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Fast Electron Transfer *C*-Alkylation of 2-Nitropropane Anion under Microwave Irradiation[§]

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Abstract: Microwave irradiation is shown to be an attractive methodology for fast electron transfer *C*-alkylation reactions of 2-nitropropane anion by different reductive alkylating agents. This method is simple, rapid and affords excellent *C*-alkylation yields. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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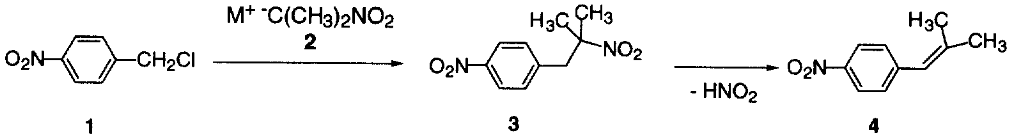
Since the initial proposal by Kornblum[1] and Russell[2] of the radical chain mechanism put forward to explain the *C*-alkylation of nitronate anions by *p*-nitrobenzyl chloride and its designation as $S_{RN}1$ by Bunnett,[3] the extensions of this reaction at sp^3 carbon have been studied extensively.[4-9] These reactions can be performed under different conditions, very often at room temperature in dipolar aprotic solvents (DMF, DMSO or HMPA) under inert atmosphere and light stimulation.

Application of microwave heating technique is currently under intensive examination since the early papers of Gedye[10] and Majetich[11] and their co-workers. Recent applications of microwave irradiation have been recently rewiewed[12] and highlighted.[13] Microwave heating techniques for 'dry' organic reactions have been developed recently.[14] We were interested in determining whether reductive alkylating agents would undergo *C*-alkylation with nitronate anions on a solid support under microwave irradiation. In order to make direct comparisons with previously studied $S_{RN}1$ reactions, we choose as first example the reaction of *p*-nitrobenzyl chloride **1** with the lithium salt of 2-nitropropane **2** which gave 95% of *C*-alkylation product **3** (Scheme 1) under Kornblum conditions (DMF, -16 °C, 2 equiv. of **2**, 35 hours).[15] In order to evaluate the influence of silica gel, water and power of microwave irradiation in this reaction, several conditions were tried (Table 1).

Scheme 1



1 **3** **4**

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§ This paper is dedicated to the late Professor Glen A. Russell. Deceased on January 1, 1998.

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Table 1: Reactions of *p*-nitrobenzyl chloride **1** with 2-nitropropane anion **2** under microwave irradiation[a]

Entry	M^+, eq.	Conditions	Time, Power	Final T °C	[b]Yield % **1**	**3**	**4**
1	Li, 2	DMF	35 hours	-16	0	95	0
2	Li, 4	Silica gel	4 min, 900 W	≈ 130	47	29	5
3	"	H_2O (2 ml), Silica gel	"	"	28	24	0
4	"	"	4 min, 350 W	≈ 95	47	16	0
5	"	H_2O (2 ml)	4 min, 900 W	≈ 100	0	9	0
6	Na, 4	H_2O (2 ml), Silica gel	"	≈ 130	18	40	0
7	"	H_2O (20 ml), Silica gel	"	"	12	23	0
8	"	H_2O (2 ml)	"	≈ 100	0	82	13
9	"	H_2O (20 ml)	"	"	27	35	0
10	"	H_2O (20 ml), 100 °C	12 hours	100	0	71	0
11	"	H_2O (20 ml), Silica gel, 100 °C	"	"	0	76	0

[a]All reactions were performed with 200 mg (1.17 mmol) of **1** and 1 g of silica gel by using open Erlenmeyer flask Pyrex, unless otherwise stated. Irradiations were carried out in a domestic microwave oven (Whirlpool MO 111). [b]Yields of pure isolated products, the complements to 100% were resins.

With $LiC(CH_3)_2NO_2$, the use of microwave irradiation with silica gel in *dry media*, gives moderate yield of *C*-alkylation and **1** remains in part unchanged with formation of resins (entry 2). With wet silica gel, the recovered **1** decreases but the formation of resins increases (entry 3). An apparent reduction in power (350 W in entry 4) which is not more than a simple cut in irradiation with sequential emission of microwaves at the maximal power gives lower *C*-alkylation yield. In water, almost only formation of resins is observed. A significant influence of the counterion is observed, sodium being more effective than lithium for *C*-alkylation reaction (entries 3 *vs* 6 and 5 *vs* 8). The best *C*-alkylation yield which is the same as in Kornblum conditions, is obtained under microwave irradiation by using $NaC(CH_3)_2NO_2$ without silica gel (entry 8). The alkene **4** formed from **3** by elimination of nitrous acid is isolated in 13% yield. The use of an excess of water (20 ml) is detrimental on *C*-alkylation (entries 7 and 9). Under conventional experimental conditions, when an aqueous solution of **1** with $NaC(CH_3)_2NO_2$ is refluxed for 12 h in the presence (entry 10) or in the absence of silica gel (entry 11), **3** is obtained in good yields.

From these interesting results, we have sought to develop a general procedure for $S_{RN}1$ reactions and we have extended these experimental conditions to heterocyclic compounds in the thiazole and imidazopyridine series. The results are summarized in Tables 2 and 3. We have previously demonstrated[16] that 2-methyl-4-chloromethyl-5-nitrothiazole **5** reacted by an $S_{RN}1$ mechanism with 2-nitropropane anion, leading to a 71% yield of isopropylidene derivative **7** formed by loss of nitrous acid from the *C*-alkylation product **6** (Scheme 2). The same reaction has been studied[17] with 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine **8** and gave the alkene **10** in 94% yield in DMF, as shown in Scheme 3. The *C*-alkylation products **6** and **9** have not been isolated under these experimental conditions.

Scheme 2

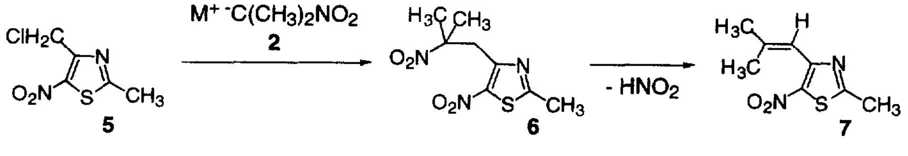

Table 2: Reactions of 2-methyl-4-chloromethyl-5-nitrothiazole **5** with 2-nitropropane anion **2** under microwave irradiation[a]

Entry	M^+, eq.	Conditions	Time, Power	Final T °C	[b]Yield **5** %	**6**	**7**
12	Li, 3	MeOH	24 hours	25	0	0	71
13	Li, 4	Silica gel	2 min, 900 W	≈ 130	23	10	19
14	"	H_2O (2 ml), Silica gel	"	"	7	31	9
15	"	"	2 min, 750 W	≈ 125	8	31	13
16	"	"	2 min, 500 W	≈ 105	10	39	12
17	"	"	2 min, 350 W	≈ 95	13	54	9
18	"	"	2 min, 160 W	≈ 80	16	72	10
19	"	"	2 min, 90 W	≈ 65	28	63	7
20	"	"	4 min, 160 W	≈ 80	8	56	19
21	"	H_2O (2 ml)	2 min, 160 W	"	60	23	0
22	Na, 4	"	"	"	21	28	5
23	"	H_2O (2 ml), Silica gel	"	"	13	31	3
24	Li, 4	H_2O (20 ml), Silica gel, 100 °C	12 hours	100	0	0	0

[a]All reactions were performed with 200 mg (1.04 mmol) of **5** and 1 g of silica gel by using open Erlenmeyer flask Pyrex, unless otherwise stated. Irradiations were carried out in a domestic microwave oven (Whirlpool MO 111). [b]Yields of pure isolated products, the complements to 100% were resins.

Scheme 3

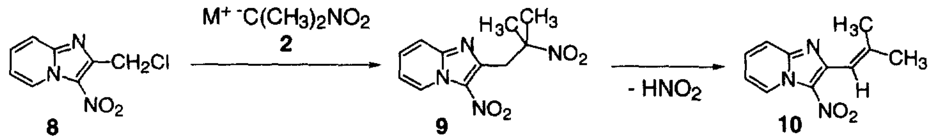

Table 3: Reactions of 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine **8** with 2-nitropropane anion **2** under microwave irradiation[a]

Entry	M^+, eq.	Conditions	Time, Power	Final T °C	[b]Yield **8** %	**9**	**10**
25	Li, 2	DMF	24 hours	25	0	0	94
26	Li, 4	Silica gel	4 min, 900 W	≈ 130	22	12	18
27	"	H_2O (2 ml), Silica gel	"	"	0	69	3
28	"	"	4 min, 650 W	≈ 115	0	91	6
29	"	"	4 min, 500 W	≈ 105	0	83	5
30	"	"	4 min, 350 W	≈ 95	0	80	6
31	"	"	4 min, 160 W	≈ 80	0	71	12
32	"	H_2O (2 ml)	4 min, 650 W	≈ 100	8	49	39
33	Na, 4	"	"	"	0	7	55
34	"	H_2O (2 ml), Silica gel	"	≈ 115	28	21	7
35	Li, 4	H_2O (20 ml), Silica gel, 100 °C	12 hours	100	0	0	73

[a]All reactions were performed with 200 mg (0.945 mmol) of **8** and 1 g of silica gel by using open Erlenmeyer flask Pyrex unless otherwise stated. Irradiations were carried out in a domestic microwave oven (Whirlpool MO 111). [b]Yields of pure isolated products, the complements to 100% were resins.

The above results show a modulation of wet silica gel-microwave irradiation balance allows the obtention of *C*-

alkylation derivatives (**6** + **7** and **9** + **10**) in good yields (82% entry 18 and 97% entry 28). With **5**, the formation of resins increases with the power of microwawe irradiation (entries 13-15). A similar effect is observed with **8** (entries 26-27). In thiazole series, $NaC(CH_3)_2NO_2$ also is more effective but more resins are formed (entries 21 *vs* 22 and 18 *vs* 23). In imidazopyridine series, $NaC(CH_3)_2NO_2$ forms more resins (entries 32 *vs* 33 and 28 *vs* 34). When silica gel is used as catalyst in water solution (12 hours, reflux), the alkene **10** is obtained (entry 35). The reaction of **5** under the same conditions gives only resins because **7** is probably unstable under these experimental conditions (entry 24).[16] Compared to Kornblum conditions, under microwave irradiation the *C*-alkylation products **6** and **9** are the predominent products. According to these results on wet silica gel and under microwave irradiation in thiazole and in imidazopyridine series, a short time of reaction favors the *C*-alkylation products **6** and **9**, whereas with *p*-nitrobenzyl chloride and $NaC(CH_3)_2NO_2$ in water the alkene **4**, which not formed under conventional experimental conditions, is obtained in 13% yield. To the best of our knowledge, these results are the first examples of $S_{RN}1$ reactions carried out under microwave irradiation.

In conclusion, the reported procedure is an attractive methodology for the $S_{RN}1$ reactions with 2-nitropropane anion, because the reactions are fast, the procedure is simple and gives good *C*-alkylation yields. Work is in progress to study the mode of action of microwaves on these $S_{RN}1$ reactions.

Standard procedure: In a typical experiment, the nitro compound (0.2 g) was intimately mixed with the indicated amounts of lithium or sodium salt of 2-nitropropane, water (2 ml) and 1 g of silica gel (Merck, Geduran SI 60, 70-230 microns, pH = 7, surface area 550 $m^2\ g^{-1}$). The glass vessel (open Erlenmeyer flask Pyrex) was irradiated in a domestic microwave oven for an appropriate length of time at the indicated power (see Tables). After cooling down, the reaction products were isolated by extraction of the silica gel with methylene chloride and purified by columm chromatography and recrystallization.

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