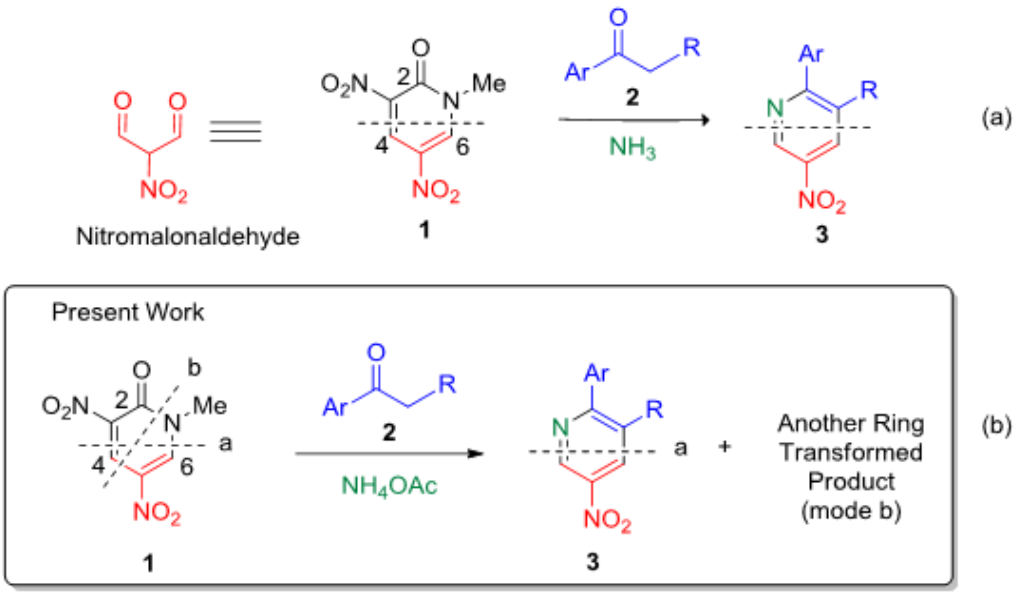
論 文 内 容 の 要 旨

1. Research Background

Nitro compounds show great importance in chemistry, biology and material sciences. Among them, nitropyridines and nitroanilines are widely used as useful intermediates for synthesis of biologically active compounds, pharmaceutical and agrochemical importance. Although nitration is the easiest way for introducing nitro group to scaffold frameworks, harsh conditions are sometimes necessary, which means the control of the reaction is quite difficult and a reactive functional group cannot be tolerated. Furthermore, a strategy to install substituents directly into pyridine framework is not easily performed because of low reactivity of pyridines and its derivatives. Thus, the development of an efficient method for synthesis of these compounds still remains a challenge.

Meanwhile, we have reported an alternative preparation method for nitropyridine derivatives by three component ring transformation (TCRT) of dinitropyridone 1 with ketones 2 in the presence of methanolic ammonia as a nitrogen source (Scheme 1, path a), in which the dinitropyridone 1 serves as a synthetic equivalent of an unstable nitromalonaldehyde. Unfortunately, this method requires preparation of methanolic ammonia beforehand, and suffers from low yields of the products because of the competitive aminolysis of substrate 1. If these disadvantages are overcome, this reaction will be a powerful protocol for synthesis of nitropyridines and nitroanilines which are not easily prepared by other methods. Therefore, the goal of this Ph.D Thesis was the development of a new method for synthesis of various kinds of nitro compounds by using a TCRT of dinitropyridone 1 with ketones in the presence of less nucleophilic ammonium acetate (NH4OAc) as nitrogen source, which avoids the aminolysis of 1 (Scheme 1, path b).



Scheme 1. A TCRT of dinitropyridone with ketones in the presence of nitrogen source

2. The Structure of Thesis

As mentioned above, the purpose of this thesis is to develop a new method for synthesis of nitro compounds. As a result, a new synthetic method was developed which leading to arylated nitropyridines, nitrated cycloalkal[b]pyridines, alkenylnitropyridines, alkynylnitropyridines, 3-substituted nitropyridines and nitroanilines. The achievement of our works and the interesting features of our synthetic method have been confirmed through several publications. The thesis has been structured by an introductory part, which gives a brief introduction about nitro compounds and their synthetic methods. The introduction of three component ring transformation will also be emphasized in this chapter. The second part of this thesis deals with the original contributions (from chapter 2 to chapter 6). The chapter 2 begins with synthesis of 2-arylated-5-nitropyridines using TCRT of dinitropyridone 1 with aromatic ketones 2 in the presence of NH4OAc. In order to investigate the scope and limitations of this TCRT, various kinds of substrates were employed and the detailed results were presented as follows: (chapter 3) synthesis of nitrated cycloalkal[b]pyridines, (chapter 4) synthesis of 2-alkenyl/alkynyl 5-nitropyridines,

(chapter 5) synthesis of 3-alkylated/arylated 5-nitropyridines, and (chapter 6) synthesis of N,N,2,6-tetrasubstituted 5-nitropyridines.

The important conclusions were presented in chapter 7 and a final part which contains a supplementary data.

3. Thesis Contents

3.1. Introduction

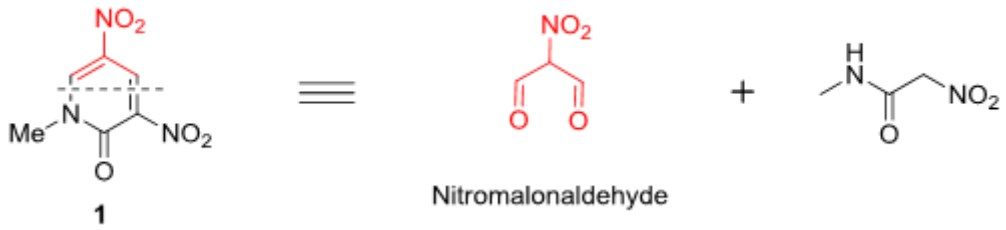
3.1.1. Synthesis of Nitro Compounds

Nitro compounds constitute an important class among organic compounds, and are widely used for various purposes. A nitro group is one of the important functional group in chemical syntheses because of the following properties: (1) a nitro group behaves as an electron-withdrawing group by both inductive and resonance effects; (2) the electron-withdrawing nitro group activates various skeletons to facilitate reactions with nucleophiles; (3) a nitro group assists the adjacent carbon-carbon bond cleavage, and can be transformed to versatile functional groups by the Nef reaction or by reduction. Thus, a large number of nitro compounds are often employed as the key intermediates leading to versatile compounds. Generally, direct nitration of the heterocyclic compounds such as pyridine is rather difficult than that of benzene ring because of low electron density and the basic nitrogen which forms a salt with acid catalyst. Therefore, supplementary protocols for construction of nitro compounds should be developed.

3.1.2. Three Component Ring Transformation

Ring transformation is a supplementary method for synthesis of nitrated heterocyclic compounds which are not easily prepared by other methods. While Diels-Alder-type and ANRORC-type ring transformations have been energetically studied, nucleophilic-type ring transformations have not been studied enough. From this viewpoint, the main parts of this thesis are emphasized to nucleophilic-type ring transformation.

Electron-deficient cyclic compounds having good leaving group are suitable substrates for nucleophilic ring transformation. Thus, dinitropyrdione 1 which behaves as synthetic equivalent of unstable nitromaloaldehyde, is considered to be a good substrate for nucleophilic ring transformation to afford versatile nitro compounds upon treatment with dinucleophilic reagents accompanied by elimination of nitroacetamide (Scheme 2).



Scheme 2. The Substrate for nucleophilic ring transformation

1,3-Dicarbonyl compounds surely behave as the excellent dinucleophilic reagents for nucleophilic ring transformation. Unfortunately, only serval kinds of ring transformation products can be obtained due to limited availability of these reagents. Thus, if we can use a simple ketones instead of dinucleophilic reagents, the synthetic utility of nucleophilic ring transformation will be improved. In this case, another nucleophilic reagent is required, which behaves as a nitrogen source or activator of substrate. This kinds of nucleophilic ring transformation is called “three component ring transformation (TCRT)”.

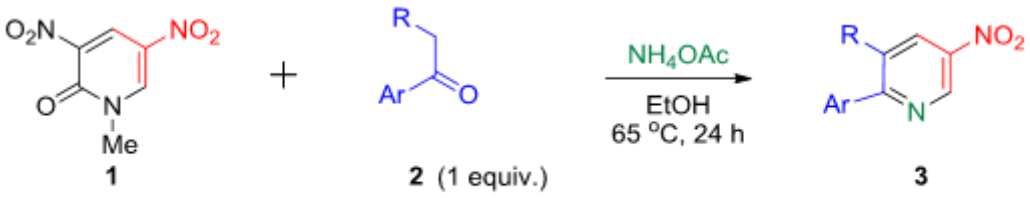
3.2. Original Contributions

3.2.1. Synthesis of 2-Arylated-5-nitropyridines

Arylated nitropyridines are widely used for synthesis of biologically active compounds or their synthetic intermediates. Although Suzuki reaction and Kumada-Tamao reaction are commonly used for synthesis of these frameworks, they suffer from poor availability of functionalized halopyridines and coupling partners.

Moreover, it is difficult to introduce an electron-deficient aryl group into the pyridine ring. Hence, development of an efficient, easily manipulated and environmentally benign method for synthesis of arylated nitropyridines remains a significant challenge.

In this part, the TCRT of dinitropyridone 1 with aromatic ketones 2 and NH4OAc was investigated, which afforded 2-arylated-5-nitropyridines 3 from good to excellent yields, as illustrated in Scheme 3. Furthermore, the application of various kinds of (het)aryl ketones as substrates for this reaction affording the corresponding (het)arylated pyridines was also studied .



Ar = Ph, R = H; **3a** (79%)
Ar = 4-MeOC$_6$H$_4$, R = H; **3b** (95%)
Ar = 3-MeOC$_6$H$_4$, R = H; **3c** (94%)
Ar = 2-MeOC$_6$H$_4$, R = H; **3d** (97%)
Ar = 4-MeC$_6$H$_4$, R = H; **3e** (88%)
Ar = 4-ClC$_6$H$_4$, R = H; **3f** (96%)
Ar = 4-NO$_2$C$_6$H$_4$, R = H; **3g** (93%)
Ar = 4-Pyridyl, R = H; **3h** (66%)
Ar = 3-Pyridyl, R = H; **3i** (97%)
Ar = 2-Pyridyl, R = H; **3j** (80%)
Ar = 2-Furyl, R = H; **3k** (87%)
Ar = 2-Thieyl, R = H; **3l** (85%)
Ar = 2-Pyrrolyl, R = H; **3m** (87%)
Ar = Ph, R = Me; **3n** (98%)
Ar = Ph, R = Pr; **3o** (97%)

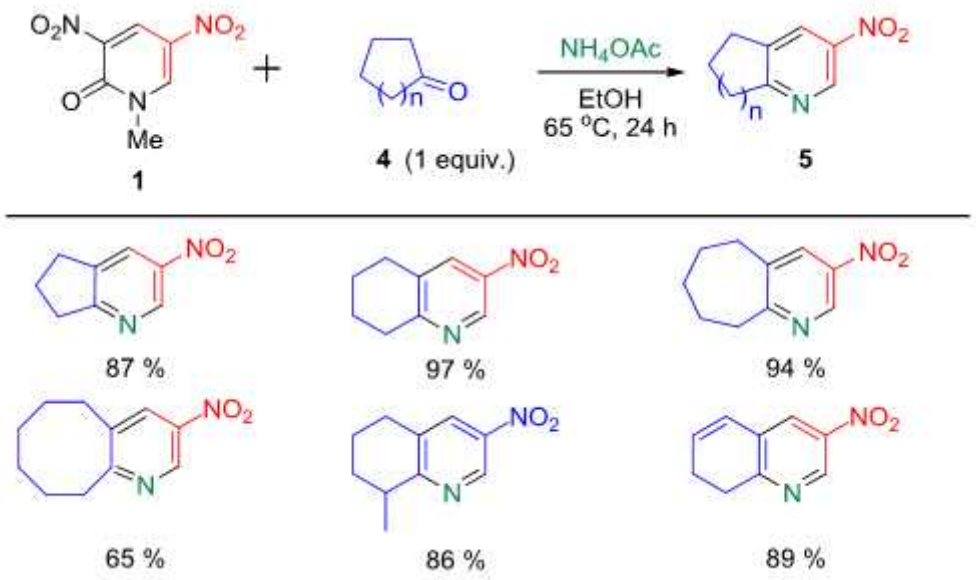
Scheme 3. The TCRT of 1 with ketones 2 and NH4OAc affording 2-arylated-5-nitropyridines 3

3.2.2. Synthesis of Nitrated cycloalka[b]pyridine

Nitrated cycloalka[b]pyridines 5 are widely employed as useful intermediates for synthesis of metacyclophane, phamacophores and biologically active compounds. Recently, some research groups reported their method for synthesis of nitropyridines derivatives, however, their reactions suffer from low yields of products.

Taking the advantages of our reported method for synthesis of nitropyridine derivatives as mention before, the substrate scope of this method was extended to a

series of cyclic ketones 4. Thus, nitrated cycloalka[b]pyridines 5 could be obtained from good to excellent yields by one-step reaction, as illustrated in Scheme 4. Furthermore, a double bond could be easily introduced to the product by changing the cycloalkanone to a cycloalkenone (Scheme 4).



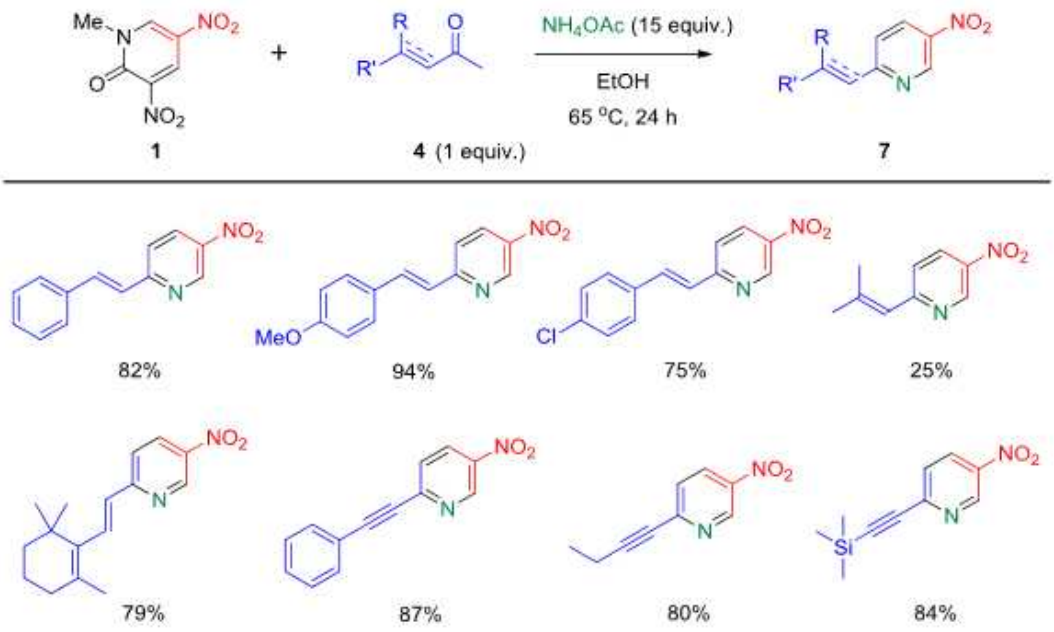
Scheme 4. A TCRT of 1 with cyclic ketones 4 and NH4OAc affording nitrated cycloalka[b]pyridines 5

3.2.3. Synthesis of 2-Alkenyl/alkynyl 5-nitropyridines

2-Alkenyl 5-nitropyridines and 2-alkynyl 5-nitropyridines are widely employed as precursors for pharmaceuticals and biologically active compounds. In addition, alkynylnitropyridines are often found in nonlinear optical materials and organic semiconductors. Although the Heck, Suzuki, Stille, and Sonogashira reactions are often used as common protocols for alkenylation/alkynylation, poisonous and expensive transition metals should be used and a purification step to avoid metal

contamination of the products is necessary. Therefore, the development of a metal-free, facile, and efficient economical methodology for the synthesis of alkenyl/alkynylpyridines is still challenging.

In this part, a metal-free, facile, and efficient protocol for synthesizing a series of 2-alkenyl/alkynyl-5-nitropyridines 7 was developed by using a three-component ring transformation of dinitropyridone 1 with α,β-unsaturated ketones 6 and NH4OAc. As a results, various kinds of 2-alkenyl/alkynyl 5-nitropyridines 7 were prepared from good to excellent yields (Scheme 5). Because these compounds are not easily prepared by Heck or Sonogashira reactions, this method will be a supplementary to these reactions.



Scheme 5. The TCRT of 1 with α, β-unsaturated ketones 6 and NH4OAc affording nitropyridines 7

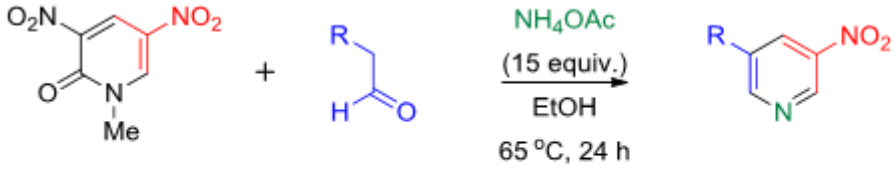
3.2.4. Synthesis of 3-Alkylated/arylated 5-nitropyridines

3-Alkylated/arylated 5-nitropyridines are widely used as synthetic intermediates for preparation of biologically active compounds such as cytokine inhibitors for treatment of various

diseases, Wnt β-catein signalling pathway inhibitors, HIV integrase inhibitors, and dihydroorotate

dehydrogenase (DHODH) inhibitors. Despite their versatile and useful applications, versatile 3-alkylated/arylated 5-nitropyridines are not easily available because ß-alkylation/arylation of the pyridine framework is particularly difficult. Thus, only a few direct ß-alkylation methods are known until now. With regard to direct phenylation, it has been realized by recent considerable efforts, however, these methods still suffer from harsh conditions or low regioselectivity. Therefore, the development of an efficient methodology for synthesis of 3-alkylated/arylated 5-nitropyridines is still significant challenge.

In this part, an alternative method for synthesis of 3-alkylated/arylated 5-nitropyridines 9 was provided which includes the three component ring transformation of dinitropyridone 1 with aldehydes 8 in the presence of NH4OAc. This method facilitates the modification of the substituent at the 3-position by only changing the aldehyde. The use of solid NH4OAc as a nitrogen source instead of ammonia improves this ring transformation as practically usable synthetic method (Scheme 6).



1 **8** (2 equiv.) **9**

Entry	R		Yield (%)
1	Me	**b**	52
2	i-Pr	**c**	71
3	Bn	**d**	34
4	t-Bu	**e**	29
5[a]	t-Bu	**e**	68
6	Ph	**f**	47
7[a]	Ph	**f**	75

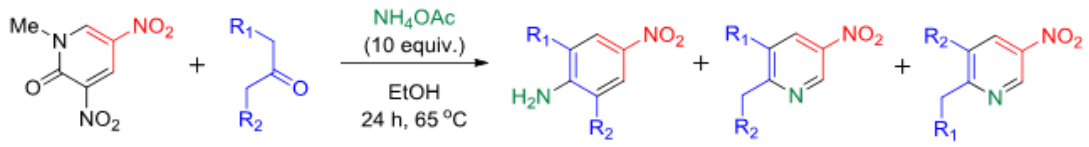
a: microwave heating was used

Scheme 6. The TCRT of 1 with aldehyde 8 and NH4OAc affording 3-Alkylated/arylated 5-nitropyridines 9

3.2.5. Synthesis of Nitroaniline Derivatives

2,6-Disubstituted 4-nitroanilines are widely used for synthesis of pharmaceutical agents and material science such as inhibitors of cholesterol acyl transferase, π-conjugated polymers. Furthermore, they are also used for synthesis of dyes, pharmaceuticals, ferromagnetic materials, organometallic complex, and garnet inhibitors. Moreover, these compounds are energetically studied as potential organic nonlinear optical materials. Generally, nitroaniline frameworks are usually prepared from the corresponding 2,6-disubstituted anilines by nitration under harsh conditions. Furthermore, the preparation of 2,6-disubstituted anilines suffers from some limitations since these alkyl groups are introduced into benzene ring by Friedel-Crafts reaction. Thus, the development of an efficient synthetic pathways is still challenging.

In this part, an efficient method for synthesis of various kinds of 2,6-disubstituted-4-nitroanilines 11 was developed by using TCRT of dinitropyridone 1 upon treatment with aliphatic ketones 10 in the presence of NH4OAc as a nitrogen source. The benzene ring as well as the amino group of the nitroaniline framework was easily modified by only changing a ketone and the nitrogen source, which afforded N,N,2,6-tetrasubstituted 4-nitroanilines 13-15 in good to excellent yields (Schemes 7 and 8).



1 **10** (1 equiv.) **11** **12** **12'**

10a : $R^1 = R^2$ = Me ; **11c**: 83% and **12c** : 13%

10b : $R^1 = R^2$ = H ; **11b**: 51% and **12b** : 47%

10c : $R^1 = R^2$ = Pr ; **11c**: 74% and **12c** : 22%

10d : $R^1 = R^2$ = Ph; **11d**: 8% and **12d** : 81%

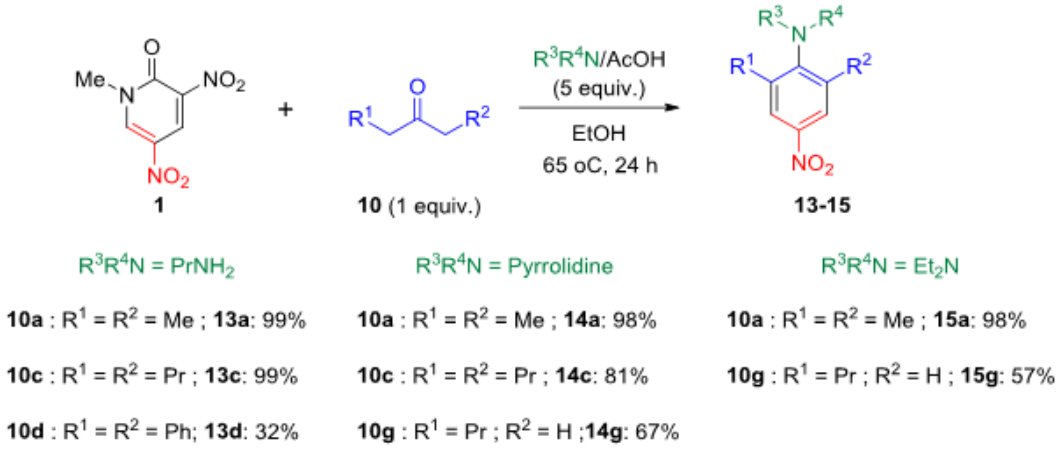
10e : R^1 = Et ; R^2 = H ; **11e**: 66% ; **12e:** 10% and **12e'** : 8%

10f : R^1 = iPr ; R^2 = H ; **11f:** 58% ; **12f** : 0% and **12f'** : 31%

10g: R^1 = Pr ; R^2 = H ; **11g**: 83% ; **12g** : 9% and **12g'** : 6%

10h : R^1 = Ph ; R^2 = Pr ; **11h**: 62% ; **12h** : 24% and **12h'** : 13%

Scheme 7. The TCRT of 1 with aliphatic ketones 10 and NH4OAc affording nitroanilines 11 and nitropyridines 12



Scheme 8. The TCRT of 1 with aliphatic ketones 10 and a combination of amine and acid acetic affording N,N,2,6-tetrasubstituted nitropyridines 13-15

3.4. Conclusions

In summary, we have successfully developed a facile and efficient method for construction libraries containing a large number of nitropyridine and nitropyridine derivatives, which are not easily prepared by other methods. This method requires only simple manipulations, single step reaction, and mild conditions. Furthermore, the modification of nitropyridine or nitroaniline frameworks can be easily obtained only chaining a commercially available substrates. These features improve the synthetic value of this method, and it will be alternative approach to nitro compounds.