β-Formyl-β-nitroenamine: An Environmentally Benign Synthetic Equivalent of Nitromalonaldehyde

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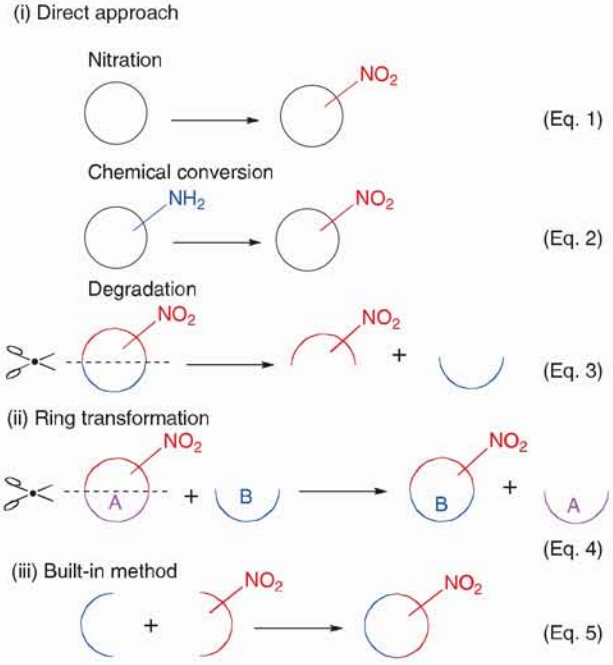
Abstract: Built-in method is one of the synthetic procedures for polyfunctionalized compounds, in which a building block having a functional group is incorporated into a new framework. β-Formyl-β-nitroenamine was found to be safe synthetic equivalent of unstable nitromalonaldehyde. The enamine is readily treatable because of high solubility into almost organic solvents with high stability. These features enable to use the enamine for organic syntheses. Indeed, nitrated pyrazoles, phenols and diazepines are available upon treatment of the nitroenamine with hyrazines, ketones, and diamines, in which 5-7 membered rings are constructed.

1. Introduction

Nitro compounds constitute a large family among organic compounds and are widely used for various purposes; millions of tons of nitro compounds are synthesized and consumed every year.[1-3] A nitro group is one of the important functional groups in organic syntheses because of strong electron withdrawing ability and diverse chemical behavior.[1] The nitro group considerably decreases electron density of the scaffold framework by both inductive and resonance electron withdrawing effects in order to facilitate reactions with nucleophiles. The α-hydrogen of a nitro group becomes highly acidic to form a stable nitronate anion, which reacts with both electrophilic and nucleophilic reagents. Furthermore, a nitro group assists the cleavage of an adjacent carbon-carbon bond, and can transform to versatile functional groups by the Nef reaction or by reduction.

Preparative methods for nitro compounds are generally divided into three categories, namely: (i) the direct approach to nitro compounds, (ii) built-in methods using a nitrated building block, and (iii) ring transformations, which are supplementary to each other.



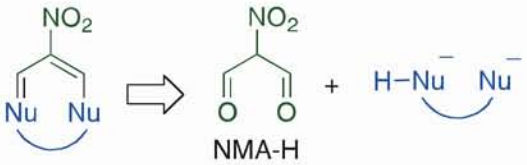
In the direct approach, three strategies are mainly employed; the most common of these is the nitration, which directly introduces a nitro group into the scaffold framework (Eq. 1). If other functional groups can be easily introduced, chemical transformation of the functional group into a nitro group becomes a useful

method for obtaining nitro compounds (Eq. 2). When nitro compounds with an additional functional group are necessary, degradation of nitrated heterocyclic compounds is often employed (Eq. 3). Ring transformation is also a useful method for synthesizing complicated skeletons that are not easily available by alternative methods (Eq. 4). The built-in method is incorporation of a nitro compound bearing an additional functional group as the building block, which is also powerful method in elaborate syntheses (Eq. 5). The direct approach is not always available because severe conditions are required, under which another functional group or a heterocyclic structure cannot tolerate. Hence, the ring transformation and the built-in method are often employed instead of the direct approach.

2. Sodium nitromaloaldehyde

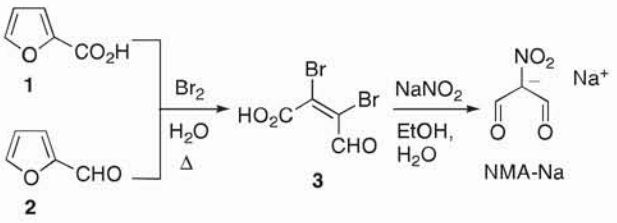
2.1 Synthetic equivalent of nitromalonaldehyde **NMA-H**

In designing synthetic schemes of nitro compounds by use of the built-in method, building blocks often appear as synthons in retrosyntheses, among which nitromalonaldehyde (**NMA-H**) is an important compound. **NMA-H** is a simple compound for a theoretical study on an intramolecular hydrogen bond, proton transfer and quasi-aromaticity.[4,5] However, **NMA-H** is too unstable in aqueous solutions to be isolated, presumably due to easily occurring hydrolysis accompanied by a C-C bond fission.[6] Thus, **NMA-H** is prepared only by bubbling dry hydrogen chloride to a suspension of sodium nitromalonaldehyde (**NMA-Na**) in dry carbon tetrachloride.[5] Hence, it is one of important subjects to develop the synthetic equivalents of **NMA-H**. From this viewpoint, **NMA-Na** has been employed for the construction of nitro compounds from old time, which was well reviewed by Fanta and Stein.[7]



2.2 Preparation of **NMA-Na**

The preparation of **NMA-Na**[8] is achieved by treating mucobromic acid **3** which is easily available from furan-2-carboxylic acid **1**[9] or furfural **2**[10] by the ring-opening reaction with bromine. However, these methods include somewhat troublesome manipulations, and a small quantity of hydrogen cyanide is evolved in each reaction.[11]

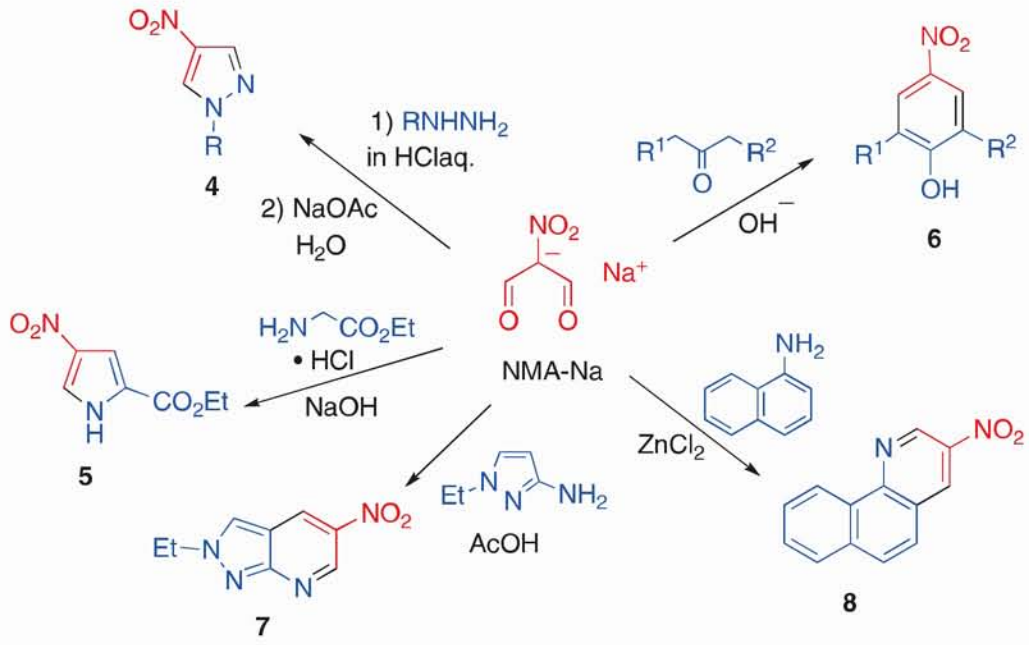


2.3 Syntheses of nitro compounds using **NMA-Na**

NMA-Na has been used for synthesizing versatile nitro cyclic compounds upon treatment with dinucleophilic reagents.[7] When **NMA-Na** is subjected to reactions with hydrazines, a five membered ring is readily formed to afford nitropyrazoles **4**. As the dinucleophilic reagents, carbon nucleophiles are also usable. For example, glicine ethyl ester reveals nucleophilicity both at the amino group and the α-carbon, which enables to afford 5-nitropyrrole-2-carboxylic acid ester **5**.

Six membered rings can be constructed in the reactions of **NMA-Na** with 1,3-dinucleophilic reagents. Nitrophenols **6** are available by condensation of **NMA-Na** with ketones, which is advantageous with regard to easy modification of substituents. The present method is applicable to the synthesis of condensed ring systems such as **7** and **8** by using aminopyrazole and aminonaphthalene as the dinucleophile, respectively.

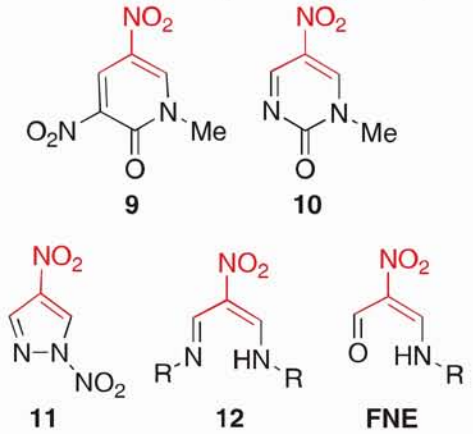
As mentioned so far, **NMA-Na** has been widely employed as the useful synthetic equivalent of **NMA-H**.[7] However, this reagent suffers from the following drawbacks. In addition to some problems mentioned in Section 2.2, it is claimed that crude **NMA-Na** is impact-sensitive and thermally unstable, and should be handled as a potentially explosive material.[7,8] Furthermore, the reactions of **NMA-Na** require to use water and/or ethanol as the solvent because of its low solubility to common organic solvents. Hence, development of the synthetic equivalent of **NMA-H** treatable in organic media is highly demanded.



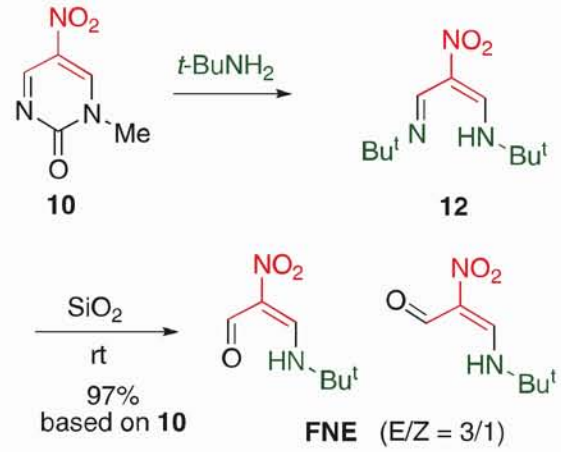
3. β-Formyl-β-nitroenamine

3.1 Preparation of formylnitroenamine

Recently, several other synthetic equivalents of **NMA-H** have been developed to overcome these disadvantages of **NMA-Na**,[12] dinitropyridone **9**,[13-17] nitropyrimidinone **10**,[18] dinitropyrazole **11**,[19] nitroazadienamines **12**,[20,21] and formylnitroenamine (**FNE**).[22,23] Among these reagents, **FNE** is the most easily treatable because of high solubility into organic solvents.



Highly electron deficiency of pyrimidinone **10** enables the aminolysis to afford azadienamines **12** in good yields upon heating with amines.[21] When azadienamines **12** are charged on silica gel for a few days at room temperature, half hydrolysis efficiently occurs to afford **FNE**s as a mixture of *E*/*Z* isomers in a ratio of about 3/1.[21]

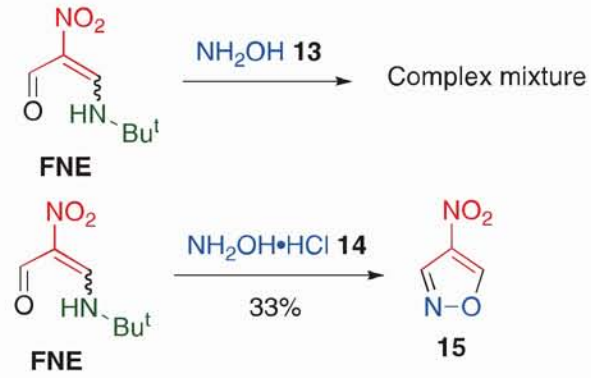


FNEs are one class of typical push-pull alkenes possessing biased electron density, which exhibit versatile reactivity. The formyl group and the α-carbon are electrophilic sites, and the amino group and the β-carbon are nucleophilic sites. In the reaction with a dinucleophile, **FNE**s serve as dielectrophiles to give nitro compounds; it means that **FNE** is a synthetic equivalent of **NMA-H**.

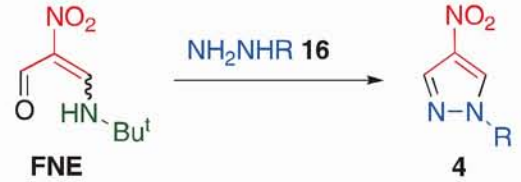
3.2. Reactions of **FNE** with N,O-and N,N-dinucleophiles

Nitroisoxazole **15** is considered to be available by condensation of **NMA-H** with hyrozylamine **13** liberated from its hydrochloride **14** in the presence of triethylamine, however, the isoxazole **15** cannot be obtained by the reaction of **NMA-Na** with **13**. Indeed, the reaction of **FNE** with hydroxylamine **13** also afforded

a complex mixture of unidentified products. This problem is overcome by employing hydrochloride **14** itself as a dinucleophile to afford nitroisoxazole **15** even though the yield is low.[23] Since isolated isoxazole **13** reacts with hydroxylamine **13** under the same conditions to furnish unidentified products, decomposition is found to be a major reason of the low yield of **13**.

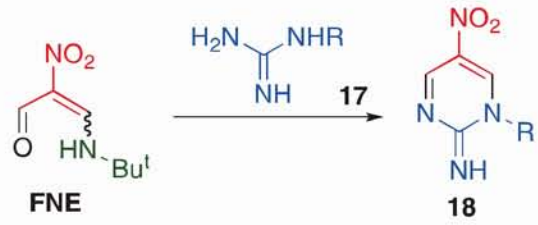


On the other hand, nitropyrazoles **4** are readily prepared by the condensation of **FNE** with hydrazines **16**.[23] The high solubility of FNE into organic solvents enables to employ various kinds of hydrazines, which consequently leads to the synthesis of nitropyrazoles having a bulky alkyl group, a functional group, or an aromatic group at the 1-position, which is one of advantageous features in comparison with a conventional synthetic equivalent, **NMA-Na**.

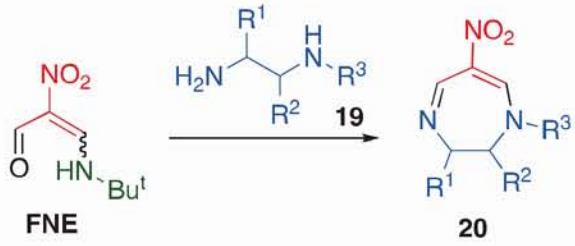


R	Yield/%
H	87
Me	96
t-Bu	59
CH_2COOEt	90
Ph	35
p-MeC_6H_4	47

When guanidines **17** are employed as the dinucleophiles, a six membered ring is constructed to afford pyrimidines **18**.[23]



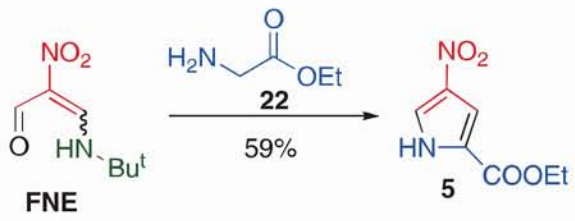
A seven membered ring can be formed to afford 6-nitro-1,4-diazepines **20** upon treatment of **FNE** with 1,2-diamines **19**.[23,24] In the present reaction, *N*-Substituted and 2,3-disubstituted diamines are also usable as the dinucleophile to afford the corresponding diazepines. When this reaction is conducted in a concentrated solution, oligomeric products **21** are also formed.



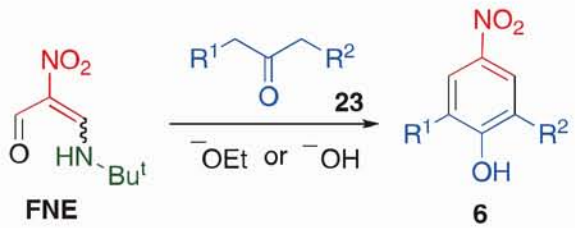
R^1	R^2	R^3	Yield/%
H	H	H	quant.
H	H	Et	80
H	Me	H	69
$-(CH_2)_4-$ (*cis*)		H	79
$-(CH_2)_4-$ (*trans*)		H	86

3.3 Reactions of **FNE** with C,N-and C,C-dinucleophiles

Carbon nucleophiles (C-nucleophiles) are also usable as the dinucleophiles instead of nitrogen nucleophiles (N-nucleophiles). Glycine ethyl ester **22** is one of the C,N-dinucleophiles which has both C- and N-nucleophilic sites. Indeed, condensation of **FNE** with **22** readily proceeds to form a five membered product, ethyl 4-nitropyrrole-2-carboxylate **5**, in 59% yield.[23]



FNE reacts with ketones **23** to undergo a double condensation affording 2,6-disubstituted 4-nitrophenols **6**.[22] In a industrial process, substituted nitrophenols are often prepared by the Friedel-Crafts alkylation of phenols followed by nitration,[25] which includes several restrictions to be overcome. In electrophilic substitutions, the control of regioselectivity is especially a significant problem; it is difficult to prepare successively trisubstituted benzenes. In addition to this problem, an aryl group nor an alkyl chain longer than an ethyl group cannot be introduced by the Friedel-Crafts reaction, and polyalkylation is another problem.



R^1	R^2	Yield/%
i-Pr	H	quant.
Et	Me	74
Ph	Ph	77
Pr	H	quant.
Pr	Pr	quant.
i-Pr	*i*-Pr	12
Ph	Pr	76
COOEt	H	55
COOEt	COOEt	80
COOMe	OMe	51

On the other hand, our approach to **6** using **FNE** is advantageous with regard to easy modification of substituents, which dissolves several problems encountered in the Friedel-Crafts reaction mentioned above. By applying this method, nitrophenols with diverse substituents are available, which are further used for developing functional materials.

4. Conclusion

FNE serves as a synthetic equivalent of **NMA-H** to afford nitro cyclic compounds. **FNE** does not show an explosive property and is highly soluble into organic solvents. These features are advantageous for practical use, compared with **NMA-Na**, with regard to safety and treatability. Furthermore, **FNE** undergoes the reactions with versatile dinucleophiles efficiently, which diminished the amount of reagents, wastes and energies. Hence, **FNE** is concluded to be an environmentally benign synthetic equivalent of **NMA-H**.

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β-ホルミル-β-ニトロエナミン：環境負荷の少ないニトロマロンアルデヒドの合成等価体

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要約：多官能化合物を合成する方法の 1 つに、官能基を有するビルディングを組み込む方法がある。本研究では、ホルミル基を有するニトロエナミンに着目し、合成ユニットとしてしばしば見られるニトロマロンアルデヒドの合成等価体として利用できることを明らかにした。本化合物は爆発性を示すことなく安定である。また、ほとんどの有機溶媒に溶解することから、簡便に取り扱うことができ、その汎用性が期待される。実際に、ヒドラジン類、ケトン類、1,2-ジアミン類などの二座求核種を作用させれば、5－7 員環を効率良く構築することができ、それぞれ対応するニトロピラゾール類、ニトロフェノール類、ニトロジアゼピン類を得ることが可能である。