ELSEVIER

Journal of Fluorine Chemistry 75 (1995) 215–216

JOURNAL OF FLUORINE CHEMISTRY

Improvements in 1,3-dipolar cycloaddition of nitrones to fluorinated dipolarophiles under solvent-free microwave activation

André Loupy [a,*], Alain Petit [a], Danièle Bonnet-Delpon [b]

[a] *Laboratoire des Réactions Sélectives sur Supports, ICMO, CNRS, UA 478, Université Paris-Sud, Bâtiment 410, 91405 Orsay, France*
[b] *Laboratoire de Synthèse Organique, BIOCIS, Centre d'Etudes Pharmaceutiques, CNRS, rue J.B. Clément, 92296 Chatenay Malabry, France*

Received 18 April 1995; accepted 29 June 1995

Abstract

1,3-Dipolar cycloadditions between ethyl trifluoracetoacetate or α-trifluoromethylstyrene and *N*-(benzylidene)methylamine *N*-oxide were performed in the absence of solvent. Under microwave irradiation in a monomode Maxidigest Prolabo reactor, quantitative yields were obtained within 3 min. Compared to conventional heating under the same conditions, the yields are significantly increased (from 55%–64% to 88.98%). Classical conditions using boiling toluene (65% within 24–48 h) are now considerably improved.

Keywords: Dipolar cycloaddition; Nitrones; Fluorinated dipolarophiles; Microwave activation; Solvent-free conditions

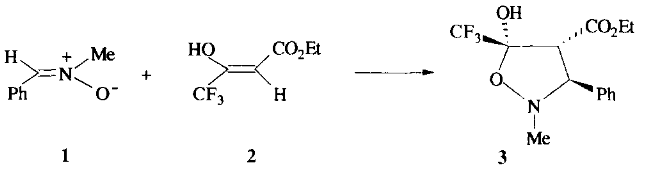
1. Introduction

Microwave activation in organic synthesis is now currently used as an efficient method for improving thermal reactions [1]. When coupled to solvent-free techniques, it has proved to be a clean and efficient technology capable of enhancing the reactivity of systems due to both concentration effects and specific activation by microwaves [2,3]. Consequently, a great number of classical organic reactions may be improved when performed in the absence of solvent under microwave irradiation. Reactions classically realized in solvents at reflux for extended times could be of interest for further improvement.

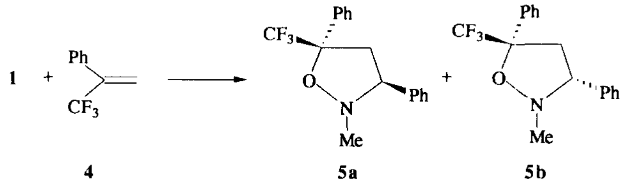
In a recent publication [4], cycloaddition between *N*-(benzylidene)methylamine *N*-oxide (**1**) and ethyl trifluoracetoacetate (**2**) (ETFAA, 80% of enol form in its *Z* configuration) afforded the isoxazolidine **3** in 65% yield regio- and stereo-selectively after 24 h in boiling toluene (Scheme 1).

Similarly, cycloaddition between the same nitrone **1** and α-trifluoromethylstyrene (**4**) afforded the two stereoisomeric isoxazolidines **5a** and **5b** (**5a**/**5b** = 50:50) in 65% yield after 48 h in boiling toluene (Scheme 2).

Hence, we performed these two experiments in the absence of solvent, i.e. the liquid fluorinated dipolarophiles **2** or **4** playing the role of both electrophile and organic phase for the reaction.



Scheme 1.



Scheme 2.

2. Results and discussion

Microwave irradiation was performed using a monomode reactor (Maxidigest MX 350 from Prolabo) with focused waves, since the energy distribution is much more homogeneous [3,5] and consequently much more efficient than with domestic ovens [3,6]. The main results are given in Table 1.

Good yields were obtained within 3 min: 76% in isolated **3** at a power of 30 W in the case of reaction (1) and 94% in pure isolated products **5a** + **5b** at 120 W for reaction (2). When performed under the same conditions of time and temperature, conventional heating led to only 64% and 55%,

---

[*] Corresponding author.

SSDI 0022-1139(95)03330-0

Table 1
1,3-Dipolar cycloaddition without solvent between nitrone **1** and compounds **2** or **4** under microwave conditions in a monomode Maxidigest MX 350 Prolabo reactor

Reaction [a]	Power (W)	Time (min)	Yield [b,c] (%)	Final temp. (°C) [d]	Conventional heating
1 [b]	60	2	84	131	3 min, 120 °C, 64% 30 min, 120 °C, 89%
	90	2	79	156	
	30	2	80	117	
	30	3	88 (76)	119	
2 [c]	120	3	81	163	3 min, 170 °C, 55% 30 min, 170 °C, 82%
	120	4	98(94)	169	
	150	3	98	171	
	180	3	90	184	

[a] Relative amounts of reactants **1**/**2** = **1**/**4** = 1:2.

[b] GC yields in **3** for reaction (1); in **5a**+**5b** for reaction (2) (**5a**/**5b** ≈ 50:50).

[c] Isolated yields in brackets after column chromatography (SiO_2 using pentane/Et_2O as eluent).

[d] Evaluated by IR detection during microwave irradiation [7].

respectively, versus 98% and 88% under microwave conditions (GC yields). The regio- and stereo-selectivities remained the same under all conditions.

Considerable improvements in yields and experimental conditions are thus obtained when compared to reflux in toluene over 24 or 48 h. The same conclusions were drawn in the case of the 1,3-dipolar cycloaddition of nitrone to acrylic esters [8], to ketene acetals [9] and of diphenylnitrilimine to various α-enones [10]. Such results are essentially due to specific microwave activation (not limited to pure thermal effects) in confirmation of some other results obtained mainly in our laboratory under solvent-free conditions [10–13]. Furthermore, microwave methods present all the advantages of reactions without solvent, i.e. safe, non-polluting, mild, economic and easy to perform.

3. Experimental details

All reactions were performed in a cylindrical Pyrex vessel using 10 mmol of nitrone **1** and 20 mmol of dipolarophiles **2** or **4**. The mixtures were introduced into the monomode reactor (Maxidigest MX 350 Prolabo) at the powers and times indicated in Table 1. Temperatures were recorded throughout the reaction using an IR detector connected to the reactor [7].

At the end of the reaction, after cooling down and extraction with CH_2Cl_2, products **3**, **5a** and **5b** were analyzed by GC methods using an internal standard and authentic samples [4] (capillary column OV1, 15 m).

References

[1] R.A. Abramovitch, *Org. Prep. Proced. Int.*, *23* (1991) 685.

[2] A. Loupy, G. Bram and J. Sansoulet, *New J. Chem.*, *16* (1992) 233.

[3] A. Loupy, *Spectra Analyse*, *175* (1993) 33.

[4] J.P. Bégué, D. Bonnet-Delpon and T. Lequeux, *J. Chem. Soc., Perkin Trans. 1*, (1991) 2888.

[5] (a) A.C. Grillo, *Spectroscopy*, *4* (1988) 16; (b) C. Desmenay and M. Olle, *Spectra Analyse*, *175* (1993) 27.

[6] A. Loupy and Le Ngoc Thach, *Synth. Commun.*, *23* (1993) 2571.

[7] P. Jacquault, Eur. Pat. 92 420 477.9, 21 Dec. 1992.

[8] D. Abenhaim, J. De Carvalho and J. Hamelin, to be published.

[9] A. Diaz-Ortiz, E. Diez-Barra, A. De la Hoz, P. Prieto and A. Moreno, *J. Chem. Soc., Perkin Trans. 1*, (1994) 3595.

[10] K. Bougrin, M. Soufiaoui, A. Loupy and P. Jacqualt, *New J. Chem.*, *19* (1995) 213.

[11] J.P. Barnier, A. Loupy, P. Pigeon, M. Ramdani and P. Jacquault, *J. Chem. Soc., Perkin Trans. 1*, (1993) 397.

[12] A. Loupy, P. Pigeon, M. Ramdani and P. Jacqualt, *Synth. Commun.*, *24* (1994) 159.

[13] E.R. Pérez, A.L. Marrero, R. Pérez and M.A. Autié, *Tetrahedron Lett.*, *36* (1995) 1779.