Isocyanate acting as a carbonyl precursor: pyridyl group-assisted formation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones from ketimines and isocyanates†

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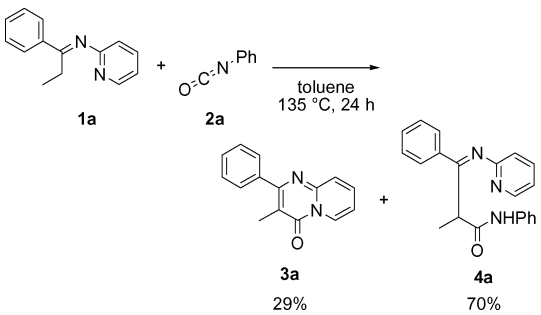
By the reactions of ketimines bearing a pyridyl or a picolyl group on a nitrogen atom of the imine moiety with tosylisocyanate, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives could be obtained in quantitative yields. In these reactions, tosylisocyanate acts as a carbonyl precursor. The pyridyl or picolyl group is a key functional group because it is not only the constituent structure of the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one framework but also the promoter of the formation of a ketene intermediate.

Synthesizing carbonyl compounds is one of the most important organic transformations in both laboratories and industries.[1] Carbon monoxide and phosgene are often used as carbonyl sources; however, they can be difficult to handle due to their toxicity and gaseous form. Therefore, there have recently been many reports on the synthesis of carbonyl compounds with substitutes for carbon monoxide and phosgene, such as formic acid, formate, formamide, formic anhydride, aldehyde, metal carbonyl, carbamoylsilane and carbamoylstannane.[2] In addition, dialkyl carbonates,[3] carbonyl diimidazoles[4] and dichloromethanimines have be used as substituents for carbon monoxide and phosgene. Instead of these substituents, we used isocyanates as carbonyl sources. We report herein that 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives are synthesized from ketimines and isocyanates.

There have been many reports on the synthesis of bioactive heterocyclic compounds bearing heteroatoms at ring junction positions.[5,6] One example is a 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton, and its 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives[7] show valuable pharmacological properties and are used as successful analgesic agents.[7e,7i]

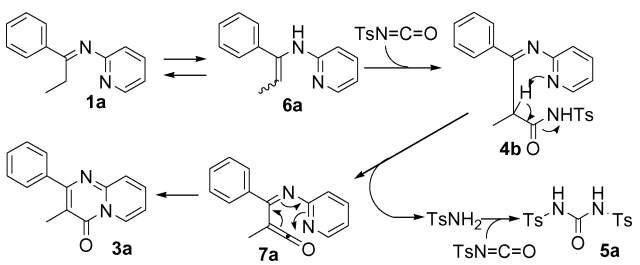
By the reaction of ketimine **1a** (1.0 equiv.) with phenylisocyanate **2a** (2.0 equiv.) in toluene at 135 °C for 24 h, the corresponding 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative **3a** and amide **4a** were obtained in 29 and 70% yields, respectively [eqn (1)].[8]



(1)

Several isocyanates were examined with the ketimine **1a**. The reaction did not occur with cyclohexylisocyanate. Arylisocyanate bearing an electron donating group (*para*-methoxy) gave **3a** in 49% yield. In order to promote the dissociation of the amine moiety from **4a**, we carried out the reactions using 2,6-dimethylisocyanate as a bulky substrate and tosylisocyanate, which has an excellent dissociation ability. In the case of 2,6-dimethylisocyanate, the yield was very low (7%). On the other hand, **3a** was obtained quantitatively with two equivalents of tosylisocyanate. In this reaction, a urea derivative **5a**, which was formed by the reaction of an amine with an isocyanate, was formed as a side product in quantitative yield. This result reveals that isocyanates act as a carbonyl source and react with ketimines to give 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives. The highly efficient transformation of the isocyanate into a carbonyl group is confirmed by the fact that this reaction needs only two equivalents of isocyanate since one equivalent of isocyanate reacts with a ketimine and another one equivalent reacts with an amine (byproduct).

A possible mechanism of the reaction is shown in Scheme 1: (1) Isomerization of the ketimine **1a** to enamine **6a**; (2) nucleophilic attack of the enamine **6a** with tosylisocyanate to give an amide intermediate **4b**;[9,10] (3) the dissociation of tosylamide from **4b** to give **7a** having a ketene moiety; (4) intramolecular cyclization of the ketene and imine moieties in **7a** to give the



Scheme 1 Proposed mechanism of the formation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

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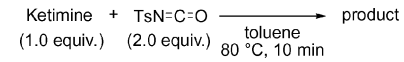
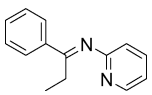
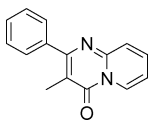
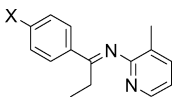
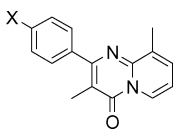
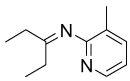
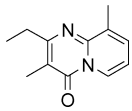
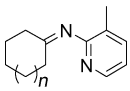
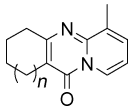
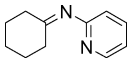
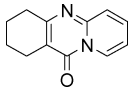
† Electronic supplementary information (ESI) available: General experimental procedure and characterization data for 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives. See DOI: 10.1039/b516916j

Table 1 Reaction of ketimines with tosylisocyanate



Entry	Ketimine	Product		Yield[a] (%)
1[b]			**3a**	93% (>99%)
2				22% (24%)
3			**3b** (X = H)	93% (>99%)
4			**3c** (X = MeO)	94% (>99%)
5			**3d** (X = Me)	92% (>99%)
6			**3e** (X = Ph)	91% (>99%)
7			**3f** (X = Cl)	93% (>99%)
8			**3g**	87% (>99%)
9			**3h** (n = 1)	74% (>99%)
10			**3i** (n = 7)	92% (>99%)
11[c]			**3j**	75% (>99%)

[a] Isolated yield. ^{1}H NMR yield is reported in parenthesis. [b] 135 °C. [c] 135 °C, 1 h.

4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative **3a**.[7f,7h] Since isocyanate must be consumed by the reaction with tosylamine, which is formed as a byproduct in step (3), this reaction needs two equivalents of tosylisocyanate to ketimine.

Next, we investigated the reaction temperature and the reaction time using ketimine **1a** and tosylisocyanate.‡ This reaction proceeded smoothly at 135 °C for 10 min, and the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative **3a** was obtained in quantitative yield (Table 1, entry 1). The yield of **3a** decreased to 24% when the reaction was conducted at 80 °C for 10 min (Table 1, entry 2).

In order to increase the yield of **3a** derived from **7a**, the lone pair of a nitrogen atom on the pyridyl group should work effectively for the deprotonation followed by dissociation of the amine, as shown in Scheme 1. Therefore, we choose a picolyl group instead of the pyridyl one. The corresponding 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative **3b** was obtained quantitatively at 80 °C for 10 min (Table 1, entry 3).[11] The reaction did not proceed with a ketimine bearing *ortho*-tolyl group. These results indicate that deprotonation by a nitrogen atom on the picolyl group is important.

In the next stage, we examined the reaction of several ketimines with tosylisocyanate (Table 1). All aromatic ketimines having an electron-withdrawing or an electon-donating group at the *para*-position of the imine moiety afforded the corresponding 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives **3c**–**f** in excellent yields (Table 1, entries 4–7). Acyclic and cyclic alkyl ketimines also gave the corresponding 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives **3g**–**i** in good to excellent yields (Table 1, entries 8–10). By the reaction of cyclohexylidene(pyridin-2-yl)-amine with tosylisocyanate at 135 °C for 1 h, the corresponding 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative **3j**, which is a successful analgesic agent,[7e] was obtained in 75% isolated yield (Table 1, entry 11).[12]

In summary, we succeeded in the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives quantitatively by the reaction of ketimines bearing a pyridyl or a picolyl group on a nitrogen atom of the imine moiety with tosylisocyanate. In the reactions, the pyridyl and picolyl groups have two functions. One is, of course, these groups are the constituent structure of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives, the other is that these groups promote the formation of a ketene intermediate. In addition, the tosylisocyanate acts as a source of carbon monoxide. To our knowledge, this is the first example of using an isocyanate as a carbonyl precursor. Since the carbonylation using isocyanates is a highly efficient in comparison with the conventional carbonylation reactions,[2] isocyanates are expected to be used as a carbonyl source in a wide range of synthetic chemistries.

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Notes and references

‡ **3,9-Dimethyl-2-phenyl-pyrido[1,2-*a*]pyrimidin-4-one (3b).** The mixture of (3-methyl-pyridin-2-yl)-(1-phenyl-propylidene)amine (112 mg, 0.500 mmol) and tosylisocyanate (197 mg, 1.00 mmol) in toluene (1.0 mL) was heated at 80 °C for 10 min. After the solvent was removed *in vacuo*, the product was isolated by silica gel column chromatography. Yield: 116 mg (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.59 (s, 3H), 7.00

(t, $J = 6.9$ Hz, 1H), 7.45–7.51 (m, 4H), 7.70 (d, $J = 8.1$ Hz, 2H), 8.94 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.96 (1C), 17.96 (1C), 111.16 (1C), 114.36 (1C), 124.75 (1C), 127.94 (2C), 128.74 (1C), 129.23 (2C), 132.95 (1C), 134.90 (1C), 139.46 (1C), 147.75 (1C), 159.66 (1C), 159.98 (1C); IR (nujol, ν / cm^{-1}) 2039 (m), 1978 (m), 1965 (m), 1941 (w), 1671 (s), 1634 (m), 1600 (w), 1540 (w), 1419 (w), 1240 (m), 1191 (w), 1169 (m), 1142 (w), 1076 (m), 1030 (w), 909 (w), 804 (w), 775 (w), 759 (s), 728 (w), 689 (m), 666 (w), 651 (w); HR-MS ([M + H]$^+$) calcd for $C_{16}H_{14}N_2O$: 251.1184; found: 251.1186.

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8 The yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

9 The 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative **3a** could be obtained when **4a** was exposed to the standard reaction conditions. This result indicates the existence of **4a** as an intermediate in the formation reaction of **3a**. Thus, **4b** must also be the amide intermediate in the case of using tosylisocyanate.

10 A referee suggested another possible mechanism for the formation of **4b** as follows: 1) the interaction between a ketimine with an isocyanate at the nitrogen atom on the pyridyl group; 2) the formation of a pyridinium salt; 3) the formation of an enamine; 4) the interaction of the enamine with the substituent, which is derived from the isocyanate, on the nitrogen atom of the pyridyl group.

11 At 50 °C, unsaturated β-lactam derivative **3b** and amide **4b** were obtained in 31 and 68% yields, respectively.

12 The structure of **3j** was determined by comparison with the data reported in ref 7e.