Solvent-Free Benzylations of 2-Pyridone. Regiospecific *N*- or *C*-Alkylation

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Regiospecific N- or C-benzylations of 2-pyridone are observed in solvent-free conditions in the absence of base. The regioselectivity is controlled by the heating technique (microwave irradiation or conventional heating) or, using microwaves, by the emitted power or the leaving group of benzyl halides.

In connection with our studies on the reactivity of heterocyclic compounds in solvent-free conditions we reported the alkylation of 2-pyridone[1] by phase transfer catalysis in the absence of solvent. In this communication we describe the benzylation of 2-pyridone in solvent-free conditions in the absence of base under microwave irradiation or conventional heating, resulting in interesting changes in the regioselectivity.

The use of microwave irradiation has an increasing interest in organic synthesis as a rapid, safe and clean synthetic method.[2-6] The rapid heating rate has been used to produce spectacular diminutions in reaction times. However, the regio[7] or quimioselectivity[8] of a known reaction can be also affected by the use of this non classical energy source. Using this technique, in solvent-free conditions, we have reported the selective alkylations of 1,2,4-triazole and benzotriazole.[9] Important changes in the mono/di selectivity were observed by comparison with conventional heating.

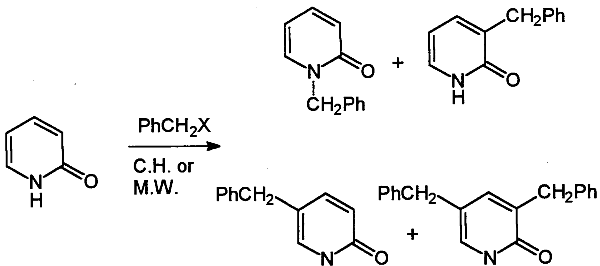
Reactions of 2-pyridone with benzyl halides under microwave irradiation have been performed in a commercial microwave oven using an open vessel. 10 Mmoles of 2-pyridone and the appropriate proportion of benzyl halide were used in all experiments. In a smaller scale (1 mmol), absorption of microwaves is not efficient enough to heat the mixture and to produce the reaction.[10]

In order to check the possible intervention of specific microwave effects (non purely thermal ones), we compared the results obtained by conventional heating in a thermostated oil bath in every conditions equal elsewhere (same temperature, reaction time and vessel). Comparative results are collected in the Table.

The regioselectivity, i.e., N- or C-alkylation, is controlled according to the leaving group of benzyl halide by the heating technique and, in some cases, by the emitted power of microwaves.

i) With benzyl chloride, whatever the activation mode is, N-alkylation is the only reaction occurring (entries 1-2). ii) Using benzyl bromide dramatic changes in the selectivity are observed either by changing the heating mode or the emitted power. After 5 min, (196 °C) exclusive C-alkylations are produced under microwaves at 450 W (entries 4-5), whereas exclusive N-alkylation is obtained by classical heating (entry 7-8), or reducing the power to 150 W (entry 6). iii) With benzyl iodide, microwave irradiation leads to exclusive C-alkylation with increased amounts of C-3 versus C-5 when compared to benzyl bromide (entries 9-11) whereas no reaction occurs in the same conditions under conventional heating (entry 12).

Table. Benzylation of 2-pyridone[a]. Product distribution



Entry	X	Power (W)	T (°C)	t (min)	N-	C-3	C-5	C-3,5
1	Cl	780	198	5	100	-----	-----	-----
2	Cl	780 [b]	176	5	100	-----	-----	-----
3	Cl	C. H.[b,c]	176	5	100	-----	-----	-----
4[d]	Br	450	196	5	-----	31	44	25
5	Br	450 [b]	171	5	-----	19	62	19
6	Br	150	81	5	100	-----	-----	-----
7	Br	C. H.[c]	196	5	100	traces	traces	-----
8	Br	C. H.[c]	130	60	100	-----	-----	-----
9	I	450	180	2,5	-----	59	41	-----
10	I	150	146	5	-----	51	49	-----
11	I	150	160	10	7	42	51	-----
12	I	C. H.[c]	180	5	traces	-----	-----	-----

2-Pyridone:benzyl halide ratio, [a] 10 : 20 mmol. [b] 10 : 10 mmol. [c] Conventional heating (C.H.), oil bath. [d] Yield of isolated products, 60%.

Considering the leaving group, C-alkylation is favored with soft leaving groups (compare for example entries 2, 5, 9). It is remarkable that two conditions are necessarily required to obtain C-alkylation, the use of solvent-free conditions and microwave irradiation. Using conventional heating N-alkylation is obtained whatever the reaction conditions may be (temperature or leaving group) (entries 3, 7, 8, 12), even in comparable experimental conditions that produce C-alkylation under microwaves (entries 4 vs 7). These results exclude any temperature effect on the regioselectivity. In solution, in DMSO, under microwave irradiation, the N-benzyl-2-pyridone is the only alkylated product detected. In consequence, an effect of the rapid heating rate[11] can be excluded because the heating rate in DMSO is even higher than under solvent-free conditions.

Moreover, a N-benzyl to C-benzyl rearrangement is excluded because the N-alkyl derivative is stable under the reaction conditions, even in the presence of benzyl bromide.[12] Therefore, such a dramatic change in selectivity can arise from purely specific microwave effect or must be a consequence of a change in the mechanism induced by the irradiation. C-alkylation can be produced by, i) a nucleophilic substitution at the benzylic carbon, ii) an aromatic electrophilic substitution, or iii) a radical substitution. Mechanisms ii) and iii) are in agreement with the fact that C-alkylation increases in the sequence Cl<Br<I.

A radical mechanism must be excluded as the addition of a radical scavenger (benzophenone or topanol, 5%), under microwave irradiation produces again, C-alkylation exclusively. Moreover, the generation of benzyl radical by classical methods[12] produces selectively N-benzylpyridone.

In favour of mechanism ii) is the selectivity observed and that reaction of 2-pyridone with benzyl alcohol, with traces of acid, under microwaves produce a 36 : 64 mixture of C-alkylation and N-alkylation respectively.

In conclusion, microwave irradiation produces an interesting and useful inversion in the selectivity. This method may constitute a simple way to introduce C-alkyl substituents in heterocyclic compounds. The observed selectivity is explained by an activation of the benzyl halide, rather than the heterocyclic compound, that favours the dissociation of the C-X bond.

Microwave irradiations[13] A. Reaction with benzyl halides in solvent-free conditions. In a Pyrex flask (25 cm^3), a mixture of 2-pyridone (0.95 g, 10 mmol) and benzyl halide (10 or 20 mmol) was introduced in the microwave oven and irradiated under the conditions described in the table. Extraction with dichloromethane (4 x 10 cm^3) and removal of the solvent afforded the crude product which was analysed by ^{1}H-NMR.

B. Reaction with benzyl bromide in DMSO. In a Pyrex flask (50 cm^3), a solution of 2-pyridone (0.95 g, 10 mmol), benzyl bromide (1.22 cm^3, 10 mmol) and DMSO (10 cm^3) was irradiated at 450 W for 38 sec (final temperature, 142°C). The reaction was poured into water (5 cm^3) and extracted with dichloromethane (3 x 3 cm^3). Removal of the solvent afforded the crude product which was analysed by ^{1}H-NMR.

C. Reaction with benzyl alcohol. In a Pyrex flask (25 cm^3), a mixture of 2-pyridone (0.95 g, 10 mmol), benzyl alcohol (1.08 g, 10 mmol) and sulfuric acid (one drop) was irradiated at 450 W for 5 min (final temperature, 207 °C), and elaborated as in A. The crude product was analysed by ^{1}H-NMR giving a mixture of 1-benzyl-2-pyridone, 64%, 3-benzyl-2-pyridone, 12%, 5-benzyl-2-pyridone, 12% and 3,5-dibenzyl-2-pyridone, 12%.

D. Conventional heating. In a round botton flask (25 cm^3) a mixture of 2-pyridone (0.98 g, 10 mmol) and benzyl halide (10 or 20 mmol) was heated in an oil bath at the temperature indicated in Table for 5 or 60 min and elaborated as indicated in method A

E. Reaction in the presence of a radical initiator.[14] A solution of 2-pyridone (0.14 g, 1.5 mmol), benzyl iodide (0.87 g, 4 mmol) and benzoyl peroxide (0.36 g, 1.5 mmol) in acetonitrile (20 cm^3) was heated to reflux until complete decomposition of the peroxide (c.a. 4 h). The solution was diluted with water (50 cm^3) and made alkaline with 10% sodium hydroxide. Extraction with ethyl acetate (50 cm^3) and removal of the solvent afforded the crude product which was analysed by ^{1}H-NMR.

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12 N-benzyl-2-pyridone (10 mmol) was irradiated at 450 W for 5 min in the absence and in the presence of benzyl bromide (10 mmol). Starting material was recovered.

13 All compounds were fully characterized, IR, ^{1}H- and ^{13}C-NMR and elemental analysis. In microwave irradiations, temperature was measured at the end of the reaction with a thermocouple thermometer. In conventional heating reactions, temperature was controlled with a contact thermometer submerged in the oil bath.

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