An efficient aerobic oxidative cyanation of tertiary amines with sodium cyanide using vanadium based systems as catalysts

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The first report on the use of vanadium-based catalysts for oxidative cyanation of tertiary amines with molecular oxygen in the presence of sodium cyanide and acetic acid to afford the corresponding α -aminonitriles in good to excellent yields is described.

Oxidative cyanation of tertiary amines is an important synthetic transformation as α -aminonitriles are extremely useful synthetic intermediates, which have widely been used in the construction of a variety of synthetically, as well as biologically important compounds such as alkaloids.¹ Molecular oxygen is an attractive oxidant and development of synthetic methodologies using molecular oxygen, as the sole oxidant is a rewarding goal both from environmental and economic view points.² To the best of our knowledge there is only one report on the oxidative cyanation of tertiary amines to α -aminonitriles using molecular oxygen as a sole oxidant and ruthenium trichloride as catalyst.³ However, the expensive nature and moisture sensitivity of the ruthenium trichloride makes its utility limited.

In continuation to our studies on oxidation of organic substrates using molecular oxygen as oxidant,⁴ herein, we report for the first time an efficient and cost-effective methodology for the oxidative cyanation of various tertiary amines to the corresponding α -aminonitriles with sodium cyanide using a catalytic amount of V₂O₅ and molecular oxygen as oxidant under mild reaction conditions (Scheme 1).

At first, we studied the catalytic efficiency of various vanadium based catalysts for oxidative cyanation of *N*,*N*-dimethylaniline with sodium cyanide using molecular oxygen as oxidant and methanol–acetic acid (4 : 1) as reaction medium. Among the various vanadium based catalysts, *viz* V_2O_5 , its supported analogues such as V_2O_5/ZrO_2 , V_2O_5/Al_2O_3 and V_2O_5/TiO_2 and complexes such as $VO(acac)_2$, VO(salen), VOPc studied, V_2O_5 was found to be most efficient catalyst for this transformation. Catalytic efficiency of V_2O_5 was also compared with RuCl₃ for oxidative cyanation of *N*,*N*-dimethylaniline,⁵ *N*-phenyl-1,2,3,4-tetrahydroisoquinoline⁵ and *N*-phenylpyrrolidine. Vanadium pentoxide yielded better conversion and selectivity than RuCl₃ for all the three tertiary amines studied. These results are summarized in Table 1.



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Table 1 Comparison of various catalysts for oxidative cyanationusing molecular oxygen as oxidant a

| Entry | Substrate | Catalyst | t/h | Conv. ^b (%) | Select. ^b (%) |
|-------|------------------|---|-----|---------------------------|-----------------------------|
| 1 | | V ₂ O ₅ | 1.5 | 99 | 97 |
| 2 | | 11% V ₂ O ₅ /TiO ₂ | 1.5 | 98 | 92 |
| 3 | | $15\% V_2O_5/Al_2O_3$ | 1.5 | 98 | 90 |
| 4 | | $17\% V_2O_5/ZrO_2$ | 1.5 | 98 | 91 |
| 5 | | VO(acac) ₂ | 1.5 | 98 | 60 |
| 6 | | VOSO ₄ ·2H ₂ O | 2.0 | 40 | 5 |
| 7 | | VOPc | 2.0 | 80 | 30 |
| 8 | | VO(salen) | 2.0 | 60 | 32 |
| 9 | | RuCl ₃ | 2.0 | — | 93 |
| 10 | N. _{Ph} | V_2O_5 | 3.0 | 87 | 82 |
| 11 | | RuCl ₃ | 4.0 | _ | 79 |
| 12 | | V_2O_5 | 2.0 | 92 | 87 |
| 13 | | RuCl ₃ | 24 | 50 | 45 |

^{*a*} Reaction conditions: N,N-dimethylaniline (1 mmol), NaCN (1.2 mmol), MeOH (1 mL), AcOH (0.3 mL), O₂, at 60 °C for 1.5 h. ^{*b*} Determined by GC-MS.

The reaction did not proceed in the absence of catalyst under similar reaction conditions. We also carried out recycling experiments using N,N-dimethylaniline as substrate and 15% V₂O₅/Al₂O₃ as catalyst under the described reaction conditions. At the end of the reaction, the catalyst was separated by filtration, washed with methanol, dried and reused for subsequent runs (for three runs). The catalytic efficiency was found to decrease in subsequent runs and afforded poor yields of the desired product (90, 75, 60% GC yields), indicating the leaching of metal during the reaction. These facts indicated that the reactions might have occurred in homogeneous phase in case of supported vanadium pentoxides.

We then generalized the protocol developed for the oxidative cyanation of various tertiary amines with sodium cyanide (1.2 mmol) in the presence of a catalytic amount of

Table 2 The aerobic oxidative cyanation of various tertiary amines catalysed by $V_2O_5{}^a$

| Entry | Substrate | t/h | Product | Yield ^b (%) | Conv./select. (%) |
|-------|----------------------|-----|---|---------------------------|----------------------|
| 1 | CH3 | 1.5 | CH ₂ CH ₃ CH ₂ CN | 95 | 99/97 |
| 2 | CH3 CH2CH3 | 1.5 | CH ₂ CH ₂ CH ₃ | 89 | 97/92 |
| 3 | Me | 1.5 | Me NCH ₂ CH ₃ CH ₂ CN | 93 | 99/96 |
| 4 | Br | 2 | | 92 | 97/94 |
| 5 | But-CH3 CH3 | 2 | But-CH3 CH2CN | 93 | 98/96 |
| 6 | | 2 | | 82 | 92/87 |
| 7 | | 2 | | 84 | 90/86 |
| 8 | ₿ N _{Ph} | 3 | CN N-Ph | 80 | 87/82 |

^{*a*} Reaction conditions: amine (1 mmol), V₂O₅ (5 mol%), NaCN (1.2 mmol), AcOH (0.3 mL), MeOH (1 mL), O₂ at 60 °C. ^{*b*} Isolated yield. ^{*c*} Determined by GC-MS.

vanadium pentoxide (5 mol%) under similar experimental conditions.[†] All the substrates were selectively and efficiently converted to the corresponding α -aminonitriles in high to excellent yields. These results are summarized in Table 2. All the products were analyzed by GCMS and their identity was confirmed by comparing their spectral data (IR and ¹H NMR) with the known compounds reported in the literature.^{3,5} Substituted N,N-dimethylanilines containing both electron donating and electron withdrawing groups on the phenyl ring were efficiently converted to the corresponding α -cyanoamines in excellent yields. Cyclic amines such as N-phenyl piperidine, *N*-phenylpyrrolidine and *N*-phenyltetrahydroisoquinoline yielded the corresponding a-cyanated compounds in high yields. In case of N-ethyl-N-methylaniline (Table 2, entry 2), the N-methyl group was oxidized chemoselectively to yield N-ethyl-N-phenylaminoacetonitrile in 92% (GC yield) along with a trace amount of the 2-(N-methyl-N-phenylamino)propionitrile (5%).

Thus the protocol developed represents an efficient, improved and cost-effective methodology for the oxidative cyanation of tertiary amines including functionalized nitrogen-containing heterocycles, which find extensive applications both as pharmaceutical agents and auxiliaries in asymmetric synthesis.

The exact mechanism of the reaction is not clear at this stage, however the reaction probably proceeds through a radical mechanism which is evident from the fact that the oxidative cyanation of N,N-dimethylaniline did not occur in the presence of 2,6-di(*tert*-butyl)-*p*-cresol (BHT) (2 eq.) as a free radical scavenger under similar experimental conditions. The plausible mechanistic pathway shown in Scheme 2 involves coordination of the tertiary amine with oxovanadium species **1** to give intermediate **2**, which yields



iminium ion intermediate 4 *via* single electron transfer (SET) from α -carbon centered radical 3. Oxidation of the intermediate 4 with molecular oxygen leads to the formation of vanadium(v) superoxo intermediate 5, which subsequently reacts with HCN (generated *in situ* from NaCN and acetic acid) to yield α -aminonitrile 6 and regeneration of oxovanadium species 1. A similar type of mechanism has been demonstrated by Murahashi *et al.*³ for the aerobic oxidative cyanation of tertiary amines in the presence of ruthenium chloride.

In summary, the present work describes the first report for the oxidative cyanation of tertiary amines with sodium cyanide in presence of vanadium-based catalysts using molecular oxygen as oxidant under mild reaction conditions. The inexpensive nature of the catalyst, use of environmentally benign oxidant, excellent product yields and wide substrate scope makes this method an improved and superior one than the existing method.

Notes and references

† *Experimental procedure*: A 25 mL double necked round-bottom flask equipped with an oxygen balloon and magnetic stirrer, was charged with *N*,*N*-dimethylaniline (1 mmol), MeOH (1 mL), AcOH (0.3 mL) and V₂O₅ (5 mol%). After the addition of NaCN (1.2 mmol), the resulting mixture was continuously stirred at 60 °C under an oxygen atmosphere. At the end of the reaction as monitored by TLC (SiO₂), the mixture was added into aqueous NaHCO₃ and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The conversion of *N*-methyl-*N*-phenylacetonitrile was determined to be 99% by GC-MS.

- 1 D. Enders and J. P. Shilvock, *Chem. Soc. Rev.*, 2000, **29**, 359, references cited therein.
- S.-I. Murahashi and D. Zhangab, *Chem. Soc. Rev.*, 2008, **37**, 1490;
 T. Punniyamurthy and L. Rout, *Coord. Chem. Rev.*, 2008, **252**, 134;
 J. Piera and J.-E. Bäckvall, *Angew. Chem., Int. Ed.*, 2006, **47**, 3506;
 T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329;
 T. Mallat and A. Baiker, *Chem. Rev.*, 2004, **104**, 3037.
- 3 S.-I. Murahashi, N. Komiya, H. Terai and T. Nakae, J. Am. Chem. Soc., 2003, 125, 15312.
- 4 S. L. Jain and B. Sain, Angew. Chem., Int. Ed., 2003, 42, 1265;
 S. L. Jain and B. Sain, Chem. Commun., 2002, 1040; V. B. Sharma,
 S. L. Jain and B. Sain, Tetrahedron Lett., 2003, 44, 2655;
 V. B. Sharma, S. L. Jain and B. Sain, J. Mol. Catal. A: Chem., 2004, 219, 61; J. K. Joseph, S. L. Jain and B. Sain, Catal. Commun., 2006, 7, 184.
- 5 S.-I. Murahashi, N. Komiya and H. Terai, *Angew. Chem., Int. Ed.*, 2005, **44**, 6931.