One-step Direct Conversion of Heterocyclic Aldehydes to Esters

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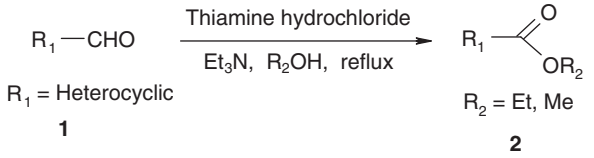
One-step direct conversion of a series of heterocyclic aldehydes to heterocyclic esters is reported here by the use of thiamine hydrochloride as a catalyst in the absence of nitrogen atmosphere in a reasonably high yield. This method exclusively produces heterocyclic esters in most cases (specially with more electron-withdrawing heterocyclic aldehydes) without the formation of side products like heteroin. Thus the method developed looks promising and general for the synthesis of electron-withdrawing heterocyclic esters from the corresponding aldehydes.

Direct conversion of esters[1] from the corresponding aldehydes is an important transformation,[2,3] particularly in the synthesis of natural products. The principal requirements for this conversion are mild conditions and short reaction times.[4] Various methods such as catalytic[5] as well as oxidative[6] reactions have been developed for the transformation of aldehydes to the corresponding esters and these generally deal only with aromatic aldehydes.[7] However, the conversion of heterocyclic aldehydes to the corresponding esters is not reported although heterocyclic esters are also important for the synthesis of various natural products, antimicrobial agents and pharmaceutical compositions.[8] But according to our knowledge there is no such easy method developed for the direct synthesis of heterocyclic aldehydes to the corresponding heterocyclic esters. In our continuous effort on the development of suitable methodology[9] for heterocyclic chemistry, here we wish to report the efficient mild synthesis of heterocyclic aldehydes to the corresponding esters using thiamine hydrochloride as catalyst in the presence of triethylamine.

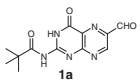
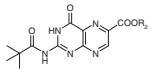
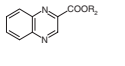
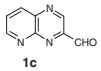
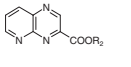
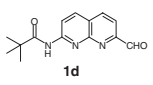
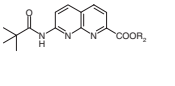
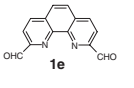
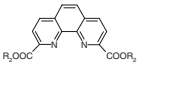
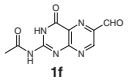
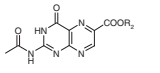
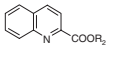
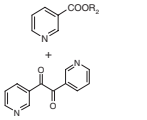
In recent years there is an increasing interest in use of thiamine hydrochloride as a catalyst[10] for the benzoin or benzoin like condensation reaction.[11] Previously some aromatic aldehydes have been converted to the corresponding esters using thiazolium ions by electrochemical oxidation[12] or by redox reaction in which aromatic aldehydes are oxidized to esters along with the reduction of several organic compounds[13,14] and the time required for these reactions is 20 h to 4 days.[15] In our investigation, treatment of catalytic amount of thiamine hydrochloride with heterocyclic aldehydes in the presence of triethylamine in dry methanol or ethanol solvent, interestingly in the period of two to three hours, methyl or ethyl ester from heterocyclic aldehydes are obtained instead of the usual benzoin like condensation reactions.

In heterocyclic systems, direct conversion of aldehydes to the corresponding esters is not much explored according to our knowledge although various reagents are available for the conversion of aromatic aldehydes to corresponding esters.[5–7] During our survey, on the addition of a catalytic amount (15 mol %) of thiamine hydrochloride in methanol or ethanol solution of various heterocyclic aldehydes **1a**–**1h** in the presence of triethylamine, the corresponding heterocyclic esters **2a**–**2o**[16] are easily obtained in high yield (Scheme 1).[17]



Scheme 1. Synthesis of heterocyclic esters from heterocyclic aldehydes (for R_1 and R_2, see Table 1).

Table 1. Synthesis of heterocyclic esters from heterocyclic aldehydes

Entry	Substrate **1**	Reaction time/h	Product **2**	Yield[a]/%	Mp/°C
1	 **1a**	2.5		80 (**2a**, R_2 = Et)	126–128
				85 (**2b**, R_2 = Me)	82–84
2	 **1b**	2.0		92 (**2c**, R_2 = Me)	115–116
				90 (**2d**, R_2 = Et)	75–76
				75 (**2e**, R_2= isopropyl)	64–65
3	 **1c**	2.5		87 (**2f**, R_2 = Et)	78–80
				89 (**2g**, R_2 = Me)	155–156
4	 **1d**	2.5		85 (**2h**, R_2 = Me)	156–158
				82 (**2i**, R_2 = Et)	168–170
5	 **1e**	3.0		76 (**2j**, R_2 = Me)	144–145
				72 (**2k**, R_2 = Et)	162–164
6	 **1f**	3.0		79 (**2l**, R_2 = Et)	238–240 (decomp.)
7	 **1g**	2.0		89 (**2m**, R_2 = Me)	70–72
				86 (**2n**, R_2 = Et)	82–84
8	 **1h**	2.0		30 (**2o**, R_2 = Et)	Liquid
				58 (**3**)	60–62

[a]Isolated yields are of chromatographically obtained pure material.

Thus we have successfully carried out the esterification reactions with a series of various heterocyclic aldehydes like pterin aldehyde, quinoxaline aldehyde, pyridopyrazine aldehyde, etc. (except pyridinecarbaldehydes) using ethanol or methanol solvent, which are shown in Table 1. In the case of pyridine-3-carbaldehyde, pyridine ethyl ester (**2o**) is obtained along with di-3-pyridyl diketone (**3**). Here initially benzoin type condensation of pyridinecarbaldehydes occurs which follows

Table 2. Effects on thiamine hydrochloride catalyst on esterification of 2-quinoxalinecarbaldehyde (**1b**)

Entry	Substrate	Thiamine hydrochloride/mol %	Reaction time/h	Product	Yield[a] /%
a	**1b**	5	2	**2c**	30
b	**1b**	10	2	**2c**	70
c	**1b**	15	2	**2c**	92
d	**1b**	20	2	**2c**	92

[a]Isolated yields are of chromatographically obtained pure material.

further aerial oxidation to give di-3-pyridyl diketone.[18] We have applied the same reaction condition on aromatic as well as aliphatic aldehydes. The esterification reaction successfully occurs only in the case of strong electron-withdrawing aromatic aldehydes such as 4-nitrobenzaldehyde. Other aromatic (without introducing any outer oxidant[13–15]) as well as aliphatic aldehydes do not get esterified by this method. In the presence of secondary alcohol such as isopropanol, the esterification occurs successfully with reasonable yield (Entry 2, compound **2e**). Tertiary alcohol does not take part in this reaction. The yields of the esters using triethylamine base are satisfactory. When a methanolic solution of KOH was used instead of triethylamine in the case of 2-quinoxalinecarbaldehyde (**1b**), most of the aldehyde is converted to its acid, with a small amount of mixture of ester and quinoxaloin products.

The effects of the catalyst thiamine hydrochloride have also been examined where 15% of the catalyst is found to be optimum and use of further excess does not change the reaction time or yield (Table 2).

We have also carried out this reaction taking 2-quinoxalinecarbaldehyde (**1b**) under inert atmosphere bubbling with nitrogen, but the desired ester **2c** was not obtained in two to three hours. After seven to eight hours, only 10–15% conversion of ester was found, but the reaction yield does not improve by increasing the reaction time. As these heterocyclic moieties of aldehydes are electron withdrawing, therefore when the reactions are carried out in the presence of oxygen, the formation of corresponding esters may be explained by the following plausible mechanistic pathway (Figure 1).

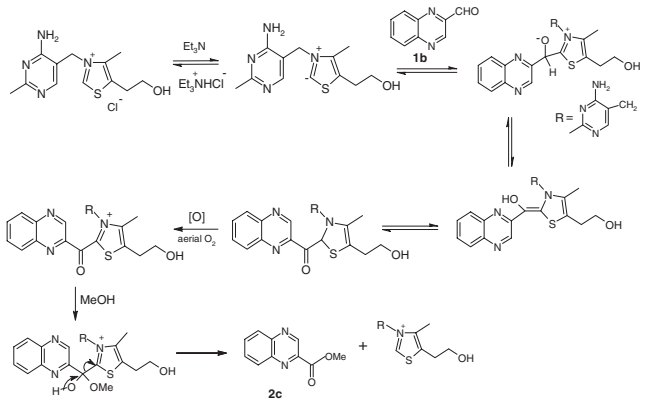


Figure 1. A plausible mechanism for the synthesis of heterocyclic esters from the corresponding heterocyclic aldehydes.

In conclusion, we have developed here a single step and straightforward methodology for the synthesis of various heterocyclic esters from the heterocyclic aldehydes in the absence of inert gas atmosphere using thiamine hydrochloride as catalyst. This method is clean, mild, rapid, and efficient for the synthesis of a series of heterocyclic esters.

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17 For general procedure and spectral data see Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
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