Three-Component Ring Transformation

Subjects: Chemistry, Organic

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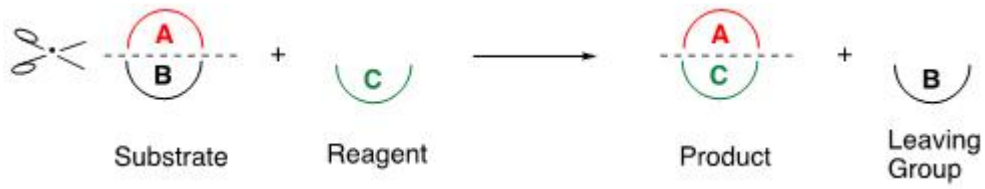
The ring transformation is a synthetic method for cyclic products including transfer of the partial structure of a cyclic substrate to a reagent, constructing a new ring system. When one substrate and two reagents are used to form a cyclic structure, it is called three-component ring transformation.

three-component ring transformation nitropyridine nitroaniline

1. General Concept of TCRT

1.1. Ring transformation

Ring transformation is a powerful synthetic method that accompanies "*Scrap & Build*" of cyclic compounds. The general concept of this method is shown in Scheme 1. When a substrate (**A** + **B**) is reacted with a reagent (**C**), the partial structure (**A**) of the substrate is transferred to the reagent to construct a new ring system (**A** + **C**), simultaneously eliminating the leaving group (**B**). This reaction facilitates the synthesis of functionalized compounds that are not easily afforded by alternative procedures.



Scheme 1. General concept of the ring transformation.

There are four types of ring transformations, namely, Diels-Alder-type, decarboxylative, degenerate, and nucleophilic-type ring transformations, among which the last nucleophilic-type ring transformation has not been studied extensively as compared to the other three ring transformations [1][2][3][4][5][6]. 1-methyl-3,5-dinitro-2-pyridone (**1**) serves as an excellent substrate for this reaction to afford functionalized 4-nitrophenols **3** upon treatment with enolate of 1,3-dicarbonyl compounds **2**.

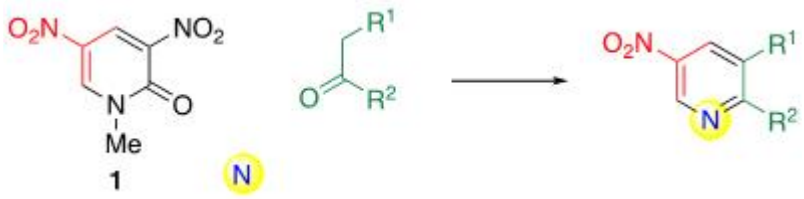
Table 1. Synthesis of functionalized 4-nitrophenols by ring transformation.

R^1	R^2	Solv.	Temp./°C	Yield/%

OEt	COOEt	**a**	pyridine	50	91
OEt	H	**b**	pyridine	70	61
Me	H	**c**	DMF	70	53
COOEt	H	**d**	pyridine	110	42

1.2. General concept of TCRT

Although 1,3-dicarbonyl compounds **2** are excellent dinucleophilic reagents, only few products **3** are synthesized because of the low diversity of the available **2**. If simple ketones **4** can be used instead of **2**, the synthetic utility of the ring transformation should be improved. In such cases, it is necessary to use a nitrogen source as ketone is a mononucleophilic reagent. This process is referred to as three-component ring transformation (TCRT) (Scheme 2).



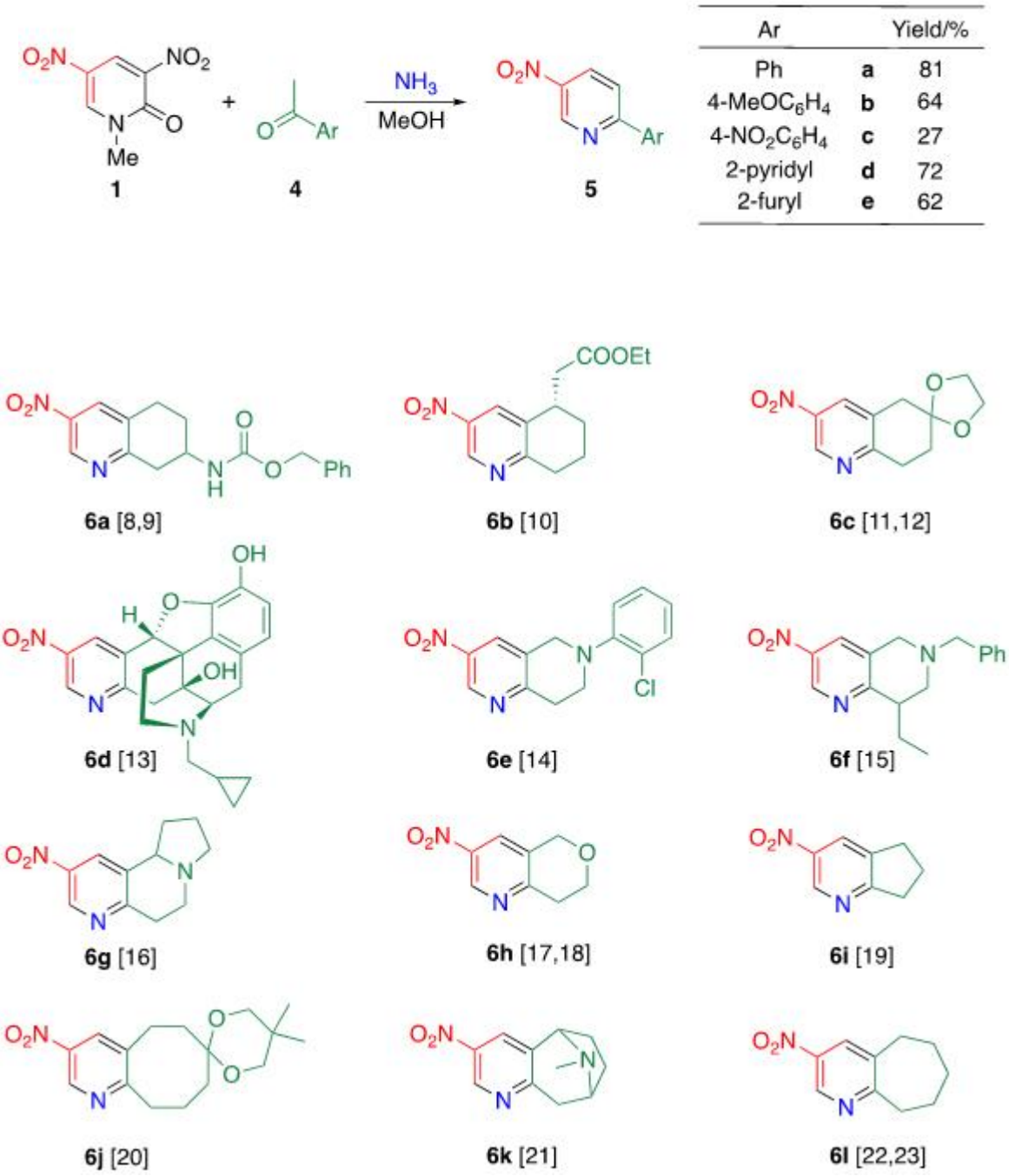
Scheme 2. The general concept of TCRT.

2. Synthesis of nitropyridines by TCRT

2.1. TCRT using ammonia as the nitrogen source

Tohda *et al.* reported the reaction of dinitropyridine **1** with ketones in the presence of ammonia (Table 2) [7]. When a methanol solution of pyridone **1** is heated with acetophenone **4a** in the presence of larger amounts of ammonia (140 equiv.) at 120 °C in an autoclave, TCRT proceeds to afford 3-nitro-6-phenylpyridine **5a** in 81% yield. This reaction is applicable to other aromatic ketones **4b–e** to afford the corresponding 2-(het)aryl-5-nitropyridines **5b–e**, respectively. This TCRT efficiently proceeds under mild conditions to afford [*b*]-fused 5-nitropyridines **6** only when cyclohexanone is used as the reagent (Figure 1).

Table 2. TCRT using dinitropyridine **1**, ketones **4** and ammonia leading to nitropyridines **5**.



Ar		Yield/%
Ph	a	81
4-MeOC$_6$H$_4$	b	64
4-NO$_2$C$_6$H$_4$	c	27
2-pyridyl	d	72
2-furyl	e	62

Figure 1. Condensed nitropyridines [8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23].

2.2. TCRT using ammonium acetate as the nitrogen source

TCRT using ammonia as the nitrogen source is an effective approach to [*b*]-fused 5-nitropyridines **6**. However, when less reactive ketones such as acetophenone **4a** are used, both electrophilic sites of **1** are attacked by ammonia, which undergoes ammonolysis to consume pyridone **1** competitively. Le *et al.* mitigated this problem by using a less nucleophilic ammonium acetate as a nitrogen source instead of ammonia. Even when either electron-rich or -poor ketones **4a–e** are used, TCRT efficiently proceeds under mild reaction conditions leading to nitropyridines **5a–e**, respectively [24].

Table 3. TCRT with other aromatic ketones **5**.

Ar		Yield/%
Ph	**a**	79
4-$MeOC_6H_4$	**b**	95
4-$NO_2C_6H_4$	**c**	93
2-pyridyl	**d**	87
2-furyl	**e**	87

This protocol is applicable to a,b-unsaturated ketones [25], cycloalkanones [26], and aldehydes [24] to afford the corresponding nitropyridines (Figure 2). For the C–C bond formation on the pyridine framework, the Heck, Suzuki, Stille, and Sonogashira reactions are commonly used. However, these methods require the use of poisonous and expensive transition metals and a purification step to avoid metal contamination of the products. In addition, troublesome multistep reactions are necessary to prepare the substrates for these reactions (2-halo-5-nitropyridines). Thus, the TCRT is a metal-free supplementary method for the above-mentioned reactions.

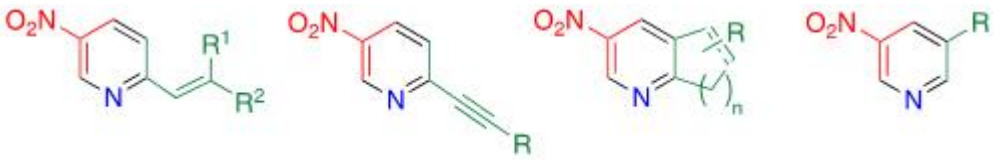


Figure 2. Other types of nitropyridines.

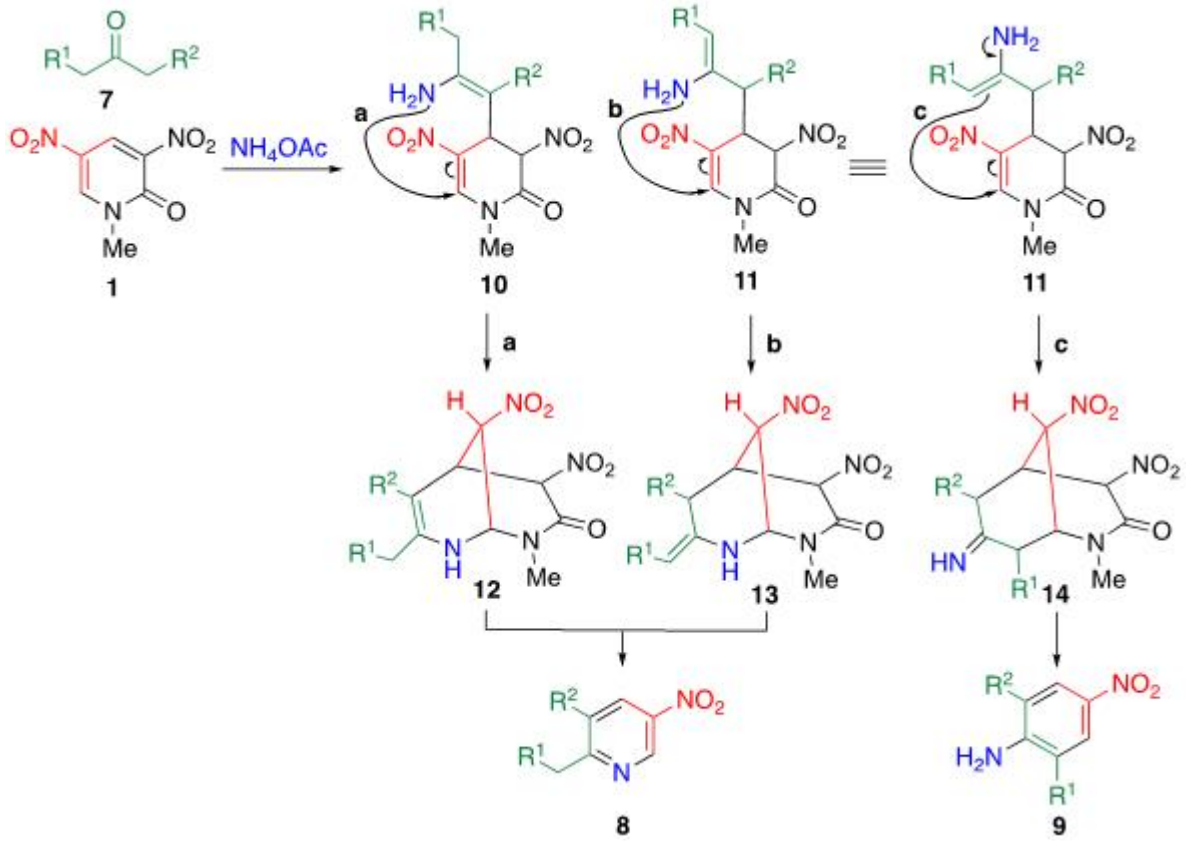
When dinitropyridone **1** is subjected to a reaction with aliphatic ketones **7** in the presence of ammonium acetate, two types of TCRT occur to afford nitropyridines **8** and nitroanilines **9** (Table 4) [27]. Generally, 2,6-disubstituted 4-nitroanilines **9** are prepared from the corresponding anilines by nitration under harsh reaction conditions, wherein protection and deprotection of the amino groups are necessary [28]. Furthermore, the preparation of this compound suffers from limitation of Friedel–Crafts alkylation. There are several limitations for the Friedel–Crafts alkylation, such as the following: (1) the monoalkylated product undergoes further alkylation; (2) it is difficult to introduce two different alkyl groups; (3) primary alkyl groups longer than the ethyl group cannot be introduced; (4) a phenyl group cannot be introduced; and (5) nitrobenzene and aniline do not facilitate the alkylation. The TCRT overcomes these disadvantages.

Table 4. Two kinds of TCRT using aliphatic ketones **7**.

Ketone			**Yield/%**		
R^1	**R^2**		**9**	**8**	**8'**
Me	Me	**a**	83	13	—

H	H	**b**	51	47	—
Et	H	**c**	66	10	8
i-Pr	H	**d**	58	0	31
Pr	H	**e**	83	9	6
Et	Et	**f**	67	24	—
Pr	Pr	**g**	74	22	—
C_6H_5	Pr	**h**	62	24	13
C_6H_5	C_6H_5	**i**	8	81	—

3. Reaction mechanism of TCRT



Scheme 2. Plausible mechanisms of TCRT when an aliphatic ketone **7** is employed as a reagent.

A plausible mechanism for this TCRT is shown in Scheme 2. The enol form of **7** attacks the electrophilic 4-position of **1**, then the adduct is converted enamines **10** and **11** by ammonium ion. Attack of the amino group attacks at the 6-position (routes **a** and **b**) furnishes bicyclic intermediates **12** and **13**, from which nitroacetamide is eliminated to afford nitropyridine **8**. On the other hand, the *C*-attack of enamine **11** at the 6-position (route **c**) leads to bicyclic intermediate **14**, which affords nitroaniline **9**.

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