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An Introduction to the Synthesis of Nitroanilines and Nitropyridines *via* Three Component Ring Transformation

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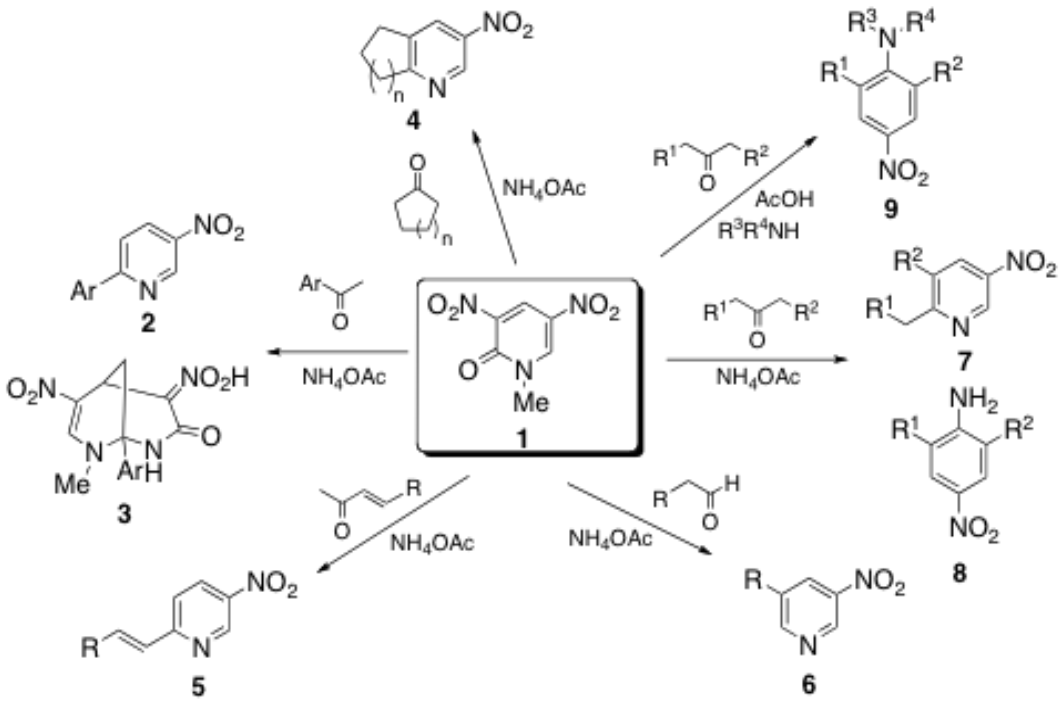
KOCHI UNIVERSITY OF TECHNOLOGY

An Introduction to the Synthesis of Nitroanilines and Nitropyridines *via* Three Component Ring Transformation



Abstract:

A file syntheis of nitropyridines and nitroanilines are achieved by using a three component ring transformation of dinitropyridone **1** with ketones in the presence of less nucleophilic ammonium acetate (NH_4OAc) as nitrogen source.

When pyridone **1** was reacted with aromatic ketone in the presence of ammonium acetate, 6-arylated 3-nitropyriines **2** were formed besides diazabicyclo compounds **3**. This method was also applicable to cycloalkanones and α,β-unsaturated ketones to afford cycloalka[*b*]pyridines **4** and 6-alkynylated/alkenylated pyridines **5**, respectively. It was found to be possible to use aldehydes as the substrate, which leading to 3,5-disubstituted pyridines **6**.

On the other hand, when aliphatic ketones were employed as the substrate, two kinds of ring transformation proceeded. Namely, 2,6-disubstituted 4-nitroanilines **8** were formed in addition to nitropyridines **7**. It was successful to apply this protocol to synthesis of *N*,*N*,2,6-tetrasubstituted nitroanilines **9** upon treatment of dinitropyridone **1** with ketone and amine in the presence of acetic acid.

Keywords: Ring Transformation; Dinitropyridone; Nitropyridine; Nitroaniline; Multi Component Reaction

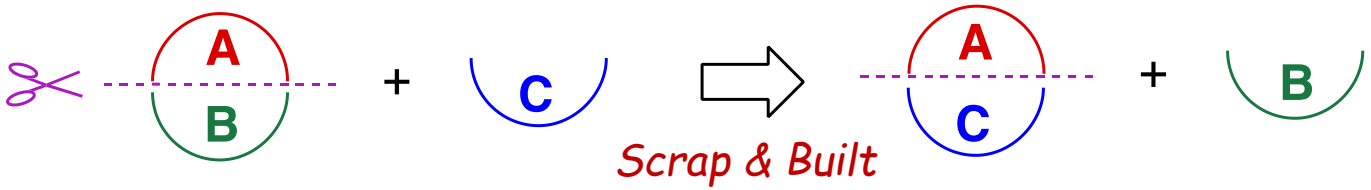
Introduction

Functionalized Heterocyclic Compounds are Useful for
Medicines, Agricultural Chemicals, Dyes,
Organic Electroluminescence etc.

However,
It is not Easy to Functionalize the Heterocyclic Framework.
Hence,
Efficient Functionalization Method should be Developed.

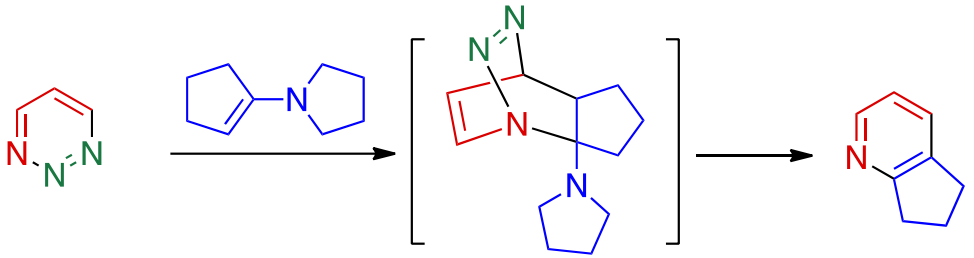
Ring Transformation is One of the Solution for This Problem !!

What is the Ring Transformation?

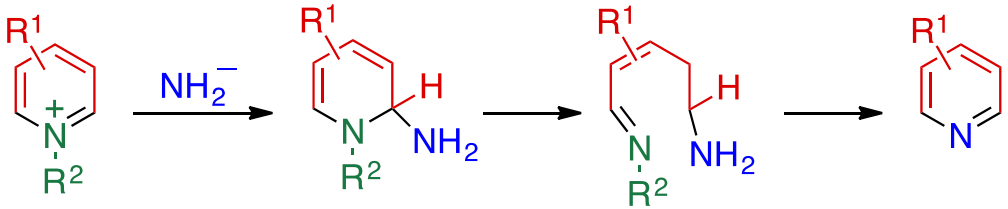


Substrate Reagent Product Leaving Group

Diels-Alder Type



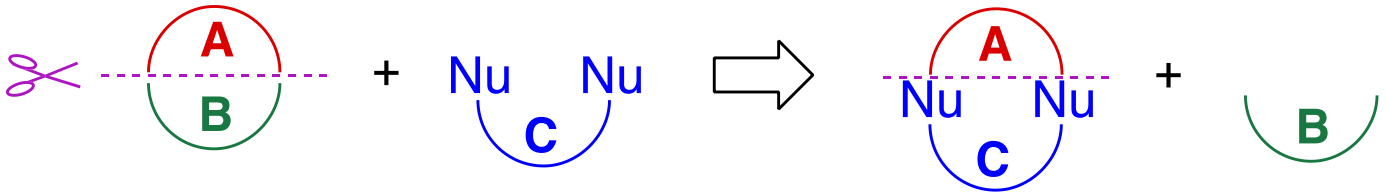
Anderson, *Org. Lett.* **2011**, *13*, 249



Degenerate Type

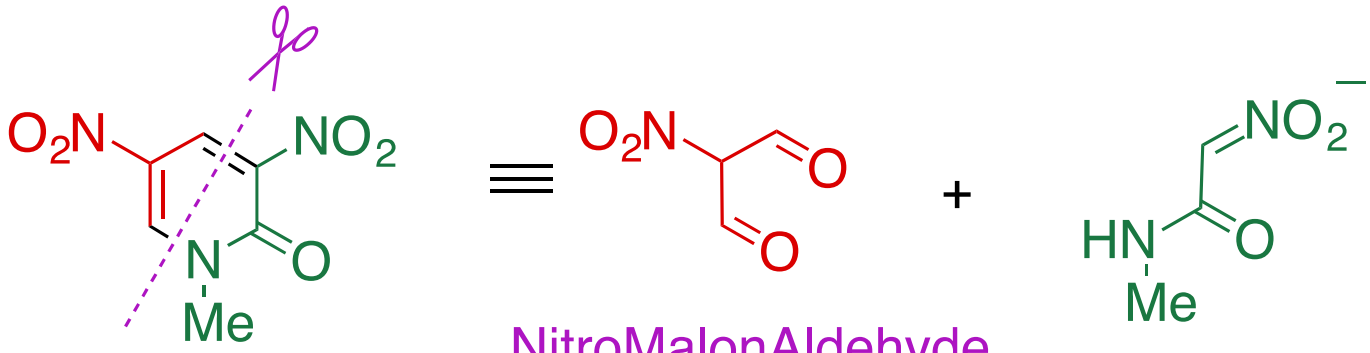
van der Plas, *J. Heterocycl. Chem.* **2000**, *37*, 427

NewType Ring Transformation (Nucleophilic Type)



Substrate Reagent Product Leaving Group

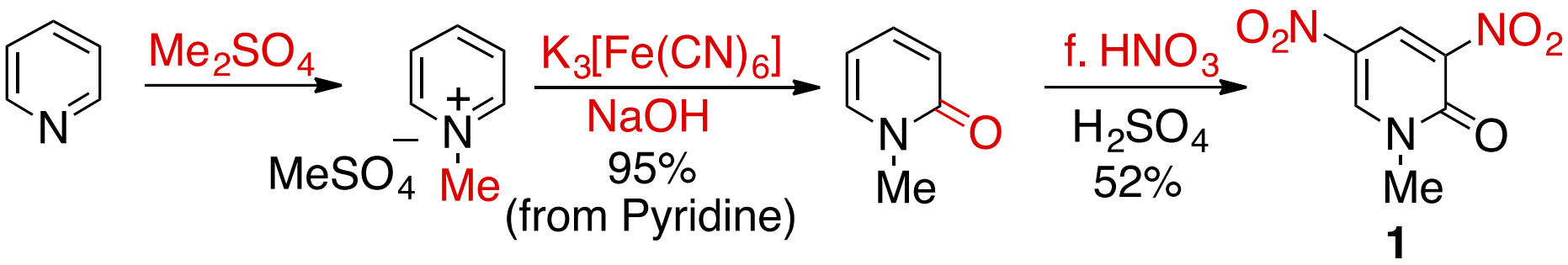
Substrate Should Have Electron-Deficiency and Good Leaving Group



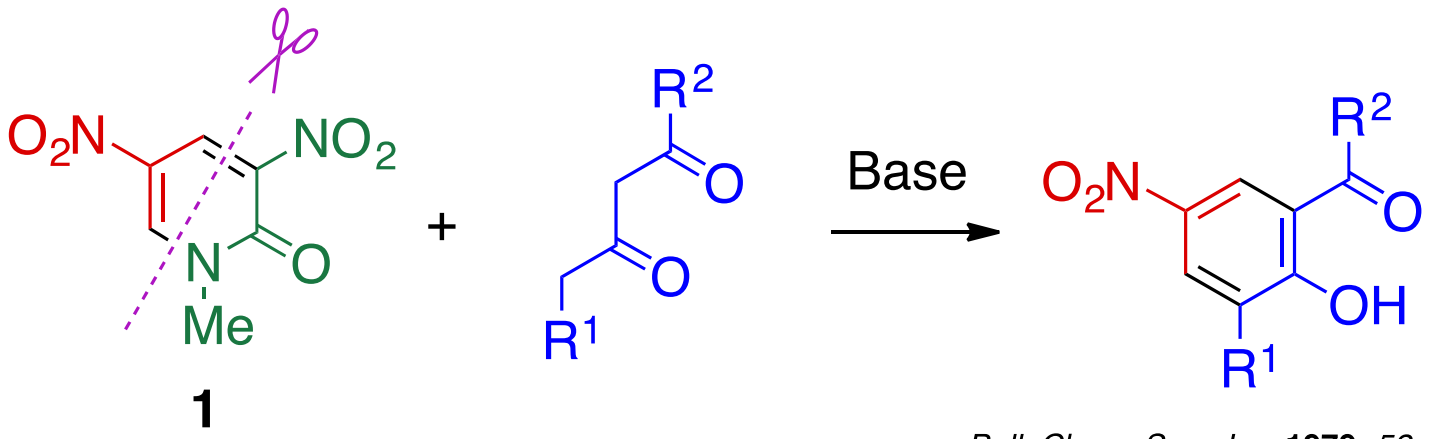
1

NitroMalonAldehyde

Preparation of 1



Reaction with 1,3-Dicarbonyl Compounds



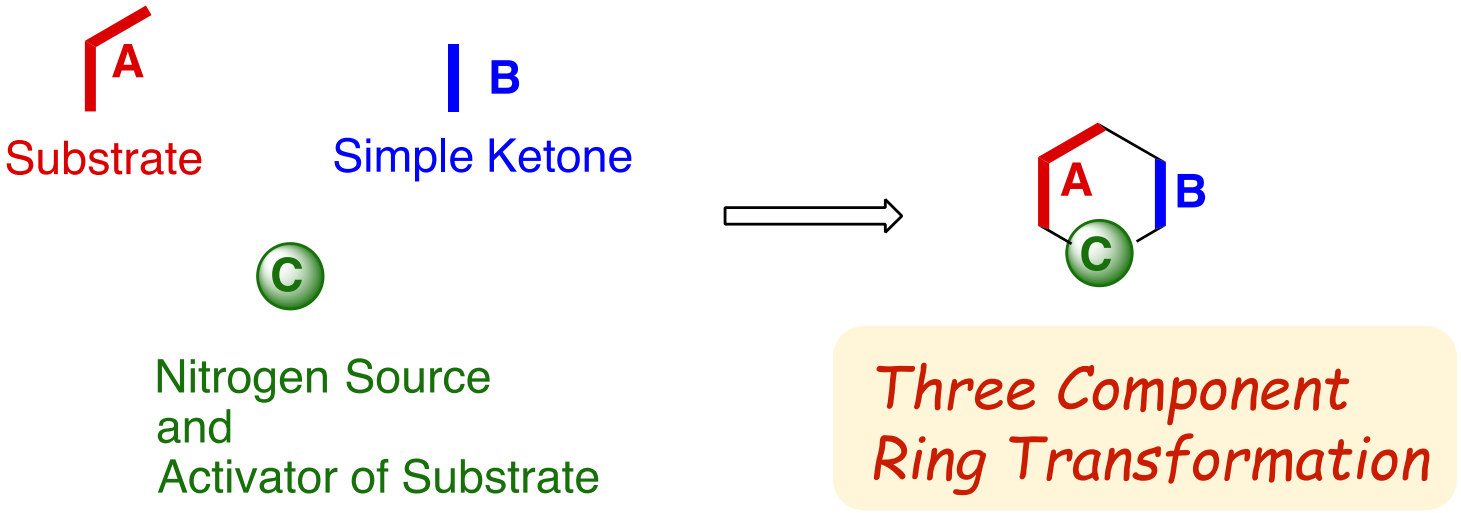
Bull. Chem. Soc. Jpn. **1979**, *52*, 2413

Problem

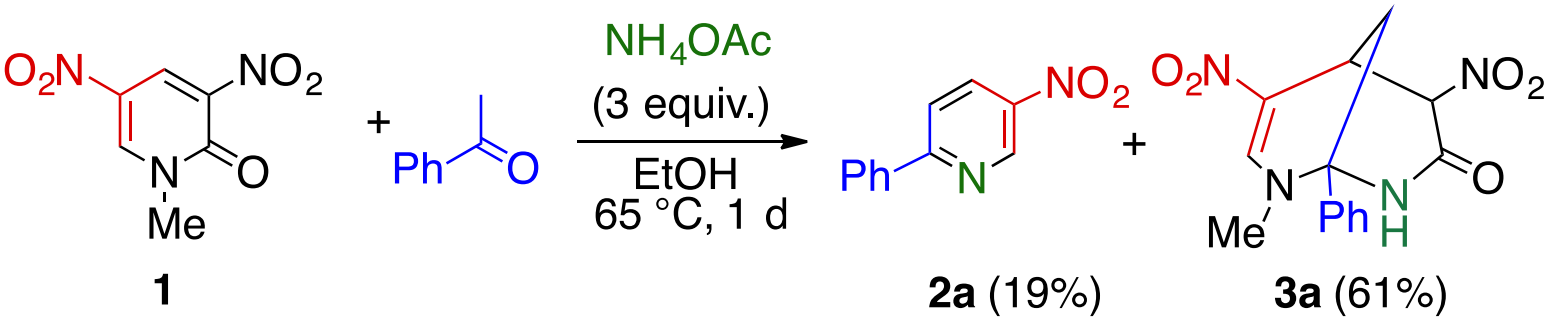
1,3-Dicarbonyl Compounds are Useful Dinucleophilic Reagents, However, the Commercially Available Versatility is Low.

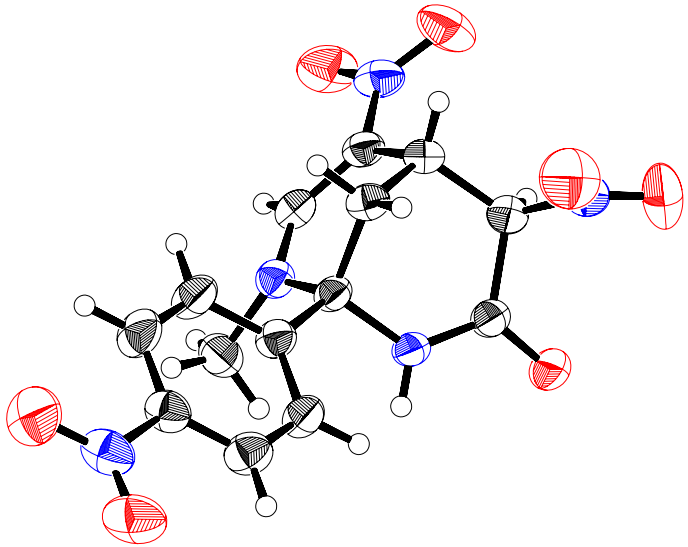
If Simple Ketones can be Used, Synthetic Utility of This Method will be Considerably Improved.

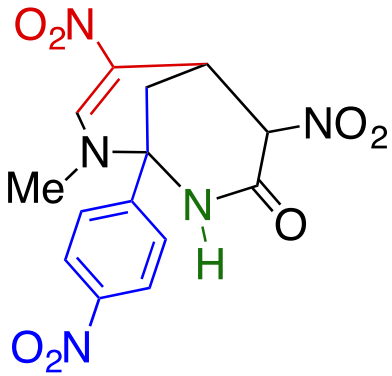
Solution



Results and Discussion



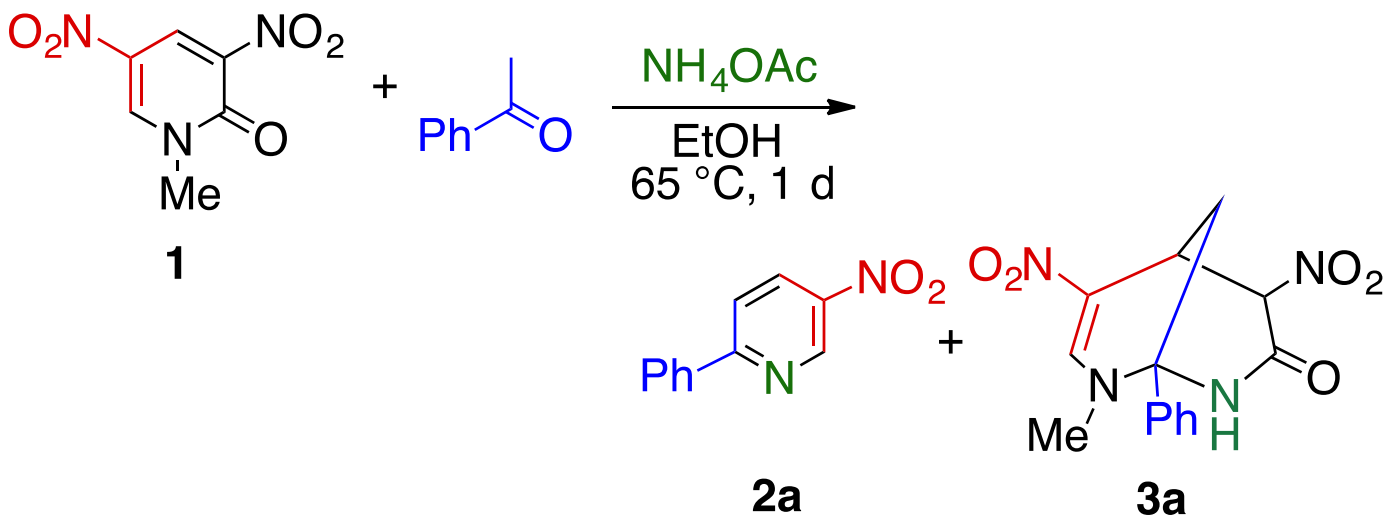




An ORTEP drawing of **3b** with 50% probability thermal ellipsoids

Asian J. Org. Chem. **2014**, *3*, 297

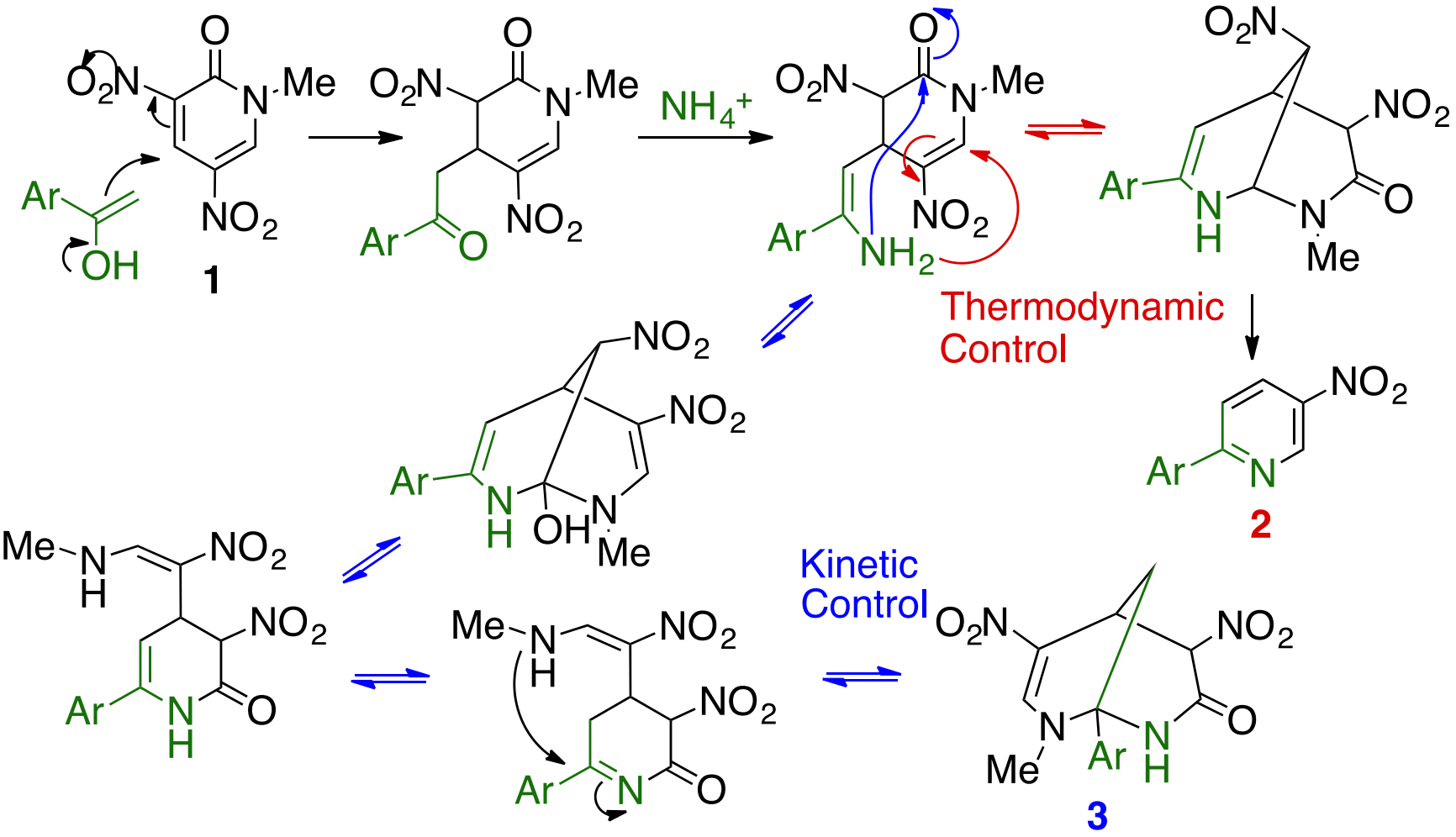
Effect of Amount of NH_4OAc



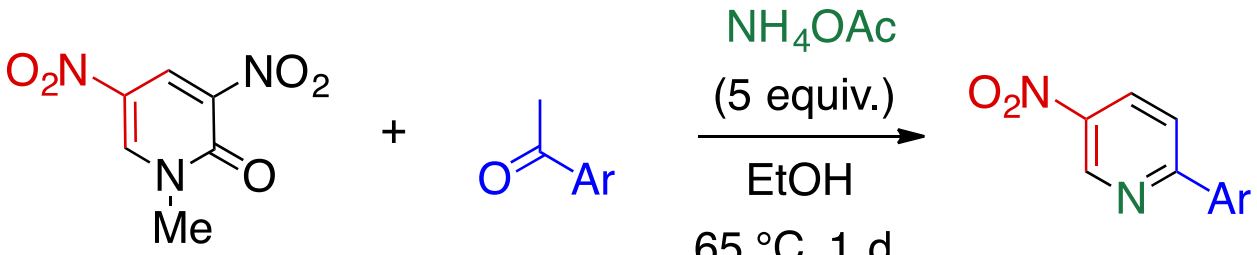
run	NH_4OAc/ equiv.	Yield/%			Ratio
		2a	**3a**	Total	**2a/3a**
1	3	19	61	80	24/76
2	5	43	46	89	48/52
3	10	64	25	89	72/28
4	15	79	0	79	100/0

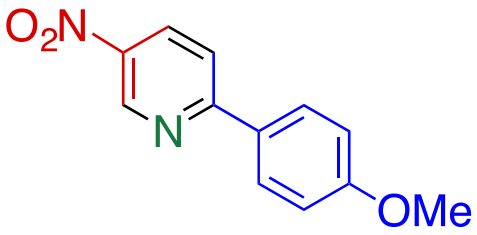
Asian J. Org. Chem. **2014**, *3*, 297

A Plausible Mechanism

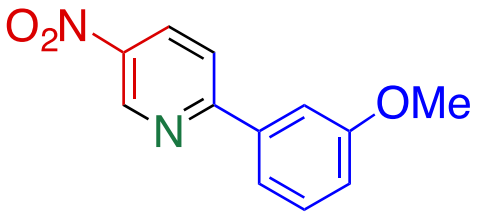


Reaction with Other Aromatic Ketones

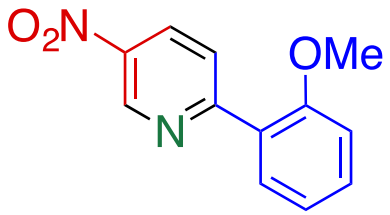




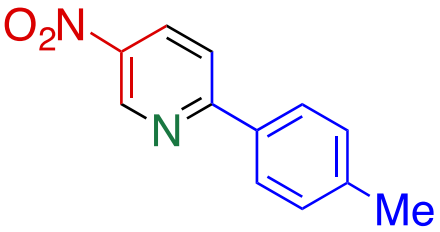
2c (95%)



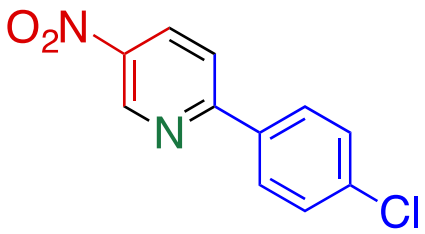
2d (97%)[a]



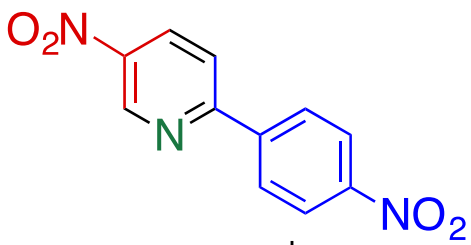
2e (94%)



2f (88%)



2g (96%)[a]

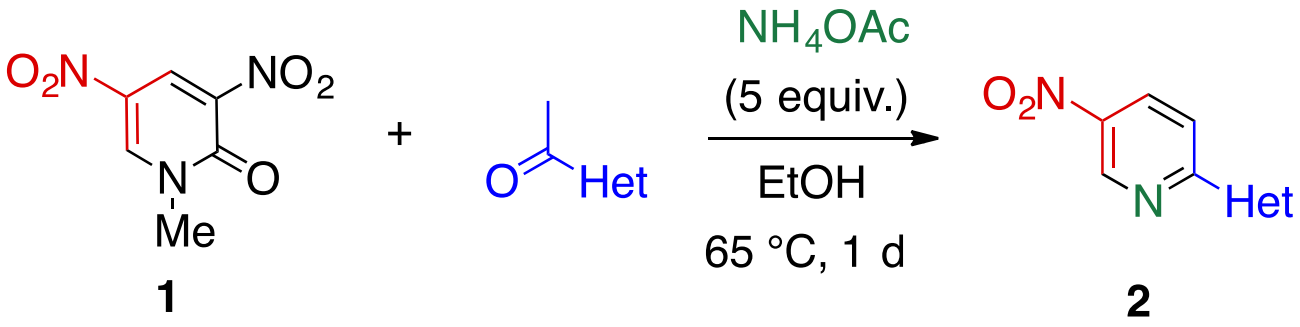


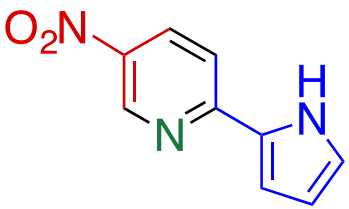
2b (95%)[b]

[a] 10 equiv. of NH_4OAc [b] 15 equiv. of NH_4OAc

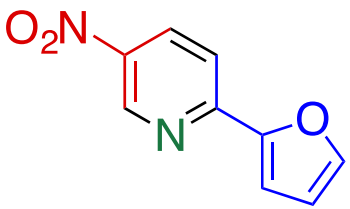
Asian J. Org. Chem. **2014**, *3*, 297

Reaction with Hetero Aromatic Ketones

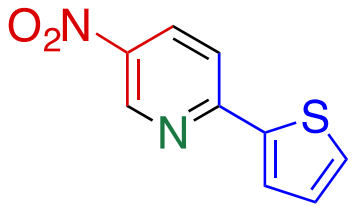




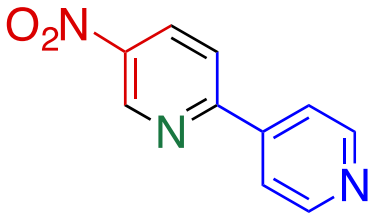
2h (87%)[a]



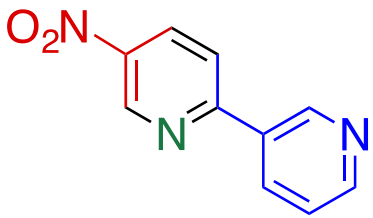
2i (87%)



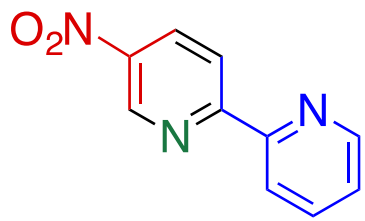
2j (85%)[a]



2k (66%)[b]



2l (97%)[b]

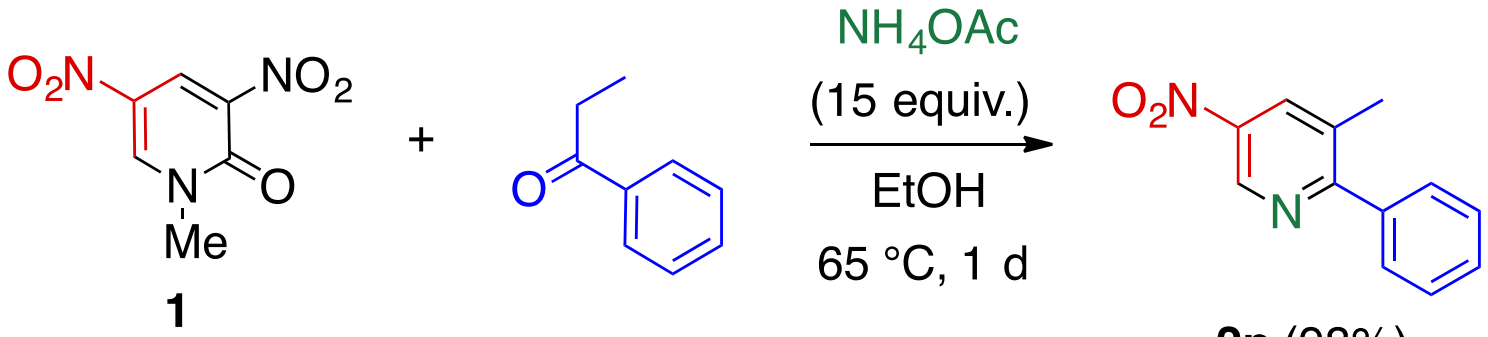


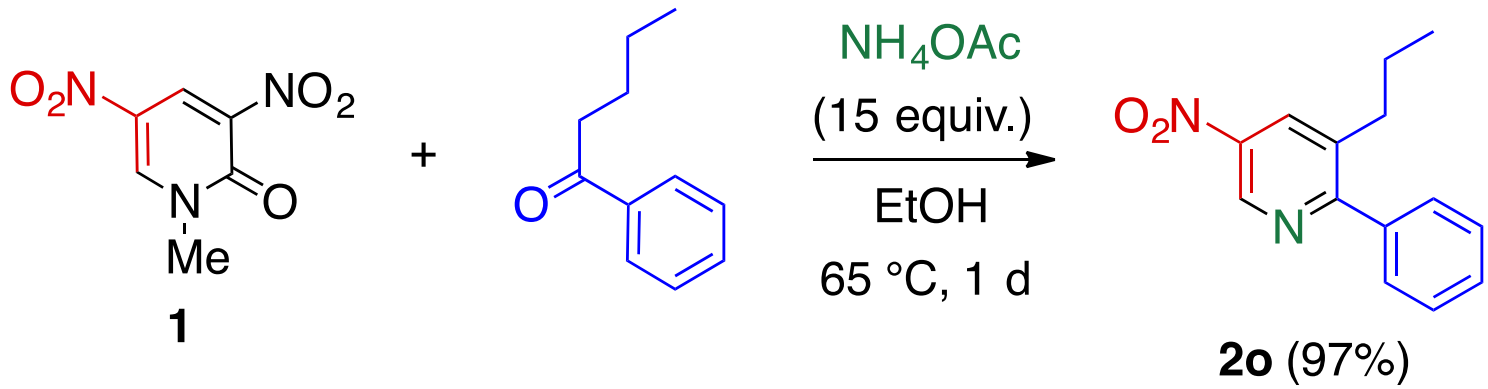
2m (80%)[b]

[a] 10 equiv. of NH_4OAc [b] 15 equiv. of NH_4OAc

Asian J. Org. Chem. **2014**, *3*, 297

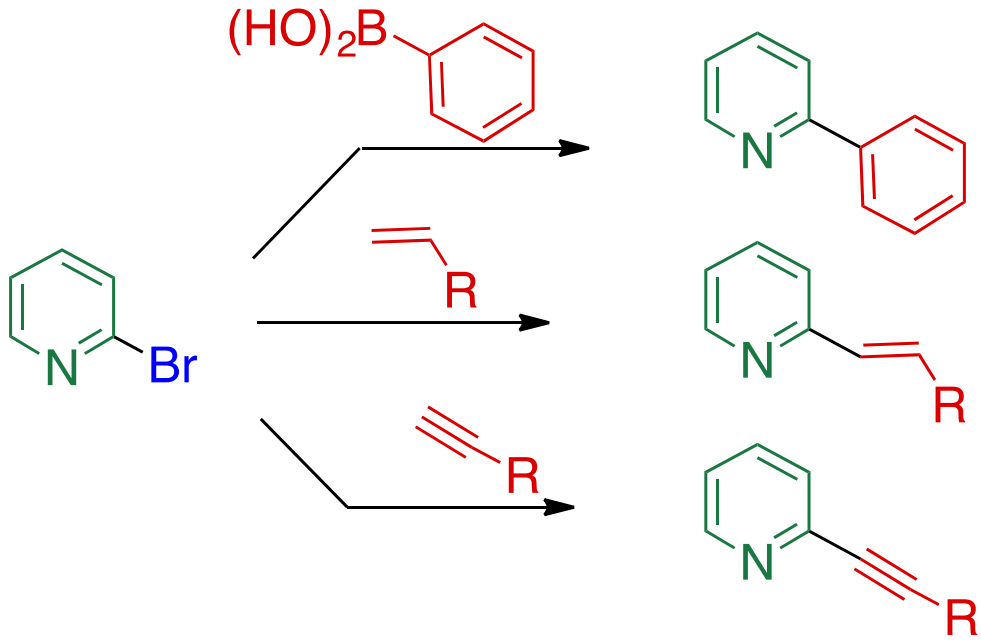
Synthesis of TriSubstituted Pyridines





Asian J. Org. Chem. **2014**, *3*, 297

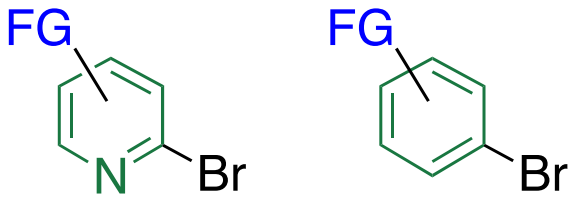
Pd Catalyzed C-C Bond Formation



Suzuki-Miyaura Coupling

Mizoroki-Heck Reaction

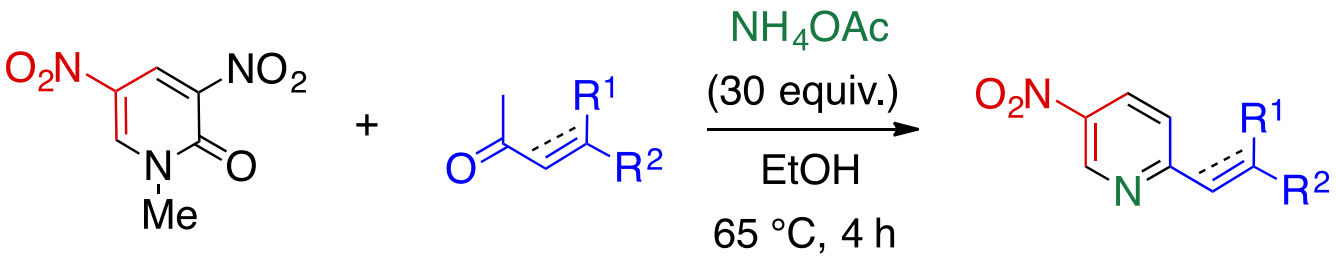
Sonogashira-Tohda Coupling

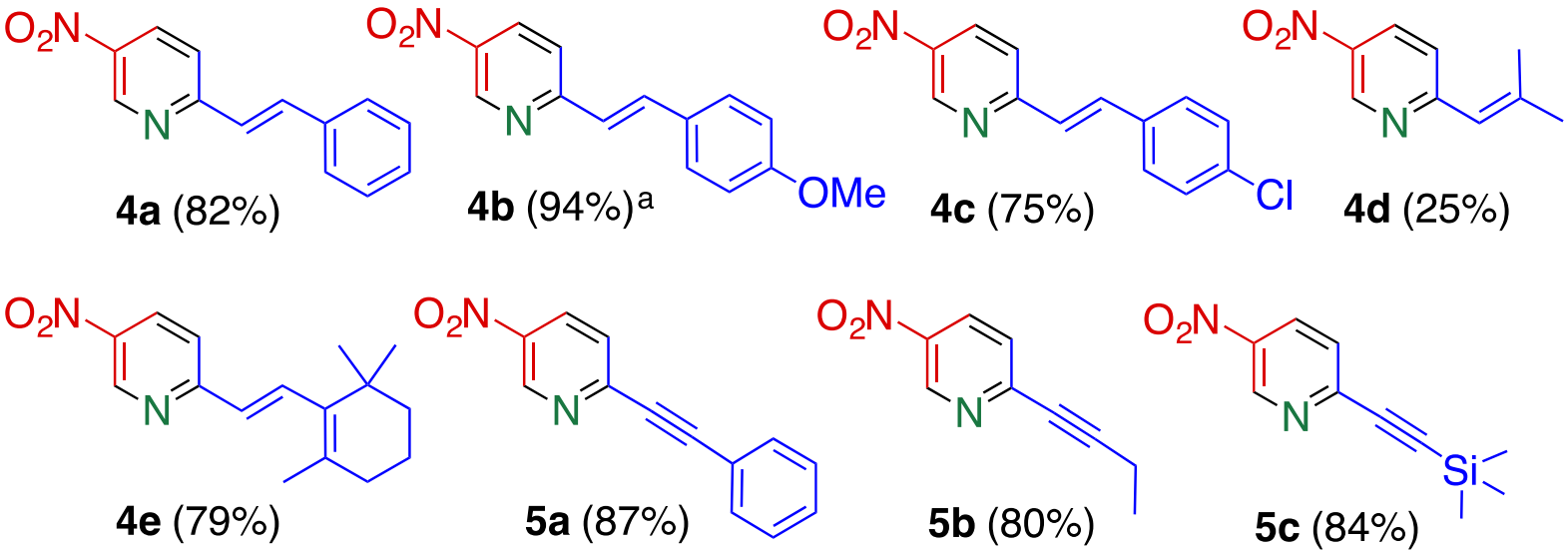


Functionalized Substrates are not Always Easily Available

Sometimes Less Reactive

Reaction with Unsaturated Ketones

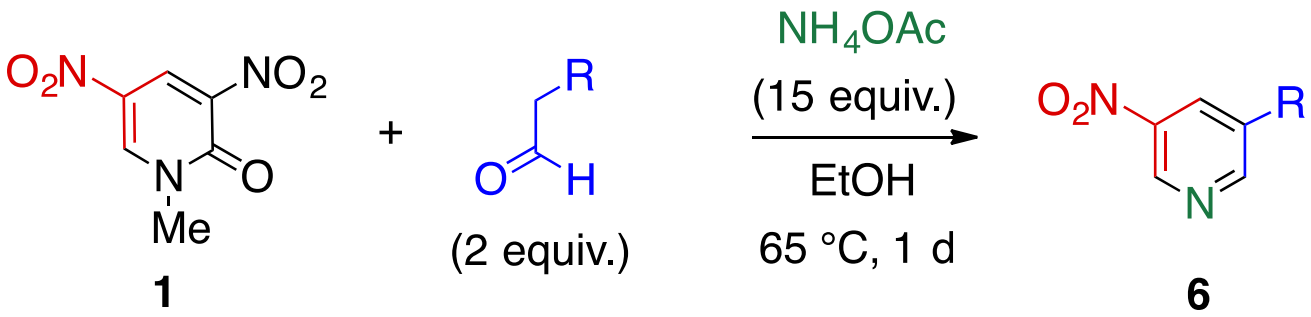


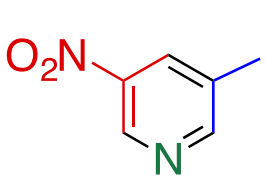


[a]Heated on a oil bath

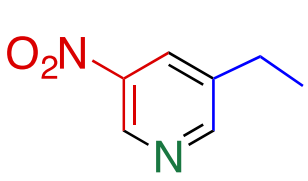
Chem. Lett. **2015**, *44*, 776

Reaction with Aldehydes

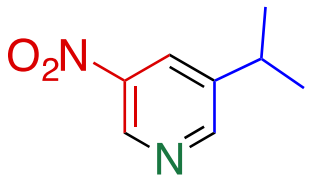




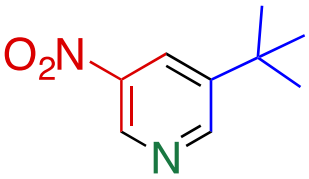
6a (52%)



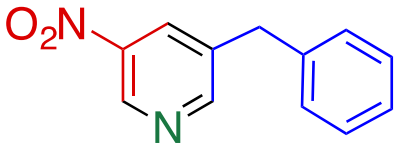
6b (85%)



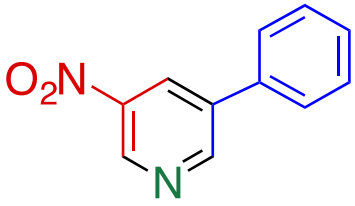
6c (71%)



6d (68%)[a]



6e (34%)

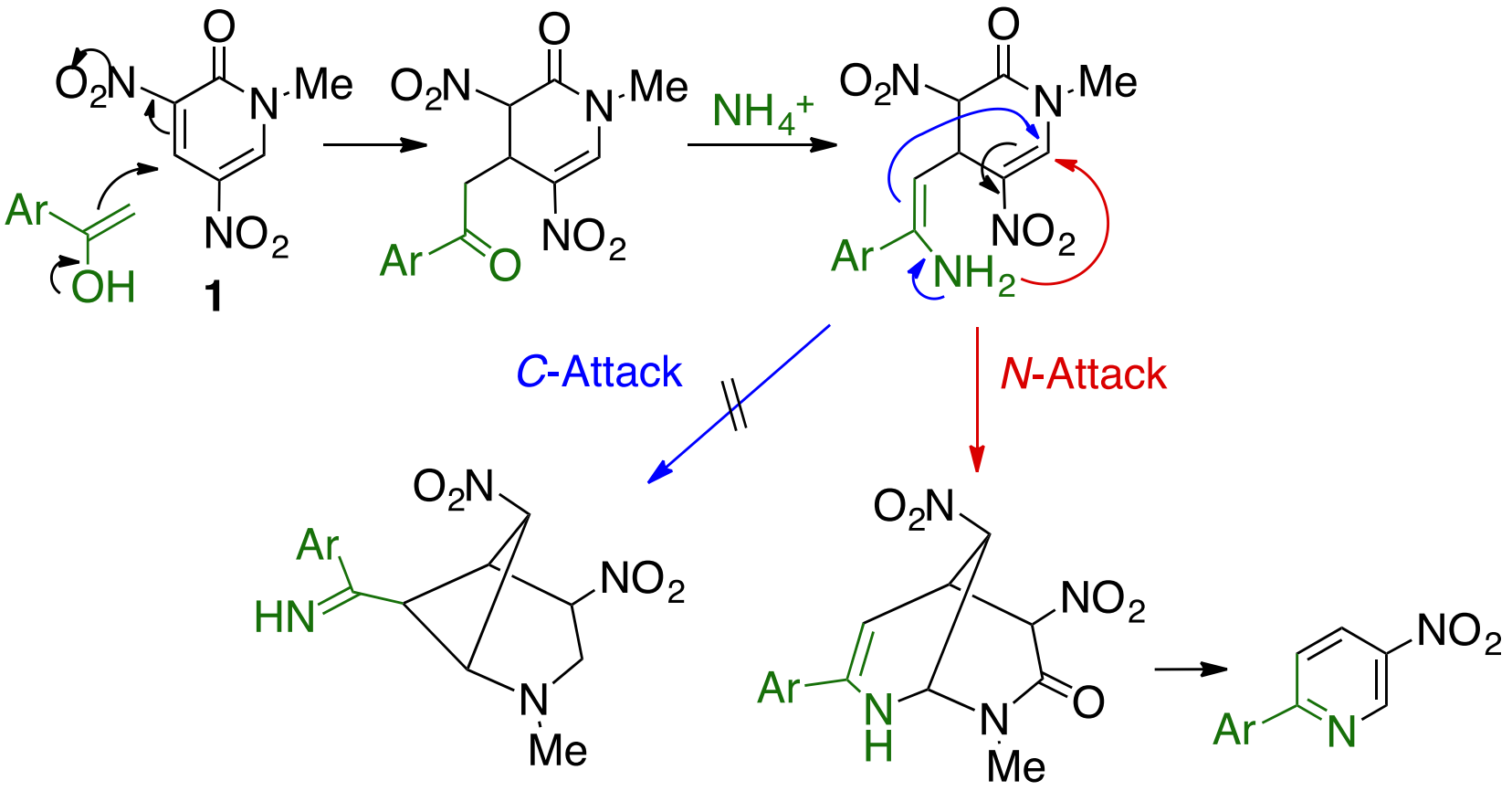


6f (75%)[a]

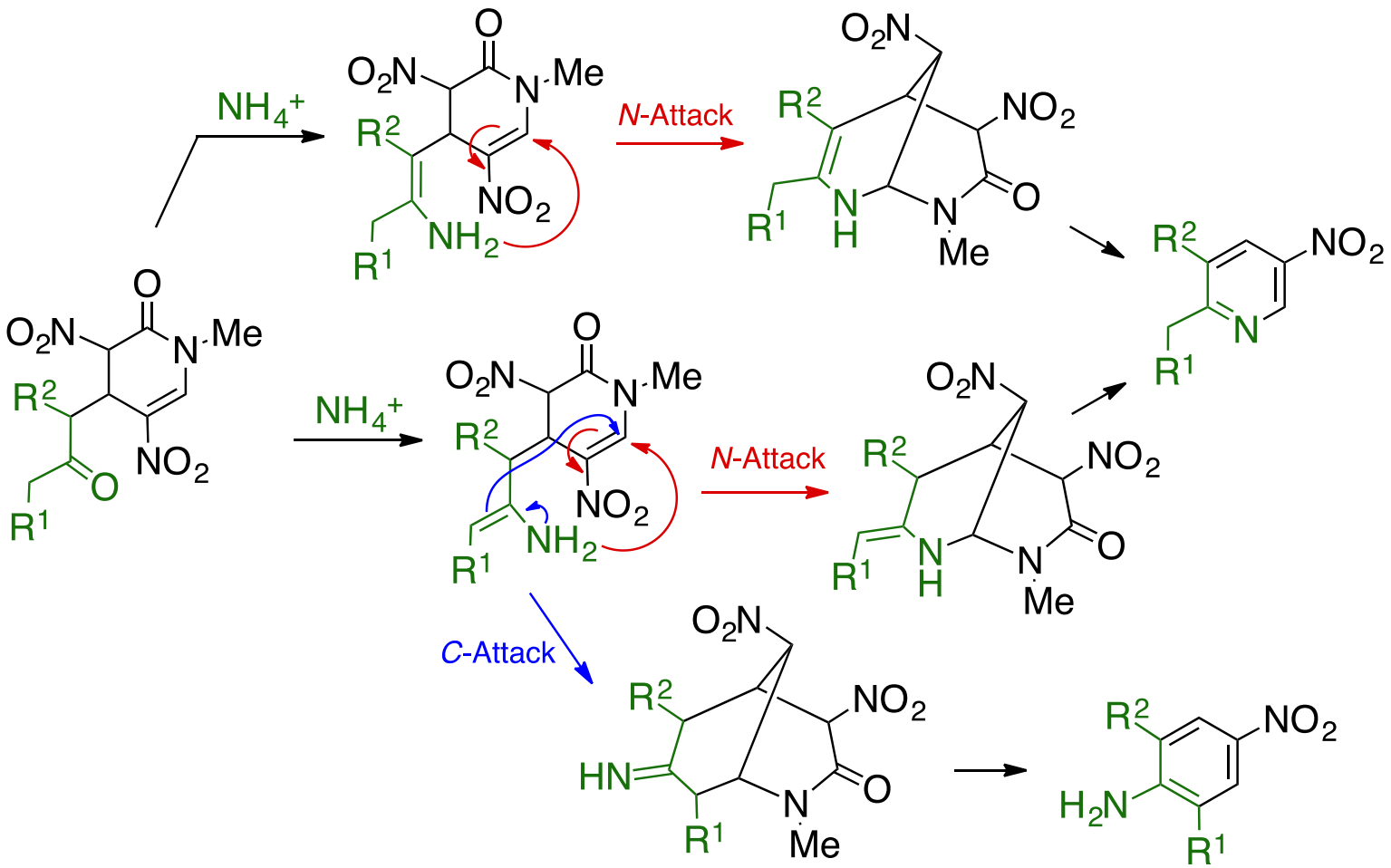
[a]Heated with microwave for 6 h

J. Org. Chem. **2015**, *80*, 8856

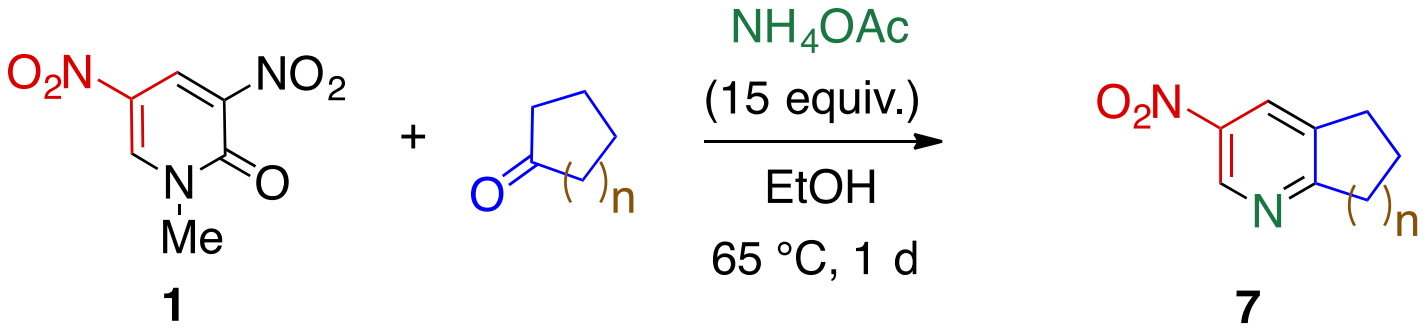
Reaction Mechanism Using Aromatic Ketones

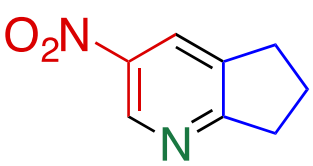


Reaction Mechanism Using Aliphatic Ketones

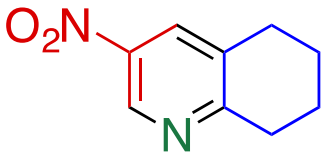


Synthesis of CycloAlka[*b*]Pyridines

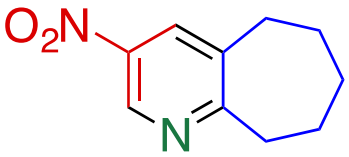




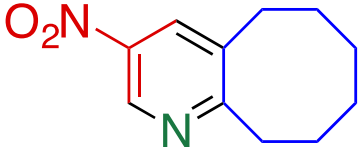
7a (87%)[a]



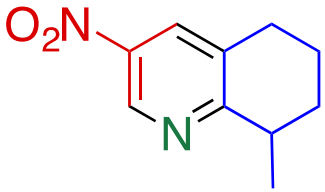
7b (95%)



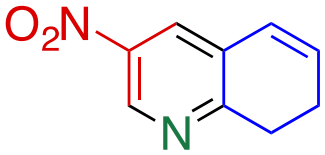
7c (94%)



7d (95%)[a]



7e (86%)

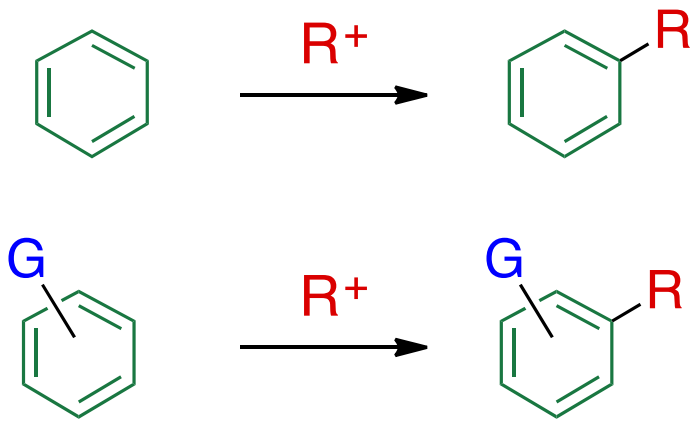


7f (89%)[a]

[a]Heated with microwave for 1-3 h

Synthesis **2014**, *46*, 2175

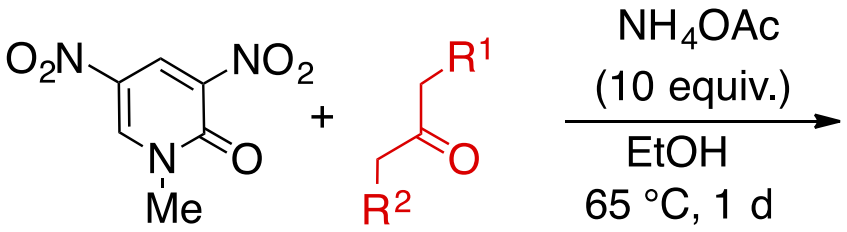
Friedel-Crafts Alkylation

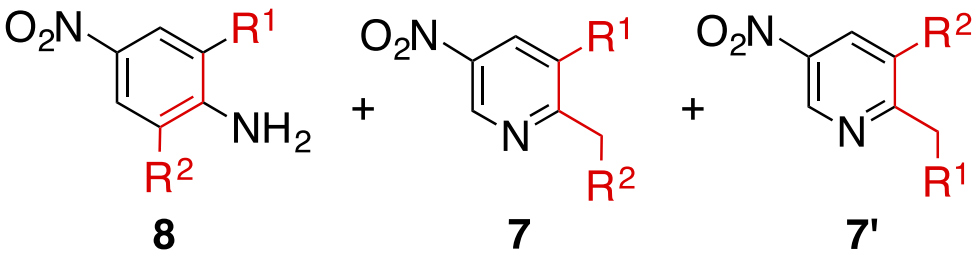


Limitations

- PolyAlkylation may Occur
- Rearrangement Proceeds to Afford Branched Alkyl Group
- Arylation cannot be Achieved
- Electron-Withdrawing Group Prevents
- Amino Group also Prevents

Synthesis of NitroAnilines





			Yield/%			
R^1	R^2		**8**	**7**	**7'**	total
H	H	**g**	51	47	—	98
Et	H	**h**	66	10	8	84
Pr	H	**i**	83	9	6	98
i-Pr	H	**j**	58	0	31	89

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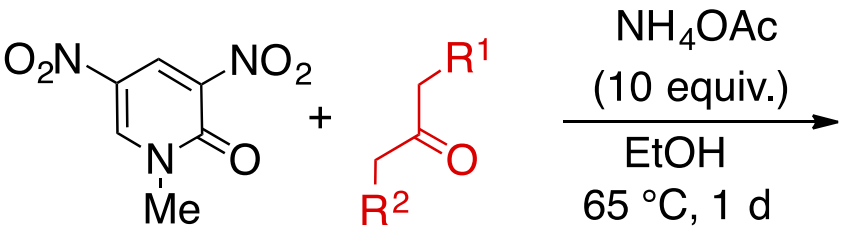
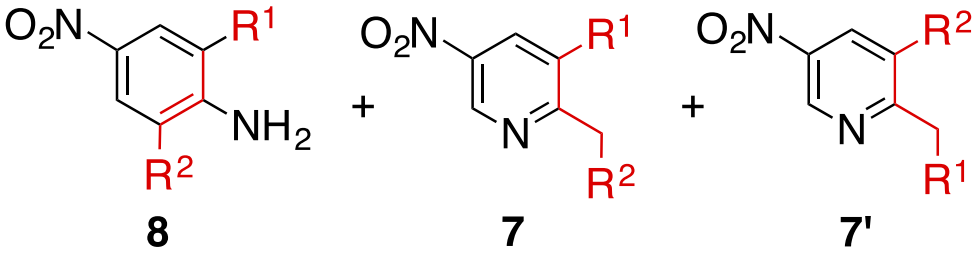
Synthesis of NitroAnilines





			Yield/%			
R^1	R^2		**8**	**7**	**7'**	total
Me	Me	**k**	83	13	—	96
Pr	Pr	**l**	74	22	—	96
C_6H_5	Pr	**m**	62	24	13	99
C_6H_5	C_6H_5	**n**	8	81	—	89

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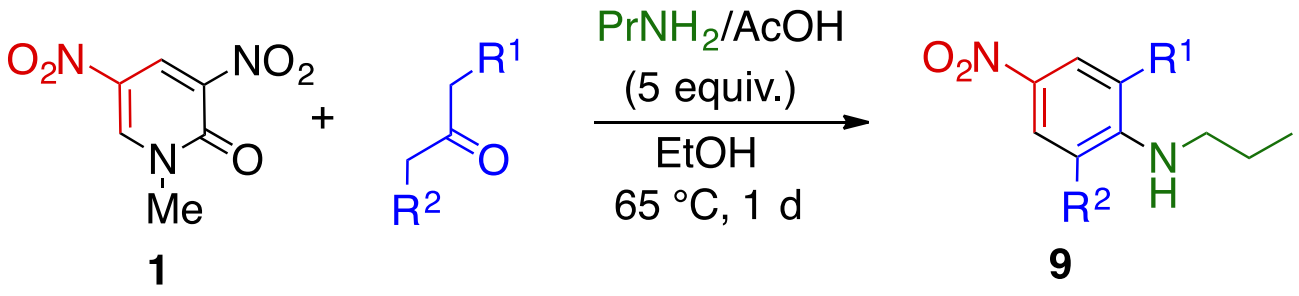
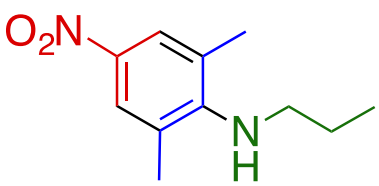
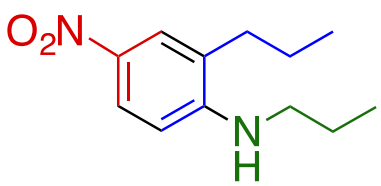
Synthesis of *N*-Modified NitroAnilines

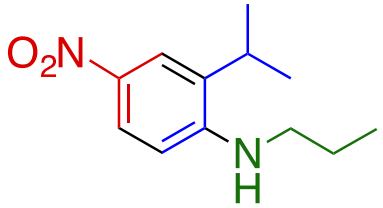




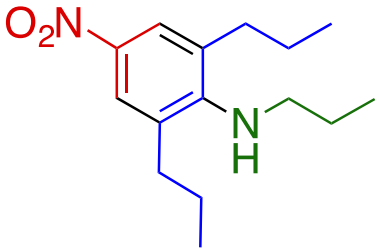
9a (99%)



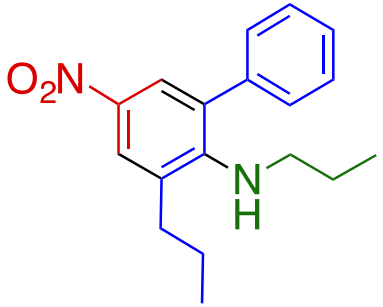
9b (83%)



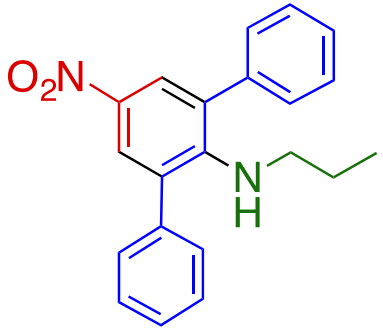
9c (83%)



9d (59%)



9e (80%)



9f (32%)

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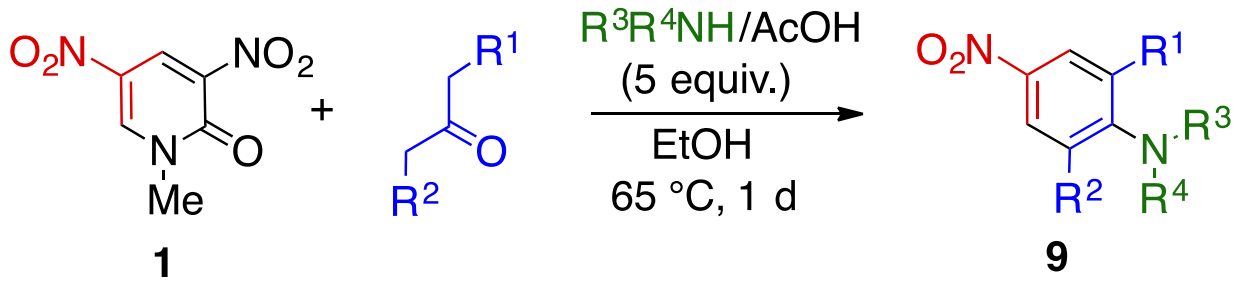
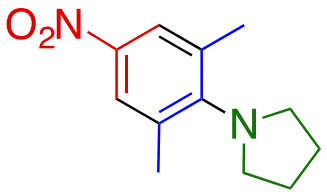
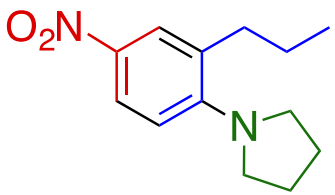
Synthesis of *N,N,2,6*-Modified NitroAnilines

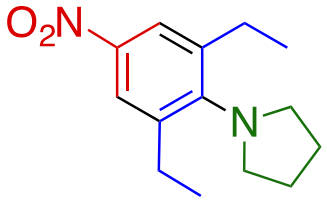




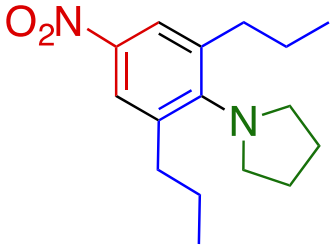
9g (98%)



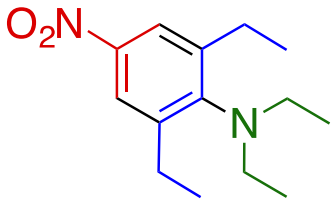
9h (67%)



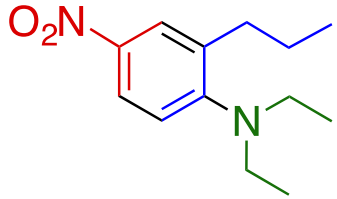
9i (68%)



9j (81%)



9k (98%)



9l (57%)

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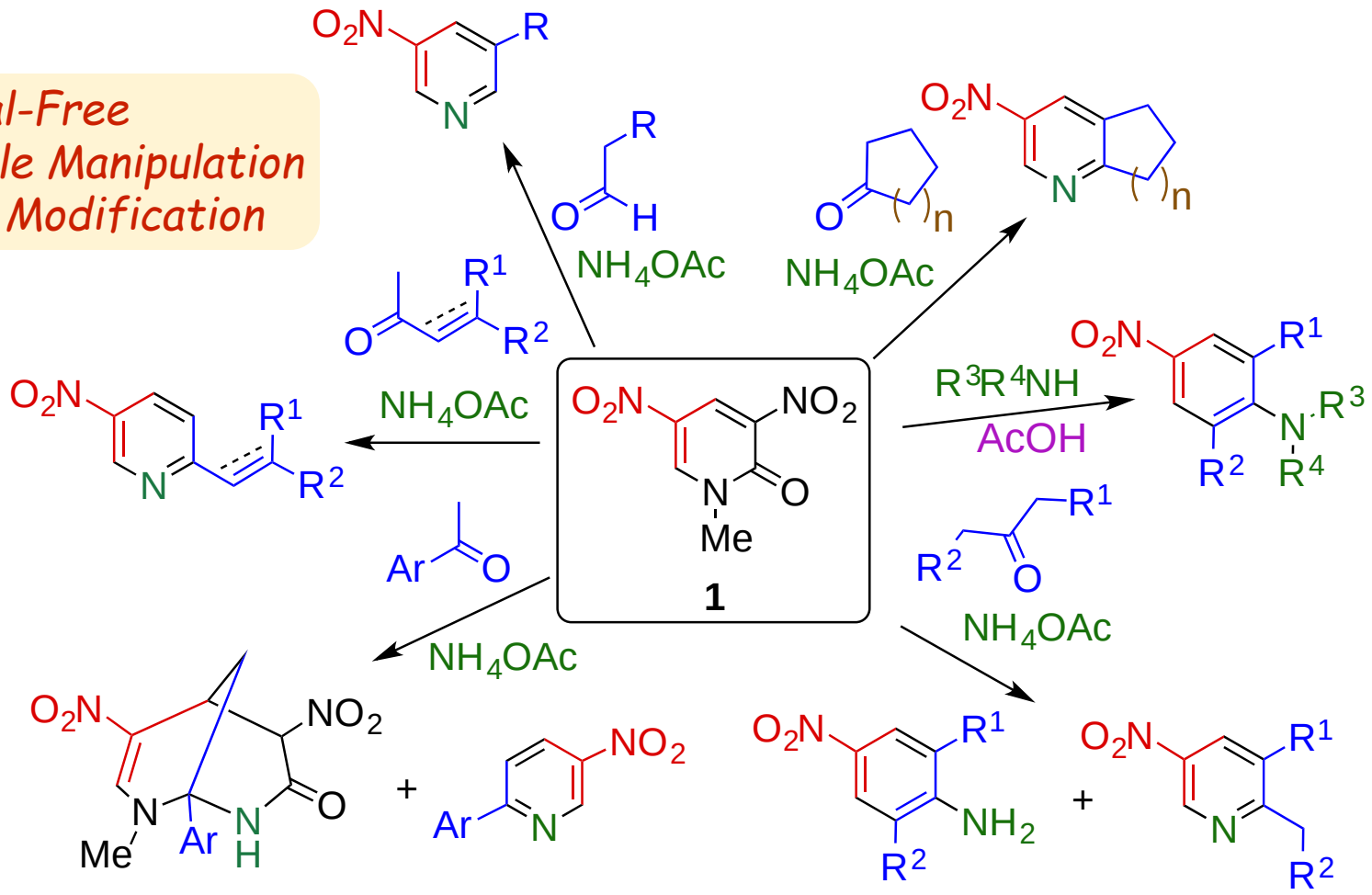
Conclusions

Metal-Free
Simple Manipulation
Easy Modification



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Nishiwaki Lab.

Special Scholarship Program (SSP) of Kochi Univ Tech

3-Year Doctoral Program
Project-based
English-medium instruction

To support living expenses,
150,000 yen/month is paid for research project work.

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