : 1)[c]
29	**6**	DMF	MW, 10 min, 180 °C	66[d]
30	**6**	DCE	3 d, 135 °C	37[e]
31	**6**	DMF	3 d, 135 °C	29[f]
32	**7**	DMF	MW, 10 min, 180 °C	94
33[a]	**7**	DCE	3 d, 135 °C	75
34	**7**	DMF	3 d, 135 °C	67

[a] Ref. 1. [b] The major isomer has a *trans*-configuration, see ref. 1. [c] The relative configuration of the major isomer was not assigned. [d] Isomer ratio *exo*-methylene : β,γ-unsaturated : γ,δ-unsaturated = 2.7 : 1.3 : 1. [e] Isomer ratio *exo*-methylene : β,γ-unsaturated : γ,δ-unsaturated = 3.9 : 1 : 1.2. [f] Isomer ratio *exo*-methylene : β,γ-unsaturated : γ,δ-unsaturated = 13.3 : 1 : 2.6.



3a (R = C_6H_{13})
3b (R = OBu)
3c (R = $(CH_2)_2Ph$)
3d (R = $(CH_2)_3OTBDMS$)
3e (R = $(CH_2)_3OC(O)OCH_3$)
3f (R = *N*-Phthalimide)

4 (X = CH_2, *trans:cis* = 2.5:1)
5 (X = O, *trans:cis* = 1.6:1)

Fig. 1 Carboaminoxylation products.

---

† Electronic Supplementary Information (ESI) available: experimental procedures and analytical data for all the described compounds. See http://www.rsc.org/suppdata/cc/b3/b313139d/

DOI: 10.1039/b313139d

classical heating under otherwise identical conditions (0.07 M, DMF, 135 °C, 3 d). A lower yield was obtained for the model reaction under these conditions (41%, run 7).

We then examined MW-assisted addition reactions of alkoxyamine **1** using various mono- and disubstituted olefins. For comparison the results obtained by classical heating under otherwise identical conditions are also included in Table 1. Furthermore, to illuminate the power of MW-induced heating the optimized results previously obtained[1] in DCE under classical heating are also reported.

Excellent results were obtained with butyl vinyl ether (→ **3b**) under all conditions tested (78–88%, runs 8–10). Addition onto 4-phenyl-1-butene (→ **3c**) is clearly more efficient under MW-conditions (71%) than under conventional heating (49% and 33%, runs 11–13). Carboaminoxylation of TBDMS-protected 5-penten-1-ol with **1** to afford **3d** can efficiently be performed under MW-irradiation and also under conventional heating in DCE (runs 14,15). However, reaction in DMF under classical heating provided a lower yield (27%, run 16). Addition of **1** onto methyl 4-penten-1-yl carbonate under MW-conditions afforded **3e** in 70% yield, whereas only moderate yields were obtained for the same reaction under classical conditions (runs 17–19). Similar results were obtained using *N*-vinylphthalimide (runs 20–22). These results clearly document the power of MW-induced heating in these thermal processes. Unfortunately, solvent-free carboaminoxylations under MW-conditions did not work, even for the most polar radical acceptor methyl 4-penten-1-yl carbonate.

MW-assisted carboaminoxylations of terminally substituted olefins such as cyclohexene (→ **4**) and 3,4-dihydro-2*H*-pyran (→ **5**) can be performed in 18 min, however, slightly lower yields were obtained (runs 23–28). As expected, the products were isolated as mixture of isomers.

We next addressed addition–elimination reactions (Fig. 2). We have previously shown that carboaminoxylations leading to tertiary alkoxyamines are followed by elimination of TEMPO-H to provide the corresponding olefins.[1] Thus, addition of **1** onto 2-methyl-1-nonene and subsequent TEMPO-H elimination (→ **6**) can be achieved in a good yield under MW-conditions (Table 1, run 29, 66%). The product was formed as a mixture of inseparable double bond isomers. The same experiment using conventional heating afforded **6** in a modest yield, again proving the efficiency of MW-induced heating (runs 30,31). If alkoxyamine **1** is heated in the presence of β-pinene, radical addition is followed by a ring opening step and subsequent regioselective TEMPO-H elimination. Product **7** was formed in excellent yield under MW-irradiation (run 32, 94%). Good yields can also be obtained using conventional heating (runs 33,34).

Finally, we focused on radical cyclization reactions. Isomerization of alkoxyamine **8** in DMF at 180 °C took only 2.5 min. The 5-*exo* product **9a** and 6-*endo* compound **9b** were isolated in 70% combined yield (Scheme 2). The unexpected low 5-*exo* : 6-*endo* ratio (2.7 : 1) for this 5-hexenyl type radical cyclization can be explained by the reversibility of the radical cyclization.[6] The same reaction in DMF under classical heating took 16 h (66% combined yield).[3a] We were also able to perform difficult radical cyclizations using our method.[7] The starting alkoxyamines **10**,**12** and **14** were readily prepared from the corresponding α-halo acid derivatives and TEMPO.[8] It turned out that these alkoxyamines could not be isomerized under the standard conditions previously developed by our group (130 °C, 0.02 M, *t*-BuOH, 24 h);[3a] the desired cyclization products **11**, **13** and **15** were not formed (Scheme 2). Encouraged by the above described MW-results, we decided to repeat the isomerizations using MW-irradiation. The reaction conditions were slightly modified. The best results were obtained at higher temperatures (210 °C) and shorter reaction times (2.5 min). Under these conditions, allyl tosyl amide **10** was efficiently isomerized to **11** (70%, *trans* : *cis* = 3.3 : 1). A lower yield was observed for the cyclization of ester **12** (→ **13**, 36%, *trans* : *cis* = 2.5 : 1). For the isomerization of amide **14** addition of camphor-10-sulfonic acid[3a] was necessary for successful isomerization. Furthermore, the reaction time had to be increased (12 min). Amide **15** was isolated in 40% yield (*trans* : *cis* = 1.9 : 1).

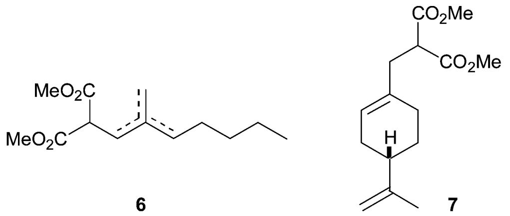
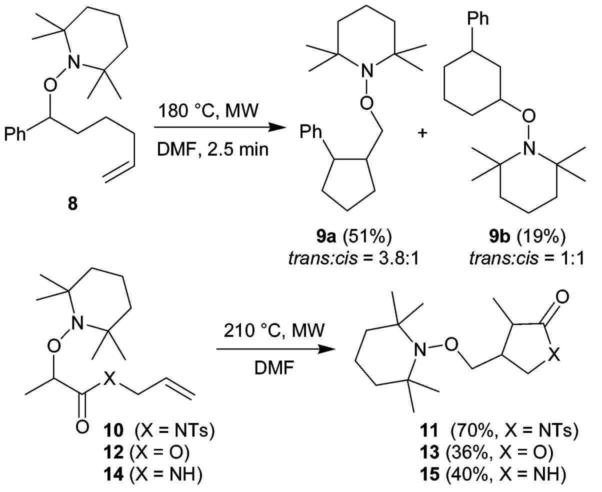


Fig. 2 Addition–elimination products.



Scheme 2 The PRE in difficult isomerization reactions.

In conclusion, we have shown that PRE-controlled environmentally benign radical processes can efficiently be performed using MW-irradiation. A 430-fold acceleration was achieved upon switching from classical to MW-induced heating. Moreover, difficult isomerizations which cannot be achieved under classical heating can be conducted with moderate to good yields using MW-irradiation.

We thank the Fonds der Chemischen Industrie (PhD stipend to C.W.) and the Deutsche Forschungsgemeinschaft (STU 280/4–1) for funding.

Notes and references

‡ A MLS-Ethos 1600 Mikrowellen System was used for the present studies. Since the reactions are performed in sealed tubes a high pressure is built up during the reaction. Therefore, special glassware and microwave equipment should be used.

1 C. Wetter, K. Jantos, K. Woithe and A. Studer, *Org. Lett.*, 2003, **5**, 2899.
2 A. Studer, *Chem. Eur. J.*, 2001, **7**, 1159; H. Fischer, *Chem. Rev.*, 2001, **101**, 3581.
3 For other nitroxide-mediated radical synthesis processes, see: (*a*) A. Studer, *Angew. Chem., Int. Ed.*, 2000, **39**, 1108; (*b*) A. D. Allen, M. F. Fenwick, H. Henry-Riyad and T. T. Tidwell, *J. Org. Chem.*, 2001, **66**, 5759; C. Leroi, B. Fenet, J.-L. Couturier, O. Guerret and M. A. Ciufolini, *Org. Lett.*, 2003, **5**, 1079.
4 For reviews, see: L. Perreux and A. Loupy, *Tetrahedron*, 2001, **57**, 9199; P. Lidström, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225.
5 A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Chaudhary and K. J. Barakat, *J. Org. Chem.*, 1991, **56**, 6968; M. Lamberto, D. F. Corbett and J. D. Kilburn, *Tetrahedron Lett.*, 2003, **44**, 1347.
6 C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, 1972, **94**, 6064.
7 D. P. Curran, M. H. Chen and D. Kim, *J. Am. Chem. Soc.*, 1989, **111**, 6265; D. P. Curran and C. T. Chang, *J. Org. Chem.*, 1989, **54**, 3140; D. P. Curan and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746; G. Stork and R. Mah, *Heterocycles*, 1989, **28**, 723; T. Sato, Y. Wada, M. Nishimoto, H. Ishibashi and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1989, 879; O. M. Musa, J. H. Horner and M. Newcomb, *J. Org. Chem.*, 1999, **64**, 1022; A. J. Clark, *Chem. Soc. Rev.*, 2002, **31**, 1.
8 K. Matyjaszewski, B. E. Woodworth, X. Zhang, S. G. Gaynor and Z. Metzner, *Macromolecules*, 1998, **31**, 5955.