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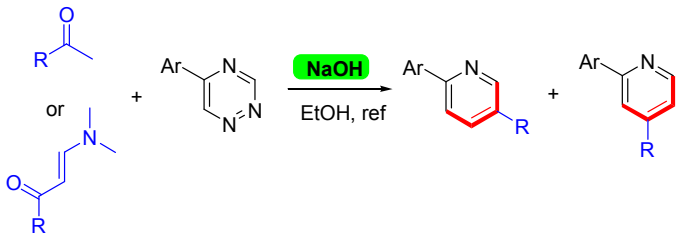
Graphical abstract

A new approach to pyridines through the reactions of methyl ketones with 1,2,4-triazines

Shu-Wen Wang, Wei-Si Guo, Li-Rong Wen,* and Ming Li*



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A new approach to pyridines through the reactions of methyl ketones with 1,2,4-triazines

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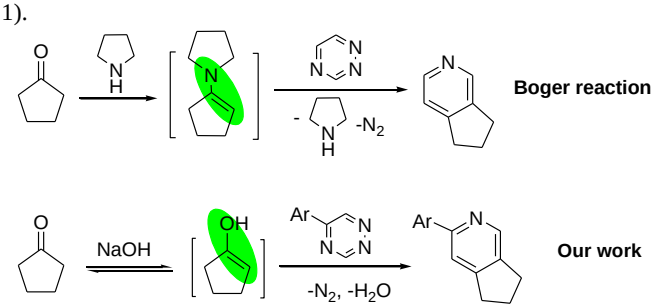
A new route to prepare pyridine derivatives based on inverse electron demand Diels-Alder/retro-Diels-Alder reactions of ketones with 1,2,4-triazines is reported. It is the first time using methyl ketones directly as a dienophile to react with 1,2,4-triazines without enamine intermediates, which is complementary to the classical Boger reaction.

Among the nitrogen heterocycles, pyridine is one of the most prevalent skeleton found in natural products, pharmaceuticals, agrochemicals, and functional materials.[1] As a consequence, pyridine synthesis has been a hot research field for a long time. Besides the transition metal-catalyzed methods to construct pyridine derivatives,[2] the traditional condensations are still the most commonly used methods because of reliability and simplicity.[3] Among the known synthetic methods, the inverse electron demand Diels-Alder/*retro*-Diels-Alder reactions of 1,2,4-triazines with electron-rich enamines across C_3/C_6 of the 1,2,4-triazine nucleus to yield pyridines, developed by Boger[4] and Tay1or,[5] are considered to be a powerful synthetic approach. However, the widely used classical methodologies have the same limitations, which required generating an enamine intermediate and long reaction time (Scheme 1).



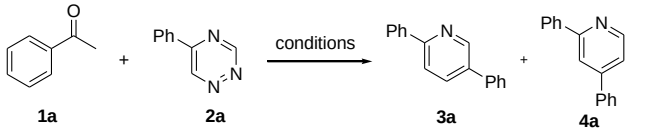
Scheme 1 The comparison of Boger reaction and our work

We speculate that the enols tautomerized from ketones under basic conditions could be used directly as dienophiles in the inverse electron demand Diels-Alder reactions. Thus, the reaction of acetophenone **1a** and 5-phenyl-1,2,4-triazine **2a** was investigated in the presence of NaOH in refluxing ethanol. To our delight, the expected pyridine products 2,5-diphenylpyridine **3a** and 2,4-dipenylpyridine **4a** were formed. To the best of our knowledge, the reactions of acetophenones and cyclic ketones as potential dienophiles with 1,2,4-triazines directly to synthesize the pyridine derivatives in the presence of NaOH have not been studied. In continuation of our research interests in exploring useful heterocyclic compounds,[6] we report herein a convenient protocol to synthesize the pyridine derivatives through the reactions of methyl ketones with 1,2,4-triazines directly without formation of enamine intermediate (Scheme 1).

The optimization of the reaction conditions was carried out with acetophenone **1a** and 5-phenyl-1,2,4-triazine **2a** as the model substrates (Table 1). Initially, 2,5-diphenylpyridine **3a** and 2,4-dipenylpyridine **4a** were obtained in a low total yield of 30% in EtOH at 40 °C with NaOH (1.0 equiv) as the base (Table 1, entry 1). Delightedly, the total yield increased with the raise of temperature, and achieved 75% yield at reflux temperature (Table 1, entry 2). The utility of other solvents, such as $CHCl_3$, THF, CH_3CN, and DMF was all unsatisfactory (Table 1, entries 3-6). Next, other bases were tested, and the results revealed that K_2CO_3 gave lower yield than NaOH (Table 1, entry 7). In the presence of Et_3N or DABCO, the reactions were sluggish, and no desired products were obtained (Table 1, entries 8 and 9). EtONa and *t*-BuONa provided the similar yields with NaOH (Table 1, entries 10 and 11). Finally, the equivalent of the base was also tested (Table 1, entries 12−14). The control experiment suggested that without any base the reaction did not take place even in refluxing ethanol (Table 1, entry 15). In addition, regarding methyl ketones could also tautomerize to the enols under acid conditions, some acids such as HOAc and HCl were employed to catalyze this reaction. However, the reaction did not occur under HOAc conditions; whereas 1,2,4-triazine hydrochloride was formed exclusively in the presence of HCl. Therefore, the optimum reaction condition was using NaOH (1.5 equiv) as the base in refluxing ethanol (Table 1, entry 13). In particular, with the optimum conditions the obtained two products were easy to be separated by flash chromatography. Interestingly, when the reaction of **1a** with **2a**

was performed in the traditional Boger's conditions (pyrrolidine as catalyst in $CHCl_3$ at 45 °C), the reaction did not proceed.

Table 1 Optimization of reaction conditions[a]



1a **2a** **3a** **4a**

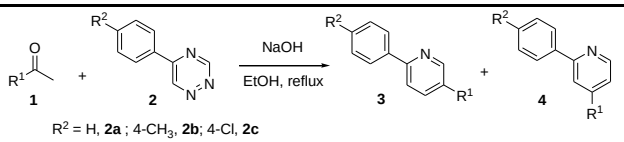
Entry	Base (equiv)	Solvent	Temp (℃)	Time (h)	Yield (%)[b]
1	NaOH (1.0)	EtOH	40	12	30
2	NaOH (1.0)	EtOH	reflux	4	75
3	NaOH (1.0)	$CHCl_3$	reflux	4	trace
4	NaOH (1.0)	THF	reflux	4	trace
5	NaOH (1.0)	CH_3CN	reflux	4	65
6	NaOH (1.0)	DMF	100	4	45
7	K_2CO_3 (1.0)	EtOH	reflux	4	42
8	Et_3N (1.0)	EtOH	reflux	4	NR[d]
9	DABCO (1.0)	EtOH	reflux	4	NR[d]
10	EtONa (1.0)	EtOH	reflux	4	73
11	*t*-BuONa (1.0)	EtOH	reflux	4	74
12	NaOH (0.5)	EtOH	reflux	4	15
13	**NaOH (1.5)**	**EtOH**	**reflux**	**1.5**	**85**
14	NaOH (2.0)	EtOH	reflux	1.5	85
15	—[c]	EtOH	reflux	12	NR[d]

[a] **1a** (1.0 mmol) and **2a** (1.0 mmol) was used. [b] Total yield of **3a** and **4a**. [c] No base. [d] No reaction.

To test the generality of this reaction, various methyl ketones **1a-1i** and 5-aryl-1,2,4-triazines **2a-2c** were examined under the optimized conditions. As shown in Table 2, the substituents on the aromatic group of triazines had no influence on the reactions (compare entries 1 with 9 and 15; entries 4 with 12 and 16). And acetophenones bearing either electron-withdrawing or electron-donating groups at 2-, 3- or 4-position of the benzene ring, in all cases, provided smoothly the desired target molecules **3** and **4** in good yields. When 1-(4-nitrophenyl)ethanone was employed to react with **2a** under the same conditions, however, the reaction did not occur, and 1-(4-nitrophenyl)ethanone could be quantitatively recovered.

Additionally, all of experimental results showed the major products were the 2,4-disubstituted-pyridines **4** rather than the 2,5-disubstituted-pyridines **3**, showing the same regioselectivity with previous reports.[7]

Table 2 Investigation on the scope of the reactions of methyl ketones **1** with 1,2,4-triazines **2**[a]



1 **2** **3** **4**

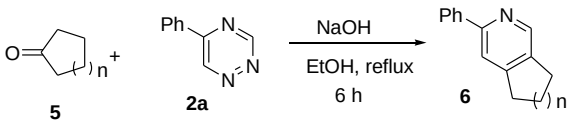
R^2 = H, **2a** ; 4-CH_3, **2b**; 4-Cl, **2c**

Entry	**1**/R^1	**2**	Time (h)	**3** (Yield %)[b]	**4** (Yield %)[b]
1	**1a** C_6H_5	**2a**	1.5	**3a** (25)	**4a** (60)
2	**1b** 4-FC_6H_4	**2a**	2	**3b** (20)	**4b** (59)
3	**1c** 4-ClC_6H_4	**2a**	2	**3c** (20)	**4c** (61)
4	**1d** 4-BrC_6H_4	**2a**	2.5	**3d** (21)	**4d** (62)
5	**1e** 4-$CH_3C_6H_4$	**2a**	2.5	**3e** (35)	**4e** (53)
6	**1f** 4-$CH_3OC_6H_4$	**2a**	3	**3f** (35)	**4f** (52)
7	**1g** 3-ClC_6H_4	**2a**	2	**3g** (19)	**4g** (56)
8	**1h** 2,4-$Cl_2C_6H_3$	**2a**	2.5	**3h** (18)	**4h** (57)
9	**1a** C_6H_5	**2b**	2	**3i** (25)	**4i** (58)
10	**1b** 4-FC_6H_4	**2b**	2.5	**3j** (18)	**4j** (57)
11	**1c** 4-ClC_6H_4	**2b**	2.5	**3k** (19)	**4k** (57)
12	**1d** 4-BrC_6H_4	**2b**	3	**3l** (20)	**4l** (58)
13	**1e** 4-$CH_3C_6H_4$	**2b**	3.5	**3m** (34)	**4m** (52)
14	**1f** 4-$CH_3OC_6H_4$	**2b**	4	**3n** (35)	**4n** (52)
15	**1a** C_6H_5	**2c**	2	**3o** (25)	**4o** (59)
16	**1d** 4-BrC_6H_4	**2c**	2.5	**3p** (20)	**4p** (61)
17	**1f** 4-$CH_3OC_6H_4$	**2c**	3	**3q** (34)	**4q** (52)
18	**1i** CH_3	**2a**	4.5	**3r** (42)	**4r** (43)

[a] Reaction conditions: methyl ketones **1** (1.0 mmol), 5-aryl-1,2,4-triazines **2** (1.0 mmol), NaOH (1.5 mmol), in 5 mL of EtOH at refluxing temperature. [b] Isolated yields by column chromatography.

Encouraged by the above results, the substrate scope was extended to cyclic ketones (Scheme 2). To our pleasure, cyclopentanone **5a**, cyclohexanone **5b**, and cycloheptanone **5c** were successfully employed to produce single pyridine isomers in excellent yields.

Scheme 2 The reactions of cyclic ketones **5** with **2a**

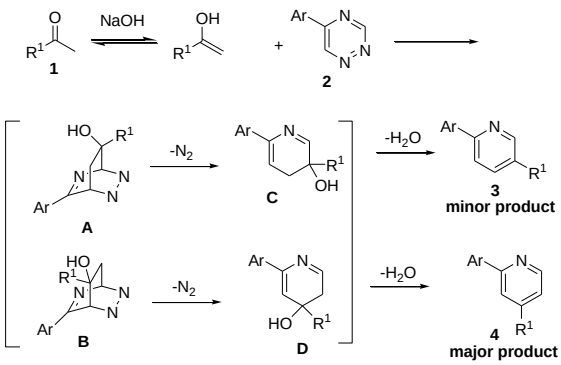


5 **2a** **6**

n = 1, **5a/6a** 92%; n = 2, **5b/6b** 90%; n = 3, **5c/6c** 88%

Based on the above experimental results, a plausible reaction mechanism is presented in Scheme 3. Initially, the methyl ketones tautomerized to the enols under the basic conditions. Then, as dienophiles, the enols reacted directly with the 1,2,4-triazines **2** through the inverse electron demand Diels-Alder reaction to give intermediates **A** and **B**. Subsequently, intermediates **C** and **D** were formed by retro-Diels-Alder process with a loss of nitrogen molecule. Finally, the target products **3** and **4** were obtained by elimination-aromatization of the intermediate **C** and **D**.

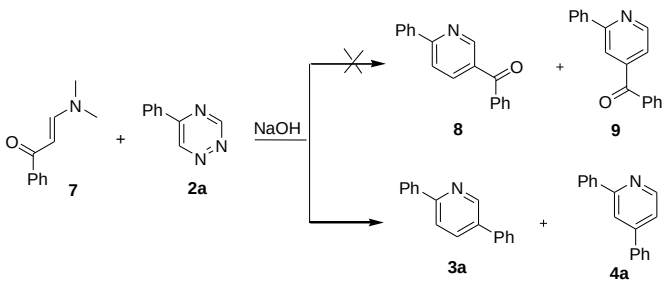
Scheme 3 Proposed mechanism for products **3**/**4**



Considering that enaminones contain the enamine motif, we attempted to use 3-(dimethylamino)-1-phenylprop-2-en-1-one **7** as a

dienophile to react with 1,2,4-triazine **2a** directly ($CHCl_3$, 45 ℃), expecting to obtain products **8**/**9** (Scheme 4). Unfortunately, none of the desired products **8**/**9** were observed. However, when this reaction was conducted under above optimum conditions, the decarbonylated products **3a**/**4a** were obtained instead of the desired products **8**/**9**. The control experiments revealed an unprecedented phenomenon that enaminone **7** could easily converted to the corresponding acetophenone **1a** under the reaction conditions. To our knowledge, this retro-aldol type conversion under basic conditions has never been reported.

Scheme 4. Reaction of enaminone **7** with triazine **2a**



Conclusions

In summary, we have successfully developed a simple and efficient synthetic protocol for pyridine derivatives by inverse electron demand Diels-Alder/retro-Diels-Alder reactions using methyl ketones and 1,2,4-triazines. The striking feature of the reaction is using methyl ketones as a potential dienophile without formation of enamine intermediate. Undoubtedly, the novel method is complementary to Boger reaction and revealed a convenient and green way to access pyridine derivatives in an atom-economic manner. We hope this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal and materials chemistry.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, full spectroscopic data for all new compounds, and crystal data for **4d** (CIF). See DOI: 10.1039/c000000x/

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