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Metal-free Synthesis of 2-Alkenyl/Alkynyl-5-nitropyridines Using a Three-component Ring Transformation

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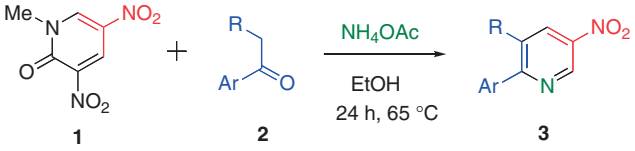
A metal-free, facile, and efficient protocol for synthesizing a series of 2-alkenyl/alkynyl-5-nitropyridines was developed by using a three-component ring transformation of 1-methyl-3,5-dinitro-2-pyridone with α,β-unsaturated ketones and ammonium acetate. As 2-alkenyl/alkynyl-5-nitropyridines are not easily prepared by the Heck or Sonogashira reactions, this method will be supplementary to these reactions.

2-Alkenyl-5-nitropyridines[1–3] and 2-alkynyl-5-nitropyridines[4] are widely employed as precursors to pharmaceuticals and biologically active compounds. In addition, alkynylnitropyridines are often found in nonlinear optical materials[5] and organic semiconductors.[6] Although the Heck,[7] Suzuki,[2a,8] Stille,[3,9] and Sonogashira[10,11] reactions are common protocols for alkenylation/alkynylation, poisonous and expensive transition metals are used and a purification step to avoid metal contamination of the products is necessary. In addition, the substrates for these reactions, 2-halo-5-nitropyridines, are commonly prepared by halogenation of 5-nitro-2-pyridone.[11,12] 2-Alkenyl-5-nitropyridines are also available by condensation reactions using 5-nitropyridine-2-carbaldehydes[13] or 2-methyl-5-nitropyridines.[14] However, troublesome multistep reactions are necessary for preparing these starting materials. Therefore, the development of a metal-free, facile, and efficient economical methodology for the synthesis of alkenyl/alkynylpyridines is still challenging.

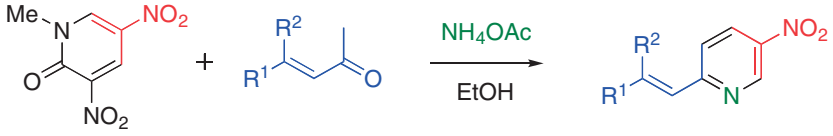
In our previous work, we developed an efficient preparative method for arylated nitropyridines **3** by three-component ring transformation (TCRT) of dinitropyridone **1** with aromatic ketones **2** in the presence of ammonium acetate as the nitrogen source (Scheme 1); this can be used as a supplementary method to the Suzuki reaction.[15] These successful experimental results prompted us to extend the substrate scope for this method to a series of α,β-unsaturated ketones **4**, thus facilitating the introduction of an alkenyl/alkynyl group into the nitropyridine framework without using a transition metal.

Dinitropyridone **1** was heated with 4-phenyl-3-buten-2-one (**4a**) at 65 °C for 24 h in the presence of 15 equivalents of ammonium acetate. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to remove unreacted ketone



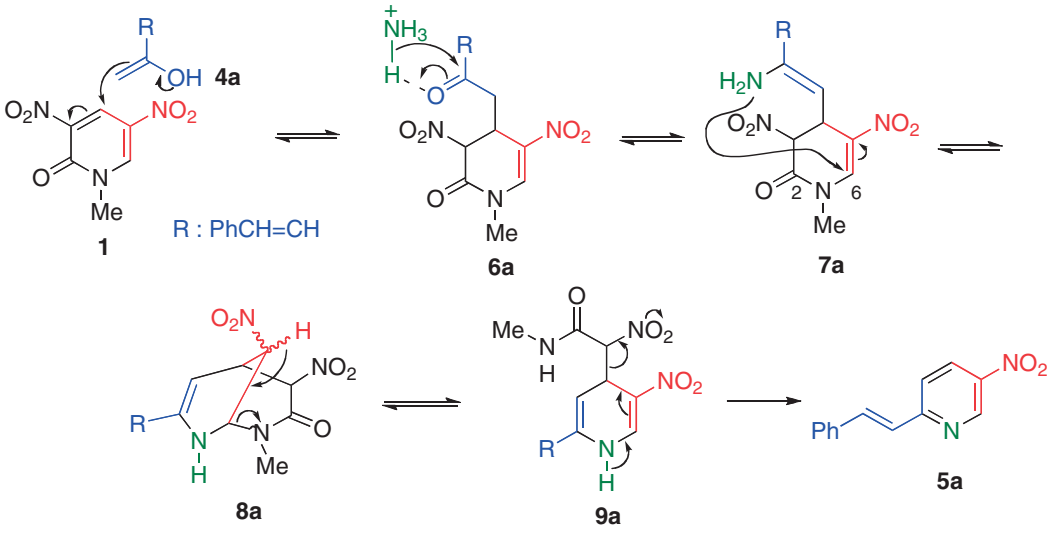
Scheme 1. TCRT of dinitropyridone **1** in the presence of ammonium acetate.

Table 1. Synthesis of 2-alkenyl-5-nitropyridines **5**



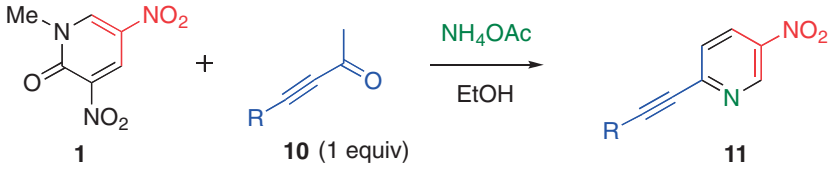
Entry	R^1	R^2		NH_4OAc /equiv	Time /h	Temp. /°C	Yield /%	Recovery of **1**/%
1	Ph	H	**a**	15	24	65	21	68
2	Ph	H	**a**	20	24	65	54	32
3	Ph	H	**a**	30	24	65	72	0
4[a]	Ph	H	**a**	15	4	80	82	trace
5	*p*-$MeOC_6H_4$	H	**b**	30	24	65	94	0
6[a]	*p*-$MeOC_6H_4$	H	**b**	15	3	80	76	trace
7	*p*-ClC_6H_4	H	**c**	30	24	65	63	0
8[a]	*p*-ClC_6H_4	H	**c**	30	4	80	75	0
9	H	H	**d**	30	24	65	0	0
10[a]	H	H	**d**	30	2	80	0	0
11	Me	Me	**e**	30	24	65	18	0
12[a]	Me	Me	**e**	15	2	80	25	0
13	2,6,6-trimethylcyclohexenyl	H	**f**	30	24	65	68	0
14[a]	2,6,6-trimethylcyclohexenyl	H	**f**	30	6	80	79	0

[a]Microwave heating was used.



Scheme 2. A plausible mechanism for the formation of 2-ethenyl-5-nitropyridine **5a**.

Table 2. Synthesis of 2-alkynyl-5-nitropyridines **11**



Entry	R		NH_4OAc /equiv	Time /h	Temp. /°C	Yield /%	Recovery of **1**/%
1	Ph	**a**	20	24	65	83	trace
2[a]	Ph	**a**	15	3	80	87	trace
3	Et	**b**	20	24	65	52	0
4[a]	Et	**b**	15	3	80	80	0
5	Me_3Si	**c**	20	24	65	**11c** 16/**11d** 35[b]	0
6[a]	Me_3Si	**c**	15	4	80	**11c** 24/**11d** 60[b]	0

[a]Microwave heating was used. [b]Desilylated product **11d** (R = H) was also obtained.

4a and was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 95/5) to afford 5-nitro-2-(2-phenylethenyl)pyridine (**5a**)[7] in 21% yield (Table 1, Entry 1). TCRT is considered to proceed as illustrated in Scheme 2. The enol form of **4a** attacks the 4-position of dinitropyridone **1** to afford the intermediate **6a**, which is then converted to enamine **7a** by reaction with ammonium ion.[15,16] The amino group of **7a** intramolecularly attacks the 6-position, leading to bicyclic product **8a**. After ring opening of **8a**, the elimination of nitroacetamide accompanied by aromatization of intermediate **9a** affords alkenylated pyridine **5a**.

In this TCRT, the competitive thermal decomposition of ammonium acetate proceeds, and gaseous ammonia escapes from the reaction mixture, depleting the nitrogen source. Thus, when all the ammonium acetate is consumed by TCRT or by thermal decomposition, the reaction cannot proceed further. Indeed, the low yield of nitropyridine **5a** was improved by increasing the amount of ammonium acetate; however, this substantially prolonged the reaction time (Table 1, Entries 2 and 3). Microwave heating was found to be more effective than conventional heating to increase the yield of **5a** within shorter reaction time (Entry 4).

The application of this TCRT to other vinyl ketones **4b**–**4f** was also studied. Substituted styryl ketones **4b** and **4c** underwent TCRT to afford the corresponding alkenylated pyridines **5b** and **5c**, respectively (Table 1, Entries 5–7). Among styryl ketones **4a**–**4c**, methoxy-substituted ketone **4b** revealed higher reactivity because electron-rich **4b** can easily approach the electron-poor dinitropyridone **1**. When aliphatic ketone **4d** was employed, the reaction was complex and alkenylpyridine **5d** was not detected (Entries 9 and 10). The reaction of mesityl oxide **4e** also afforded a complex mixture, from which alkenylpyridine **5e** was isolated in low yield (Entry 11). Although microwave heating was somewhat effective for increasing the yield of **5e**, the yield was still low because of side reactions and the instability of the product (Entry 12). These problems were solved by employing a bulkier alkyl group to afford alkenylpyridine **5f** in high yield (Entries 13 and 14).

This TCRT also facilitated alkynylation of the nitropyridine framework by using alkynyl ketones as substrates. Both aromatic and aliphatic alkynyl ketones **10a** and **10b** underwent TCRT to afford **11a**[5b,11] and **11b**, in good yield, respectively (Table 2, Entries 1–4). Next, we conducted the ring transformation using trimethylsilylethynyl ketone **10c** to prepare the corresponding pyridine **11c**,[11] which is regarded as an equivalent of the unsubstituted ethynylpyridine **11d** (R = H).[17] As a result, desilylation also proceeded under the employed reaction conditions to afford a mixture of **11c** and **11d** with high total yield (Entries 5 and 6).

In summary, we have developed a novel method for the synthesis of alkenylated/alkynylated nitropyridines **5a**–**5f**/**11a**–**11c** through the TCRT of dinitropyridone **1** with unsaturated ketones **4**/**10** and ammonium acetate. This method requires simple manipulations during both the reaction and work-up. Moreover, this method is metal-free, which enables the omission of a purification step for removing poisonous transition metal contamination and reduces the cost of preparation. Hence, this TCRT is considered supplementary to other methods, including the Heck and Sonogashira reactions.

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Supporting Information is available electronically on J-STAGE.

References and Notes

1 Recent reports are shown in refs. 1–3: S. Hameed P, M. Chinnapattu, G. Shanbag, P. Manjrekar, K. Koushik, A. Raichurkar, V. Patil, S. Jatheendranath, S. S. Rudrapatna, S. P. Barde, N. Rautela, D. Awasthy, S. Morayya, C. Narayan, S. Kavanagh, R. Saralaya, S. Bharath, P. Viswanath, K. Mukherjee, B. Bandodkar, A. Srivastava, V. Panduga, J. Reddy, K. R. Prabhakar, A. Sinha, M. B. Jiménez-Díaz, M. S. Martínez, I. Angulo-Barturen, S. Ferrer, L. M. Sanz, F. J. Gamo, S. Duffy, V. M. Avery, P. A. Magistrado, A. K. Lukens, D. F. Wirth, D. Waterson, V. Balasubramanian, P. S. Iyer, S. Narayanan, V. Hosagrahara, V. K. Sambandamurthy, S. Ramachandran, *J. Med. Chem.* **2014**, *57*, 5702.

2 a) V. Birault, A. J. Campbell, S. Harrison, J. Le, L. Shukla, PCT Int. Appl. WO 2013160419, **2013**. b) R. Frank, T. Christoph, B. Lesch, J. Lee, PCT Int. Appl. WO 2013013817, **2013**. c) A. Kakizuka, S. Hori, T. Shudo, T. Fuchigami, PCT Int. Appl. WO 2012014994, **2012**.

3 J. L. Yap, X. Cao, K. Vanommeslaeghe, K.-Y. Jung, C. Peddaboina, P. T. Wilder, A. Nan, A. D. MacKerell, Jr., W. R. Smythe, S. Fletcher, *Org. Biomol. Chem.* **2012**, *10*, 2928.

4 Recent reports: S. Hoelder, J. Blagg, S. Solanki, H. Woodward, S. Naud, V. Bavetsias, P. Sheldrake, P. Innocenti, J. Cheung, B. Atrash, PCT Int. Appl. WO 2014037750, **2014**; A. G. Cole, R. A. James, Y. Shao, J. J. Letourneau, J. G. Quintero, C. M. Riviello, L Zhi, PCT Int. Appl. WO 2013025628, **2013**; D. A. Coates, R. Gilmour, J. A. Martin, E. M. Martin De La Nava, PCT Int. Appl. WO 2012074761, **2012**; M. Henrich, U. Abel, S. Muller, H. Kubas, U. Meyer, M. Hechenberger, V. Kauss, R. Zemribo, PCT Int. Appl. WO 2012052451, **2012**.

5 a) Y. L. Si, C. G. Liu, E. B. Wang, Z. M. Su, *Theor. Chem. Acc.* **2009**, *122*, 217. b) A. S. Karpov, F. Rominger, T. J. J. Müller, *J. Org. Chem.* **2003**, *68*, 1503. c) R. H. Naulty, A. M. McDonagh, I. R. Whittall, M. P. Cifuentes, M. G. Humphrey, S. Houbrechts, J. Maes, A. Persoons, G. A. Heath, D. C. R. Hockless, *J. Organomet. Chem.* **1998**, *563*, 137.

6 A. K. Flatt, S. M. Dirk, J. C. Henderson, D. E. Shen, J. Su, M. A. Reed, J. M. Tour, *Tetrahedron* **2003**, *59*, 8555.

7 E. Rafiee, A. Ataei, S. Nadri, M. Joshaghani, S. Eavani, *Inorg. Chim. Acta* **2014**, *409*, 302; A. Ataei, S. Nadri, E. Rafiee, S. Jamali, M. Joshaghani, *J. Mol. Catal. A: Chem.* **2013**, *366*, 30.

8 A. Saxena, H. W. Lam, *Chem. Sci.* **2011**, *2*, 2326.

9 A. Nuñez, B. Abarca, A. M. Cuadro, J. Alvarez-Builla, J. J. Vaquero, *J. Org. Chem.* **2009**, *74*, 4166.

10 A. El Kadib, K. McEleney, T. Seki, T. K. Wood, C. M. Crudden, *ChemCatChem* **2011**, *3*, 1281.

11 G. P. Sagitullina, M. A. Vorontsova, A. K. Garkushenko, N. V. Poendaev, R. S. Sagitullin, *Russ. J. Org. Chem.* **2010**, *46*, 1830.

12 H. Wang, K. Wen, L. Wang, Y. Xiang, X. Xu, Y. Shen, Z. Sun, *Molecules* **2012**, *17*, 4533.

13 T. C. Henninger, X. C. Xu, PCT Int. Appl. WO 2002046204, **2002**.

14 P. Chand, P. L. Kotian, P. E. Morris, S. Bantia, D. A. Walsh, Y. S. Babu, *Bioorg. Med. Chem.* **2005**, *13*, 2665; J. Siu, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2004**, *2*, 160.

15 S. T. Le, H. Asahara, K. Kobiro, R. Sugimoto, K. Saigo, N. Nishiwaki, *Asian J. Org. Chem.* **2014**, *3*, 297.

16 S. T. Le, H. Asahara, N. Nishiwaki, *Eur. J. Org. Chem.* **2015**, 1203; S. T. Le, H. Asahara, N. Nishiwaki, *Synthesis* **2014**, *46*, 2175.

17 J. Kraft, D. Schmollinger, J. Maudrich, T. Ziegler, *Synthesis* **2015**, *47*, 199.