Selective N-propargylation of imidazole under microwave irradiation using some magnesium oxides as catalysts

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The alkylation of imidazole ($C_3H_4N_2$) with propargyl bromide (C_3H_3Br) using some magnesium oxides as catalysts under microwave irradiation was carried out with a high activity and selectivity. It has been found that it is possible to prepare efficiently N-alkyl derivatives of heterocycles under microwave irradiation in absence of solvent. Under these experimental conditions N-alkylated heterocycles can be obtained with higher selectivities than when using other basic media.

Keywords: microwave irradiation; basic catalysis; propargylation; magnesium oxide

1. Introduction

Basic solids and base-catalyzed reactions constitute a field which offers possibilities for selectively catalyzed reactions to produce fine chemicals [1–3].

Recently, basic solid catalysts have received a great deal of attention to perform efficiently, and in absence of solvent, some organic synthesis in different heterogeneous conditions [4,5]. Among all the experimental procedures induced by heterogeneous media, such as reactions on solid inorganic supports, solid–liquid phase transfer catalysts [6,7], and uncatalyzed solid–liquid heterogeneous reactions, the microwave irradiation exhibits an interesting reactivity, giving rise to a peculiar selectivity, and it has been used recently to activate some organic reactions catalyzed by inorganic solids [8–10].

Among these organic reactions, the anionic alkylation of N-heterocycles is the primary route to obtain pharmaceutically important intermediate products [11]. N-propargyl derivatives A (scheme 1) of heterocycles are of interest because of

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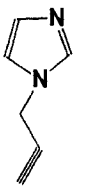


Scheme 1. N-propargyl derivative of type A.

their pharmacodynamic properties, but their usual synthesis in basic media affords low yields of the desired product.

Galons et al. [12] carried out the alkylation of imidazole with propargyl bromide using Al_2O_3 and KOH as catalysts. In the present work, we have studied the same reaction in very mild conditions under microwave irradiation in "dry media", in the presence of some magnesium oxides as catalysts.

2. Experimental

2.1. CATALYSTS

Three magnesium oxides were used as catalysts in the present work. The first sample, MgO, is a commercial magnesium oxide, provided by Fluka. The second one was obtained by calcination (873 K, 6 h) of a magnesium hydroxide, supplied also by Fluka. It is named as MgO_{hyd}. And the third catalyst was prepared by calcination (873 K, 5 h) of the hydroxide formed by precipitation of magnesium nitrate (Fluka) with 0.5 M NH_4OH. It is named as MgO*.

The BET surface areas and the pore volume distribution of the catalysts were calculated from N_2 adsorption isotherms at 77 K in a Micromeritics ASAP 2000 equipment. The diffraction patterns were recorded and evaluated with a Phillips 1730/10 diffractometer, using Cu K_α radiation.

2.2. REACTANTS

Imidazole and propargyl bromide are reagent grade and they were supplied by Fluka.

2.3. REACTION PROCEDURE

Imidazole (2 mmol) and different amounts of magnesium oxide were blended in a flask and propargyl bromide (2 mmol) was added. The mixture, placed in a Teflon 60 ml closed flask, was irradiated in a microwave oven (Sanyo EM 881) at 2450 MHz at different powers. After cooling, the reaction products were extracted with acetone (20 ml) and filtered. The reaction was followed by GC using a Konik

Table 1
Some physical characteristics of the MgO samples

Catalyst	S_{BET} (m^2/g)	V_p (cm^3/g)	Pore size (Å)	d^a (Å)
MgO	51.4	0.13	98.8	153
MgO_{hyd}	61.4	0.23	148.8	181
MgO*	55.7	0.21	154.0	131

[a] Crystal size determined by Debye–Scherrer's equation.

KNK-3000-HRGC gas chromatograph with a BP1 capillary column of 25 m length. The mass spectra of the products were obtained on a Hewlett-Packard HP 5971A spectrometer. The reactivity is expressed in terms of the amount of A obtained in wt%.

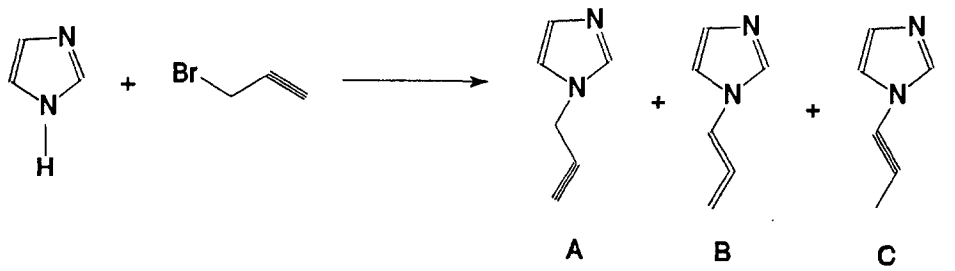
3. Results and discussion

3.1. PHYSICAL CHARACTERISTICS

In table 1 some physical characteristics of the magnesium oxides are given. The BET surface areas, the pore volumes and the average pore sizes, together with the crystal sizes determined by Debye–Scherrer's equation are included. It can be seen that the three samples have similar area values, the one corresponding to the oxide formed by calcination of the hydroxide being slightly higher. On the other hand the commercial oxide has a pore volume and average pore size which are approximately half of the other two synthesized samples. In all cases the cubic phase (periclase) was obtained and the degree of crystallization is similar, with a crystal size of the samples between 130 and 180 Å.

3.2. SELECTIVE N-PROPARGYLATION OF IMIDAZOLE

It is well known that the propargylation of N-heterocycles in basic media generally affords several products (scheme 2) with low yield and selectivity for the



Scheme 2. Propargylation of imidazole in basic media.

desired N-propargyl derivative A [13]. Together with the compound A, allenes B and ynamines C are formed, which are stabilized by resonance.

Under our experimental conditions, we have found that N-propargyl derivative A is selectively obtained when imidazole is alkylated with propargyl bromide. The mass spectrum of the reaction product [MS *m/s*: 106(M^+), 79(100), 52, 39] confirms that the only product obtained is the compound A.

In the present work some reaction parameters, such as irradiation time and power and the amount of catalyst have been studied in order to know their influence on the activity and selectivity of the reaction.

3.2.1. Effect of the amount of catalyst

The influence of the amount of catalyst has been studied during the alkylation of imidazole with propargyl bromide using, 0.1, 0.3 and 0.5 g of the catalyst samples (MgO, MgO_{hyd} and MgO*). Besides, in order to study the possible influence of the irradiation powers and times on the results obtained with a determined amount of catalyst, the corresponding experiments were carried out.

The conversion values with two different magnesium oxides are shown in tables 2 and 3. The product A is the only one obtained in all cases, with conversion values comprised between 45 and 90%, depending on the microwave power employed. It is observed that, in general, for a determined amount of catalyst, the amount of A increases with the irradiation time.

Fig. 1, as an example, shows the effect of the amount of catalyst in the propargy-

Table 2
Alkylation of imidazole (2 mmol) with propargyl bromide (2 mmol) using MgO in different reaction conditions

Power (W)	Catalyst amount (g)	Time (min)	Compound A (%)
300	0.3	1	44.8
		3	45.6
		5	52.3
300	0.5	1	32.5
		3	45.2
		5	59.5
450	0.3	1	44.2
		3	63.0
		5	65.5
450	0.5	1	55.1
		3	64.9
		5	57.2
750	0.3	1	59.9
		3	69.8
		5	78.3
750	0.5	1	55.7
		3	62.8
		5	70.6

Table 3
Alkylation of imidazole (2 mmol) with propargyl bromide (2 mmol) using MgO_{hyd} in different reaction conditions

Power (W)	Catalyst amount (g)	Time (min)	Compound A (%)
300	0.3	1	48.8
		3	58.2
		5	69.5
300	0.5	1	48.8
		3	55.1
		5	62.4
450	0.3	1	65.5
		3	72.2
		5	69.1
450	0.5	1	63.2
		3	65.5
		5	77.5
750	0.3	1	77.8
		3	74.6
		5	87.3
750	0.5	1	64.3
		3	72.0
		5	85.5

lation of imidazole at 750 W for 1, 3 and 5 min of irradiation, using the commercial MgO. It can be seen that, for all the reaction times studied, the highest values of amount of A are obtained for 0.3 g of catalyst. In general, the same order of activity is observed for all the magnesium oxides employed, and for all the irradiation times studied.

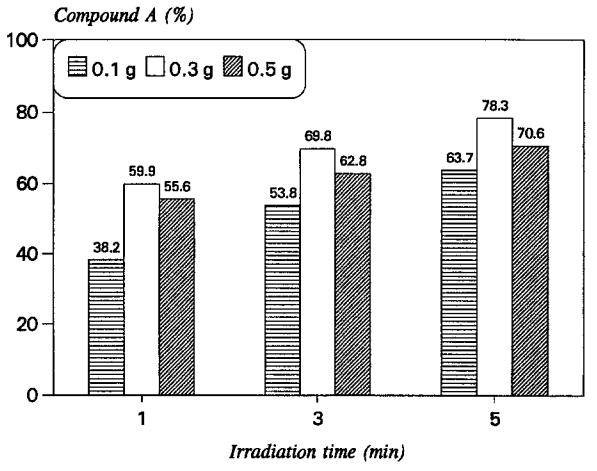


Fig. 1. Effect of the amount of catalyst (commercial MgO) in the propargylation of imidazole at 750 W and different irradiation times.

On the other hand, in order to know if the reaction takes place in absence of catalyst, a blank experiment with only the reactants was carried out at 750 W for 5 min, which are respectively the highest irradiation power and time used in the rest of the experiments with catalysts. A conversion of about 25% of A was obtained (it can be due to the effect of the microwave irradiation), opposite to the 70–80% values obtained with the magnesium oxides for the same time and power, results which combine the effect of the microwave and the catalyst.

3.2.2. Effect of the type of catalyst

The effect of the origin and the way of preparation of the magnesium oxides employed as catalysts has been studied carrying out several microwave irradiation experiments using the three magnesium oxides for different reaction times, for a fixed power and amount of catalyst. As a representative example, in fig. 2, the results obtained with 0.3 g of each oxide at a power of 300 W are shown. It can be seen that, for the lowest time, 1 min, values quite similar (between 45 and 50%) are obtained for the three oxides, but for higher times the difference of activities increases considerably, being the activities of the oxides prepared (which have the double of pore volume) almost 1.4 times higher than the one for the commercially available MgO.

3.2.3. Effect of the microwave irradiation power

The effect of the power of the microwave irradiation has also been investigated. Powers of 300, 450 and 750 W have been selected to carry out the propargylation of imidazole with all the catalysts at different experimental conditions. As an example, in figs. 3 and 4, the results obtained using MgO (0.3 g) and MgO_{hyd} (0.5 g) have been respectively plotted. From these results, it can be said that, in all cases,

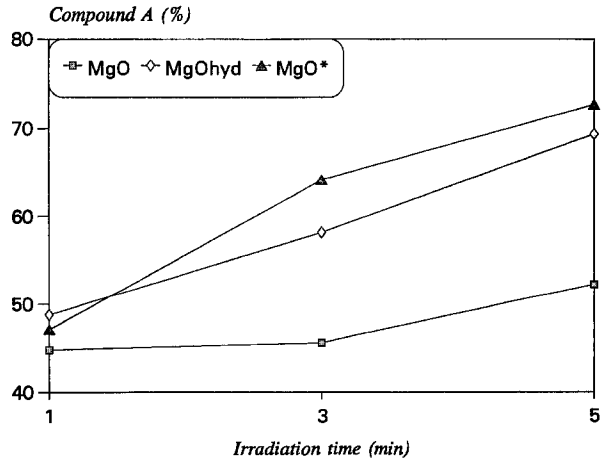


Fig. 2. Effect of the type of catalyst in the propargylation of imidazole at 300 W, using 0.3 g of catalyst.

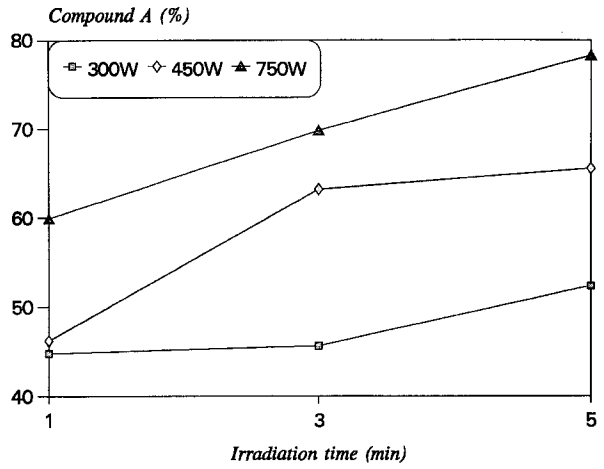


Fig. 3. Effect of the irradiation power in the propargylation of imidazole using 0.3 g of commercial MgO.

the reactivity increases with the microwave irradiation power, being the order of activity 300 < 450 < 750 W, and getting values near 90% for the highest power, that is almost 1.5 times higher than for the lowest power. The same order of reactivity was observed for other amounts of catalyst and for the MgO*.

4. Conclusions

N-propargyl derivatives of heterocycles which present clinical applications can be obtained under mild microwave irradiation using magnesium oxide as base cata-

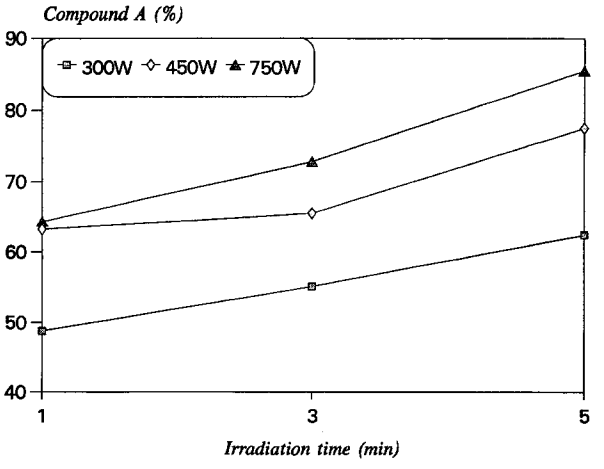


Fig. 4. Effect of the irradiation power in the propargylation of imidazole using 0.5 g of MgO_{hyd}.

lyst. We have found that the magnesium oxides employed in the present work are active and very selective catalysts for the alkylation of imidazole with propargyl bromide. It has been shown that the commercial MgO is almost 1.4 less active than the other two prepared by calcination, which have twice pore volume. It has been also concluded that, in general, under our experimental conditions, the reactivity increases with the microwave irradiation power and the irradiation time, giving the highest values of the desired product A when 0.3 g of catalyst are used. Values of 70–80% and 100% for conversion and selectivity respectively, which are higher than the results of other conventional reaction procedures, can be obtained in only 5 min of reaction. All these results show the great utility of microwave irradiation (combined with the use of base catalysts) in this type of processes, which allows to get excellent results of reactivity under easy experimental conditions and in a very short time.

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