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RSC Advances Accepted Manuscript

Journal Name

ARTICLE

Received 00th January 20xx,

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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CROYAL SOCIETY OF CHEMISTRY

Highly Practical Sodium ($\rm I$)/ Azobenzene Catalyst System for Aerobic Oxidation of Benzylic Alcohols

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An economic, environmental and practical aerobic oxidation of benzylic alcohols and hetero aryl alcohols to the corresponding carbonyl compounds with good substrate scope is disclosed firstly. Good to excellent yields were obtained by employing economic and commercial available sodium bromide and catalyst amount of azobenzene under metal-free and ligand-free conditions. Moreover, aldehydes and acids, the oxidation products of benzylic 1° alcohols, could be obtained using sodium bromide and sodium hydroxide as the co-catalyst respectively in high yields.

Introduction

From both economic and environmental viewpoints, the selective oxidation of benzylic alcohols to the corresponding carbonyl compounds is one of the most challenging transformations. Many traditional and novel methods have been developed with the efforts of many researchers over the past few decades. Manganese¹⁻⁴ and chromium oxides⁵⁻⁷ may be still the most used oxidants in the oxidation of alcohols, such as KMnO₄, MnO₂ and PCC. Unfortunately, stoichiometric heavy metal waste was produced at the same time, which limits these reagents into the small-scale. Besides, iodine reagent,⁸⁻¹⁰ such as Dess-Martin reagent, and activated-DMSO reagent,^{11, 12} such as Swern reagent were built, and the oxidation products of alcohols were obtained smoothly. However, either economics (The iodine reagents were usually costly) or the difficulty of the operation (Low temperature should be kept when Swern reagent was used), limits the use of these reagents. Besides these reagents, DDQ (2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone),¹³⁻¹⁶ TEMPO (2, 2, 6, 6tetramethylpiperidinooxy)¹⁷⁻¹⁹ and NaClO²⁰⁻²² were also used as the oxidant of benzylic alcohols. Unfortunately, some drawbacks were existent, such as high cost, using complex ligands and danger. In summary, dioxygen should be the most practical oxidant. In recent years, many oxidation systems of dioxygen have been developed. The most common systems were dioxygen together with noble metals (e.g, Pd, Pt, Au, Ru)²³⁻²⁶ or complex and commercially unavailable ligands.^{27, 28}

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Consequently, the development of green, economical and practical oxidation process is still a big challenge.

Azo compounds have been used as the oxidant of alcohols for decades.²⁹ And, researchers were devoted to finding efficient catalysts and co-catalysts because of the low-reactivity and high cost of azo compounds. Many oxidation systems have been developed, such as azo compounds together with Grignard reagent³⁰ or AZADO (2-Azaadamantane-N-oxyl).³¹ And, many metal compounds were proved to be efficient catalyst for the oxidation of alcohols by azo compounds, such as Cu,³²⁻³⁴ Mg,³⁵ Ni³⁵ and Zn³⁵. Moreover, copper was used mostly. Lately, the azo compounds were often used as the ligands of the copper to catalyse the oxidation reaction.

Results and discussion

Within the context, we desired to develop a novel oxidation system using catalytic amount of azo compounds together with dioxygen without any heavy metal or complex co-catalyst. The 4-Nitrobenzyl alcohol was chosen as the model substrate for our initial study. The detailed results were summarized in Table 1.

Firstly, the reaction did not occur when azo compounds were used alone, which indicated that these azo compounds showed lower reactivity (Table 1, entries 1-6). To our delight, the expected oxidation product was obtained when NaBr, the inexpensive and readily available reagent, was added (Table1, entry 8). However, the reaction did not proceed when DIAD was used. The instability of DIAD may be the main reason (Table1, entry 7). Fortunately, the decrease of the equivalent of the catalyst azobenzene did not cause the obvious drop of the yield (Table1, entry 9). Further solvent screening indicated that 1, 4-Dioxane was the best one among N, N-dimethylformamide, Dimethyl sulfoxide, Acetonitrile and Toluene (Table1, entries 9-13). An obvious lower yield was obtained when polar solvent was used, which indicated possible critical complex was unstable in these polar solvent.

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Electronic Supplementary Information (ESI) was available. See DOI: 10.1039/x0xx00000x

Published on 15 September 2015. Downloaded by Stockholms Universitet on 15/09/2015 14:00:31

	OH conditions			0		
	O ₂ N		-	O2N		
	1a			2a		
Entry	Catalyst	Co-	Т	Solvent	T(h)	Yield
	(mol%)	catalyst	(°C)			(%) ^b
1	DIAD (200)	-	80	DMSO	24	trace
2	DIAD (200)	-	80	Toluene	24	trace
3	DIAD (200)	-	80	Dioxane	24	trace
4	Azobenzene	-	80	DMSO	24	trace
	(200)					
5	Azobenzene	-	80	Toluene	24	trace
	(200)					
6	Azobenzene	-	80	Dioxane	24	trace
	(200)					
7	DIAD (200)	NaBr	80	Dioxane	24	trace
8	Azobenzene	NaBr	80	Dioxane	24	90
	(200)					
9	Azobenzene(5)	NaBr	80	Dioxane	48	88
10	Azobenzene(5)	NaBr	80	DMF	48	5
11	Azobenzene(5)	NaBr	80	DMSO	48	8
12	Azobenzene(5)	NaBr	80	Acetonit	48	8
				rile		
13	Azobenzene(5)	NaBr	80	Toluene	48	42
14	Azobenzene(5)	NaBr	65	Dioxane	48	78
15	Azobenzene(5)	NaBr	50	Dioxane	48	22
16	Azobenzene(5)	TBAB	80	Dioxane	48	trace
17	Azobenzene(5)	KBr	80	Dioxane	48	trace
18	Azobenzene(5)	NH ₄ Cl	80	Dioxane	48	trace
19	Azobenzene(5)	NaCl	80	Dioxane	48	35
20	Azobenzene(5)	NaHCO₃	80	Dioxane	48	trace
21	Azobenzene(5)	Na_2CO_3	80	Dioxane	48	64
22	Azobenzene(5)	NaOH	80	Dioxane	48	
23	Azobenzene(5)	Na_2SO_4	80	Dioxane	48	82
24 ^c	Azobenzene(5)	NaBr	80	Dioxane	48	/

^areaction conditions: 1a (1mmol), catalyst, co-catalyst (2mmol), solvent (3 mL), T ($^{\circ}$), under O₂ (O₂ balloon), DIAD: diisopropyl azodicarboxylate. ^byield: isolated yield. ^cunder N₂.

When the temperature was decreased to 65 $^{\circ}$ C, a little drop of the yield was obtained even though the reaction time was extended (Table1, entry 14). Even worse, the yield was dropped to 22 % when the temperature was decreased to 50 $^{\circ}$ C, which indicated that temperature affected this oxidation reaction obviously (Table 1, entries 9, 14, 15). In addition, further co-catalyst screened showed that this catalytic process was promoted by the Na⁺ rather than Br⁻ or K⁺ (Table 1, entries 9, 16, 17). And, different Na⁺ source have different catalytic activity (Table1, entries 9, 19-23). NaBr was the best choice. It was possible that the catalytic performance of different Nabased co-catalysts was influenced by pKb. And, neutral co-catalysts showed higher catalytic activity. So, relatively good yields were obtained when NaBr, Na₂SO₄ and NaCl were

DOI: 10.1039/C5RA15286K Journal Name

involved. Moreover, further investigation of the equivalent of NaBr showed the amount of the co-catalyst influenced the reaction process obviously (Table SI). It might be the reason why Na_2CO_3 gave a higher yield compared with $NaHCO_3$. No product was detected when the reaction was conducted under Ar atmosphere, which suggested dioxygen was the actual oxidant (Table 1, entries 9, 24).

We set out to explore the methodology with respect to the substitution of the aryl ring and aliphatic alcohols (Table 2) .In general, the oxidation reaction is affected by steric hindrance and electronic factors moderately.^{18, 36}And, aliphatic alcohols often show lower reactivity. One set of alcohols oxidation was performed following the optimized procedure above. It was observed that both electron-rich and electron-deficient benzylic alcohols could be oxidized smoothly in moderate to good yields (Table 2, entries 1- 10). Nevertheless, electronwithdrawing groups attached to the phenyl rings of substrate showed lower reactivity obviously (Table 2, entries 1-3). As, more reaction time should be needed to reach the full conversion. To our delight, the efficiency of this reaction was not affected obviously by substituents at different positions of the aryl ring and steric hindrance (Table 2, entries 1-3, 9, 10). Moreover, there was no obvious effect observed between 1° benzylic alcohols and 2° benzylic alcohols and hetero aryl alcohols were oxidized to afford the corresponding products in good yields (Table 2, entries 1-13). Unfortunately, almost no desired product was obtained when aliphatic alcohols were texted (Table 2, entries 14, 15).

Table 2 NaBr/azobenzene-promoted oxidation of alcoholsa

$$\begin{array}{c} OH \\ R_1 \\ 1 \\ R_2 \end{array} \xrightarrow{azobenzene} R_1 \\ NaBr/O_2 \\ R_1 \\ 2 \\ R_2 \\ R_1 \\ 2 \\ R_2 \\ R_2 \\ R_1 \\ R_2 \\ R_2 \\ R_2 \\ R_1 \\ R_2 \\ R_2 \\ R_1 \\ R_2 \\ R_2 \\ R_1 \\ R_2 \\$$

Entry	Substrates		Т	Product	Yield
	R ¹	R ²	(h)	No	(%) ^b
1	<i>o</i> -NO₂Ph	Н	48	2b	86
2	<i>m</i> -NO₂Ph	н	48	2c	85
3	<i>p</i> -NO₂Ph	н	48	2a	88
4	<i>p</i> -OMePh	н	24	2d	94
5	<i>p-</i> ClPh	н	24	2e	96
6	<i>p-</i> ClPh	CH₃	24	2f	96
7	<i>p</i> -BrPh	н	24	2g	94
8	<i>p</i> -BrPh	CH₃	24	2h	95
9	Ph	Ph	24	2i	92
10	2,6-dichloro-Ph	н	24	2j	93
11	2-Furan	н	24	2k	92
12	2-Thiophene	н	24	21	93
13	3-Pyridine	н	36	2m	89
14	Hexyl alcohol		48	2n	trace
15	Cyclohexanol		48	2o	trace

^areaction conditions: 1 (1mmol), azobenzene (0.05 mmol), NaBr (2 mmol), 1,4-Dioxane (3 mL), 80 $^{\circ}$ C, under O₂ (O₂ balloon). ^byield: isolated yield.



Scheme 1 library synthesis of aldehydes and ketones

The standard reaction conditions: 1 (1 mmol), azobenzene (0.05 mmol), NaBr (2 mmol), 1, 4-Dioxane (3 mL), 80 $^\circ\! C$, under O_2 (O_2 balloon). Yields shown were the isolated products.

The experimental results above showed that this oxidation system was applicable to all kinds of 1° benzylic alcohols, 2° benzylic alcohols and hetero aryl alcohols. The limitation of steric hindrance and electronic nature could be ignored. A library of aldehydes and ketones were synthesized from various alcohols in good yields (scheme 1).

As we all know, the dismutation reaction could occur under the strong alkaline condition when the aldehyde did not involve any α -H.³⁷⁻³⁹ And, the corresponding alcohol and acid were got. In table 1, when NaOH was chosen as the cocatalyst, the oxidation of alcohol and the cannizzaro reaction occurred smoothly. And, the acids were obtained in good yields as the final product. To our knowledge, a special base (sodium pyrazolide) could promote the oxidation of 1° benzylic alcohol to the corresponding acid successfully. Afterwards, NaH was found to be a useful replacer in this oxidation system.⁴⁰ Similarly, NaOH here may be used as the promoter just like the NaH before. In other words, we guessed the transformation could occur normally without any azobenzene. Finally, we found that lei and his co-workers⁴¹ reported on aerobic oxidation of benzylic alcohols into the corresponding acids under NaOH/air/THF conditions in 2013. Nevertheless, the oxidation system of azobenzene/NaOH/O2 was still meaningful. As, higher yields of heterocyclic alcohols were obtained compared with oxidation system without azobenzene. Especially, 2, 5-furandicarboxylic acid was obtained in excellent isolated yield from oxidation of 5hydroxymethylfurfural under azobenzene/sodium methanolate/ O_2 . However, an obvious decrease of the yield

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was observed in the absence of azobenzene, which would be discussed detailed in another paper later.

Following this new protocol, a wide range of acids were obtained from the oxidation of 1° alcohols in excellent yields (scheme 2). The 1° benzylic alcohols could be oxidized to acid efficiently. Fortunately, the effect of different electronic properties (electron-donating or electron-withdrawing) of the substituents could be ignored. Moreover, the desired products could be got when hetero aryl 1° alcohols were investigated, which indicated that the Na⁺/azobenzene oxidation system was very practical.



Scheme 2 library synthesis of acids

The standard reaction conditions: 1 (1 mmol), azobenzene (0.05 mmol), NaOH (2 mmol), 1, 4-Dioxane (3 mL), 80 $^\circ\! C$, under O2 (O2 balloon). Yields shown were the isolated products.

Conclusions

In summary, a practical and economical oxidation system of Na⁺/azobenzene/O₂ was built firstly, although some oxidation systems of Cu/azo compounds (CuCl.Phen.DEAD-H₂.K₂CO₃/CuCl.dpPhen.DBAD.Cs₂CO₃⁴²) were reported before. A series of benzylic alcohols and hetero aryl alcohols could be oxidized to the corresponding carbonyl compounds smoothly. Moreover, the products of 1° alcohols could be controlled by the different co-catalyst. And, the aldehydes and acids were obtained accordingly. Although the exact mechanism was uncertain, it was easy to believe that the Na⁺ here played a similar role as Cu⁴² above.

Acknowledgements

The research has been supported by National Key Basic Research Program of China (973 Program) 2012CB725204; the National High Technology Research and Development Program of China (863 Program) 2014AA022101; the National Natural Science Foundation of China (Grant No.U1463201 and 81302632); the National Science and Technology Major Projects for "Major New Drugs Innovation and Development" (2013ZX09103001-004).

DOI: 10.1039/C5RA15286K

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