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Nitroacetonitrile and Its Synthetic Equivalents

Kento Iwai and Nagatoshi Nishiwaki*

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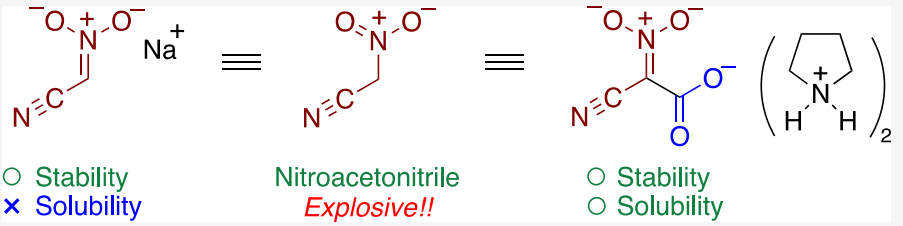


ABSTRACT: Nitroacetonitrile (NAN) serves as a cyano(nitro)methylating agent facilitating the construction of polyfunctionalized compounds; however, its explosive property is a significant drawback in terms of practical handling. Alkali metal salts of NAN are thermally stable, but their insolubility in organic solvents restricts their use as a synthetic reagents. On the contrary, dipyrrolidinium cyano-*aci*-nitroacetate is soluble in common organic solvents and thermally stable, allowing for its use as an alternative synthetic equivalent of nitroacetonitrile for the construction of polyfunctionalized frameworks via cyano(nitro)methylation.

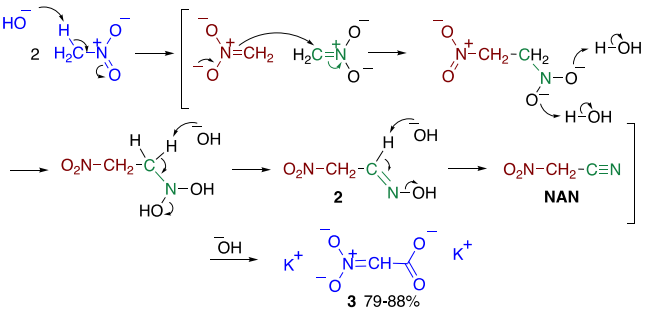
Active methylene compounds, represented by 1,3-dicarbonyls,[1−7] constitute an important family of compounds in organic chemistry. The acidity of a methylene group is considerably increased when flanked by two electron-withdrawing functionalities, such as carbonyl, nitro, cyano, sulfonyl, and 2-pyridyl, allowing for the generation of resonance-stabilized nucleophiles, which are widely employed as readily available carbon nucleophiles in diverse and elaborate syntheses.[1−16] Active methylene compounds act as ambident nucleophiles under basic conditions resulting in diverse reactivity. Furthermore, versatile polyfunctionalized frameworks can be constructed to harness the combination of the nucleophilicity and the respective functionalities. Although extensive research into active methylene compounds has been conducted, their chemistry remains fascinating and worthy of pursuit.

Examples of active methylene compounds wherein the carbonyl groups have been replaced with other functional groups are relatively less common. Malononitrile,[8−10] cyanoacetate,[11−13] and nitroacetate[14−16] are commercially available low-cost reagents and are thus frequently employed in organic synthesis; however, other active methylene compounds are not general reagents due to disadvantages such as low availability, high cost, and instability. Nitroacetonitrile (NAN, O_2NCH_2CN) is an attractive building block for the introduction of a cyano(nitro)methyl group. The cyano group exhibits similar reactivity to a carbonyl, but is additionally capable of unique reactivity via an imino group, enabling the synthesis of versatile frameworks. On the other hand, the nitro group is a strongly electron-withdrawing through both inductive and resonance effects. Nitro compounds can act as both a nucleophiles and electrophiles, depending on the counterpart, and a nitro group serves as a good leaving group.[17−19] Hence, the incorporation of a cyano(nitro)methyl group is favorable for the construction of polyfunctionalized compounds via subsequent chemical transformation.

NITROACETONITRILE

The dimerization of nitromethane is an effective approach for the preparation of NAN (Scheme 1).[20] When nitromethane is treated with potassium hydroxide, the generated nitronate attacks another molecule of nitronate to form a C−C bond.

Scheme 1. Base-Induced Dimerization of Nitromethane



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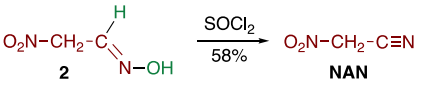
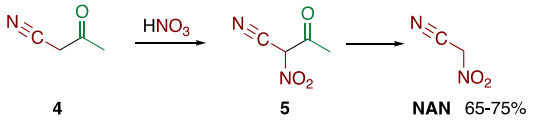
Scheme 2. Dehydration of 2 Leading to NAN



Scheme 3. Alternative Approach to NAN



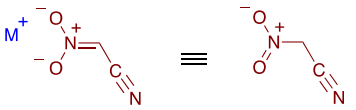
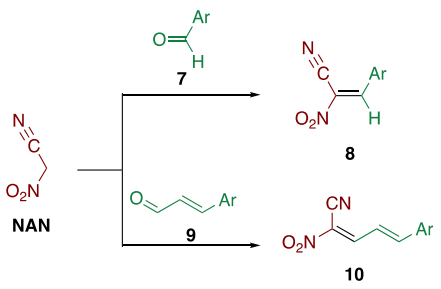
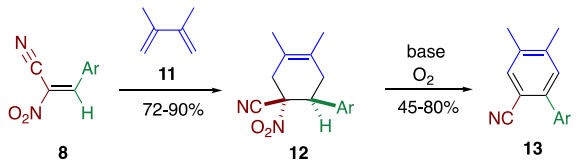


Figure 1. Alkali metal salts **6** as a synthetic equivalent of NAN.

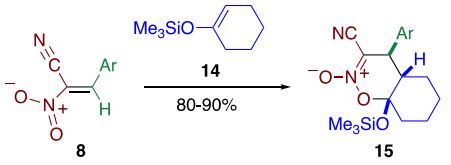
Scheme 4. Synthesis of Difunctionalized Alkenes 8



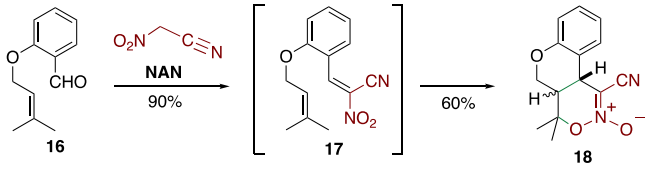
Scheme 5. Diels−Alder Reaction of 8 and Subsequent Aromatization



Scheme 6. Hetero-Diels−Alder Reaction of 8

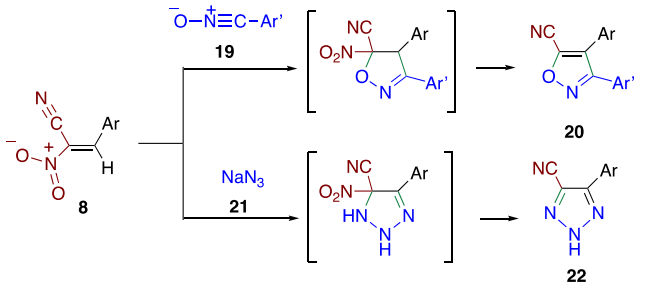


Scheme 7. Intramolecular Hetero-Diels−Alder Reaction of 17

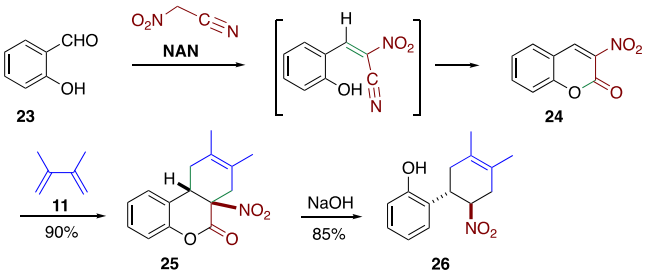


Subsequent dehydration furnishes oxime **2** (methazonic acid). Gentle heating of this reaction mixture results in further dehydration to afford NAN; however, this method is not commonly employed due to the difficulty in controlling the reaction temperature. Namely, when more severe conditions are employed, further hydrolysis of the cyano group occurs, producing the dipotassium salt of nitroacetic acid **3**.

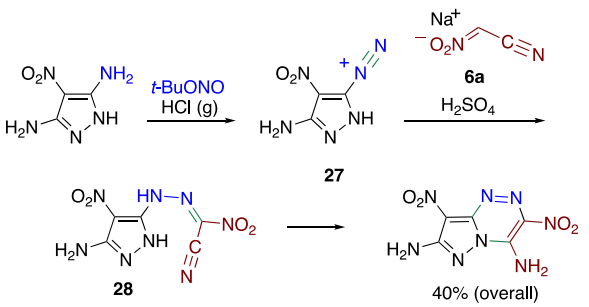
Scheme 8. 1,3-Dipolar Cycloaddition of 8



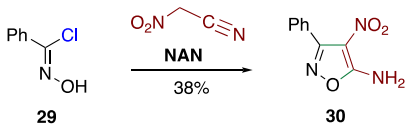
Scheme 9. Synthesis of Nitrocoumarin 24 Followed by Diels−Alder Reaction and Ring Opening to Deliver 26



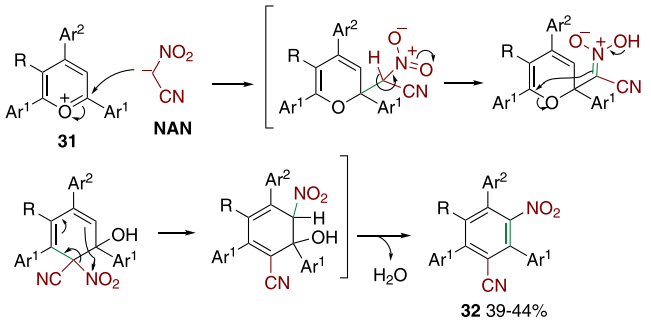
Scheme 10. Reaction of Diazonium Ion 27 with 6a Followed by Cyclization



Scheme 11. Synthesis of Functionalized Isoxazole 30



Scheme 12. Ring Transformation Leading to Fully Substituted Benzene 32



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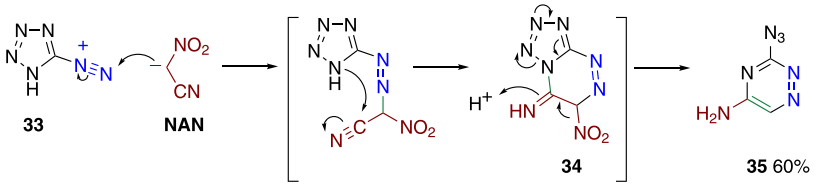
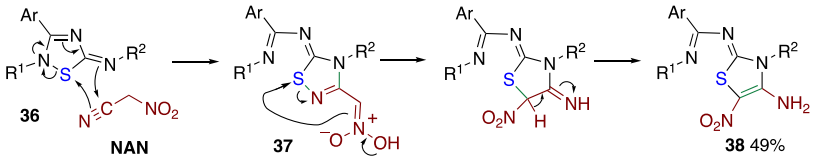
Scheme 13. Ring Expansion of Tetrazole 33 to Triazine 35



Scheme 14. Conversion of Thiadiazole 36 to Thiazole 38 via Intramolecular Ring Transformation



Although NAN is generally prepared via dehydration of **2** using thionyl chloride, this method suffers from low yields and inconsistent product purity (Scheme 2).[21,22] Semenov and co-workers have developed an efficient preparative method for NAN via nitration of α-cyanoketone **4** entailing a two-phase system and subsequent deacylation of nitrated product **5** (Scheme 3).[23]

As NAN is thermodynamically unstable, careful treatment under 50 °C is required.[24−26] Thomas reported the explosion of a flask containing NAN, allegedly due to decomposition.[25] According to the UN Orange Book,[27] organic substances with a decomposition energy of 800 J/g or more are classified as explosive materials. Indeed, NAN rapidly decomposes in air at 109 °C, releasing 874 J/g of energy, as evaluated by differential scanning calorimetry (DSC).[28] This explosive property has been useful in developing energetic materials[24] but has conversely prevented its use in organic synthesis as a common reagent. In contrast, sodium and potassium salts of NAN (**6a** and **6b**) are thermally stable, allowing for straightforward storage and handling (Figure 1).

Both NAN and its alkali metal salts **6** have been widely utilized in organic synthesis as cyano(nitro)methylating agents. In some cases, NAN is generated from **6** in situ. As the reactions of NAN and **6** are essentially the same, we will discuss their reactivity without distinction in the following sections.

The Knoevenagel reaction entails the condensation of active methylene compounds and aromatic aldehydes (Ar = substituted phenyl, heteroaryl) for the synthesis of alkenes possessing two electron-withdrawing groups in excellent yields. Thus, NAN serves as a nucleophile leading to alkenes **8** substituted with cyano and nitro groups (Scheme 4). This protocol is useful for generating a library of compounds by simply altering aldehydes **7**, which facilitates biological activity evaluation.[29−31] The synthesis of push−pull alkenes (Ar = electron rich aryl), applicable in the development of nonlinear optical materials, is readily achieved upon treatment of NAN with electron-rich aldehydes.[32,33] When α,β-unsaturated aldehydes **9** (Ar = substituted phenyl, heteroaryl) are used, nucleophilic attack of NAN (1,2-addition) occurs at the formyl group to afford butadienes **10** in moderate yields (Scheme 4).[34,35] Thioamides are also applicable as substrates in place of aldehydes **7** for condensation with NAN.[36] Several green processes have been developed, such as conducting the condensation of NAN with aldehydes **7** in aqueous media[37,38] and using the recyclable natural catalyst, dolomite [$CaMg(CO_3)_2$], in water.[39]

The obtained alkenes **8** are highly electron-deficient and can thus serve as reactive dienophiles, efficiently undergoing Diels−Alder reaction under mild reaction conditions with dienes, such as 2,3-dimethylbutadine **11** (Scheme 5)[31,40] and 1,3-cyclopentadiene.[41] Because the nitro group is readily eliminated as a nitrous acid,[18,42,43] the cycloadduct **12** can be readily converted to functionalized biphenyls **13** upon treatment of **12** with base under solvent-free conditions in the presence of oxygen (Scheme 5).[40]

Nitroalkenes are known to exhibit dual behavior in the Diels−Alder reaction: as a dienophile and as a heterodiene.[44−46] Cyanated nitroalkene **8** is also usable as an electron-deficient heterodiene, affording oxazine framework **15** in the reaction with electron-rich dienophile **14** (Scheme 6).[47,48] Fused oxazine derivative **18** is obtained when *O*-allylated salicylaldehyde **16** is condensed with NAN, whereby intermediate **17** undergoes an intramolecular hetero-Diels−Alder reaction (Scheme 7).[38]

The resonance effect of nitro and cyano groups considerably decreases the electron density at the β-position in **8** to bias the electron density on the C−C double bond. This electronic feature enables its use as a dipolarophile. Indeed, 1,3-dipolar cycloaddition with nitrile oxide **19** affords 4-cyanoisoxazole **20** and its regioisomers in 65% total yield,[49] and that with sodium azide **21** furnishes 4-cyano-1,2,3-triazole **22** via aromatization accompanied by elimination of nitrous acid (Scheme 8).[50]

Because a cyano group can serve as an electrophile, further ring construction is possible to afford 3-nitrocoumarin **24** in the condensation of NAN with salicylaldehyde **23** (Scheme 9). The double bond of **24** (C3−C4) provides a good dienophile for the Diels−Alder reaction yielding cycloadduct **25** upon treatment with diene **11**. When cycloadduct **25** is treated with sodium hydroxide, hydrolysis of the lactone ring predominantly occurs rather than elimination of nitrous acid, and subsequent decarboxylation furnishes cyclohexene **26** possessing a nitro group and a phenol ring at the vicinal positions.[51]

NAN readily executes nucleophilic addition to diazonium ions, and subsequent annulation furnishes polyazabicyclic compounds. This protocol is effective for obtaining energetic materials.[24] For example, pyrazole-3-diazonium ion **27** reacts with in situ generated NAN, and the ring nitrogen intramolecularly attacks the cyano group to form pyrazolotriazine **28** in 40% overall yield (Scheme 10).[52,53] Aminotriazole can be

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used instead of aminopyrazole for the synthesis of triazolotriazines.[54−56]

Chloroaldoxime **29** can be used as an electrophile for the reaction with NAN.[57] Nucleophilic substitution at the imino carbon followed by cyclization involving the hydroxy and the cyano groups affords vicinally functionalized isoxazole **30** (Scheme 11).

NAN serves as a nucleophile and contains reactive cyano and nitro functionalities. The combination of these reactivities facilitates ring transformation yielding polyfunctionalized heterocyclic compounds, which are not readily accessible via alternative methods.[58] When NAN is allowed to react with triarylpyrylium ion **31**, ring transformation accompanied by rearrangement of the nitro group proceeds to afford fully substituted benzene **32** (Scheme 12).[59]

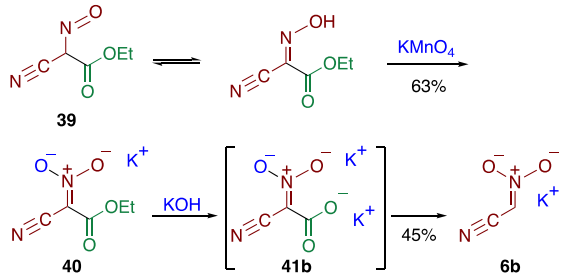
In the reaction of NAN with tetrazole-5-diazonium ion **33**, ring closure proceeds, as the reaction in Scheme 10, to form tetrazolotriazine **34**. However, due to the instability of the fused tetrazole ring, ring opening reaction and denitration proceed readily to afford azide-substituted 1,2,4-triazine **35** (Scheme 13).[60]

The cyano group of NAN serves as a dipolarophile in the reaction with 5-imino-1,2,4-thiadiazole **36** to form a new five-membered ring **37** (Scheme 14). The subsequent C−S bond formation concomitant S−N bond fission furnishes thiazole derivative **38**.[61]

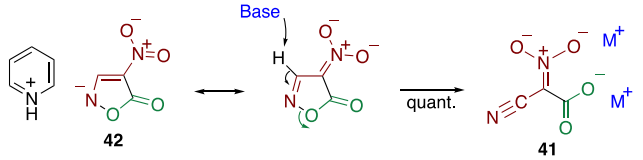
CYANO-*aci*-NITROACETATE

The diverse reactivity of NAN provides a useful synthetic tool for accessing versatile polyfunctionalized compounds; however,

Scheme 15. Ester 40 as a Precursor of 6b via Dipotassium Salt 41b



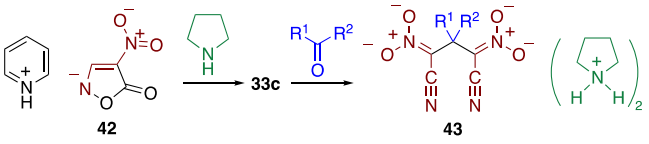
Scheme 16. Ring-Opening Reaction of Nitroisoxazolone 42



its explosive property curtails its practical use in organic synthesis. On the other hand, salt **6** sacrifices solubility in organic solvents while gaining thermal stability and ease of handling, which significantly narrows the substrate scope. Hence, achieving both ease of handling and stability while retaining solubility in organic solvents has been a long-standing challenge. From this viewpoint, cyano-*aci*-nitroacetates have recently attracted considerable attention.

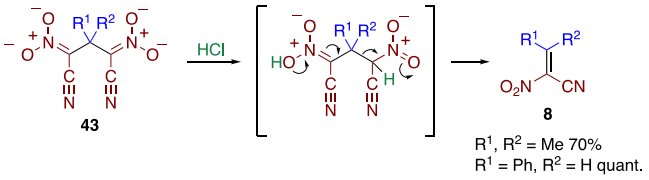
Ethyl cyano-*aci*-nitroacetate **40** is an easy-to-handle compound prepared via the oxidation of ethyl cyano(nitroso)-acetate **39** using potassium permanganate (Scheme 15).[62]

Table 1. Synthesis of Glutaronitriles 43

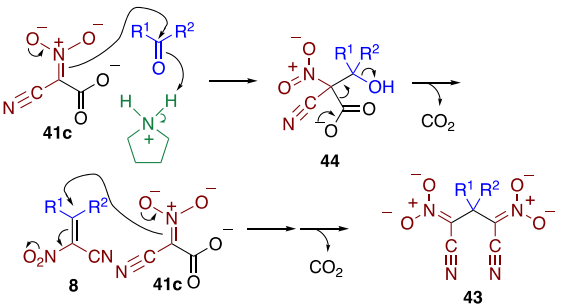


R^1	R^2	yield (%)
Ph	H	90
p-$MeOC_6H_4$	H	quant
Et	H	95
t-Bu	H	92
Me	Me	83
Et	Et	73
$-(CH_2)_4-$		64
$-(CH_2)_5-$		82

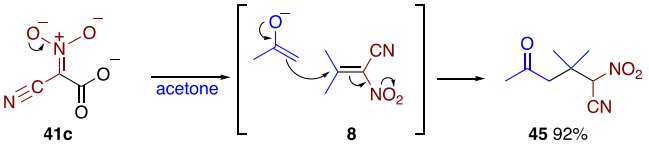
Scheme 17. Conversion of 43 to Electron-Deficient Alkene 8



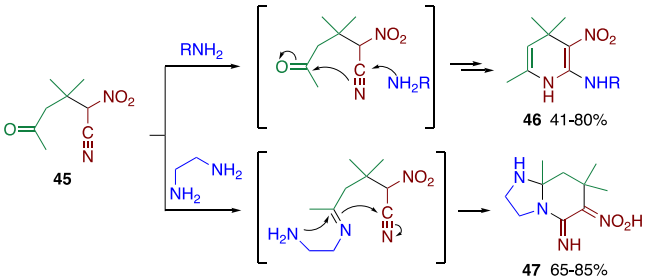
Scheme 18. Mechanism for the Condensation of 41c with Ketones



Scheme 19. Synthesis of *α*-Nitro-*δ*-keto Nitrile 45.



Scheme 20. Synthesis of Polyfunctionalized Heterocycles via a Pseudo-intramolecular Process



When ester **40** is treated with potassium hydroxide, potassium salt **6b** is obtained accompanied by decarboxylation (Scheme

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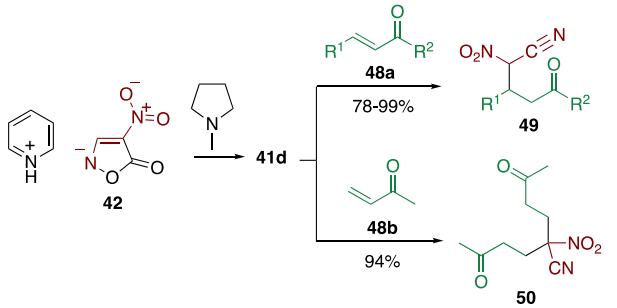
Scheme 21. Conjugate Addition of Dianion 41d to Enones 48



15).[63] The dianionic cyano-*aci*-nitroacetate intermediate **41** is stable and can be isolated. Barium salt **41a** was first synthesized by Ulpiani in 1912 via hydrolysis of ester **40** with barium hydroxide.[64] Due to the negative charge repulsion, it is considered that dianion **41** is more reactive than monoanionic reagent **6**; however, it has not been employed in organic synthesis owing to its inadequate solubility in common organic solvents.

Anionic nitroisoxazolone **42** is readily prepared from commercially available ethyl nitroacetate in two steps.[65] Although **42** is an anionic species, ring opening reaction proceeds efficiently at room temperature to afford dianionic cyano-*aci*-nitroacetate **41** upon treatment with base, such as a hydroxide, carbonate, ethoxide, or amines (Scheme 16).[65] The counter cations of **41** can be modified by altering the base. While the dimetal salt is insoluble, diammonium salt **41c**, prepared by using pyrrolidine, is soluble in common organic solvents. Dianion **41** and its precursor **42** are stable even at 140 °C and release considerably less energy (250 and 163 J/g, respectively) than NAN (874 J/g). These DSC results indicate that both compounds **41** and **42** are safe to handle in air.[28]

As already mentioned, neutral NAN and anionic nitroacetonitrile **6** efficiently react with aromatic aldehydes **7** to form the corresponding electron-deficient alkenes **8** (*α*-nitroacrylonitriles). In the case of cyano-*aci*-nitroacetate **41c**, not only aromatic aldehydes but also aliphatic aldehydes and ketones can be used as substrates; in this reaction, two molecules of **41c** react with one molecule of aldehyde to give glutaronitriles **43** with concomitant decarboxylation (Table 1).[66] Alkenes **8** are obtained via C−C bond cleavage initiated by acidification of **43** (Scheme 17).[66]

The condensation is initiated by nucleophilic attack of dianion **41c** onto the carbonyl functionality yielding adduct **44**. Subsequent decarboxylation affords *α*-nitroacrylonitrile derivatives **8**. The high electron-deficiency of **8** allows for a second addition of **41c**, forming glutaronitrile **43** (Scheme 18). When this reaction is conducted in acetone, intermediate alkene **8** undergoes nucleophilic attack by the enol of acetone instead of **41c**, affording *α*-nitro-*δ*-keto nitrile **45** (Scheme 19).[67]

The obtained product **45** contains an acidic hydrogen as well as electrophilic cyano and carbonyl functionalities. These structural features allow for a pseudo-intramolecular process, via which the efficient synthesis of polyfunctionalized heterocycles **46** and **47** can be realized in a single step (Scheme 20).[1,68]

While NAN enacts 1,2-addition to *α*,*β*-unsaturated aldehyde **9**, dianion **41d** (*N*-methylpyrrolidinium salt) effects conjugate addition (1,4-addition) to various *α*,*β*-unsaturated ketones **48** and esters.[69] This reaction affords distinct products depending on the level of steric hindrance in **48**; that is, only single addition proceeds in the case of *β*-substituted enones **48a**, whereas double addition proceeds in the case of enone **48b** without a substituent at the *β*-position to afford double adduct **50** (Scheme 21).

Double adduct **50** can be converted to naphthyridine **52** upon heating with ammonium acetate (Scheme 22).[69] In this reaction, the formation of intermediate bis(enamine) **51** is a likely first step, whereupon the amino group attacks the cyano group, followed by aromatization accompanied by elimination of nitrous acid and ammonia and by air oxidation to afford **52**.

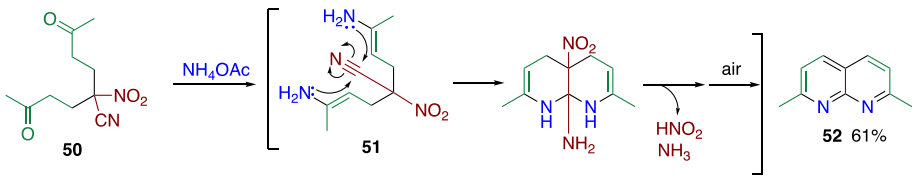
When the conjugate addition of **42** is applied to *α*-chloro-*α*,*β*-unsaturated ketones **53**, intramolecular nucleophilic substitution of the chloro group with the nitronate and subsequent dehydration proceed to afford polyfunctionalized isoxazoles **54** (Scheme 23).[28] The vicinal functionalities can be manipulated for ring construction, as demonstrated by the synthesis of isoxaloquinoline derivative **55** in 35% overall yield from **54a** via three steps: oxime formation, *O*-acetylation, and cyclization (Scheme 24).[28]

While the oxygen atom of a nitronate exhibits nucleophilicity, the carbon atom of *O*-acylated nitronates is highly electrophilic toward nucleophilic addition.[70] As glutaronitrile **43** contains two nitronates, one serves as a nucleophile and the *O*-acetylated nitronate serves as an electrophile to yield isoxazoline **56**. As the formed isoxazoline **56** has an electrophilic moiety, intramolecular ring transformation proceeds to afford polyfunctionalized isoxazoline **57** (Scheme 25).[71] In the case of glutaronitriles derived from aldehydes (R^1 = H), 3,5-dicyanoisoxazole is obtained as a result of further aromatization accompanied by elimination of nitrous acid.

■ CYANONITRILE OXIDE

1,3-Dipolar cycloaddition is one of the most powerful synthetic tools whereby a heterocyclic framework is generated through the formation of two new bonds in a single reaction.[72] Although numerous reports are found in the literature, the number of reports dealing with functionalized nitrile oxides is relatively low, despite the high synthetic utility thereof.[73] Regarding cyano-substituted nitrile oxide (cyanogen *N*-oxide) **58**, only a few generation methods are known. Although dehydrochlorination of cyanoformhydroximic chloride **59**[74,75] and flash pyrolysis of furazan derivative **60**[76] are known,

Scheme 22. Synthesis of Naphthyridine 52



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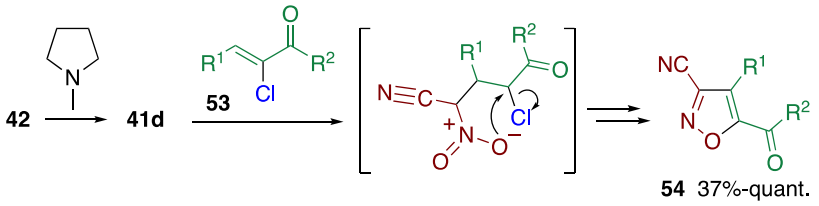
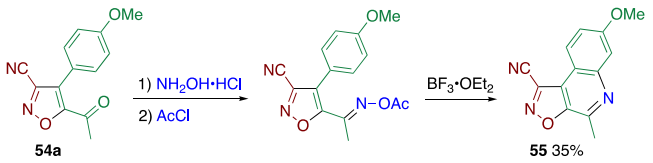
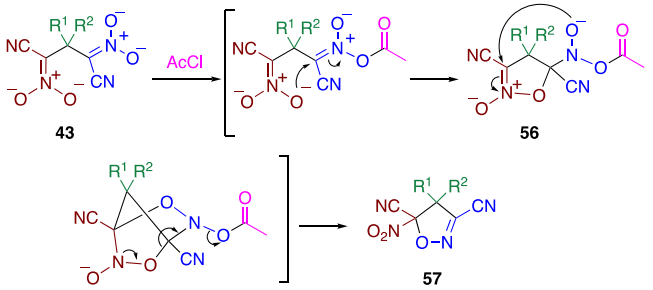
Scheme 23. Synthesis of Cyanoisoxazoles 54



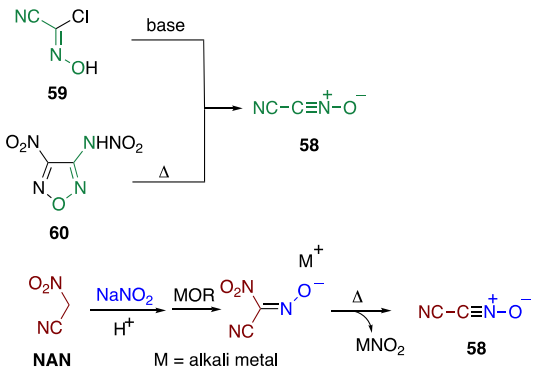
Scheme 24. Synthesis of Isoxazoloquinoline 55



Scheme 25. Synthesis of Polyfunctionalized Isoxazoline 57



Scheme 26. Methods for Generating Cyanonitrile Oxide 58



neither method is suitable for practical use because the precursors are not readily available (Scheme 26). NAN serves as a precursor of **58**, accessed via nitrosoation followed by thermal decomposition.[77]

On the other hand, decarboxylation of cyano-*aci*-nitroacetate **41a** readily occurs to afford NAN upon acidification. The nitronic acid tautomer of NAN is a 1,3-dipole and can therefore undergo cycloaddition upon heating with dipolarophiles, such as alkynes **61**, under acidic conditions to afford 3-cyanoisoxazoles **62** (Scheme 27).[78] Methacrylic acid **63** can be used as a dipolarophile without any modification, resulting in the formation of cyanoisoxazoline-5-carboxylic acid **64**. Products **62** and **64** are the same as cycloadducts as those obtained from the analogous reaction with nitrile oxide **58**; thus, NAN serves as a synthetic equivalent of cyanonitrile oxide **58**.

Evidently, NAN is a useful building block for the simultaneous introduction of a cyano and nitro group; however, its explosive property impedes its practical use in organic synthesis. Its alkali metal salt **6** is thermally stable, but its low solubility in organic solvents is a drawback that needs to be addressed. On the other hand, dianionic cyano-*aci*-nitroacetate **41** possessing organic counter cations is thermally stable and soluble in common organic solvents, allowing for its use as a safe, easy-to-handle synthetic equivalent of NAN. Indeed, versatile polyfunctionalized compounds can be synthesized via cyano(nitro)methylation using dianion **41**. Hence, dianion **41** is a useful building block broadly applicable under various conditions in organic synthesis.

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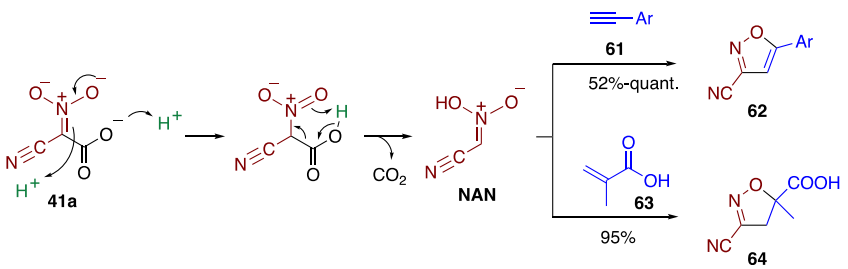
Scheme 27. NAN as a Synthetic Equivalent of Nitrile Oxide 58



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Notes

The authors declare no competing financial interest.

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