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Microwave assisted solid additive effects in simple dry chlorination reactions with *n*-chlorosuccinimide

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ABSTRACT

Solid additives participate in the dry microwave assisted chlorination reaction of *N*-chlorosuccinimide with the xylenes affecting both yields and chemoselectivities. Total yields can be increased up to nine times for simple alkylaromatics and chemoselectivities can be altered according to the desired ring or α-side chlorination product by choosing the appropriate additive. We believe that in these reactions the solid additives play a very important role by increasing yields and affecting chemoselectivities, as well as behaving as microwave energy absorbers that consequently aid the transfer of heat to the active reagents.

1. Introduction

In general, all of the participants—reagents, catalysts, solvents—have a particular chemical role to play in a chemical reaction that is promoted by using conventional energy sources. However, this role can be modified when interactions with certain physical phenomena are possible, such as, for example, when techniques involving ultrasound or microwave irradiation are used whereby high energy micro-environments can develop.[1] The outcome of a microwave assisted chemical reaction depends on the efficiency of the coupling of the microwave energy with all the chemical species present in the reaction mixture. As a result, much attention has been directed towards the use of ionic liquids,[2] which can absorb microwave energy very well and in this way act as heating aids.[3] Some insoluble inorganic supports (silica, Celite, montmorillonite K-10 clay), due to their ability to absorb reagents on their surface, have also been used in the microwave-assisted synthesis of heterocyclic compounds.[4] In these reactions the catalytic effect has been ascribed to the presence of acidic sites in the solid support.

Numerous industrially valuable products carry halogen functionality and halogenated aromatic compounds are key intermediates in the synthesis of organometallic molecules and play important roles in transition metal coupling reactions.[5] *N*-Chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) are among the most common halogenating reagents. A disadvantage in the use of them for the halogenation of aromatic compounds can sometimes be their tendency to give benzylic halogenation rather than ring halogenation, although it has been found that under appropriate conditions the reaction pathways can often be differentiated.[6] The first reported reactions involving these reagents were performed in organic solvents and were solvent dependent,[7] and it was found that the lower the refractive index of the solvent, the greater was the yield of the benzylic halogenated product.[8] On the other hand, Lewis acids and solvents with high dielectric constant were observed to promote aromatic ring halogenation.[9] The promotion of this reaction by light and other so-called high energy techniques has also been examined in solvent free reactions, in water or in ionic liquids, with variable results.[10] From the large number of papers that have appeared, especially during recent years, and the ongoing demand for cheaper and cleaner products, it is apparent that there is a need to increase reaction yields and to develop more practical and economical procedures for the selective synthesis of isomeric halogenated compounds. In connection with this we herein describe our work on the halogenation of some simple alkylaromatics by NCS involving the use of microwaves under solvent-free conditions in the presence of a range of solid additives.

2. Results and discussion

We have recently reported the contrasting diverse chemoselectivities in the ultrasound and microwave assisted bromination

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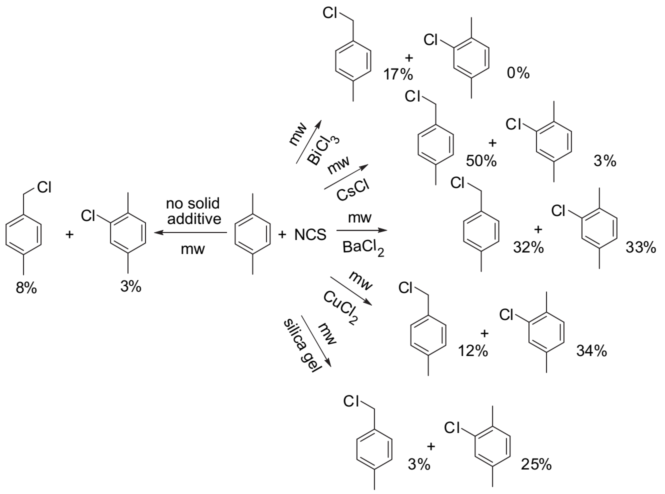
reactions of NBS with substituted alkylaromatics,[11] and we have now turned our attention to the effect of solid additives on the chemoselectivities and yields in the microwave promoted reaction of NCS with similar compounds in the absence of solvent. For this study we chose NCS instead of NBS, because the latter gives higher yields of benzylic bromination products under microwave irradiation with *o*-xylene (62%), *m*-xylene (56%) and *p*-xylene (50%), whereas NCS affords yields of only 20%, 3% and 8%, respectively. Therefore, we considered that the use of NCS as a halogenation reagent would be more suitable for study in model systems involving microwave irradiation, since it would be easier to gauge the significance of any improvement in conversions and chemoselectivities that might be observed (Scheme 1).



Scheme 1. *p*-Xylene and NCS microwave assisted reaction in the presence or absence of a salt.

The effect of salts, such as lithium chloride, sodium chloride, potassium chloride, rubidium chloride, caesium chloride, ammonium chloride, calcium chloride, barium chloride, copper (II) chloride, potassium bromide, potassium nitrate, monopotassium phosphate, sodium acetate, sodium oxalate, sodium carbonate, potassium carbonate, bismuth trichloride, and other compounds such as aluminium oxide, sand, powdered glass, silica gel and graphite on the halogenation reactions of xylene under microwave irradiation was studied (Table 1). While it is known that microwave irradiation is often a convenient way to obtain higher yields in very short times, in our reactions the addition of almost all of the additives to the reaction mixture was shown to effectively boost the conversions to chlorinated products and also to significantly affect the chemoselectivity of the reaction. In the presence of almost all of the additives, the total conversion, i.e., the sum of the products of ring and benzylic chlorination of the xylenes was considerably higher than that obtained in their absence.

The microwave promoted reactions were carried out using equimolar amounts (3.0 mmol) of the xylene, NCS and the additive and in the absence of solvent. For *o*-xylene the maximum total conversion was obtained with $CuCl_2$ (55%), and powdered glass (54%). With CsCl the reaction gave essentially only α-side-chain substitution (52%) while with $BiCl_3$ only the ring product (11%) was obtained. The highest ring conversion was obtained with $CuCl_2$ (44%) and for α-side-chain substitution with CsCl (52%) and KH_2PO_4 (51%). For *m*-xylene the highest total conversion was obtained with $CuCl_2$ (77%), $BaCl_2$ (69%) and Al_2O_3 (68%). $BiCl_3$ gave only ring conversion (18%) and $CuCl_2$ and silica gel gave almost clean ring conversion, 75% and 40%, respectively. For *p*-xylene the highest total conversion was obtained with $BaCl_2$ (65%) while Group 1 salts, as well as NH_4Cl, KBr and KH_2PO_4, gave almost only the α-side-chain substituted product (ca. 48%) and silica gel was the only additive that gave almost only ring substitution. It is interesting to note that, of all the additives that were tested, only $CuCl_2$ gave predominantly ring halogenation for all three xylenes and that

Table 1
Dry microwave assisted chlorination reactions yields of xylenes with NCS in the presence of a solid additive[a]

Solid additive	*o*-Xylene			*m*-Xylene			*p*-Xylene		
	Ring product (%)	Side-chain product (%)	Total (%)	Ring product (%)	Side-chain product (%)	Total (%)	Ring product (%)	Side-chain product (%)	Total (%)
None	3	20	**23**	10	3	**13**	3	8	**11**
LiCl	6 (9)[b]	46 (2)[b]	**52** (11)[b]	36	8	**44**	8 (11)[b]	45 (4)[b]	**53** (15)[b]
NaCl	5	42	**47**	8	2	**10**	4	47	**51**
KCl	4	49	**53**	20	10	**30**	3	48	**51**
RbCl	3	42	**45**	42	17	**59**	3	47	**50**
CsCl	1	52	**53**	42	17	**59**	3	50	**53**
NH_4Cl	3	47	**50**	26	25	**51**	3 (2)[b]	47 (8)	**50** (10)[b]
$CaCl_2$	6	43	**49**	36	17	**53**	7	43	**50**
$BaCl_2$	10	41	**51**	57	12	**69**	33	32	**65**
$CuCl_2$	44	11	**55**	75	2	**77**	34	12	**46**
KBr	5	32	**37**	17	7	**24**	3	48	**51**
KNO_3	2	10	**13**	15	3	**18**	5	9	**14**
KH_2PO_4	50	1	**51**	18	8	**26**	2	44	**46**
CH_3CO_2Na	0	0	**0**	3	1	**4**	1	0	**1**
$C_2Na_2O_4$	6	41	**47**	33	10	**43**	2	26	**28**
Na_2CO_3	2	6	**8**	6	2	**8**	2	4	**6**
K_2CO_3	0	2	**2**	7	2	**9**	5	13	**18**
$BiCl_3$	11	0	**11**	18	0	**18**	17	0	**17**
Al_2O_3	8	12	**20**	53	15	**68**	7	9	**16**
Sand	5	48	**53**	37	23	**60**	5	45	**50**
Glass	3	51	**54**	12	6	**18**	3	47	**50**
Silica gel	16	2	**18**	40	1	**41**	25	3	**28**
Graphite	6	44	**50**	—[c]	—[c]	—[c]	7	12	**19**

[a] General experimental conditions: Temperature 102 °C, time 4 min, max. pressure 3.5 bar, microwave power 120 W, no water. The average yields presented are within 6%, after 3 repetitions and only for the monochlorinated products. Some dichlorides were observed by GC–MS in a number of the reactions although the products were not characterised. For *o*-xylene ring conversion represents the sum of both isomers, 1-chloro-2,3-dimethylbenzene and 4-chloro-1,2-dimethylbenzene, which are formed in almost all our experiments in 1:3 ratio, respectively. Yields were calculated from the GC of the products.

[b] Yields in parentheses are for microwave experiments performed in water.

[c] The reaction was interrupted due to the very high pressure observed in the reaction vessel.

$BiCl_3$ gave only clean α-side conversion for all the xylenes. With CH_3CO_2Na we had almost no conversion and this is ascribed to the preferential chlorination of the methyl group of the salt.

In an attempt to see if the use of a lower amount of salt would benefit the reactions in the same way, we repeated some of them using a small amount of salt, e.g., 0.3 mmol instead of 3.0 mmol that we used in the previously described protocol. With *p*-xylene, NCS and KBr the conversions were almost identical: 3% ring and 49% side products. But when 0.03 mmol of KBr was used the yields dropped significantly (2% ring and 25% side, respectively). With KCl and $CaCl_2$ we observed the same behaviour. Thus when 10% of the equimolar amount was used the yields were similar to those when equimolar amounts were used, but when 1% was used the yields were very low. We also repeated some reactions with equimolar reagents in water. With *o*-xylene or *p*-xylene, and NCS and LiCl, the yields dropped dramatically (Table 1). Similar results were obtained with other additives.

We have also compared the results of some of these reactions with those obtained using classical heating conditions in the presence or absence of a solid additive. For example, *o*-xylene with NCS in the presence of CsCl afforded 5% the side-chain product while in the absence of CsCl a 9% yield was observed. Under MW irradiation the side-chain product yield was 52% (Table 1). Similar results were observed with other additives. It is obvious that, in contrast to the microwave assisted reactions, the presence of the salt diminishes the yields under classical heating conditions although the reason for this is not yet clear. It must be noted that the heating profile of the reaction of *p*-xylene and CsCl and NCS, under classical heating is a straight line, even when it was heated over 150 °C (preheated oil bath to 160 °C) and that all the reactions under classical heating are not triggered, in contrast to those under MW conditions where there is a sudden temperature jump within the first 1–2 min of the reaction (Fig. 1).

Recently, Passive Heating Elements (PHE), that are composed of chemically inert substances such as SiC, have been used in MW assisted reactions.[12] They possess a strong ability to absorb microwave energy and to convert it to heat which is then transferred very effectively to their environment. In this way, even reagents that do not absorb MW energy can be heated. In order to obtain a more in depth understanding of our results, we performed several of our reactions in the presence of SiC. The yield results obtained for the reaction of *p*-xylene and NCS in the presence of SiC and LiCl, KCl, CsCl, KBr or sand were similar to those obtained in the absence of SiC (Table 2). Lower yields were observed, however, when $BaCl_2$, and $CuCl_2$ were used. The various maximum temperatures for each reaction in the presence of SiC were lower (for the same additive), but were reached in a shorter time. We also performed the reaction in the presence of two salts, e.g., LiCl and CsCl and although the total yield (48%) was similar to those obtained when they were used separately (53%), the yield of the ring product was increased, while the side-chain product yield was decreased.[13] The heating profiles of most of the reactions can be found in the Supplementary data section.

Table 2
Dry MW assisted chlorination reactions yields of *p*-xylene with NCS, in the presence of a solid additive and PHE (SiC)[a]

Solid additive	Ring product (%)	Side-chain product (%)	Total (%)
None	6	46	52
LiCl	12	40	52
KCl	4	49	53
CsCl	3	50	53
$BaCl_2$	14	36	50
$CuCl_2$	26	12	38
KBr	4	50	54
KNO_3	6	12	18
K_2CO_3	12	16	28
$BiCl_3$	12	8	20
Sand	5	46	51

[a] General experimental conditions: As those prescribed in Table 1.

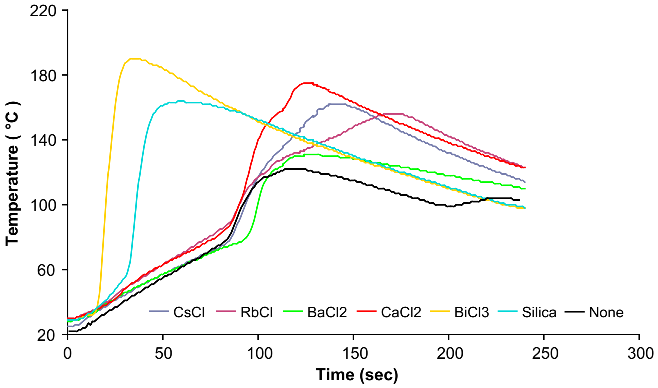


Figure 1. Heating profiles of the reaction of *p*-xylene with NCS, in the presence of different solid additives.

In order to see if our method could be applied to other simple molecules, we tested 1-methylnaphthalene, 2-methylnaphthalene and 1-*tert*-butyl-4-methylbenzene, in the presence and absence of a salt (CsCl, $BaCl_2$, KH_2PO_4). As we can see from Table 3, in all the examined reactions the presence of a salt increased the yield up to nine times and affect the chemoselectivity. The fact that yields are increased and chemoselectivities vary in all these reactions can be attributed to variations in how each additive absorbs microwave energy and dissipates it to the other reagents that are adsorbed on the additive surface. The mechanism by which this energy transfer occurs and how it affects the subsequent course of the reaction remains a matter of speculation. The heating profiles indicate that the solid additive absorbs and transfer energy to the other reagents in almost the same manner. Therefore it appears that, through a similar physical process, the solid additives enable the activation energy barrier of the reactions to be overcome, thus leading to the reaction products. However, these heating profiles are a result of complex processes occurring at different rates, which involve simultaneous absorption and transfer of energy and we believe that this may be the source of the characteristic chemoselectivities for each of the additives. It remains to be demonstrated whether these processes are the result of established mechanisms of energy transfer or whether it is necessary to hypothesise the involvement

Table 3
Dry microwave assisted chlorination reactions yields of simple alkylaromatics with NCS in the presence of a solid additive[a]

Substrate	Product %	No additive	CsCl	$BaCl_2$	KH_2PO_4
1-Methyl-naphthalene	Ring[b]	5	23	45	11
	Side	2	37	18	4
	Total	**7**	**60**	**63**	**15**
2-Methyl-naphthalene	Ring[c]	16	49	59	25
	Side	3	20	8	8
	Total	**19**	**69**	**67**	**33**
1-*tert*-Butyl-4-methylbenzene	Ring[d]	6	4	13	4
	Side	4	49	33	40
	Total	**10**	**53**	**46**	**44**

[a] General experimental conditions: Temperature 102 °C, time 4 min, max. pressure 3.5 bar, microwave power 120 W, no water. The average yields presented are within 6%, after 3 repetitions and only for the monochlorinated products. Yields were calculated from the GC of the products.

[b] 1-Chloro-4-methylnaphthalene.

[c] 1-Chloro-2-methylnaphthalene.

[d] 4-*tert*-Butyl-2-chloro-1-methylbenzene.

of some type of intermediary such as microwave induced phonons, which have been invoked by others to explain certain physicochemical phenomena.[14,15]

3. Conclusions

The microwave promoted chlorination reaction of simple alkylaromatics with NCS, in the presence of an ionic species (salt, metal oxide, etc.) and in the absence of water produced interesting results. Total yields were increased up to ninefold when compared with the reactions in the absence of these compounds. In addition, chemoselectivities varied according to the additive used and in some cases it was possible to obtain exclusively either the ring or the side-chain chlorinated isomer. These additives play little or no chemical role in these reactions but, as the main instantaneous absorbers of microwave energy, they consequently transfer part of this energy to the active reagents, thus increasing their reactivity via a complex mechanism. The heating aid behaviour of these ionic species in our microwave assisted reactions is similar to that observed with the use of ionic liquids. The solid additives used in this study have the advantage that they are very cheap and, since they are easily separated from the reaction products, can also be used repeatedly. We therefore believe that our microwave assisted method is of synthetic interest, since it dramatically increases yields (up to 77%, nine times) and by choosing the appropriate salt can afford almost exclusively the desired isomer.

4. Experimental section

4.1. General MW experimental procedure

The microwave-assisted experiments were carried out in the dark with a CEM Discover 300 W monomode microwave instrument. The closed vessels used were special glass tubes with self-sealing septa that controlled pressure with appropriate sensors on the top (outside the vial). The temperature was monitored through a non-contact infrared sensor centrally located beneath the cavity floor. Magnetic stirring was provided to assure complete mixing of the reactants. Under these conditions the pressure in the tubes never exceeded 4 bars, except with *m*-xylene and graphite. The 10 mL reaction vessels were charged in air with 0.32 g (3.0 mmol) of xylene and 0.39 g (3.0 mmol) of NCS and 3.0 mmol of salt or 0.39 g of sand, powdered glass, silica gel or graphite. Using 120 W initial power, which is moderated during the reaction by the microwave instrument software in order to try to maintain a constant temperature of 102 °C, the reaction temperature rises in a similar way from room temperature up to a certain different 'trigger' temperature for each additive. Then it rapidly jumps undergoing a spontaneous exothermic reaction reaching different maximum temperatures for each additive. After a total reaction time of 4 min, the mixture was rapidly cooled to room temperature. Hexane was added after cooling and the whole reaction mixture was transferred to a separation funnel. The organic layer was washed three times with 3×15 mL of water, dried over Na_2SO_4 and analysed by GC and GC–MS. For the NMR samples the solvent was evaporated prior to analysis. The reactions were very reproducible with results differing by not more than 6%. The general work up for the reaction with CH_3CO_2Na was the same as with all the other solid additives (see above) but in order to find out why the reaction did not proceed, we added sulfuric acid 10% to combined aqueous extracts and then extracted with ether. After drying the ether extract with anhydrous Na_2SO_4, and removal of the solvent ^1H NMR analysis of the residue indicated that the products contained $CH_2ClCOOH$. This was confirmed by conversion of the acid to its methyl ester by using CH_2N_2 followed by analysis with GC–MS.

4.2. General classical heating experimental procedure

In a 25 mL round bottom flask equipped with a water-cooled condenser and covered by aluminium foil for protection from light, were added 0.39 g (3.0 mmol) of NCS and 3.0 mmol of salt. The mixture was pre-heated to 102–104 °C for 10 min with stirring using an oil-bath on a stirrer hot-plate equipped with an electronic temperature feedback system. Subsequently, 0.32 g (3.0 mmol) of xylene was added and stirring was continued for 60 min. The mixture was then rapidly cooled to room temperature and the same work-up procedure followed as described above for the microwave assisted experiments.

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Supplementary data

Supplementary data associated with this article can be found in the online version doi:10.1016/j.tet.2010.01.033.

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