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# A chemoselective aerobic oxidation of benzylic azides catalyzed by molybdenum xanthate in an aqueous medium

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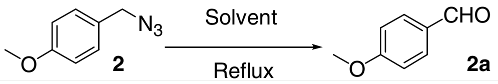
## ABSTRACT

A mild molybdenum-catalyzed, aerobic, chemoselective oxidation of benzylic azides to the corresponding aldehydes in an aqueous medium that tolerates a variety of functional groups including alcohols, esters, ketones, halides and olefins is described.

Transition metal-catalyzed oxidations in water using molecular oxygen as the reoxidant are of importance in both academia and industry.[1–4] Furthermore, the use of molybdenum catalysts for oxidation is a well-explored area.[5] Research in this direction, apart from aiding the understanding of the role of molybdenum and its derivatives in oxo-transfer reactions, has produced numerous methods which are useful in organic synthesis.[5–8] In this context, herein we present an efficient chemoselective aerobic oxidation of benzylic azides to the corresponding aldehydes catalyzed by molybdenum complex **1**[9] using molecular oxygen as the reoxidant.

For optimization of the reaction conditions, we chose *p*-methoxybenzyl azide (**2**) as a model substrate and treated it with various Mo(VI) reagents. As shown in Table 1, the reaction of azide **2** with ammonium molybdate and sodium molybdate, either in toluene or in water, did not produce any significant amount of product even after prolonged reaction times (Table 1, entries 1–4). However, the reaction of azide **2** with a stoichiometric amount of dioxobis(*N*,*N*-diethyldithiocarbamato)molybdenum **1** ($MoO_2[S_2CNEt_2]_2$) in toluene under refluxing conditions furnished the corresponding aldehyde **2a** in excellent yield (87%, 8 h, entry 5, Table 1). Surprisingly, the reaction of **2** with **1** in water resulted an 85% yield of the aldehyde **2a** under reflux (10 h, entry 6, Table 1). Reaction of azide **2** with $MoO_2(acac)_2$[10] in water, DMSO or toluene (in stoichiometric amount) under reflux was not effective and the starting material was recovered unchanged (Table 1, entries 7–9). Also, control experiments in the absence of **1** under refluxing conditions for >48 h did not produce any aldehyde, and the starting material was recovered unchanged (Table 1, entries 10 and 11).

**Table 1**
Reaction of *p*-methoxybenzyl azide with different Mo-reagents



| Entry | Reagent[a] | Solvent | Time[b] (h) | Yield[c] |
|---|---|---|---|---|
| 1 | $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ | $H_2O$ | 20 | No reaction |
| 2 | $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ | Toluene | 20 | No reaction |
| 3 | $Na_2MoO_4\cdot 2H_2O$ | $H_2O$ | 20 | No reaction |
| 4 | $Na_2MoO_4\cdot 2H_2O$ | Toluene | 20 | No reaction |
| 5 | $MoO_2(Et_2NCS_2)_2$ | Toluene | 8 | 87% |
| 6 | $MoO_2(Et_2NCS_2)_2$ | $H_2O$ | 10 | 85% |
| 7 | $MoO_2(acac)_2$ | $H_2O$ | 20 | No reaction |
| 8 | $MoO_2(acac)_2$ | Toluene | 20 | No reaction |
| 9 | $MoO_2(acac)_2$ | DMSO | 20 | No reaction |
| 10 | — | Toluene | 20 | No reaction |
| 11 | — | $H_2O$ | 20 | No reaction |

[a] Stoichiometric amount.
[b] Heated at 100 °C.
[c] Isolated yields.

Oxidants such as $H_2O_2$ and NMO did not produce any significant result under refluxing conditions either in toluene or in water (Table 2, entries 1–4). However, reaction of azide **2** with a catalytic amount **1** and DMSO in toluene produced aldehyde **2a** (36 h, yield 40%, entry 5, Table 2). Similar reaction of **2** with a catalytic amount

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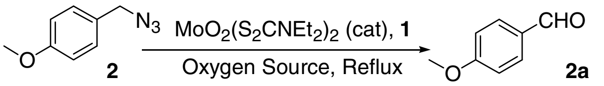
**Table 2**
Optimization of the reaction conditions



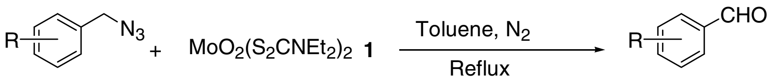
| Entry | Oxygen source | Solvent | Time$^{a}$ (h) | Yield$^{b}$ (%) |
|---|---|---|---|---|
| 1 | $H_2O_2$ | Toluene | 36 | No reaction |
| 2 | $H_2O_2$ | $H_2O$ | 36 | No reaction |
| 3 | NMO | Toluene | 36 | No reaction |
| 4 | NMO | $H_2O$ | 36 | No reaction |
| 5 | DMSO | Toluene | 36 | 40 |
| 6 | DMSO | $H_2O$ | 3 | 90 |
| 7 | *m*-CPBA | $H_2O$ | 5 | 80 |
| 8 | *m*-CPBA | Toluene | 36 | 10 |
| 9 | $O_2$ | Toluene | 8 | 86 |
| 10 | $O_2$ | $H_2O$ | 10 | 83 |

[a] Heated at 100 °C.
[b] Isolated yields.

of **1** and DMSO in water produced **2a** in good yield (90%) after 3 h (Table 2, entry 6). Use of a catalytic amount of **1** in the presence of *m*-CPBA in water turned out to be a good reaction medium producing **2a** in 80% yield (5 h, entry 7, Table 2). However, the yield was poor on similar reaction in toluene (10%, 36 h, entry 8, Table 2). The reaction of **2** with **1** in the presence of molecular oxygen (1 atm) in toluene resulted in the formation of **2a** in good yield (8 h, reflux, 86%, entry 9, Table 2). A similar reaction in water produced **2a** in 83% yield (Table 2, entry 10). Accordingly, we continued our study using molecular oxygen as the reoxidant.[11]

Under the optimized reaction conditions, 10 mol % of **1** in toluene/water, $O_2$ atmosphere, 100 °C, a wide range of benzylic azides were smoothly converted to the corresponding aldehydes in excellent yields (Table 3). *p*-Methoxybenzyl azide (**2**) produced the corresponding aldehyde **2a** in excellent yield both in water and in toluene (Table 3, entry 1). Benzyl azide (**3**) produced benzaldehyde (**3a**) in almost quantitative yield in toluene and in good yield in water (99% and 78%, respectively, entry 2, Table 3). Similarly,

**Table 3**
Catalytic oxidation of benzylic azides



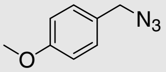
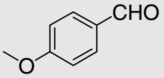
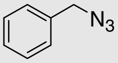
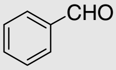
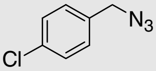
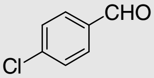
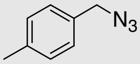
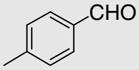
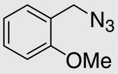
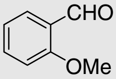
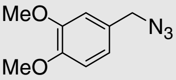
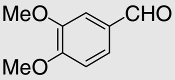
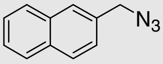
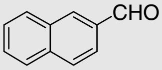
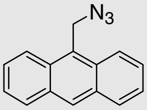
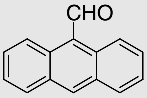
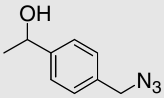
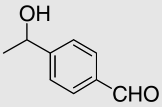
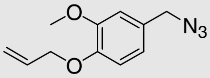
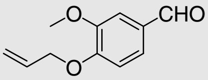
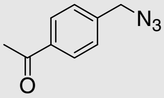
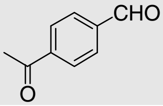
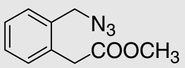
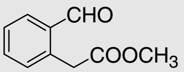
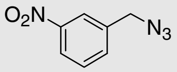
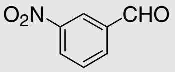
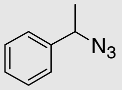
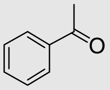
| Entry | Substrate | | Time$^{a,b}$ (h) | Product | | Yield$^{c,d}$ |
|---|---|---|---|---|---|---|
| 1 |  | **2** | 10 (8) |  | **2a** | 83 (86) |
| 2 |  | **3** | 8 (10) |  | **3a** | 99 (78) |
| 3 |  | **4** | 16 (14) |  | **4a** | 78 (61) |
| 4 |  | **5** | 10 (3) |  | **5a** | 82 (95) |
| 5 |  | **6** | 20 (3) |  | **6a** | 80 (81) |
| 6 |  | **7** | 10 (8) |  | **7a** | 74 (82) |
| 7 |  | **8** | 15 (12) |  | **8a** | 92 (90) |
| 8 |  | **9** | 10 (12) |  | **9a** | 88 (80) |
| 9 |  | **10** | 16 (17) |  | **10a** | 86 (88) |
| 10 |  | **11** | 12 (7) |  | **11a** | 92 (92) |
| 11 |  | **12** | 12 (6) |  | **12a** | 50 (48) |

**Table 3** (*continued*)

| Entry | Substrate | | Time[a,b] (h) | Product | | Yield[c,d] |
|---|---|---|---|---|---|---|
| 12 |  | **13** | 18 (8) |  | **13a** | 45 (40) |
| 13 |  | **14** | 20 (8) |  | **14a** | 19 (24) |
| 14 |  | **15** | 36 (36) |  | **15a** | 5 (10) |

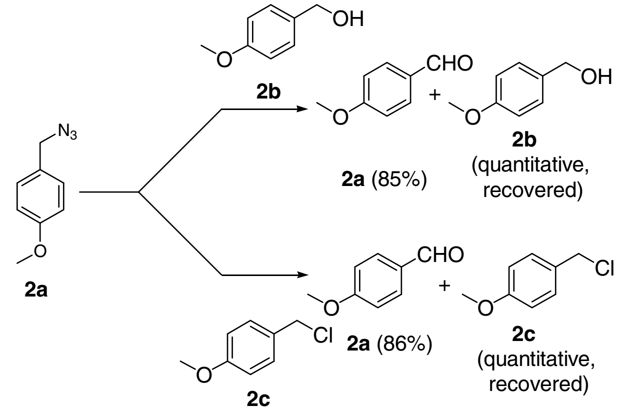
[a] Heated at 100 °C.

[b] Time in parentheses indicates the reaction in toluene.

[c] Isolated yields.

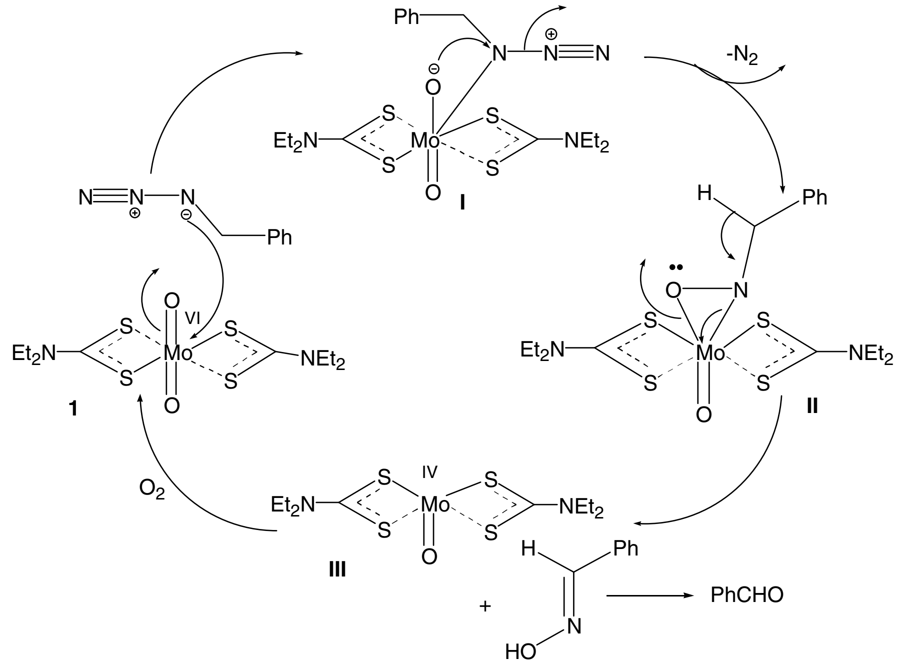
[d] Value in parentheses indicates the yield in toluene.

*p*-chlorobenzyl azide **4**, *p*-methylbenzyl azide **5** and *o*-methoxybenzyl azide **6** afforded the corresponding aldehydes **4a**, **5a** and **6a** in excellent yields (Table 3, entries 4–6). 3,4-Dimethoxybenzyl azide (**7**) produced the corresponding aldehyde **7a** in good yields both in toluene and in aqueous medium (Table 3, entry 7). 2-(Azidomethyl)naphthalene (**8**) and 10-(azidomethyl)anthracene (**9)** gave the corresponding aldehydes **8a** and **9a** in very good yields both in water and in toluene (Table 3, entries 7 and 8). The oxidation of azides was chemoselective and tolerates a variety of functional groups as exemplified in entries 9–12 (Table 3). Functional groups such as alcohols and olefins were unaffected (Table 3, entries 9 and 10). In the reaction of *p*-acetylbenzyl azide (**12)** with **1**, the ketone group remained inert to provide *p*-acetylbenzaldehyde **12a** in moderate yield. Similarly, reaction of methyl 2-(azidomethyl)benzoate (**13**), with **1** provided aldehyde **13a** in moderate yield and the ester group was unaffected. However, *m*-nitrobenzyl azide (**14**) and α-methylbenzyl azide (**15**) produced the expected products in low yields. Reaction of aliphatic azides with **1** did not produce any products even after prolonged reactions.

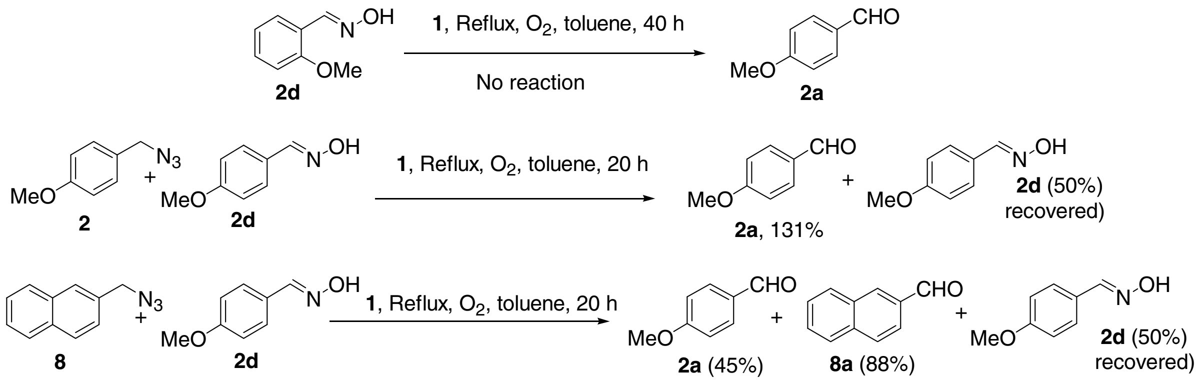


**Scheme 1.** Chemoselective oxidation.

The chemoselectivity of the above oxidation was demonstrated further by performing additional experiments as presented in



**Scheme 2.** Proposed catalytic cycle.



**Scheme 3.** Reaction of various azides and oxime **2d** with **1**.

Scheme 1. The alcohol **2b** and *p*-methoxybenzyl chloride remained unaffected under these reaction conditions. Clearly, this method provides an opportunity to synthesize aldehydes from azides in the presence of alcohols, chlorides, olefins, esters and ketones. Also, this strategy produces only the corresponding aldehyde, without any over-oxidation.

Interestingly, the reaction of azide **2** and reagent **1** (10 mol %) in $H_2O$ (or toluene) in the absence of molecular oxygen (reflux, 40 h) produced the corresponding aldehyde **2a** in 10% yield, 90% of the starting material was recovered (by $^1$H NMR).[12] This experiment indicates that molecular oxygen is essential for the reaction. This observation contrasts that observed in the reaction of xanthine with xanthine oxidase where the oxygen is transferred from water.[13]

A tentative mechanism based on the available information in the literature is presented in Scheme 2.[5] Reagent **1** reacts with benzyl azide to form complex **I**, which in turn could lose nitrogen to generate complex **II**.[14] Further, the complex **II** could lose a proton to furnish **III**, along with the oxime. The oxime thus generated could be converted to the corresponding aldehyde under the reaction conditions. Furthermore, the complex **III** could react with molecular oxygen to produce the reagent **1** and the cycle continues. The catalytic cycle persists until at the end of the reaction the cycle terminates in producing a molybdenum complex, which can no longer catalyze the oxygen transfer reaction.[15]

To substantiate the proposed intermediacy of an oxime, we performed a few control experiments (Scheme 3). Surprisingly, the reaction of *p*-methoxybenzaldoxime (**2d**) and **1** under an oxygen atmosphere (toluene or water as the solvent) at reflux (40 h) did not furnish the expected aldehyde; however, the starting material was recovered unchanged. Similar reaction of *p*-methoxybenzaldoxime (**2d**) and *p*-methoxybenzyl azide (**2**) with **1** under the standard reaction conditions produced the aldehyde **2a** in 131% yield, indicating that the oxime is also converted to aldehyde **2a** under the reaction conditions employed for the oxidation. The reaction of *p*-methoxybenzaldoxime (**2d**) and 2-(azidomethyl)naphthalene (**8**) in toluene with **1** under an oxygen atmosphere produced 2-naphthaldehyde (**8a**, 88% yield) and *p*-methoxybenzaldehyde (**2a**, 45%). Presumably, the species formed from azides may be essential for the conversion of oximes to aldehydes.

In conclusion, we have reported a useful, chemoselective aerobic oxidation of benzylic azides to the corresponding aldehydes.[16] Interestingly, over-oxidation to the acid was not observed. Preliminary studies indicate that the oxygen is transferred from molecular oxygen and not from the solvent. This aerobic reaction may be helpful in understanding the role of molybdenum in molybdo-enzyme-catalyzed oxidations in Nature.

## Acknowledgements

We are thankful to Professor S. Chandrasekaran for encouragement and laboratory facilities. We are grateful to IISc. for the financial support.

## Supplementary data

The analytical data, spectral data, and $^1$H and $^{13}$C NMR spectra of compounds **2**–**13** and **2a**–**13a** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.047.

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12. It was confirmed by an independent experiment that a stoichiometric amount of reagent **1** was essential to convert *p*-methoxybenzyl azide **2** to the corresponding aldehyde **2a** under a nitrogen atmosphere (or in the absence of oxygen). Therefore, the reaction of azide **2** with 10 mol % of **1** under a nitrogen atmosphere converts only 10% of the azide to the corresponding aldehyde **2a**, which is consistent with our observations.
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15. After isolating the product aldehyde **2a** in the reaction of *p*-methoxybenzyl azide (**2**) with **1**, the aqueous solution was reacted again with another equivalent of azide **2** under similar aerobic reaction conditions. However, even after a prolonged reaction time, the starting material was recovered unchanged. This indicates that the reaction cycle proposed in Scheme 2, terminates in producing a molybdenum complex, which does not facilitate the oxo-transfer reaction.
16. *Typical experimental procedures: Method A*: A well-stirred solution of benzylic azide (1 mmol) and **1** (10 mol %) in water (3 mL) under an oxygen atmosphere was refluxed until completion of the reaction (monitored by TLC). The reaction mixture was cooled, extracted with dichloromethane, concentrated and purified by silica gel column chromatography (hexane–EtOAc, 9:1) to furnish the corresponding aldehyde. *Method B*: A well-stirred solution of benzylic azide (1 mmol) and **1** (10 mol %) in toluene (3 mL) under an oxygen atmosphere was refluxed until completion of the reaction (monitored by TLC). The reaction mixture was concentrated and purified by silica gel column chromatography (hexane–EtOAc, 9:1) to furnish the corresponding aldehyde.