Carbon-Heteroatom Bond-Forming Reactions Mediated by Cerium(IV) Ammonium Nitrate: An Overview

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Abstract: As a powerful one-electron oxidant, cerium(IV) ammonium nitrate (CAN) is useful for a variety of oxidative transformations including carbon-carbon bond formation. Recent work has also demonstrated the usefulness of CAN in carbon-heteroatom bond-forming reactions. Particularly noteworthy is the effectiveness of CAN in building C–N, C–S, C–Se, C–Br, and C–I bonds. This account is aimed at creating awareness among organic chemists about such reactions with potential application in the synthesis of a variety of building blocks.

Key words: cerium(IV) ammonium nitrate, radical reactions, bond-forming reactions, heteroatoms, oxidations

1   Introduction

Although radicals have been known since the ground breaking discovery by Gomberg in 1900,[1] and notwithstanding the pointers to their potential application in synthesis presented in the work of Hey and Waters,[2a] Kharasch,[2b] and Mayo,[2c] no serious attempts to incorporate radical methodology in rational organic synthesis was made until the last quarter of the twentieth century. A paradigm shift, resulting in explosive growth in the area of radical methodology during the last two decades can be attributed in large measure to the conceptualization and demonstration by Stork that the controlled formation, as well as the addition of vinyl radicals to alkenes, constitutes a unique and powerful method for complex carbocyclic construction.[3] Important contributions made by many research groups, most notably those of Julia,[4] Beckwith,[5] Giese,[6] Ingold,[7] Curran[8] and Pattenden[9] have also contributed immensely to the general acceptance of radical methodology. As an integral part of this rapidly growing area of organic synthesis,[3–9] the application of carbon centered

radicals resulting from redox processes mediated by high-valent metal salts such as Mn(III), Co(III), V(V), Ce(IV) etc has emerged as a powerful tool for carbon-carbon bond-formation in recent years.[10]

The use of Ce(IV) reagents as convenient oxidants for a variety of substrates is well established;[10a,11] their use in carbon-carbon bond-forming reactions was demonstrated by Heiba and Dessau as early as 1971.[12] Subsequent investigations have shown that Ce(IV) reagents, especially cerium(IV) ammonium nitrate (CAN) are powerful one-electron oxidants, which are useful for various synthetic transformations.[10c,13] Comparative studies have shown that in intermolecular reactions, CAN is superior to the more commonly used Mn(III) acetate in many respects.[14] The experimental simplicity, ease of handling and non-toxicity combined with its solubility in organic solvents like MeOH and MeCN, has made CAN attractive in organic synthesis. The use of CAN in carbon-carbon bond-forming reactions is now well documented[13] and it is noteworthy that there has been a flurry of activity in this area since our original review appeared.[15] Interestingly, there has also been considerable effort towards exploring the use of CAN in C-heteroatom bond-formation. This account focuses on the recent progress in CAN-mediated reactions involving carbon-nitrogen, carbon-sulfur, carbon-selenium and carbon-halogen bond formation, highlighting the results of our own investigations in this area. To put things in perspective, a brief account of the use of CAN in carbon-carbon bond formation is given as a prelude.

2   Carbon-Carbon Bond-Forming Reactions Mediated by CAN: A Brief Outline

It is evident from the literature that there has been considerable recent interest in the use of Ce(IV) reagents especially CAN in the construction of carbon-carbon bonds.[15] As might be expected of a very powerful one-electron oxidant, oxidation of organic molecules by CAN is dominated by radical and cation radical chemistry. Oxidative additions of electrophilic radicals to alkenes,[16] enol ethers,[17] dienes,[18] glycals,[19] and allyl silanes[20] are representative of the many reports on the use of CAN in carbon-carbon bond-forming reactions. Nitromethylation,[21] malonylation,[22] and acetonylation[23] of arenes were also reported earlier.

Biographical Sketches
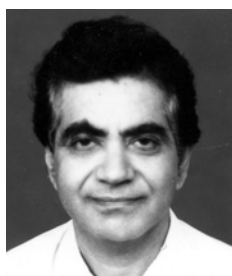
Vijay Nair was born and raised in Konni, Kerala state, India. He has PhD degrees from Banaras Hindu University (with Professor R. H. Sahasrabudhey) and the University of British Columbia (with Professor James P. Kutney). He has done post-doctoral work with Josef Fried (Chicago), Peter Yates (Toronto) and Gilbert Stork (Columbia). He joined the Medical Research Division (Lederle Laboratories) of American Cyanamid Company as Senior Research Chemist in 1974 and became Principal Research Chemist in 1987. In 1981 he received the Outstanding Scientist Award of Cyanamid Company. In 1990, he returned to India to join the Regional Research Laboratory (CSIR) in Trivandrum as its Deputy Director. During 1997–2001, Dr Nair was the Director of the Laboratory and presently he is continuing as Director-grade Scientist. He has lectured in a number of Universities in Germany in 1998 under the INSA–DFG exchange fellowship. He has been an Invited Speaker at the 17th ICHC in Vienna in 1999 and the MCR 2000, International Symposium in Munich. He was a Visiting Professor at the University of Pernambuco in Brazil in May 2001. Dr Nair is a Fellow of the Indian Academy of Sciences. His research interests include cycloadditions, radical-mediated C–C and C–heteroatom bond-forming reactions, multicomponent reactions and heterocyclic synthesis.

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Anu Augustine was born in Pala, Kerala state, India. She received her BSc and MSc in Chemistry (St. Thomas College, Pala) from Mahatma Gandhi University. She received her Ph.D. (2002, Kerala University) working under the supervision of Dr Vijay Nair at the Regional Research Laboratory (CSIR), Trivandrum. Currently she is a post-doctoral fellow at ETH Zürich in the research group of Professor Dr. Andrea Vasella.

Investigations in our laboratory have revealed that oxidative addition of 1,3-dicarbonyl compounds to alkenes,[24] dienes,[25] and exocyclic alkenes[26] provides a facile synthesis of dihydrofuran and spirodihydrofuran derivatives. An interesting and mechanistically fascinating reaction was observed in the oxidative addition of malonate to styrenes.[27] We have reported the CAN mediated single electron transfer reaction (SET) of methoxy styrenes yielding dimerization products via the intermediacy of cation radicals.[28] Very recently, we have reported a facile one-pot synthesis of 1-amino 4-aryl tetralin derivatives by the CAN-induced cyclodimerization of various styrenes.[29]

In comparison to Mn(III)acetate, there are very few reports on intramolecular cyclization reactions induced by (CAN).[30,31] The CAN mediated Pictet–Spengler cyclization[32] and cyclization of α-methoxycarbonyl acetyl enamides and acetoacetyl enamides leading to highly functionalized β-lactams[33] are noteworthy in this context. Very recently, we have reported that the intramolecular cyclization of cinnamyl ethers using CAN results in the stereospecific formation of 3,4-*trans* disubstituted tetrahydrofuran derivatives.[34]

3   Carbon-Heteroatom Bond-Forming Reactions Mediated by CAN

All CAN-mediated reactions, in general, can be broadly classified into two categories. The first one involves the formation of a cation radical by the oxidation of the substrate and subsequent transformations mediated by the cation radical. Since almost all these reactions involve incorporation of the solvent, carbon heteroatom bond formation is common to them. The second category involves the addition of heteroatom-centered radicals, formed by the oxidation of the anions by CAN, to alkenes or alkynes; this review is focused on such reactions.

3.1   Carbon-Nitrogen Bond Formation

#### 3.1.1   Introduction of Azide Functionality

Apart from the CAN-mediated reactions in which solvent incorporation results in carbon-heteroatom bond formation, the first example of such a reaction using an added nucleophile was reported by Trahanovsky in 1971.[35] Trapping of azide radicals, generated by the oxidation of sodium azide with CAN in MeCN, by olefins such as hexene, stilbene and acenaphthalene resulted in the formation of *trans*-α-azido-β-nitratoalkanes (Scheme 1).
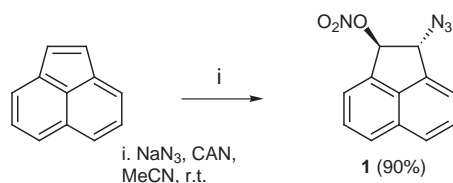
Scheme 1

The mechanism suggested for this reaction involves the addition of azide radical or the cerium-azide complex to the alkene. The reaction was reported to have failed with α,β-unsaturated carbonyl compounds (vide infra). With sterically hindered olefins only 1,2-diazides were formed in very low yields.[36]

Since the initial report on azidonitration using CAN by Trahanovsky, the method has been widely used for functionalization of double bonds, especially in carbohydrates as exemplified by the reaction of 3,4,6-tri-*O*-acetyl-D-galactal with excess CAN and sodium azide in MeCN yielding the 2-azido-1-nitrate (Scheme 2).[37]
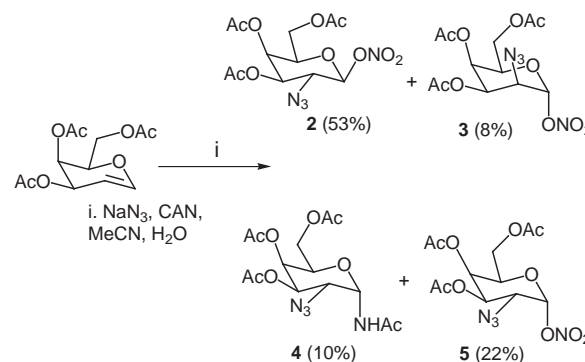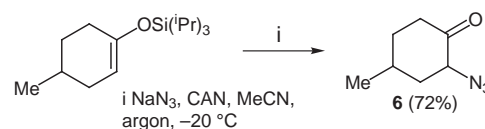
Scheme 2

A drawback of this reaction is that a large excess of CAN and sodium azide are needed to compensate for the loss due to oxidation of azide to nitrogen gas. Evidently, the acetamido product is formed by Ritter trapping of the carbocation by MeCN and hydration of the resulting iminium ion.

It is noteworthy that the non-nucleophilicity, acid tolerance and ease of reduction of azide to amine, makes the introduction of azide group a very important process in the synthesis of amino sugars. The importance of the reaction is evinced by the application of this or related processes discernible in the literature.[38]

Recently, the oxidative azidation of triisopropylsilyl enol ethers has been used for the synthesis of α-azido ketones by Magnus (Scheme 3).[39]
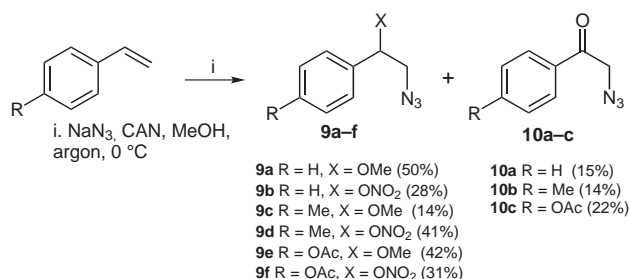
Scheme 3

It may be mentioned that in earlier work, Vogel has used this method as an intermediate step in the total synthesis of deoxypolyoxin.[40] CAN-mediated azidonitration has also been applied in the synthesis of amino acids (Scheme 4).[41] CAN-mediated azidation of enol ethers has been reported to afford azido acetals.[42]
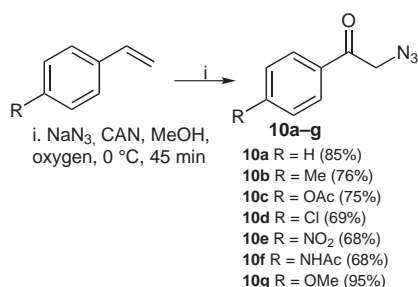
Scheme 4

i. NaN$_3$, CAN
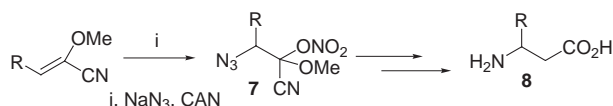
In the azidonitration and diazidation of styrenes, reported by Trahanovsky, the solvent used was MeCN.[35] Recently, we observed a remarkably different reactivity in methanol. The reaction of styrene with sodium azide and CAN in methanol illustrates this; the azidomethyl ether was formed as the major product along with smaller amounts of the azido nitrate and the azido ketone (Scheme 5).[43]

i. NaN$_3$, CAN, MeOH, argon, 0 °C

9a R = H, X = OMe (50%)
9b R = H, X = ONO$_2$ (28%)
9c R = Me, X = OMe (14%)
9d R = Me, X = ONO$_2$ (41%)
9e R = OAc, X = OMe (42%)
9f R = OAc, X = ONO$_2$ (31%)

10a R = H (15%)
10b R = Me (14%)
10c R = OAc (22%)

Scheme 5

In an oxygen atmosphere, the azido ketone was formed exclusively (Scheme 6).[43]

i. NaN$_3$, CAN, MeOH, oxygen, 0 °C, 45 min

10a–g
10a R = H (85%)
10b R = Me (76%)
10c R = OAc (75%)
10d R = Cl (69%)
10e R = NO$_2$ (68%)
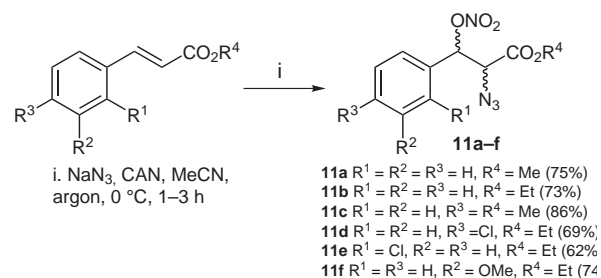**10f** R = NHAc (68%)
10g R = OMe (95%)

Scheme 6

Mechanistically, the reaction can be conceived to involve the addition of azide radical, formed by the oxidation of azide anion by CAN, to styrene generating a benzylic radical. The latter reacts either with molecular oxygen to give the phenacyl azide **10** via the intermediacy of a peroxy radical, or gets converted to the nitrato product by ligand transfer from CAN. The oxidation of the benzylic radical to the cation and its subsequent reaction with methanol leads to azidomethyl ether **9**.
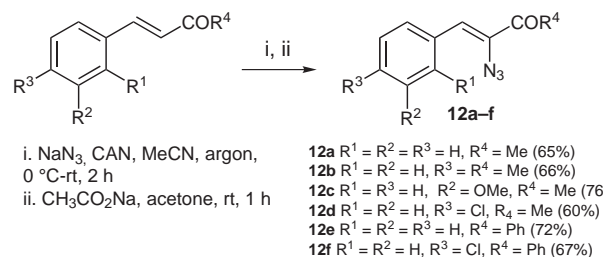
Earlier workers have reported that CAN-mediated azidation fails with α,β-unsaturated carbonyl compounds.[35] Contrary to these, we have observed a facile CAN-mediated addition of azide to such systems. Cinnamic acids, esters and cinnamamides on treatment with sodium azide and CAN in MeCN under deoxygenated conditions, afforded the corresponding α-azido-β-nitrato compounds in

excellent yields.[44] An illustrative example involves the reaction of ethyl cinnamate with sodium azide and CAN in MeCN under an argon atmosphere leading to the corresponding α-azido-β-nitrate in good yield (Scheme 7).

i. NaN$_3$, CAN, MeCN, argon, 0 °C, 1–3 h

11a–f
11a R^1 = R^2 = R^3 = H, R^4 = Me (75%)
11b R^1 = R^2 = R^3 = H, R^4 = Et (73%)
11c R^1 = R^2 = H, R^3 = R^4 = Me (86%)
11d R^1 = R^2 = H, R^3 = Cl, R^4 = Et (69%)
11e R^1 = Cl, R^2 = R^3 = H, R^4 = Et (62%)
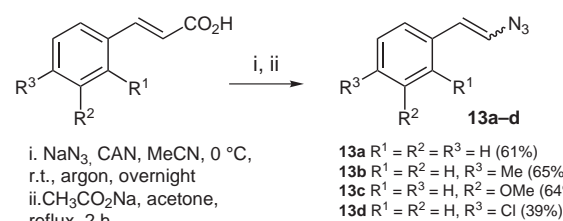**11f** R^1 = R^3 = H, R^2 = OMe, R^4 = Et (74%)

Scheme 7

Further studies in our laboratory have shown that, sequential treatment of cinnamic esters and α,β-unsaturated ketones with sodium azide and CAN in MeCN followed by sodium acetate in dry acetone yielded the corresponding α-azido cinnamates and α-azido-α,β-unsaturated ketones respectively in good yield (Scheme 8).[44]

i. NaN$_3$, CAN, MeCN, argon, 0 °C-rt, 2 h
ii. CH$_3$CO$_2$Na, acetone, rt, 1 h

12a–f
12a R^1 = R^2 = R^3 = H, R^4 = Me (65%)
12b R^1 = R^2 = H, R^3 = R^4 = Me (66%)
12c R^1 = R^3 = H, R^2 = OMe, R^4 = Me (76%)
12d R^1 = R^2 = H, R^3 = Cl, R$_4$ = Me (60%)
12e R^1 = R^2 = R^3 = H, R^4 = Ph (72%)
12f R^1 = R^2 = H, R^3 = Cl, R^4 = Ph (67%)

Scheme 8

Similarly, cinnamic acids can be converted to β-azido styrenes (Scheme 9).[44]

i. NaN$_3$, CAN, MeCN, 0 °C, r.t., argon, overnight
ii. CH$_3$CO$_2$Na, acetone, reflux, 2 h

13a–d
13a R^1 = R^2 = R^3 = H (61%)
13b R^1 = R^2 = H, R^3 = Me (65%)
13c R^1 = R^3 = H, R^2 = OMe (64%)
13d R^1 = R^2 = H, R^3 = Cl (39%)

Scheme 9

Epoxides on treatment with catalytic amount of CAN and sodium azide in *tert*-butanol underwent oxidative ring-opening to afford 1,2-azido alcohols.[45] The reaction is highly regioselective (Scheme 10).

i. NaN$_3$, CAN, *t*-BuOH, reflux **14**   **15**
65% (98:2)
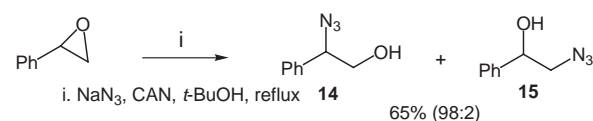
Scheme 10

3.1.2   Introduction of Nitro Functionality

Nitro compounds are important intermediates in organic synthesis and recently CAN has been used for the introduction of nitro group into a variety of substrates. Hwu et al. have reported that alkenes on treatment with an excess of sodium nitrite in the presence of CAN and acetic acid in chloroform in a sealed tube under sonication afforded nitroalkenes (Scheme 11).[46]

i. NaNO$_2$, CAN, AcOH, CHCl$_3$, 25–73 °C   **16** (90%)
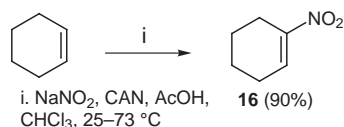
Scheme 11

It was speculated that the nitrous acid formed from sodium nitrite under acidic conditions is the source of nitrite radical. The latter on addition to the alkene generates a carbon radical, which undergoes oxidation by CAN and subsequent elimination of a proton leading to the formation of the nitroalkene. In order to increase the concentration of nitrite radical, the reaction is done in sealed tube. When the solvent is MeCN, a novel one-pot nitroacetamidation occurs (Scheme 12).[47]

i. NaNO$_2$, CAN, MeCN, rt   **17** (64%)
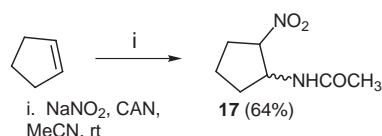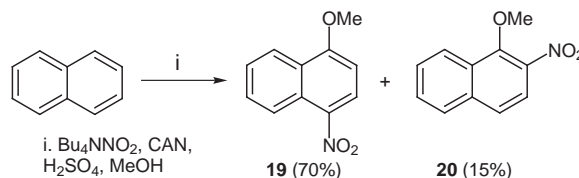
Scheme 12

It is evident that quenching of the cationic intermediate by MeCN in a Ritter fashion and subsequent transformation of the iminium ion leads to the acetamido product. With styrene and cinnamyl acetate, however, the product is β-nitro styrene. Attempted nitroacetamidation of cyclopentene carboxaldehyde, under similar reaction conditions, resulted in the formation of the unexpected dinitro-oxime; the mechanism of this transformation is unclear (Scheme 13).[48]

i. NaNO$_2$, CAN, MeCN, rt   **18** (21%)
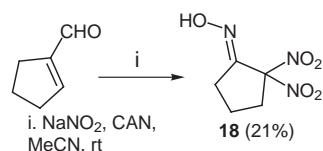
Scheme 13

3.1.3   Nitration of Aromatic Nucleus

Silica gel-supported CAN has been shown to nitrate polynuclear aromatic systems.[49,50] CAN-mediated nitration of naphthalene in presence of catalytic amount of H$_2$SO$_4$ and *tert*-butylammonium nitrite in methanol, afforded 1-nitro-4-methoxynaphthalene as the major product (Scheme 14).[51]

i. Bu$_4$NNO$_2$, CAN, H$_2$SO$_4$, MeOH   **19** (70%)   **20** (15%)

Scheme 14

The suggested mechanistic rationale for this reaction involves the addition of nitrite radical to naphthalene and oxidation of the resulting radical to the cation followed by methanol quenching.

3.2   Carbon-Sulfur Bond Formation

3.2.1   Sulfonylation

Oxidation of sulfinates using one-electron oxidants, especially CAN provides an easy way to generate sulfonyl radicals, which otherwise would require photolytic conditions or action of peroxides. Narasaka has extensively studied the addition of sulfinate to various olefins, especially electron-rich ones in the presence of different one-electron oxidants such as manganese(III) 2-pyridine carboxylate [Mn(pic)$_3$], tetrabutyl ammonium cerium(IV) nitrate (TBACN) and CAN.[52] An illustrative example is the reaction of sodium-2-naphthalenesulfinate with 1-vinyl-cyclobutanol in the presence of CAN in MeCN resulting in the formation of ring enlarged product (Scheme 15).[52]

i. NapSO$_2$Na, CAN, MeCN, 0 °C   **21** (72%)
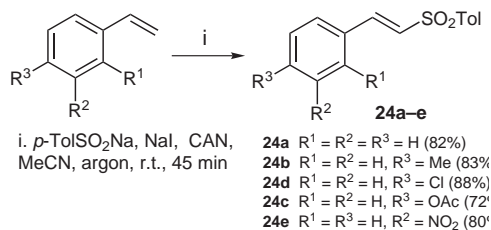
Nap = 2-Naphthyl
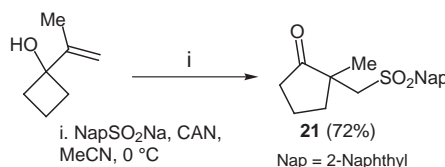
Scheme 15

We have observed that CAN-mediated oxidative addition of sulfinates to styrene proceeds very efficiently to afford keto and nitrato sulfinates (Scheme 16).[53]

i. ArSO$_2$Na, CAN, MeCN, r.t., 45 min   **22** (61%)   **23** (20%)
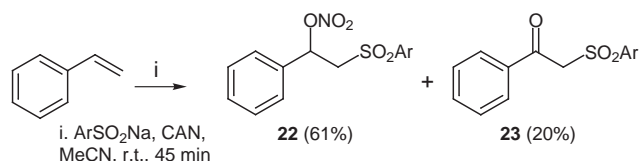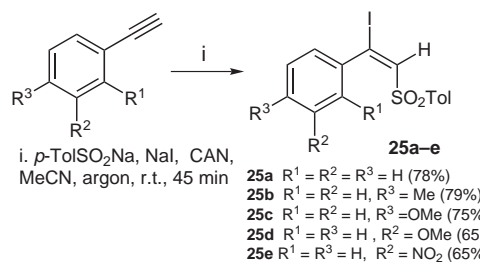
Scheme 16

When sodium iodide is present in the reaction medium, vinyl sulfones are formed (Scheme 17).[54]

It is speculated that the vinyl sulfones are formed via the dehydroiodination of the intermediate iodovinyl sulfones. The formation of iodovinyl sulfones from alkynes under similar reaction conditions indirectly supports this postulate (Scheme 18).[54]
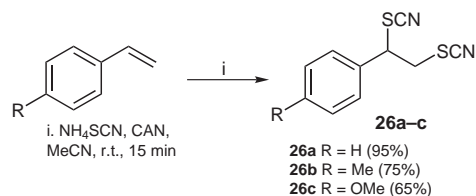
Scheme 17

i. *p*-TolSO$_2$Na, NaI, CAN, MeCN, argon, r.t., 45 min

24a R^1 = R^2 = R^3 = H (82%)
24b R^1 = R^2 = H, R^3 = Me (83%)
24d R^1 = R^2 = H, R^3 = Cl (88%)
24c R^1 = R^2 = H, R^3 = OAc (72%)
24e R^1 = R^3 = H, R^2 = NO$_2$ (80%)

Scheme 18

i. *p*-TolSO$_2$Na, NaI, CAN, MeCN, argon, r.t., 45 min

25a R^1 = R^2 = R^3 = H (78%)
25b R^1 = R^2 = H, R^3 = Me (79%)
25c R^1 = R^2 = H, R^3 =OMe (75%)
25d R^1 = R^3 = H , R^2 = OMe (65%)
**25e** R^1 = R^3 = H, R^2 = NO$_2$ (65%)

3.2.2 Thiocyanation

Thiocyanation of arenes and olefins constitutes an important method for introducing sulfur functionality into a molecule. Treatment of an alkene with ammonium thiocyanate and CAN in MeCN at ice cold temperature results in the formation of dithiocyanates in excellent yields. The reaction is general; the product yield ranges from 50–95% (Scheme 19).[55]
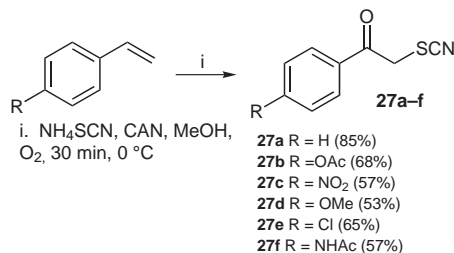

i. NH$_4$SCN, CAN, MeCN, r.t., 15 min

26a–c
26a R = H (95%)
26b R = Me (75%)
26c R = OMe (65%)

Scheme 19

A different reactivity pattern leading to the phenacyl thiocyanate as the principal product was observed in methanol (Scheme 20).[43]
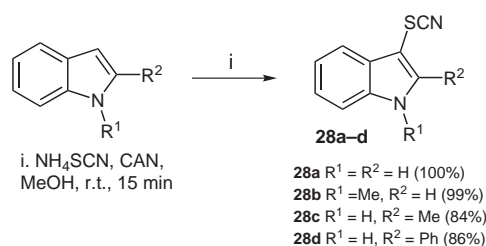

i. NH$_4$SCN, CAN, MeOH, r.t.

27a (60%)   **26a** (10%)
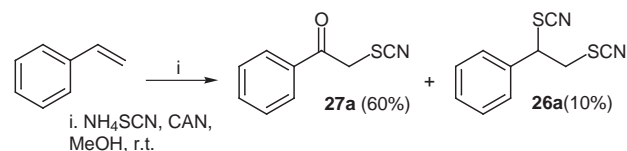
Scheme 20

In an atmosphere saturated with oxygen, the predominant product is the phenacyl thiocyanate (Scheme 21).[43]

i. NH$_4$SCN, CAN, MeOH, O$_2$, 30 min, 0 °C

27a–f
27a R = H (85%)
27b R = OAc (68%)
27c R = NO$_2$ (57%)
27d R = OMe (53%)
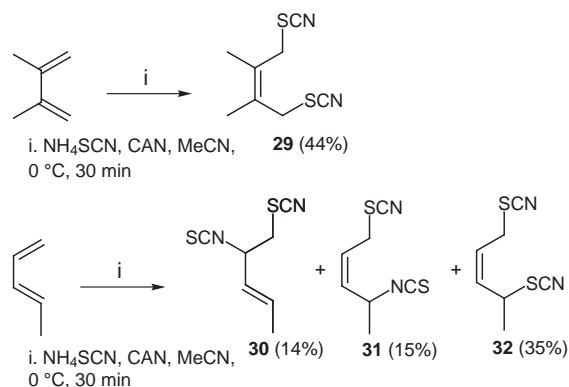**27e** R = Cl (65%)
27f R = NHAc (57%)

Scheme 21

In the case of vinyl naphthalene, in addition to the dithiocyanate, nitratothiocyanate is formed as a byproduct in low yield. With 4-acetoxystyrene, gem-dithiocyanates are also isolated.[43]

The same combination of reagents effects the thiocyanation of indole and substituted indoles (Scheme 22) [56]

i. NH$_4$SCN, CAN, MeOH, r.t., 15 min

28a–d
28a R^1 = R^2 = H (100%)
28b R^1 =Me, R^2 = H (99%)
28c R^1 = H, R^2 = Me (84%)
28d R^1 = H, R^2 = Ph (86%)

Scheme 22

Pyrroles and thiophene also undergo thiocyanation at 3-position on treatment with CAN and ammonium thiocyanate.[57] 1,3-Dienes, on reaction with CAN and ammonium thiocyanate in MeCN afforded the corresponding 1,4-dithiocyanates and in some cases the dithiocyanates formed underwent [3,3] sigmatropic rearrangement affording the isothiocyanato-thiocyanates (Scheme 23).[57]

i. NH$_4$SCN, CAN, MeCN, 0 °C, 30 min   **29** (44%)

i. NH$_4$SCN, CAN, MeCN, 0 °C, 30 min   **30** (14%)   **31** (15%)   **32** (35%)
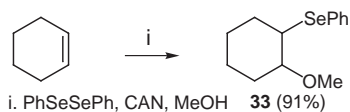
Scheme 23

3.3 Carbon-Selenium Bond Formation

Introduction of phenylseleno group into an organic molecule is of great synthetic importance. The common reagents for such transformations are phenyl-selenenylbromide and phenylselenenylchloride. Oxidation of diphenyl diselenide to the cation radical using

CAN and subsequent trapping of the latter with olefins in MeOH leads to β-methoxyalkyl phenyl selenides in excellent yields (Scheme 24).[58] The reaction with trisubstituted olefins or enol ethers is highly regioselective, always leading to Markovnikov orientation.


i. PhSeSePh, CAN, MeOH **33** (91%)

Scheme 24

With 5-hexene-2-ol, intramolecular reaction afforded the selenide substituted tetrahydrofuran (Scheme 25).[58]
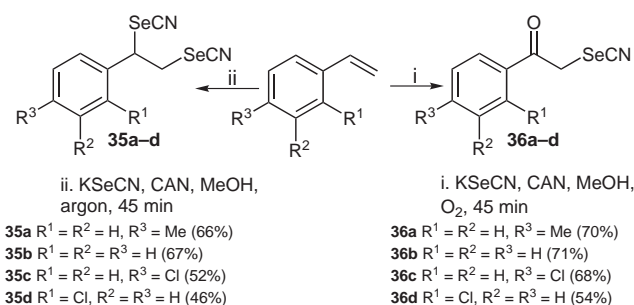

Scheme 25

We have observed that the oxidative addition of selenocyanates to alkenes constitutes a highly efficient method for the synthesis of diselenocyanates and keto selenocyanates (Scheme 26).[59]

i. KSeCN, CAN, MeOH, 0°C, 30 min   **35a** (60%)   **36a** (20%)
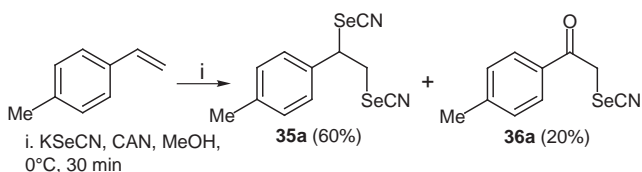
Scheme 26

The reaction can be forced in the desired direction to get either of the two products, simply by changing the reaction conditions. In a completely deoxygenated atmosphere, the diselenocyanate is formed exclusively whereas under oxygen saturated conditions, the phenacyl selenocyanate is formed as the sole product (Scheme 27).[59]


ii. KSeCN, CAN, MeOH, argon, 45 min
35a $R^1 = R^2 = H$, $R^3 = Me$ (66%)
35b $R^1 = R^2 = R^3 = H$ (67%)
35c $R^1 = R^2 = H$, $R^3 = Cl$ (52%)
35d $R^1 = Cl$, $R^2 = R^3 = H$ (46%)

i. KSeCN, CAN, MeOH, O$_2$, 45 min
36a $R^1 = R^2 = H$, $R^3 = Me$ (70%)
36b $R^1 = R^2 = R^3 = H$ (71%)
36c $R^1 = R^2 = H$, $R^3 = Cl$ (68%)
36d $R^1 = Cl$, $R^2 = R^3 = H$ (54%)
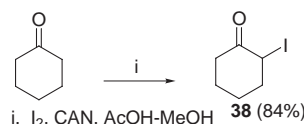
Scheme 27

3.4 Carbon-Halogen Bond Formation

3.4.1 Iodination and Bromination

There are a number of reports on halogenation reactions mediated by CAN. Regioselective iodination of an aromatic nucleus has been achieved using CAN and an iodide such as tetrabutylammonium iodide or any alkali metal iodide or molecular iodine. With molecular iodine, CAN serves as a catalyst, whereas in the case of iodide the latter is oxidized to the radical by CAN. Benzylic iodination has not been observed in the case of methylbenzenes under these conditions (Scheme 28).[60] Polymethoxy benzenes are also iodinated under the same reaction conditions.

i. Bu$_4$NI, CAN, MeCN

37 (83%)
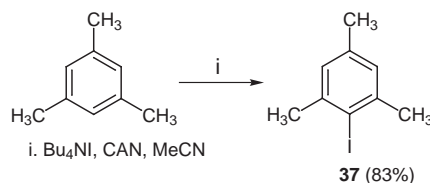
Scheme 28

A method for α-iodination and α,α′-diiodination of ketones has been reported using a combination of iodine and CAN in solvents such as acetic acid or methanol (Scheme 29). The reaction is applicable to both cyclic and acyclic ketones. In the case of unsymmetrical ketones, the most substituted position is iodinated. With aqueous methanol as the solvent, both the 1- and 3- positions get iodinated.[61, 62]
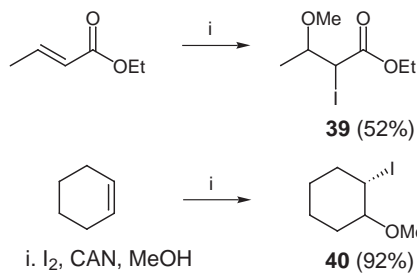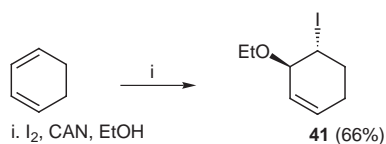

i. I$_2$, CAN, AcOH-MeOH   **38** (84%)

Scheme 29

The reaction of α,β-unsaturated ketones and esters with iodine and CAN in methanol, ethanol or *iso*-propanol, under reflux conditions afforded the corresponding β-alkoxy α-iodo-ketones and esters in very good yields.[63] In MeCN, β-hydroxy α-iodo-ketones and esters are obtained.[63] Iodination of simple olefins also leads to similar products. Cycloalkenes on treatment with iodine and CAN in alcohols such as methanol, ethanol, 1-propanol or 2-propanol under reflux conditions gave the corresponding vicinal alkoxyiodo cycloalkanes (Scheme 30).[64] When the solvent is *tert*-butanol, the product is *trans*-iodonitrate.[64]

Cyclic 1,3-dienes afford the corresponding *trans*-2-alkoxy-1-iodo compounds as the major products on treatment with iodine and CAN in alcohols (Scheme 31).[65] The reaction is generally applicable to the synthesis of a variety of 1,2-*trans* alkoxyiodides.
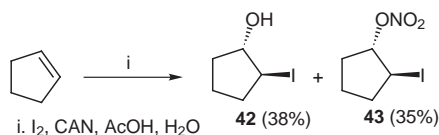
The reaction of cycloalkenes with iodine and CAN in MeCN–water afforded a mixture of the corresponding *trans*-iodohydrins and *trans*-iodonitrates (Scheme 32).[66]

i. I$_2$, CAN, MeOH

Scheme 30

i. I$_2$, CAN, EtOH   **41** (66%)

Scheme 31



i. I$_2$, CAN, AcOH, H$_2$O   **42** (38%)   **43** (35%)

Scheme 32

The CAN-mediated iodination of styrenes afforded only the iodohydrin, presumably by the hydrolysis of the intermediate iodonitrates.[66]

Asakura et al. have reported the bromination of C-5 of uracil nucleosides using CAN and lithium bromide in MeCN. In this reaction, they have used stoichiometric amounts of CAN and lithium bromide. A mechanism involving the intermediacy of a bromonium ion has been postulated (Scheme 33).[67]

i. LiBr, CAN, MeCN   R = glycosyl
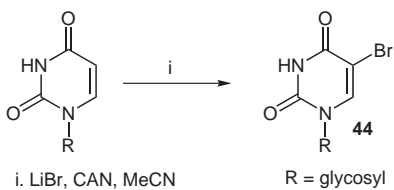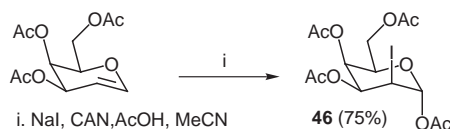
Scheme 33

They have also reported the CAN-catalyzed iodination at C-5 of protected uracil nucleosides in MeCN or DMF.[68]

Very recently, the regioselective iodination of pyrazoles using iodine and CAN has been reported (Scheme 34).[69]

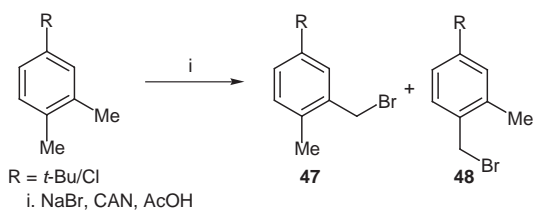i. I$_2$, CAN, MeCN   **45** (98%)
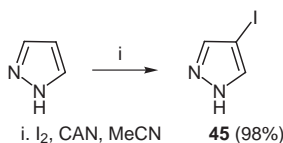
Scheme 34

Roush and co-workers have reported a stereoselective iodoacetoxylation of glycals using sodium iodide and CAN in a mixture of MeCN and acetic acid (Scheme 35).[70]


i. NaI, CAN, AcOH, MeCN   **46** (75%)

Scheme 35

Side chain bromination of alkyl aromatics has been reported by Baciocchi et al. using sodium bromide and CAN (Scheme 36).[71]

R = *t*-Bu/Cl
i. NaBr, CAN, AcOH

Scheme 36

Very recently, it has been reported that activated cinnamyl esters or ketones on reaction with CAN and lithium bromide with an excess of propargyl alcohol at room temperature afforded the corresponding bromoethers. The reaction, however, is of limited scope since it is ineffective in the case of unactivated cinnamyl systems (Scheme 37).[72]

i. LiBr, CAN, propargyl alcohol, MeCN   **49** (87%)
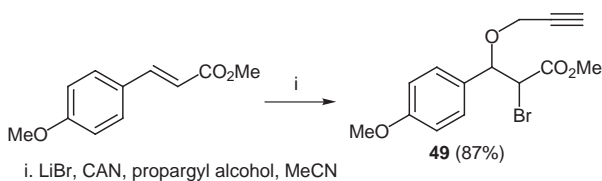
Scheme 37

A method for the dibromination of alkenes has been developed by us using potassium bromide and CAN in a two-phase system of water and dichloromethane. The reaction is found to be general for the dibromination of alkenes such as styrenes, cycloolefins, α,β-unsaturated carbonyl compounds etc (Scheme 38).[73]

i. KBr, CAN, CH$_2$Cl$_2$, H$_2$O, r.t., 30–45 min

50a–d

50a R = H (91%)
50b R = Me (67%)
50c R = Cl (85%)
50d R = NO$_2$ (62%)
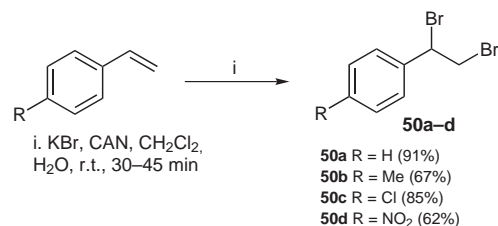
Scheme 38

If the solvent is methanol, MeCN or acetic acid, phenacyl bromide and nitrato bromide are obtained (Scheme 39).[73]

i. LiBr, CAN, MeCN,
r.t., argon, 2 h

51 (65%)   **52** (12%)
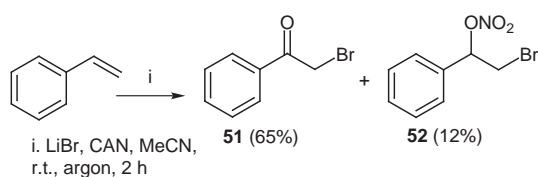
Scheme 39

A mechanism involving the oxidation of bromide ion to bromine radical and subsequent addition of the latter to the alkene leading to a benzylic radical can be invoked to account for the above reaction. Further transformations of the benzylic radical lead to different products.

Since the combination of potassium bromide and CAN has been shown to be an excellent brominating agent for various alkenes we extended the reaction to cinnamic acids. This resulted in a one-pot conversion of the latter to the β-bromostyrene (Scheme 40).[74]
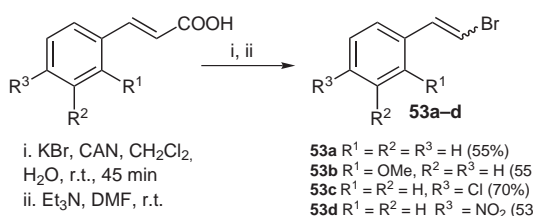

i. KBr, CAN, CH$_2$Cl$_2$,
H$_2$O, r.t., 45 min
ii. Et$_3$N, DMF, r.t.

53a R^1 = R^2 = R^3 = H (55%)
53b R^1 = OMe, R^2 = R^3 = H (55
53c R^1 = R^2 = H, R^3 = Cl (70%)
53d R^1 = R^2 = H, R^3 = NO$_2$ (53

Scheme 40

3.4.2   Azido-Iodination and Iodo-Thiocyanation

Bis-functionalization of double bonds, in particular cohalogenation of olefins, constitutes a very useful organic transformation. A number of methods are available to introduce an azide functionality and iodine together into an organic molecule. Of these, the CAN-mediated azidoiodination offers the most convenient protocol due to the experimental simplicity. It is remarkable that, simply stirring a solution of an alkene, sodium azide, sodium iodide and CAN in methanol yields the azidoiodide. The reaction is applicable to a variety of alkenes (Scheme 41).[75]

i. NaN$_3$, NaI, CAN, MeOH,
0 °C, 30 min

54a R = H (71%)
54b R = Me (70%)
54c R = Cl (78%)
54d R = NO$_2$ (66%)
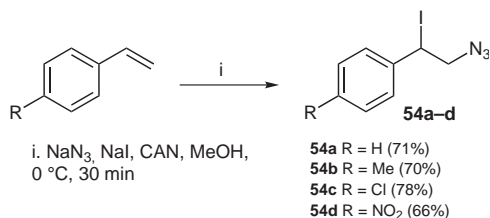
Scheme 41

Styrene yields iodothiocyanate and phenacyl thiocyanates on treatment with ammonium thiocyanate, sodium iodide, and CAN in methanol at ice bath temperature. With cyclohexene and octane, iodothiocyanate is the only product.[76]

4   Conclusion

An impressive number of publications that appeared during the last few years is testimony to the enormous interest in the use of CAN in carbon-heteroatom bond-forming reactions, many of which ultimately have a bearing on the synthesis of building blocks such as heterocycles, amino acids, deoxysugars etc. Experimental simplicity and mild reaction conditions are among the most attractive features of CAN-mediated reactions. Although much fascinating chemistry of CAN is already known, further explorations are sure to uncover even more interesting and useful reactions and processes. Two specific issues that remain to be addressed are: i) to make CAN catalytic in its reactions, and ii) to devise asymmetric transformations using CAN or related species. It is quite remarkable that, even in stoichiometric use, CAN is finding general acceptance for the laboratory scale synthesis of a variety of organic compounds and it is anticipated that CAN will continue to find increasing application in synthesis.

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