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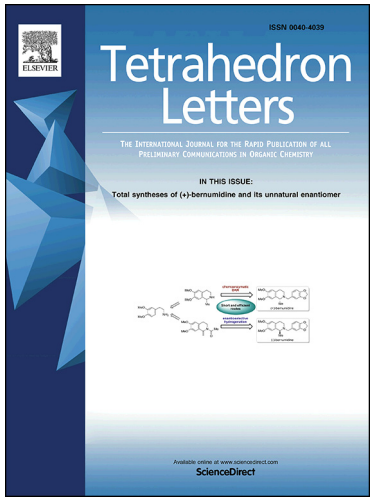

A new method using 1,3,5-triazine as an umpolung hydrogen cyanide equivalent toward the syntheses of isoquinolinone and 2-pyridone derivatives

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A new method using 1,3,5-triazine as an umpolung hydrogen cyanide equivalent toward the syntheses of isoquinolinone and 2-pyridone derivatives.

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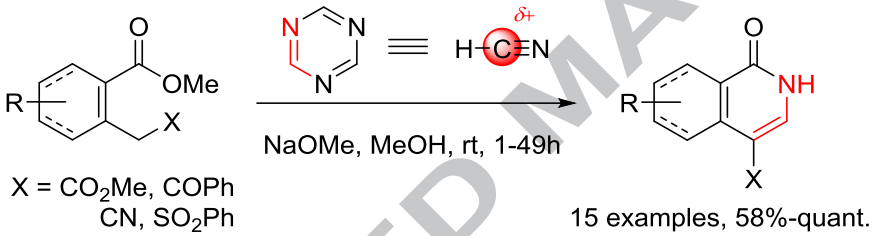
Abstract

An investigation of Hermecz and Hartenstein's cyclization methods was conducted. Overcoming the limited substrate scope allowed the expansion of the synthetic application of 1,3,5-triazine as an umpolung hydrogen cyanide equivalent. The reaction proceeded under mild conditions to provide various isoquinolinone and 2-pyridone derivatives with excellent yields.

Graphical Abstract



Keywords

triazine

cyclization

umpolung

isoquinolinone

2-pyridone

1,3,5-Triazines are widely known as common building blocks in various functional materials such as melamine resins, dyes, and bioactive compounds.[1] As synthetic tools, triazine derivatives are often utilized in halogenation and peptide coupling reactions.[2] For instance, Kunishima's 4-(4,6-Dimethoxy-1,3,5-triazine-2-yl)-4-methylmorpholinium chloride (DMTMM) is recognized as an effective and durable coupling reagent in aqueous media.[3] However, most of these reactions are categorized as either complete or no carbon frame incorporation. An example of partial structural transformation is the case of Gattermann-Koch formylation[2,4]: 1,3,5-triazine (**1**) is used as a -CH=O source under acidic conditions. Although triazine **1** is also considered as a trimer of hydrogen cyanide, its application as a –CH=N- unit is limited. HCN tends to form a cyanide anion and act as a nucleophile due to a low pKa of approximately 9. Therefore, if triazine **1** behaves as an umpolung hydrogen cyanide synthetic equivalent, it would be an interesting reagent for the community.

During our course of the study on ASP3700 (**4**), an osteoarthritis drug discovered by Astellas Pharma Inc.,[5] we encountered an opportunity to explore an effective and robust method to synthesize the key intermediate **3** (Figure 1). As described in our previous paper, the use of 1,3,5-triazine and NaOMe with diesters **2** allowed us to achieve the sequential transesterification, olefin isomerization, 2-pyridone ring formation, followed by hydrolysis to afford the methanoisoquinoline **3** in 63.3% yield without silica gel column chromatography.[6] Here, we describe our investigation on this new cyclization strategy in comparison with

related reports by Hermecz[7] and Hartenstein[8] and its application to various isoquinolinones and 2-pyridones syntheses. In addition, our novel approach toward the amino-isoquinoline derivatives is discussed.

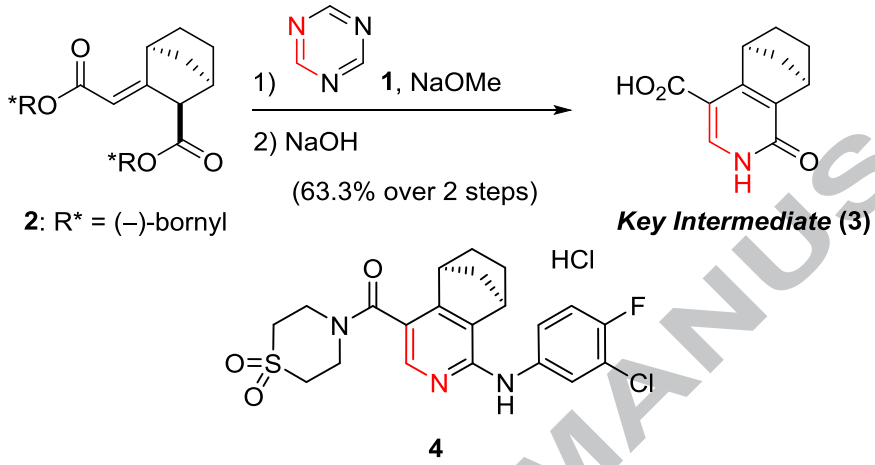


Figure 1. 1,3,5-triazine promoted cyclization for the synthesis of the key intermediate of ASP3700 (**4**).

In 1980, Hermecz *et al*. discovered that the reaction of ethyl acetoacetate with **1** and NaOEt in EtOH afforded 11.8% of the pyrimidopyridinone as a major byproduct along with the desired 4-pyridone. Later, the reaction was applied to the synthesis of naphthyridinones from 2,6-dimethyl pyridines-3,5-dicarboxylate derivatives[7] (Figure 2). In their reports, the reaction proceeded smoothly to give various aza-isoquinolinones in 21-97% yield. However, the substrate scope was quite limited at the 4-position. On the other hand, Hartenstein *et al.* showed that Hantzsch esters and their derivatives showed similar reactivity.[8] Although a stronger base and high temperature (NaH/DMF/100°C) were required, a number of 2- and 4-

substituted cyclic products were obtained in 11-85% yield. Curiously, both research groups utilized rather sophisticated substrates but not simpler starting materials such as methyl 2-methylbenzoate (**5**) or methyl 2-methylnicotinate (**6**). Therefore, we began investigating the cyclization with these compounds.

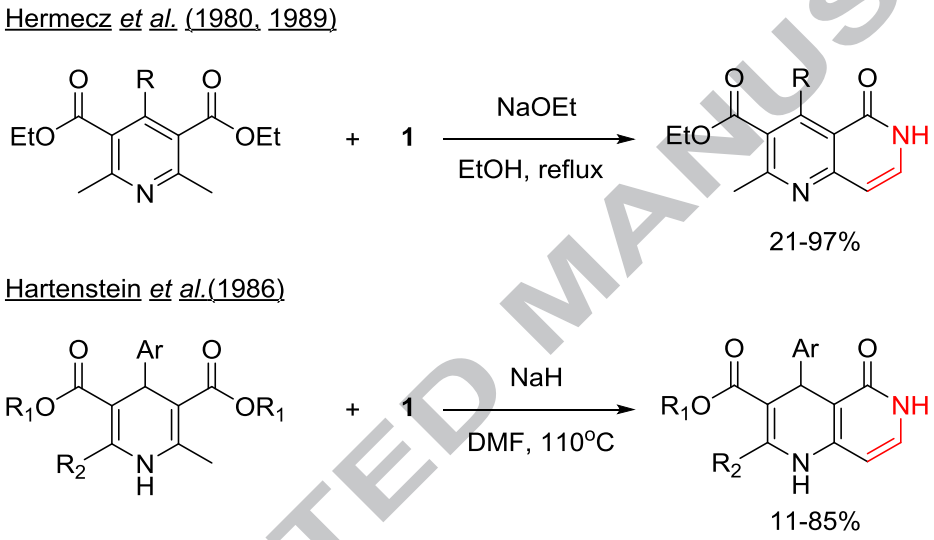
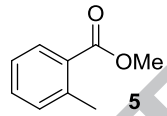
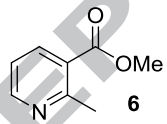
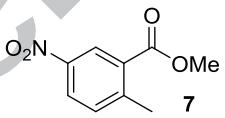
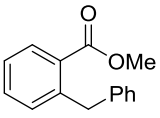
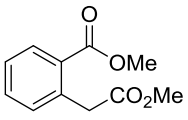


Figure 2. Hermecz and Hartenstein's previous works

Following the Hermercz report, ester **5** was treated with alkoxides in alcohol (Table 1, Entry 1, condition A and B). Surprisingly, the reaction did not proceed at all. Next, we tried the much harsher Hartenstein's method, NaH/DMF/100°C, as well as NaHMDS/THF (condition C and D). However, no desired product was observed. Based on their reports, sodium cation coordination to the nitrogen lone pair seemed to play an important role in the deprotonation stage. Therefore, we switched the substrate to 2-methylnicotinate **6**. Unfortunately, the

reaction still did not provide the target compound (Entry 2). Furthermore, to increase the acidity and stabilize the generated anion at the benzylic position, the compounds bearing nitro **7** and phenyl **8** groups were tested (Entries 3 and 4). Nevertheless, the desired cyclization did not take place. These results indicate that the key for this reaction is balancing the acidity to form an anion intermediate and sufficient nucleophilicity to attack triazine **1**. Therefore, along with our success in ASP3700 synthesis,[6] CO_2Me attached ester **9** was investigated. To our delight, the reaction proceeded smoothly to afford the desired isoquinolinone **10** in quantitative yield.

Table 1. Hermecz and Hartenstein's method with simple substrates.

Entry	Substrate	Conditions	Yield %
1	 **5**	condition A: **1**(5.0 equiv.), NaOMe(10.0 equiv.), MeOH, 24 h, reflux	No reaction
		condition B: **1**(5.0 equiv.), NaOEt(10.0 equiv.), EtOH, 24 h, reflux	No cycloadduct
		condition C: **1**(5.0 equiv.), NaH(5.0 equiv.), DMF, 24 h, 110°C	Complex mixture
		condition D: **1**(5.0 equiv.), NaHMDS(1.3 equiv.), THF, 24 h, RT	Complex mixture
2	 **6**	condition B	No cycloadduct
		condition C	Complex mixture
3	 **7**	condition A	Complex mixture
4	 **8**	condition A	No reaction
5	 **9**	condition E: **1**(5.0 equiv.), NaOMe(10.0 equiv.), MeOH, 1 h, RT	Quantitative

Next, the optimization of the reaction was conducted (Table 2). The use of triazine **1** was able to be reduced to 1.2 equivalents (Entries 1 and 2). Interestingly, despite that one molecule of triazine **1** could provide three -HC=N- sources, the reaction with 0.4 equivalent formed only 34.8% of the cycloadduct (Entry 3). As described in the reaction mechanism for our ASP3700 synthesis[6], the sequential addition to triazine **1** followed by amide bond formation is the key for this transformation. This result implied that the potential formamidine source is not the -HC=N- donor. Next, base selection showed that inorganic salts such as Na_2CO_3, K_2CO_3 and NaOAc can also lead to the desired cyclization but with insufficient yield (Entries 4-6). These poor results could be caused by the lower solubility of these inorganic bases. Although using an extended reaction time, a strong organic base such as DBU promoted the reaction as effectively as NaOMe with 99.3% yield (Entry 8). Solvent screening revealed that aprotic solvents such as MeCN and toluene are also applicable in this reaction (Entries 9-14). Not surprisingly, proper tuning of the base and solvent seemed to be vital for the reaction behavior (Entry 11 vs. 14). Reducing the amount of base to 5 equivalents affected the reaction efficiency less so using NaOMe/MeOH than the DBU/MeOH system (Entry 15 vs 16). Further sodium methoxide reduction showed a significant yield drop of 83.6% (Entry 17). This phenomenon indicates that the quick elimination of the formamidine unit in intermediates **IV** described in our proposed mechanism[6] seemed a crucial factor for their

reaction presumably due to the instability. Considering reaction time and robustness, the reaction condition in entry 15 was selected as our primary condition.

Table 2. Optimization of the cyclization of diester **9**.

Entry	**1** amount (equiv.)	Base (10 equiv.)	Solvent (0.2 M)	Time	Temp.°C	Yield %[a]
1	5.0	NaOMe	MeOH	1 h	RT	Quant.
2	1.2	NaOMe	MeOH	1 h	RT	99%
3	0.4	NaOMe	MeOH	24 h	RT	35%
4	1.2	Na_2CO_3	MeOH	24 h	50°C	47%[b]
5	1.2	K_2CO_3	MeOH	24 h	50°C	46%[b]
6	1.2	NaOAc	MeOH	24 h	50°C	15%[b]
7	1.2	DIPEA	MeOH	24 h	60°C	15%[b]
8	1.2	DBU	MeOH	24 h	RT	99%
9	1.2	NaOMe	MeCN	9 h	RT	81%
10	1.2	NaOMe	TBME	7 h	RT	77%
11	1.2	NaOMe	DMF	3 h	RT	35%
12	1.2	NaOMe	Toluene	3 h	RT	80%
13	1.2	DBU	TBME	24 h	RT	92%
14	1.2	DBU	DMF	7 h	RT	90%
15[c]	1.2	NaOMe	MeOH	1 h	RT	98%
16[c]	1.2	DBU	MeOH	20 h	RT	77%
17[d]	1.2	NaOMe	MeOH	2 h	RT	84%

[a] HPLC yield.

[b] The incomplete reactions after 24 hours.

[c] 5 equivalents of base were used.

[d] 2.5 equivalents of NaOMe were used.

With the optimal reaction condition in hand, we examined the substrate scope in 1,3,5-triazine mediated isoquinolinone synthesis (Figure 3). The compounds bearing various functional groups, such as NO_2, Me, OMe, Cl, and F, converted smoothly to give the corresponding isoquinolinones in excellent yields. (83.8-98.4%). Particularly, in the pharmaceutical industry, fluoride attached isoquinolinone **15** seemed to be useful for future drug discovery. These results indicated the reaction is feasible with both electron-withdrawing

and electron-donating groups. Interestingly, methyl group attached diesters afforded the desired product **12** in 69.5% yield under NaOMe/MeOH conditions. On the other hand, the DBU/MeOH system showed a much better result of 84.4%. With these favorable results on diester derivatives, we assumed other alpha carbon activating functionalities such as ketone, cyanide, sulfone, and phosphorus ester would also facilitate the cyclization. As expected, benzoyl, cyano, and benzenesulfonyl, which substituted isoquinolinones **16-18**, were also obtained in excellent yields.[9] Based on these results, activating the benzylic position to enhance nucleophilicity with proper functional groups seems to be a more crucial factor than the electron density in the aromatic ring.

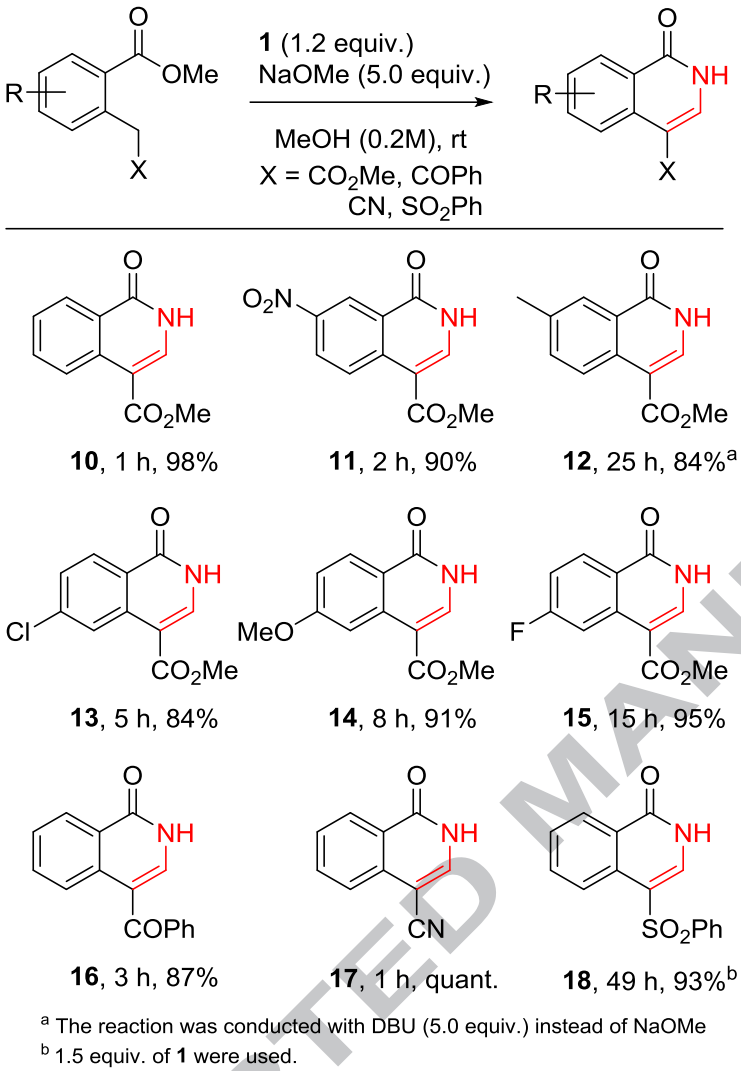
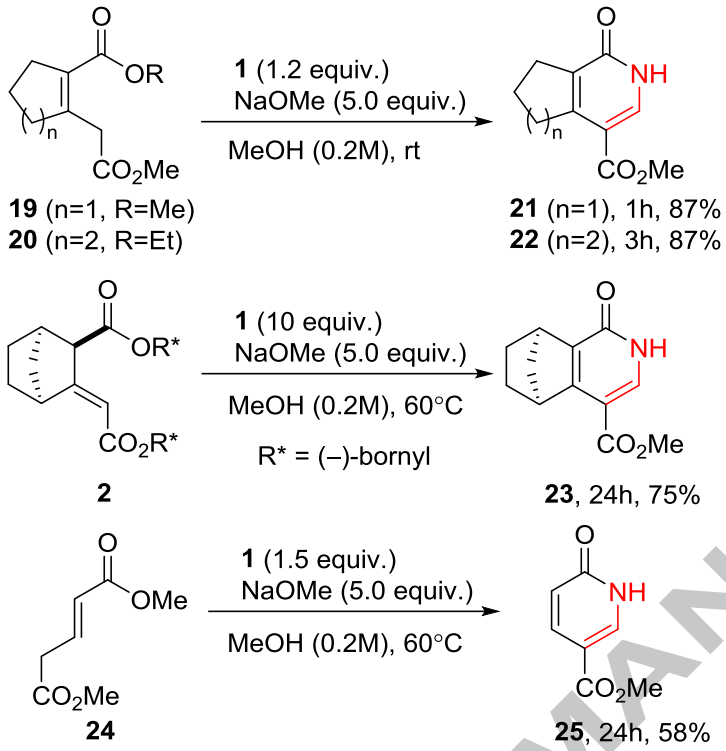


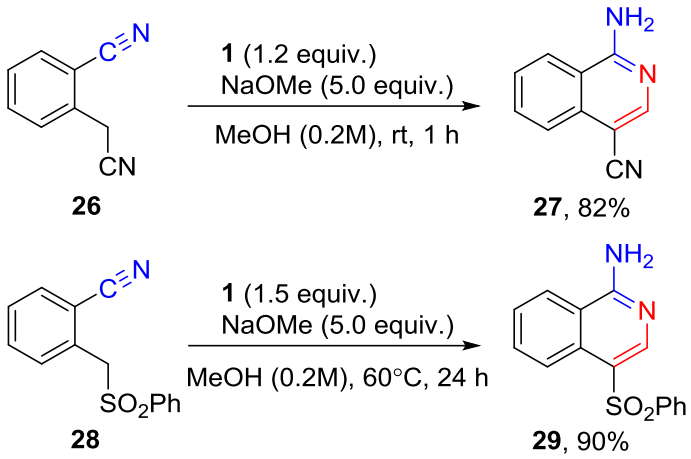
Figure 3. The substrate scope.

Next, the reaction was applied to aliphatic substrates (Scheme 1). The compounds containing 5-membered and 6-membered rings proceeded smoothly to afford the desired 2-pyridones in 75.3-87.1% yield. Furthermore, the linear substrate **24** also gave **25** with 58.0% yield[10], although the reaction efficacy dropped presumably due to the loss of the Thorpe-Ingold effect.[11] Overall, our 1,3,5-triazine mediated cyclization well suits 2-pyridone synthesis, as well.



Scheme 1. The reaction with aliphatic substrates.

Finally, we attempted to switch the ester moiety in the substrate for other functional groups. In principle, the proposed anionic intermediate[6] could be trapped with various intramolecular electrophiles. Inspired by classical Kreutzberger's aminoquinazoline synthesis,[12] 2-cyanophenylacetonitrile (**26**) was treated with triazine **1** and NaOMe in MeOH. (Scheme 2). To our delight, the cyclization proceeded smoothly to give a desired amino-isoquinoline **27** of 81.6%. Moreover, compound **28** bearing a benzenesulfonyl group also underwent cyclization with excellent yield. These preliminary results imply that our 1,3,5-triazine mediated cyclization strategy would be applicable for various types of heteroaromatic compound syntheses by switching intramolecular anion acceptors.



Scheme 2. Application to amino-isoquinoline synthesis.

In conclusion, we have investigated the Hermecz and Hartenstein's reports on the use of 1,3,5-triazine as an umpolung hydrogen cyanide equivalent. Overcoming the limited substrate scope allowed the discovery of a new method for synthesizing various isoquinolinone and 2-pyridone derivatives in an efficient manner. Finally, converting the intramolecular electrophile to nitrile showed further potential applications toward the syntheses of various heteroaromatic compounds.

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Declaration of interest

Conflicts of interest: none

Acknowledgements

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Highlight

- An efficient and simple approach to access various isoquinolinone and 2-pyridones derivatives.
- A useful application of 1,3,5-trizaine as an umpolung hydrogen cyanide synthetic equivalent.
- A novel cyclization for the synthesis of amino-isoquinoline derivatives.