Nafion supported molybdenum oxychloride: Recyclable catalyst for one-pot synthesis of nitrones *via* direct condensation/oxidation of primary amines and aldehydes using UHP as oxidant

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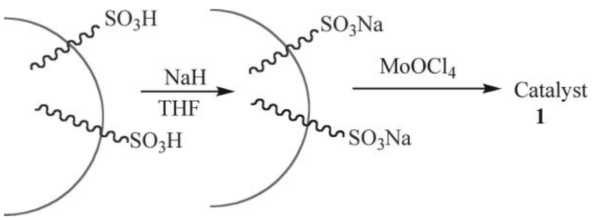
Immobilization of molybdenum(VI) oxychloride to the surface of perfluorinated ion-exchange polymer "Nafion" *via* an ion exchange method was carried out for the first time. The prepared Nafion immobilized molybdenum(VI) oxychloride catalyst was used for the direct synthesis of nitrones *via* one-pot condensation/oxidation of primary amines with aldehydes using solid urea-hydrogen peroxide (UHP) as oxidant under very mild reaction conditions. The developed polymer immobilized catalyst showed better activity than its analogous homogeneous catalyst with the added benefits of facile recovery and recyclability of the catalyst without leaching and loss in catalytic activity.

Nitrones are valuable synthones in the realm of organic synthesis which are extensively used in the synthesis of biologically active compounds,[1] as spin trap reagents,[2] as therapeutic agents[3] and also behave like 1,3-dipoles in cycloaddition reactions.[4] Two main synthetic methods commonly used for the preparation of nitrones are: i) condensation of carbonyl compounds with N-monosubstituted hydroxylamines,[5] ii) the oxidation of secondary amines or hydroxylamines.[6] However both methods have certain drawbacks; the condensation method is limited due to the limited accessibility of the precursors (*e.g.* hydroxylamines) and it is difficult to apply it to the preparation of non-conjugated cyclic nitrones and bulky group containing ketonitrones. However, the direct oxidation of secondary amines, although a straightforward approach for the preparation of nitrones, is less favorable in the case of secondary amines bearing two different groups due to the formation of two possible isomeric products. Formation of nitrones through N-alkyaltion of aldoximes with α,β-unsaturated carbonyl compounds and their use as 1,3-dipoles for intermolecular cycloaddition reactions has also been reported in the literature.[7] Recently, Goti *et al.*[8] reported an efficient one-pot synthesis of nitrones from primary amines and aldehydes using methyltrioxorhenium as catalyst. This method is particularly advantageous from the economic as well as green chemistry viewpoints as it involves a single step synthesis without isolation of any intermediate, which helps in saving time and energy as well as reducing waste production. However, the major drawbacks of this method are its expensive nature, tedious synthesis and particularly the non-recyclability of the catalyst. In recent decades, considerable attention has been devoted to the immobilization of homogeneous transition metal complexes onto solid supports[9] due to the added benefits of increased catalyst stability, catalyst recycling, and ease of product separation. In this regard, transition metal complexes have widely been supported on silica and other inorganic oxides, in clays, in siloxanes, exchanged into ion-exchange resins and attached to polystyrene and other organic polymers through covalent bonding to the ligands in the metal complexes.[9,10] Nafion, a perfluorinated ion exchange polymer developed by Dupont has many practical applications in catalysis. Owing to the presence of a strongly electron withdrawing fluorocarbon backbone, the sulfonic acid sites within Nafion are quite strong. This has led to the use of Nafion as a solid acid catalyst for a variety of organic reactions such as alkylation, esterification, acylation, olefin oligomerization, and isomerization,[11] whereas catalytic active site modified Nafion resins for synthetic applications have seldom been reported.[12] Oxo-molybdenum complexes are versatile catalysts and have extensively been used as homogeneous catalysts for the oxidation of organic substrates. Heterogenization of molybdenum catalysts is an emerging area of current research interest and a variety of supports, such as mesoporous materials, polymers and ionic liquids, have hitherto been used for this purpose.[13] In the present study, we have used Nafion NR-50 ion-exchange resin as a support for the immobilization of an oxo-molybdenum compound. To the best of our knowledge this is the first report on the immobilization of a molybdenum catalyst to Nafion support. The heterogenization of $MoOCl_4$ to the Nafion support was carried out, as shown in Scheme 1. Immobilization of Mo catalyst to the polymer support was confirmed by IR spectroscopy as it showed clear bands of ν Mo=O (at ν 951, very sharp). The metal loading onto the polymer was calculated by TGA analysis and was found to be 2.6% (0.18 mmol g^{-1}).†



Scheme 1 Immobilization of $MoOCl_4$ to the Nafion support.

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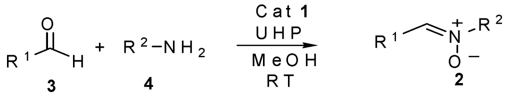
Table 1 One-pot oxidative synthesis of nitrones **2** from aldehyde **3** and amine **4**[a]

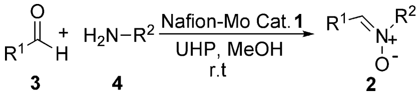


Entry	Aldehyde **3**	Amine **4**	**4** [eq]	Nitrone **2**	t/h	Yield[b](%)
1	**3a**: R^1 = Ph	**4a**: R^2 = $PhCH_2$	1.0	**2a**: R^1 = Ph; R^2 = $PhCH_2$	4.0	75
2	**3a**: R^1 = Ph	**4a**: R^2 = $PhCH_2$	1.2	**2a**	4.0	78
3	**3a**: R^1 = Ph	**4a**: R^2 = $PhCH_2$	1.5	**2a**	6.0	50
4	**3a**: R^1 = Ph	**4a**: R^2 = $PhCH_2$	2.0	**2a**	8.0	—[c]
5	**3a**: R^1 = Ph	**4a**: R^2 = $PhCH_2$	1.2	**2a**	4.0	65[d]
6	**3a**: R^1 = Ph	**4a**: R^2 = $PhCH_2$	1.2	**2a**: R^1 = Ph; R^2 = $PhCH_2$	4.0	80
7	**3a**	**4b**: R^2 = *n*Bu	1.2	**2b**: R^1 = Ph; R^2 = *n*Bu	4.5	68
8	**3a**	**4b**: R^2 = *n*Bu	1.2	**2b**: R^1 = Ph; R^2 = *n*Bu	5.0	70
9	**3a**	**4c**: R^2 = *t*Bu	1.2	**2c**: R^1 = Ph; R^2 = *t*Bu	5.5	64
10	**3b**: R^1 = 4-$MeOC_6H_4$	**4a**	1.2	**2d**: R^1 = 4-$MeOC_6H_4$; R^2 = $PhCH_2$	4.5	70
11	**3b**: R^1 = 4-$MeOC_6H_4$	**4a**	1.2	**2d**: R^1 = 4-$MeOC_6H_4$; R^2 = $PhCH_2$	4.5	71
12	**3b**	**4b**	1.2	**2e**: R^1 = 4-$MeOC_6H_4$; R^2 = *n*Bu	5.0	64
13	**3b**	**4b**	1.2	**2e**: R^1 = 4-$MeOC_6H_4$; R^2 = *n*Bu	5.5	65
14	**3b**	**4c**	1.2	**2f**: R^1 = 4-$MeOC_6H_4$; R^2 = *t*Bu	6.5	56
15	**3c**: R^1 = 4-O_2N–C_6H_4	**4a**	1.2	**1**: R^1 = 4-$NO_2C_6H_4$; R^2 = $PhCH_2$	7.0	70
16	**3c**: R^1 = 4-O_2N–C_6H_4	**4a**	1.2	**2g**: R^1 = 4-$NO_2C_6H_4$; R^2 = $PhCH_2$	7.0	68
17	**3c**	**4b**	1.2	**2h**: R^1 = 4-$NO_2C_6H_4$; R^2 = *n*Bu	5.0	65
18	**3c**	**4c**	1.2	**2i**: R^1 = 4-$NO_2C_6H_4$; R^2 = *t*Bu	6.0	58
19	**3d**: R^1 = 2-furyl	**4a**	1.2	**2j**: R^1 = 2-furyl; R^2 = $PhCH_2$	3.5	74
20	**3d**: R^1 = 2-furyl	**4a**	1.2	**2j**: R^1 = 2-furyl; R^2 = $PhCH_2$	3.5	72
21	**3e**: R^1 = $CH_3(CH_2)_2CH_2$	**4a**	1.2	R^1 = $CH_3(CH_2)_2CH_2$ R^2 = $PhCH_2$	5.0	—[e]

[a] Reaction conditions: Aldehyde (1 mmol), amine (1.2 mmol), catalyst (2 mol%), UHP (3 eq.), MeOH (3 ml) at room temp. [b] Isolated yields. [c] Intricate mixture obtained. [d] Using homogeneous MoOCl4 as catalyst. [e] Intricate mixture obtained.

Catalytic activity

The catalytic activity of the prepared Nafion immobilized $MoOCl_4$ was studied for the direct synthesis of nitrones from the one-pot condensation/oxidation of primary amines and aldehydes using solid UHP as oxidant under mild reaction conditions (Scheme 2).



Scheme 2 One-pot synthesis of nitrones **2**.

The present method has the added benefits of easy handling, facile recovery and reusability of the catalyst without loss in catalytic activity and importantly, no metal leaching was observed during this course. The protocol developed for the one-pot synthesis of nitrones consists of the addition of solid UHP and Nafion-Mo catalyst **1** (2 mol%, 0.11 g) into the stirred mixture of aldehyde and primary amine in methanol. Anhydrous sodium sulfate was added in order to facilitate the reaction and the resulting mixture was stirred at room temperature. After completion of the reaction (as analyzed by TLC), the polymer beads were easily separated *via* decantation, washed with methanol, dried and reused for subsequent runs. Evaporation of the solvent under reduced pressure followed by the usual work-up of the resulting residue gave nitrones in good yields. The results for the one-pot condensation/oxidation of a variety of primary amines and aldehydes to nitrones are summarized in Table 1. Among the various aldehydes studied, aromatic aldehydes were found to be more efficient in terms of yield of the desired product, whereas aliphatic aldehydes showed limitations and yielded an intricate mixture of the products (Table 1, entry 21). The addition of a slight excess (1.2 equiv.) of amine in comparison to the aldehyde (1 mmol) improved the yield of the nitrone; however, the use of greater excess (1.5 mmol, 2 mmol) of amine adversely affected the reaction and no nitrone formation was occurred even after prolonged reaction time, these results are presented in Table 1, entry 1–4. We also compare the catalytic efficiency of Nafion immobilized $MoOCl_4$ **1** with its homogeneous analogues $MoOCl_4$ (Table 1, entry 5). The Nafion immobilized catalyst was found to be better and afforded better yield of the desired product than its homogeneous analogues with the added benefits of having facile recovery and recycling ability of the polymer immobilized catalyst. These facts establish the superiority of the heterogenized catalyst over homogeneous ones.

We also studied the reaction of benzaldehyde and benzylamine in the absence of the molybdenum catalyst under the described reaction conditions. The reaction afforded the corresponding imine (easily detectable by TLC) as the only product at the end of the reaction without undergoing further oxidation to nitrone. Also, the use of aq. hydrogen peroxide as oxidant in the absence of Mo-catalyst, afforded the corresponding imine only, albeit in lower yield without any formation of the nitrone. The use of aq. H_2O_2 as oxidant in the presence of the Nafion supported molybdenum catalyst afforded the nitrone; however, the yield of the product was found to be lower, along with the formation of a mixture of many side products. Similarly, the use of other solid peroxy compounds, such as sodium perborate and sodium percarbonate, in place of urea-hydrogen peroxide although gave the corresponding nitrone selectively but afforded poor yields

Table 2 Results of recycling experiments[a]

Run	Aldehyde	Amine	t/h	Yield[b](%)
1	Benzaldehyde	Benzylamine	4	78
2	Benzaldehyde	Benzylamine	4	78
3	Benzaldehyde	Benzylamine	4	78
4	Benzaldehyde	Benzylamine	4	76
5	Benzaldehyde	Benzylamine	4	77
6	Benzaldehyde	Benzylamine	4	77

[a] Reaction conditions as described in text. [b] Isolated yields

under similar reaction conditions. These results established the superiority of the urea-hydrogen peroxide adduct over other peroxy compounds/hydrogen peroxide.

We also performed the reactions *via* first formation of imine (easily detectable by TLC) by the reaction of aldehyde (1 mmol) and amine (1.2 mmol) before adding the catalyst and oxidant under otherwise similar reaction conditions. It is worthy to mention that in both cases, *i.e.* when adding all the substrates, UHP and catalyst in the beginning or by the preformed formation of imine by the condensation of aldehyde and amine followed by the addition of UHP and catalyst into the reaction mixture, nitrones were obtained as the only product at the end of the reaction and the reaction times and yields of the products remained almost the same (Table 1, entries 2 *vs.* 6, 7 *vs.* 8, 10 *vs.* 11, 12 *vs.* 13, 15 *vs.* 16, 19 *vs.* 20). These findings clearly indicate the advantages of performing the two steps in the same reaction vessel, without additional steps for the isolation of intermediates, and also it helps in saving time, energy and production of waste. The presence of anhydrous sodium sulfate was found to be vital, as its absence led to the formation of nitrones in lower yields.

To check the reusability and recyclability of the catalyst we have carried out the condensation/oxidation of benzaldehyde and benzyl amine using solid UHP as oxidant under similar reaction conditions. After completion of the reaction, the catalyst was separated by decantation, washed with methanol, dried and reused as such for subsequent experiments (6 runs), after adding fresh substrates and oxidant (UHP), under the described reaction conditions (Table 2). In these experiments, the reaction times and yield of the nitrone remained the same, establishing the recyclability and reusability of catalyst without significant loss in catalytic activity. To check the leaching of the metal during the experiments, we first stirred the Nafion immobilized $MoOCl_4$ beads in methanol at room temperature for 8 h. The polymer beads were separated by filtration and the filtrate thus obtained was used for the condensation/oxidation of benzaldehyde and benzyl amine with UHP under similar reaction conditions. No nitrone formation was observed, even at a longer reaction time (8 h), establishing that there was no metal leaching occurring and the reaction is truly heterogeneous in nature.

The exact mechanism of the reaction is not clear at the stage, however the reaction probably involves the *in situ* formation of imine *via* the condensation of aldehyde and primary amine which subsequently reacts with peroxo-molybdenum species (generated by the reaction of Mo=O and UHP) to afford the nitrone.

Conclusions

In summary, we demonstrated for the first time the use of Nafion-NR-50 (commercially available) polymer resin as a solid support for the immobilization of molybdenum oxychloride. The immobilization could be achieved in a very simple manner and the resulting Nafion immobilized $MoOCl_4$ was found to be an efficient catalyst for the direct synthesis of nitrones in good yields *via* one pot condensation/oxidation of primary amines with aldehydes using solid UHP as oxidant under mild reaction conditions. The key advantages, like the direct one step synthesis of nitrones without isolation of any intermediate, green synthesis, facile recovery and recycling ability of the catalyst without loss in catalytic activity and leaching of metal, make the present method superior and more advantageous than existing methods.

Notes and references

† **Preparation of catalyst**: Commercially available Nafion NR-50 was taken as a support. Into a stirred mixture of Nafion beads (2 g) in dry THF (10 ml) was added NaH slowly over 30 min at lower temperature (5–10 °C). After completion of the addition, the mixture was stirred for 3 h at room temperature. A solution of molybdenum(VI) oxychloride (0.2 g) in dry THF was added drop wise to the stirred mixture of Nafion in THF. The suspension was further stirred for 3 h under nitrogen atmosphere at room temperature. The solution became light colored while Nafion beads became highly colored during this period. The dark colored polymer beads were easily separated by filtration and washed thoroughly with THF, MeOH and then dried under vacuum. IR (cm^{-1}): 2355, 1670, 1522, 986, 981, 951. Metal loading was determined by TGA analysis and was found to be 0.18 mmol g^{-1} of polymer.

General procedure for the synthesis of nitrones 1 (*protocol I*): Into a stirred solution of aldehyde (1 mmol) in MeOH (3 ml) was added anhydrous Na_2SO_4, UHP (3 mmol) and Nafion immobilized Mo catalyst **1** (2 mol%, 0.11 g). The resulting solution was cooled to 0 °C and after 5 min the amine (1.2 mmol) was added drop-wise. The reaction mixture was stirred at room temperature for 4–8 h. After completion as analyzed by TLC, the catalyst could readily be separated from the reaction by decantation, washed thoroughly with water, methanol and dried and reused for subsequent experiments. The filtrate so obtained was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and the organic layer was washed with water (3 times), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product, which was purified by flash column chromatography on silica gel using ethyl acetate–hexane (1 : 9) as eluent. Results obtained for the one pot condensation/oxidation of a variety of aldehydes and primary amines to nitrones are summarized in Table 1. All the products were characterized by comparing their physical and spectral data to the reported compounds.

General procedure for the synthesis of nitrones *via* first formation of imine (***Protocol II***): Into a 25 ml round bottomed flask, a mixture of aldehyde (1 mmol) and primary amine (1.2 mmol) in MeOH (3 ml) was stirred until the formation of imine was completed (as analyzed by TLC). After completion, UHP (3 mmol) and Nafion immobilized Mo catalyst **1** (2 mol%, 0.11 g) was added into the above mentioned reaction mixture. The resulting mixture was stirred at room temperature for 4–8 h (completion of the nitrone formation was analyzed by TLC). At the end of the reaction, the catalyst was separated by decantation and resulting residue was subjected to usual workup to crude product, which was purified by flash column chromatography on silica gel using ethyl acetate–hexane (1 : 9) as eluent.

1 (*a*) R. Bloch, *Chem. Rev.*, 1998, **98**, 1407; (*b*) K. V. Gothelf and K.A. Jorgensen, *Chem. Rev.*, 1998, **98**, 863; (*c*) F. Cardona and A. Goti, *Angew. Chem., Int. Ed.*, 2005, **44**, 7832.

2 F. A. Villamena, S. Xia, J. K. Merle, R. Lauricella, B. Tuccio, C. M. Hadad and J. L. Zweier, *J. Am. Chem. Soc.*, 2007, **129**, 8177 and references cited therein.

3 J. E. Slemmer, J. J. Shacka, M. I. Sweeney and J. T. Weber, *Curr. Med. Chem.*, 2008, **15**, 404.

4 Reviews: (*a*) P. Merino, in *Science of Synthesis*, ed. A. Padwa, vol. 27, Thieme, Stuttgart, 2004, pp. 511–580; (*b*) J. J. Tufariello, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, vol. 2, John Wiley & Sons, New York, 1984, pp. 83–168; (*c*) M. Frederickson, *Tetrahedron*, 1997, **53**, 403; (*d*) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; (*e*) R. C. F. Jones and J. N. Martin, in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products (Series: The Chemistry of Heterocyclic Compounds)*, ed. A. Padwa and W. H. Pearson, Vol. 59, John Wiley & Sons, New York, 2002, pp. 1–81.

5 (*a*) K. S. Chan, W.-K. Yeung, R.-J. Chan, T.-C. Wang and W. Mak, *J. Org. Chem.*, 1995, **60**, 1741; (*b*) S. R. Sandler, W. Karo, in *Organic Functional Group Preparations*, 2nd edn, Academic Press: San Diego, 1989, vol. 3, pp. 351–376; (*c*) G. Masson, S. Py and Y. Vallee, *Angew. Chem.*, 2002, **114**, 1850, (*Angew. Chem., Int. Ed.*, 2002, **41**, 1772); (*d*) I. S. Young and M. A. Kerr, *Angew. Chem.*, 2003, **115**, 3131, (*Angew. Chem., Int. Ed.*, 2003, **42**, 3023); (*e*) F. Cardona and A. Goti, *Angew. Chem.*, 2005, **117**, 8042, (*Angew. Chem., Int. Ed.*, 2005, **44**, 7832).

6 (*a*) A. H. Fenselau, E. H. Hamamura and J. G. Moffatt, *J. Org. Chem.*, 1970, **35**, 3546; (*b*) P. A. S. Smith and S. E. Gloyer, *J. Org. Chem.*, 1975, **40**, 2508; (*c*) M. Nojima, K. Takeuchi, E. Fukui and N. J. Tokura, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2202.

7 (*a*) S. K. Hota, A. Chatterjee, P. K. Bhattacharya and P. Chattopadhyay, *Green Chem.*, 2009, **11**, 169; (*b*) K. Nakama, S. Seki and S. Kanemasa, *Tetrahedron Lett.*, 2001, **42**, 6719.

8 F. Cardona, M. Bonanni, G. Soldaini and A. Goti, *ChemSusChem*, 2008, **1**, 327.

9 (*a*) *Chiral Catalysts Immobilization and Recycling*, ed. D. E. De Vos, I. F. J. Vankelecom and P. A. Jacobs, Wiley-VCH, Weinheim, 2000; (*b*) C. A. McNamara, M. J. Dixon and M. Bradley, *Chem. Rev.*, 2002, **102**, 3275; (*c*) M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401; (*d*) A. Sakthivel, W. Sun, G. Raudaschl-Sieber, A. S. T. Chiang, M. Hanzlik and F. E. Kühn, *Catal. Commun.*, 2006, **7**, 302.

10 (*a*) R. H. Grubbs, L. C. Kroll and E.M. J. Sweet, *J. Macromol. Sci., Part A: Pure Appl. Chem.*, 1973, **7**, 1047; (*b*) G. Strukul, M. Bonivento and M. Graziani, *Inorg. Chim. Acta*, 1975, **12**, 15; (*c*) D. E. Bergbreiter and R. Chandran, *J. Am. Chem. Soc.*, 1987, **109**, 174; (*d*) K. G. Allum, R. D. Hancock, I. V. Howell, R. C. Pitkethly and P.J. Robinson, *J. Organomet. Chem.*, 1975, **87**, 189.

11 (*a*) M. Kenneth and R. B. Moore, *Chem. Rev.*, 2004, **104**, 4535; (*b*) L. A. Paquette, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, New York, 1995, vol. 6; (*c*) S. L. Jain and B. Sain, *Appl. Catal., A*, 2006, **301**, 259; (*d*) M. Schneider, F. Aquino and W. Bonrath, *Appl. Catal., A*, 2001, **220**, 51; (*e*) W. Laufer and W. F. Hoelderich, *Chem. Commun.*, 2002, 1684.

12 (*a*) A. J. Seen, *J. Mol. Catal. A: Chem.*, 2001, **177**, 105; (*b*) D. E. Bryant and M. Kilner, *J. Mol. Catal. A: Chem.*, 2002, **178**, 1; (*c*) S. Kanemoto, H. Saimoto, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1984, **25**, 3317.

13 (*a*) E. F. M. Barradas, A. R. Cestari, C. Airoldi and R. Buffon, *Braz. J. Chem. Eng.*, 1998, **15**(2), DOI: 10.1590/S0104-66321998000200008; (*b*) K. Heinze and A. Fischer, *Eur. J. Inorg. Chem.*, 2007, 1020; (*c*) X. Huang, J. Liu, J. Chen, Y. Xu and W. Shen, *Catal. Lett.*, 2006, **108**, 79; M. Seman, J. N. Kondo, K. Domen, C. Reed and S. T. Oyama, *J. Phys. Chem. B*, 2004, **108**, 3231.