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HIGH CHEMOSELECTIVE SYNTHESIS OF CARBOXAMIDES BY USING SYN-PHENYLPYRIDYL-O-ACYL OXIMES(PPKO)

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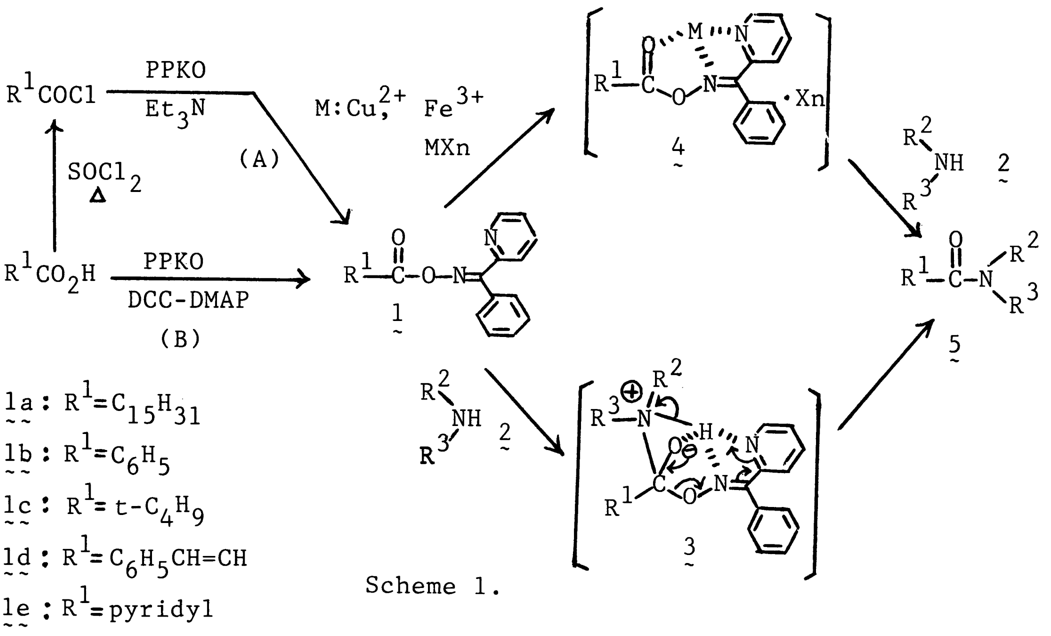
Various carboxamides are prepared chemoselectively in good yields by using syn-phenylpyridyl ketoxime(PPKO) as functional leaving group.

Although a number of synthetic methods for the preparation of amides and esters have been reported,[1-3] relatively little works have been reported on the preparation of amides by using metal chelating agents as functional leaving group.[4,5] As mentioned by Mukaiyama[1] and Lloyd,[6] there are several excellent advantages to use a metal chelating agent, syn-phenylpyridyl ketoxime(PPKO),[7] as functional leaving group: (1) Pyridyl and oxime group of PPKO serve as intramolecular base, and catalyze deprotonation step in the transition state 3 of the reaction. (2) Since all the reaction species are in close proximity to the central cationic proton or metal, the condensation reaction should be entropically advantageous. (3) Since syn-phenylpyridyl-O-acyl oximes(PPAO) can be highly activated in the presence of some cation or metal, even in nonpolar solvent.

We wish to report a high chemoselective synthesis of carboxamides by using PPAO. Synthetic sequence is shown in Scheme 1.



1a : $R^1=C_{15}H_{31}$
1b : $R^1=C_6H_5$
1c : $R^1=t\text{-}C_4H_9$
1d : $R^1=C_6H_5CH=CH$
1e : R^1=pyridyl

Scheme 1.

PPAO 1 can be easily prepared by treatment of carboxylic acid chloride with PPKO and Et_3N, method A (77-99%), and usual DCC-DMAP method B (67-90%).[8] A typical procedure for carboxamide is described: A solution of benzylamine (59 mg, 0.55 mmol) in CH_2Cl_2 (5 ml) was added to a solution of PPAO 1a (218 mg, 0.5 mmol) in CH_2Cl_2 (5 ml). After the reaction mixture was stirred at room temperature under N_2 atmosphere for 24 h, evaporation of the solvent, followed by silica gel column chromatography ($CHCl_3$) afforded amide 5a (170 mg, 99%). In a similar manner, various amides were prepared as summarized in Table 1.

Table 1. Reaction of syn-phenylpyridyl-O-acyl oximes with several amines

R^1	R^2	R^3	Time/h		Yield/%	PPKO/% [b]
$C_{15}H_{31}$	$C_6H_5CH_2$	H	24	5a	99	100
	$n\text{-}C_4H_9$	H	24	5b	91	96
	$s\text{-}C_4H_9$	H	24	5c	98	100
	$t\text{-}C_4H_9$	H	48	5d	<5[a]	
	$-(CH_2)_5-$		48	5e	40[a]	
	$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	48	5f	8[a]	
	C_6H_5	H	48	5g	<5[a]	
	$CH_3C_6H_5$	H	48	5h	<5[a]	
	HOC_2H_4	H	2	5i	92	
C_6H_5	$C_6H_5CH_2$	H	24	5j	99	94
$t\text{-}C_4H_9$	$C_6H_5CH_2$	H	48	5k	<5[a]	
$C_6H_5CH{=}CH$	$C_6H_5CH_2$	H	24	5l	99	100
pyridyl	$C_6H_5CH_2$	H	2	5n	97	98

a) The yield of amide was calculated from NMR spectrum.

b) The recovery of PPKO.

Table 2. Activation by metal halides

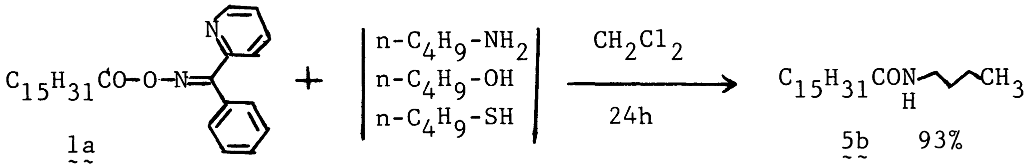
R^1	R^2 (R^3= H)	MXn[c]	Time/h		Yield/%
$C_{15}H_{31}$	$C_6H_5CH_2$[a]	$CuCl_2\cdot 2H_2O$	2(30min)[d]	5a	93
	$t\text{-}C_4H_9$[b]	$FeCl_3$	2(30min)[d]	5d	87
	C_6H_5[a]	$CuCl_2$	5(30min)[d]	5g	94
$t\text{-}C_4H_9$	$C_6H_5CH_2$[a]	$CuCl_2$	5(30min)[d]	5k	71
	$C_6H_5CH_2$[b]	$FeCl_3$	0.5(1h)[d]	5k	85
	C_6H_5[b]	$FeCl_3$	12(1h)[d]	5m	66

a) 1.5 equiv. of amine was used.

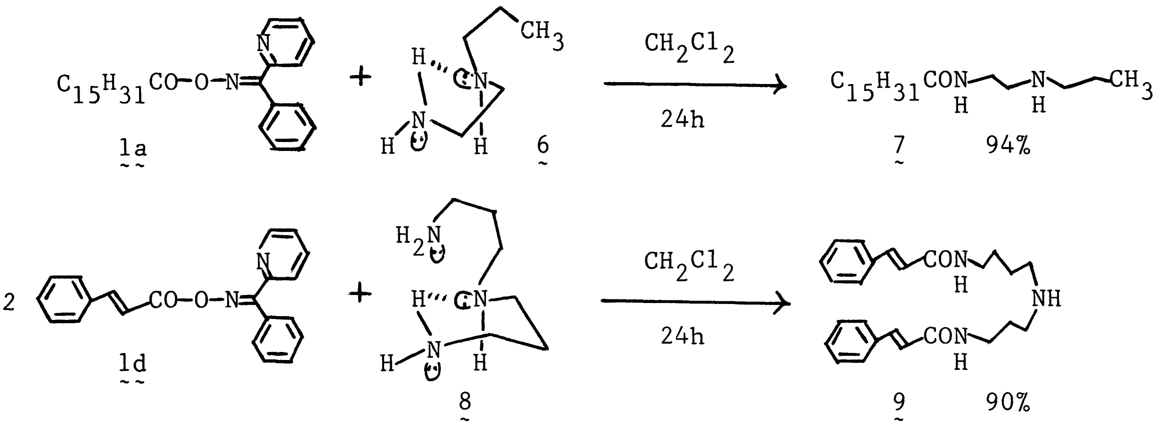
b) 2.2 equiv. of amine was used.

c) 1.1 equiv. of metal halide was used.

d) Prior to the addition of amine, metal halide was added to the reaction mixture, and which was stirred for 30 min or 1 h under N_2 atmosphere at room temperature.



Scheme 2.



Scheme 3.

It was found that the reaction was applicable to the chemoselective preparation of amides from sterically unhindered carboxylic acid and primary amine, and the product yields exactly reflect the electron density on the nitrogen atom of the amine and its steric surroundings. Comparison of the reaction rate of amines led to the following order ; $\text{R-NH}_2 > {}^{\text{R}}_{\text{R}}{>}\text{NH}$, aliphatic amine > aromatic amine.

Interestingly, when Cu^{2+} or Fe^{3+} was added to the reaction mixture prior to the condensation reaction, even the amides from sterically hindered carboxylic acid and amine were easily obtained in good yields under mild conditions (Table 2).

A competitive reaction between 1a and three kinds of nucleophilic compounds (butylamine, butane-1-thiol, and butan-1-ol) afforded only amide 5b in 93% (Scheme 2). Furthermore, PPAO recognizes the five or six-membered intramolecular hydrogen-bonding between a primary amino group and a secondary amino group.3) When PPAO 1a was similary treated with a diamine 6, the amide 7 was obtained chemoselectively in high yields,9) the secondary amino group being kept intact. This reaction was conveniently applied to the synthesis of a spermidine alkaloid, maytenine 9 was synthesized in high yield (Scheme 3).9)

Further detail investigation and synthetic utilization of PPAO are now in progress.

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