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Microwave-assisted 1,3-Dipolar Cycloaddition Reactions of Nitrilimines and Nitrile Oxides†

Hafida Kaddar,[a] Jack Hamelin[b] and Hadj Benhaoua*[a,b]

[a] *Institut de Chimie, Université d'Oran Es-senia, Algérie*

[b] *Université de Rennes I. Laboratoire de Synthèse et Electrosynthèse organiques 3, UMR 6510, Avenue du Général Leclerc, F-35042 Rennes, France*

The 1,3-dipolar activity of hydrazonoyl chlorides and oxime chlorides over alumina with various alkenes and alkynes under microwave irradiation is studied; a comparative study between dry media conditions and the procedure in homogeneous solution under microwave and classical heating is described.

In view of the synthetic importance of cycloaddition reactions, there is an increasing interest in the development of special methods and catalysts to enhance the selectivity and shorten reaction times. Some studies related to microwave-assisted cycloadditions in the presence of solvents or under solvent-free conditions have been described recently.[1] Our current research programme involving organic synthesis under microwave activation led us to explore the possibility of performing 1,3-dipolar cycloadditions under these conditions.

Recently, it was shown in our laboratory, that dehydrohalogenation occurs over alumina under microwave irradiation and in solvent-free conditions.[2] According to these results, we have extended this work to the 1,3-dipolar activity of both hydrazonoyl chlorides and oxime chlorides over alumina acting both as base and support with various alkenes and alkynes. Here we report the results obtained under various experimental conditions.

Table 1 Cycloaddition of 1,3-dipoles generated over alumina under MW irradiation

Dipole precursor	Ar	Dipolarophile	T/°C	Yield(%)[a]
1a	Ph	AC≡CE[b]	120[c]	40
1b	p-ClC$_6$H$_4$	EC≡CE	120	60
2a	Ph	EC≡CE	140	50
2a	Ph	HC≡CCO$_2$Et	110	40[d]
2b	p-ClC$_6$H$_4$	(EC≡CE	140	40
1a	Ph	PhCH=C(CN)E[b]	120	0
1b	p-ClC$_6$H$_4$	PhCH=C(CN)E	120	0
2a	Ph	PhCH=C(CN)E	120	0
2b	p-ClC$_6$H$_4$	PhCH=C(CN)E	140	0
1a	Ph	ECH=CHE[b]	110	60
1b	p-ClC$_6$H$_4$	Maleimide	110	50

[a] Yields estimated by ^{1}H NMR and not optimized, the remainder being starting materials. [b] E = CO$_2$Me. [c] Maximum temperature monitored by the oven in the cylindrical quartz reactor (diameter = 4 cm). [d] Yield of **4** + **5**.

We first studied the dehydrohalogenation of hydrazonoyl chlorides and oxime chlorides over alumina under microwave irradiation. The 1,3-dipoles generated *in situ* were trapped with various alkenes and alkynes.[4] Reactions were carried out without solvent under microwave irradiation using a monomode reactor over 30 min with monitoring of temperature. Results and experimental conditions are reported in Table 1.

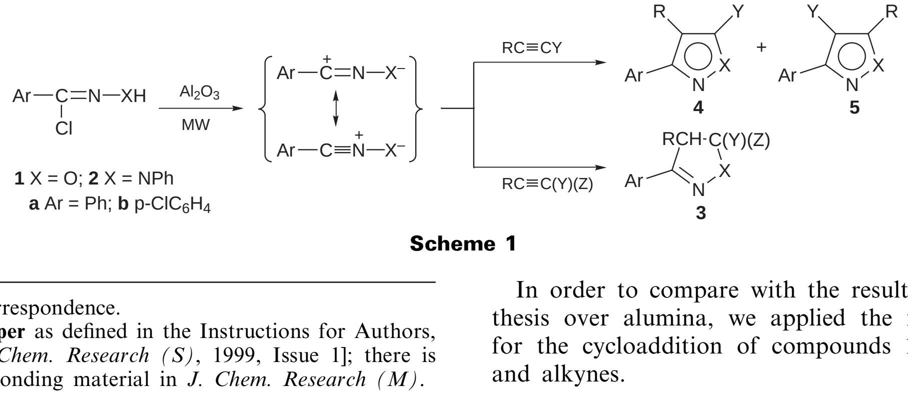
Experiments carried out under these conditions show that reactions with alkynes and disubstituted alkenes give moderate yields (40–60%) of the cycloadducts, whereas no reaction of **1** and **2** with trisubtituted alkenes was observed. These results are not surprising as trisubstituted alkenes generally react more slowly than disubstitute alkenes.[3] Our experimental results show that generation of the dipole can be achieved over alumina.

Manhas and coworkers have shown that the reaction of imines with acid chlorides in the presence of *N*-methylmorpholine (NMM) in chlorobenzene under microwave irradiation provides a rapid access to β-lactams. Unfortunately, however, a domestic oven was used without accurate control of the temperature.

Table 2 Reactions with alkenes in xylene in the presence of NMM under MW irradiation and classical heating

Dipole precursor	Ar	Alkene	**3**[a] (%) MW	**3**[a] (%) Heat
1a	Ph	PhCH=C(CN)E[b]	0	0
2a	Ph	PhCH=CHE	0	0
1a	Ph	ECH=CHE	65	30
1b	p-ClC$_6$H$_4$	ECH=CHE	85	40
2a	Ph	ECH=CHE	80	40
2b	p-ClC$_6$H$_4$	ECH=CHE	75	40
1a	Ph	Maleimide	55	22
1b	p-ClC$_6$H$_4$	Maleimide	75	42
2a	Ph	Maleimide	80	40

[a] Yields estimated by ^{1}H NMR are not optimized. [b] E = CO$_2$Me



1 X = O; **2** X = NPh
a Ar = Ph; **b** p-ClC$_6$H$_4$

Scheme 1

In order to compare with the results of the above synthesis over alumina, we applied the following procedure for the cycloaddition of compounds **1** and **2** to alkenes and alkynes.

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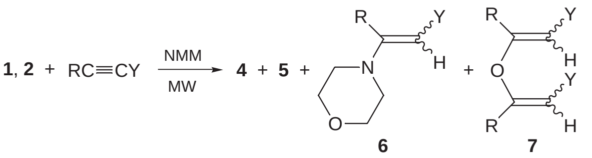
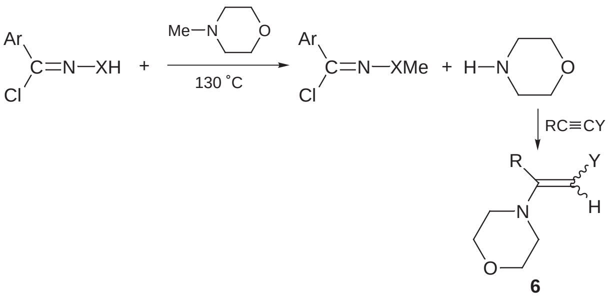
* To receive any correspondence.

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 2



Scheme 3

Compounds **1** and **2** were reacted with a variety of alkenes in the presence of NMM in xylene at 130 °C during 30 min under focused microwave irradiation. A comparison with classical heating shows the superiority of the microwave procedure. The same products are obtained and the yields are better than for the reactions in dry media (Table 1). Results are summarized in Table 2.

Reactions with alkynes under the same conditions (30 min, 130 °C) gave the desired cyclized products **4** and **5** together with enamine **6** and the compound **7**. The formation of **6** is not unexpected as it is well known that tertiary amines[7] react with alkynes to give enamines. Results collected in Table 3 show that the course of the reaction is the same as when applying classical methods. Scheme 3 accounts for the formation of the enamine **6**.

Product **7** results from the transformation of ethyl propiolate in the presence of water, as already mentioned in the literature.[6]

In summary, microwave heating accelerates the cycloaddition processus when performed in a non-polar solvent but the yields depend on the experimental conditions. It is obvious that the use of NMM as a base is not a better way to generate 1,3-dipoles in the presence of alkynes.

Experimental

Experiments were performed in a Synthewave 402$^{(R)}$ from Prolabo.[7] The reactions were run in a quartz reactor of 4 cm diameter, fitted with a refluxing condenser for the reactions in solution. All the reactions were run with monitoring of the temperature. All compounds were analyzed by ^{1}H and ^{13}C NMR (200 MHz) spectroscopy, the data are identical to those from the literature.

Table 3 Reactions with alkynes in xylene in presence of NMM under MW irradiation[a]

Dipole precursor	Ar	Alkyne	**4**/**5**[b] (%)	**6**[b] (%)	**7**[b] (%)
1a[c]	Ph	$EC\equiv CE$[d]	41/0	59	0
1b	p-ClC$_6$H$_4$	$EC\equiv CE$	73/0	27	0
2a	Ph	$EC\equiv CE$	50/0	50	0
2b	p-ClC$_6$H$_4$	$EC\equiv CE$	44/0	56	0
1a	Ph	$HC\equiv CCO_2Et$	25/13	50	12
1b	p-ClC$_6$H$_4$	$HC\equiv CCO_2Et$	52/22	26	0
2a	Ph	$HC\equiv CCO_2Et$	32/12	35	21
2b	p-ClC$_6$H$_4$	$HC\equiv CCO_2Et$	38/13	38	11

[a] Yields estimated by ^{1}H NMR are nearly quantitative. [b] Relative proportions. [c] In this case the selectivity is the same under classical heating. [d] $E = CO_2Me$.

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