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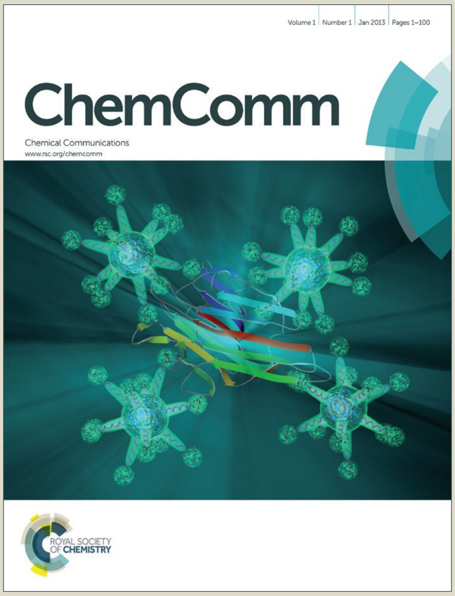

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Conversion of Nitroalkanes into Carboxylic Acids *via* Iodide Catalysis in Water

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We report a new method for the conversion of nitroalkanes into carboxylic acids that achieves this transformation under very mild conditions. Catalytic amounts of iodide in combination with a simple zinc catalyst are needed to give good conversions into the corresponding carboxylic acids.

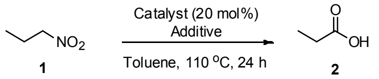
Organic molecules containing nitro group are synthetically important due to the fact the nitro group can be converted into several other functional groups such as ketones,[1] aldehydes,[2] carboxylic acids,[3] amines,[4] alkenes[5] and alkanes.[6]

The use of nitroalkanes in organic synthesis often relies on their easy conversion into the corresponding nitronate anions facilitated by the nitro group lowering the pKa of the hydrogen at the α-position.[7] Nitronate salts can act as carbon nucleophiles with a range of electrophiles such as haloalkanes[8] and aldehydes,[9] or they can be used as well as Michael acceptors.[10] In particular, the reduction of the nitro group along with the Nef reaction have become the most important transformations.

The Nef reaction has been applied not only to the synthesis of aldehydes and ketones but also to carboxylic acids under oxidative conditions. Current methodologies use a large excess of oxidant such as $KMnO_4$,[3a,3b] $NaNO_2$-AcOH[3f-3i] or oxone.[3c,3d]

McMurry's method employs $TiCl_3$ to reduce nitronate salts or nitro compounds to aldehydes and ketones by means of oxime formation.[1f,11] At the same time, oximes can be efficiently converted into amides in the presence of copper and zinc salts.[12] Moreover, it is well known that nitroalkanes under acidic conditions are in equilibrium with the corresponding nitronic acids.[3f]

Table 1 Optimization of reaction conditions for the conversion of nitropropane into propionic acid



Entry	Catalyst	Additive[b]	Conversion (%)[a]
1	CuO	AcOH	0
2	$Cu(OAc)_2$	AcOH	4
3	$CuCl_2$	AcOH	0
4	$ZnCl_2$	AcOH	0
5	$Zn(OAc)_2$	AcOH	4
6	**ZnI_2**	**AcOH**	**100**
7	ZnI_2	--	60
8	ZnI_2	AcOH[c]	50
9	ZnI_2	HCl[d]	44
10	--	AcOH	0
11	**--**	**TBAI[e] - AcOH[b]**	**100[f]**
12	**$Zn(OAc)_2$[g]**	**TBAI[h] - AcOH[d]**	**100**

[a] Conversions were determined by analysis of the ^{1}H-NMR spectra. [b] 2 equivalents of additive were used. [c] 4 equivalents of additive were used. [d] 1 equivalent of additive was used. [e] 1 equivalent of TBAI was used. [f] 10% of propionamide and 10% of *N*-ethylformamide were also observed along with the acid. [g] 10 mol% of $Zn(OAc)_2$ was used. [h] 2 mol% of TBAI was used.

Herein we describe a new method for the conversion of nitroalkanes and nitromethylbenzenes into carboxylic acids under very mild conditions using catalytic amounts of an iodide source. The new reaction conditions allow both aromatic and aliphatic carboxylic acids to be obtained without the need to pre-form the nitronate species usually required in the Nef reaction.

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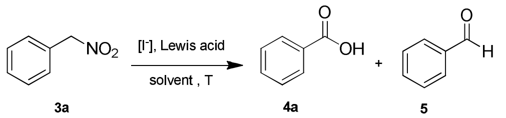
Furthermore, the reactions can be performed in water. Alternatively, for more complex substrates that are non-compatible or insoluble in water a combination of toluene and urea can also be employed (further details are given in the supporting information).

We decided to explore the possibility of converting nitroalkanes into carboxylic acids in the presence of a simple Lewis acid. Acetic acid was employed as an additive to enhance the reactivity of the nitro group (Table 1).

We initiated our investigations using nitropropane as a model substrate in the presence of copper salts using two equivalents of AcOH in toluene at 110 ^oC for 24 h. Under these conditions only traces of product or no conversion to the desired propionic acid were obtained (Table 1, entries 1-3). When the Lewis acid was changed to $ZnCl_2$ and $Zn(OAc)_2$ no improvement was observed (Table 1, entries 4 and 5). However, the use ZnI_2 gave the desired final product in 100% conversion (Table 1, entry 6). The amount of additive was also studied. It was observed that decreasing or increasing the amount of acetic acid, or the use of HCl, resulted in lower reaction conversion (Table 1, entries 7-9). Control experiments in the absence of additive or catalyst showed that while the presence of acetic acid is key for an optimum reaction outcome (Table 1, entry 7), the use of ZnI_2 is also essential for the reaction to take place (Table 1, entry 10).

In light of these results, we became intrigued about the role of iodide in this transformation and decided to test several iodide sources. The treatment of 1-nitropropane with several iodide sources showed that TBAI (tetrabutylamonium iodide) and KI in the presence of acetic acid also promoted the formation of propionic acid. While the use of Lewis acid improved conversions and avoided the formation of byproducts, it is not absolutely essential for obtaining the carboxylic acid, showing that the iodide is the key factor in this transformation (Table 1, entry 11). The best conditions found involved the use of 2 mol% of TBAI, 10 mol% of $Zn(OAc)_2$ and 1 equivalent of AcOH (Table 1, entry 12).

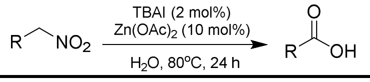
Table 2 Optimization of reaction conditions for the conversion of nitromethylbenzene into benzoic acid

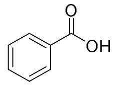


Entry	[I$^-$] source	Solvent	Lewis acid	Conversion (%)[a]
1	TBAI[b]	toluene	--	62
2	TBAI[b]	H_2O	--	80
3	TBAI[c]	H_2O	--	77
4	TBAI[d]	H_2O	$Cu(OAc)_2$	100 **4a**:**5** 80:20
5	TBAI[d]	H_2O	$ZnCl_2$	88
6	TBAI[d]	H_2O	$Zn(OAc)_2$	100 **4a**:**5** 95:5
7	--	H_2O	--	0

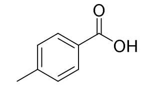
[a]Conversions were determined by analysis of the ^1H-NMR spectra. [b]2 equiv of AcOH and 5 mol% of TBAI were used. [c]5 mol% of TBAI without AcOH. [d]2 mol% of TBAI and 10 mol% of Lewis acid were used.

Table 3 Conversion of nitrobenzyl compounds into carboxylic acids[a]

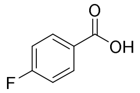




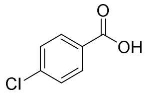
4a, 81%



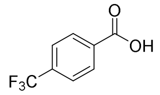
4b, 92%



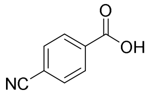
4c, 89%



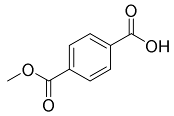
4d, 88%



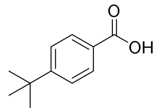
4e, 76%



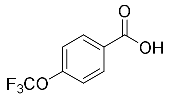
4f, 81%



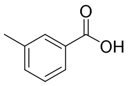
4g, 93%



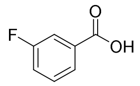
4h, 50%



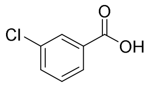
4i, 77%



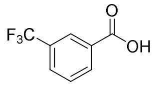
4j, 84%



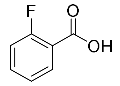
4k, 90%



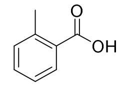
4l, 91%



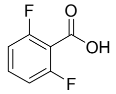
4m, 88%



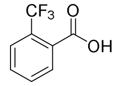
4n, 94%



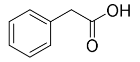
4o, 90%



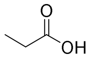
4p, 89%



4q, 88%



2b, 0%[b]



2a, 0% (95%)[c]

[a] Isolated yields. [b] The reaction was also performed using 1 equiv TBAI and 2 equiv of AcOH and the starting material was recovered. [c] Isolated yield using 1 equiv of AcOH as additive.

In order to study the scope of the reaction, nitromethylbenzene **3a** was treated with TBAI in the presence of AcOH giving a significant reduction in the reaction conversion (Table 2, entry 1). In light of the results, the reaction was re-optimized for the transformation of nitromethylbenzene.

Water was the best solvent to obtain benzoic acid in the presence of 5 mol% of TBAI and 2 equivalent of AcOH (Table 2, entry 2). In contrast to nitroalkanes, nitromethylbenzene can react in the absence of AcOH with no decrease of the reaction conversion (Table 2, entries 2 and 3). Several Lewis acids were also tested in this transformation. The addition of 10 mol% of $Cu(OAc)_2$ or $ZnCl_2$ provided the benzoic acid in high conversions allowing to decrease the amount of TBAI to 2 mol% (Table 2, entry 4 and 5). The use of $Zn(OAc)_2$ turned out to be the best Lewis acid leading to the formation of benzoic acid in 95% conversion along with traces of benzaldehyde (Table 2, entry 6).

With the optimized reaction conditions in hand, the substrate scope was explored (Table 3). This transformation is compatible with a wide range of substituents at the phenyl ring. The presence of electron-withdrawing and electron-donating groups were well-tolerated at the *ortho*-, *meta*- and *para*-positions affording the corresponding benzoic acid in excellent

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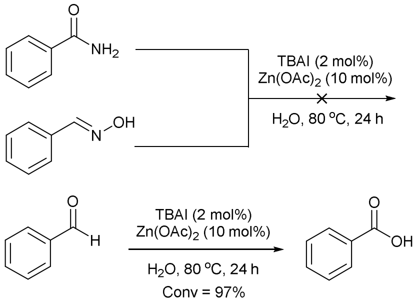
yields. Only when the reaction was performed on 4-*tert*-butyl(nitromethyl)benzene, was the acid obtained in moderate yield. Surprisingly, the treatment of 1-nitro-2-phenylethane with 1 equivalent of TBAI and 2 equivalent of AcOH did not lead to the formation of the carboxylic acid with only starting material returned. In contrast, propionic acid could be achieved in excellent yield when 1 equivalent of AcOH was employed as additive.

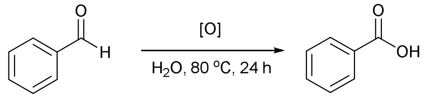
Intrigued by the mechanism of this reaction we decided to explore which could be the most likely intermediates for the conversion of nitro compounds to the corresponding acids. For this purpose, benzaldoxime, benzamide and benzaldehyde were subjected to the reaction conditions (Scheme 1). Interestingly, benzaldoxime and benzamide were recovered after the reaction. In contrast, benzaldehyde was transformed into benzoic acid in excellent conversions. We assume that oxygen is the terminal oxidant present in this process.



Scheme 1

In order to study the role of each reagent in the oxidation step benzaldehyde was treated with $Zn(OAc)_2$, TBAI and water obtaining the benzoic acid in high conversions in all the cases (Table 4). This experiment pointed out that if the reaction goes through the formation of an aldehyde as intermediate, no further oxidants are required to convert them into the corresponding benzoic acids.

Table 4 Oxidation of benzaldehyde



Entry	Catalyst	Conversion (%)
1	$Zn(OAc)_2$[a]	80
2	TBAI[b]	90
3	--	96

[a] 10 mol%. [b] 2 mol%

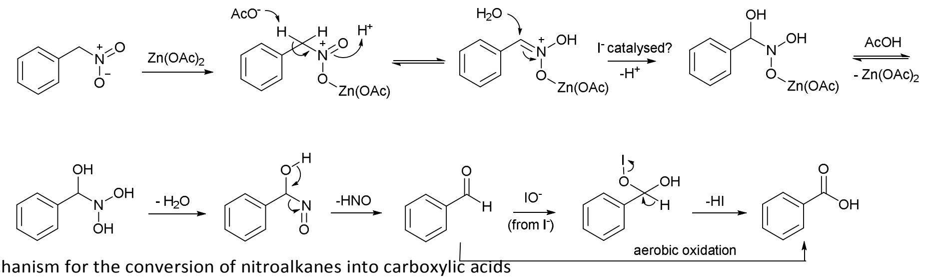
The roles of water and oxygen in the overall transformation were also explored. The conversion of nitromethylbenzene to benzoic acid under anaerobic conditions provided the final product in 60% yield, suggesting that oxygen is involved in this process (see ESI). The same reaction was carried out under anhydrous conditions using toluene as solvent. The analysis of the reaction crude by ^{1}H-NMR showed a very complex reaction mixture in which the final products could not be identified (see ESI). Finally, we decided to perform this transformation using H_2O^{18} (10 atom % ^{18}O) to determine if water was in fact taking part in this process. Analysis of the reaction crude by ESI-HRMS showed the incorporation of ^{18}O into the final product. This fact suggested that the oxygen from the carbonyl could come from the incorporation of water during the reaction course (see ESI).

Considering these results, and taking into account that the main by-product detected in the optimization of the reaction conditions was benzaldehyde, a possible mechanism starts by the formation of the aldehyde which is then oxidised under the reaction conditions.

The fact that this transformation takes place *via* the formation of the nitronate species would also explain why the transformation of nitro compounds is more favoured for benzylic substrates. The lower pKa of the benzylic position leads to the production of the nitronate species just in the presence of a Lewis acid. In contrast, nitroalkanes required stronger acid conditions such as 2 equivalents of AcOH to form the same intermediate species.

Thus, the coordination of $Zn(OAc)_2$ to the nitro group would facilitate the formation of the nitronate species (Scheme 2).† Then the attack of water to the α-position would lead to the (dihydroxyamino)(phenyl)methanol intermediate which can evolve to the aldehyde by a Nef reaction mechanism. Once the aldehyde is formed, oxidising conditions are needed to convert the aldehyde into a carboxylic acid. In that sense, we initially assumed that this step was being catalysed by the addition of IO^- (which would be formed by oxidation of I^- by either liberated HNO or by nitroalkane),[13,14,15,16] but the results in Table 4 indicate that at least for benzylic oxidation, this is not required, with simple aerobic oxidation providing the more likely pathway. The role of iodide is therefore not entirely clear, but may assist with the hydrolysis of the nitronate by nucleophilic addition.[17]

In summary, this is the first example of the conversion of nitroalkanes and nitromethylbenzenes into carboxylic acids catalysed by the presence of $Zn(OAc)_2$ and TBAI. It has been shown that this transformation tolerates a variety of substituents on the phenyl ring.



Scheme 2 A plausible mechanism for the conversion of nitroalkanes into carboxylic acids

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Notes and references

† The reaction using $ZnCl_2$ provided lower conversions than $Zn(OAc)_2$. This may suggest that the AcO^- could be involved in the formation of the nitronate species.

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