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CONVERSION OF PRIMARY AMIDES INTO ACTIVE ACYLATING AGENTS VIA ACYLPYRROLES.

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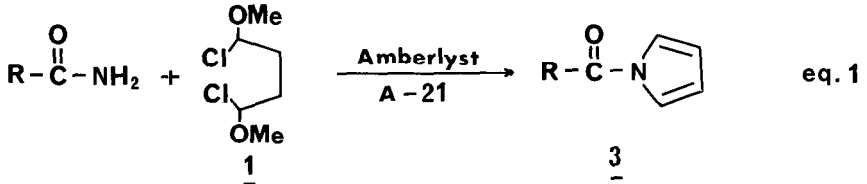
Abstract: Several primary amides were converted to N-acylpyrroles on reaction with 1,4-dichloro-1,4-dimethoxybutane (1) and Amberlyst A-21 resin. The acylpyrroles act as active acylating agents.

Because of resonance interaction, the carbon-nitrogen bond of amides possesses partial double bond character. Chemically, this is manifested in the difficulty by which amides undergo hydrolysis, alcoholysis and aminolysis. The carbonyl group in primary amides are resistant to reduction by sodium borohydride. With the more powerful lithium aluminum hydride, primary amides are normally reduced to primary amines, with the carbon-nitrogen bond intact.

In this communication, we wish to report a reaction by which primary amides are converted to acylpyrroles, thus rendering them in one step, under mild conditions, active acylating agents. This permits the facile transformation of primary amides into esters, secondary and tertiary amides as well as aldehydes and alcohols.

1,4-Dichloro-1,4-dimethoxybutane (1), a compound obtained from the reaction of trimethylchlorosilane with 2,5-dimethoxytetrahydrofuran (2)[1], reacts with primary amides to give acylpyrroles (3) in good yields according to equation 1.

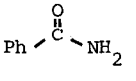
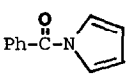
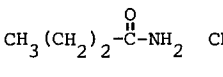
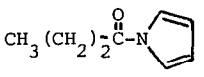
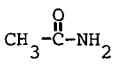
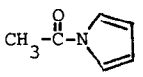
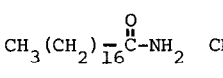
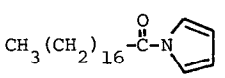


1 3 eq. 1

The experimental conditions are as follows (Table 1). To a solution of the amide (1 mmol) in 5 ml organic solvent was added 1.2 eq. of 1 and 0.5 g of Amberlyst A-21 resin. The mixture was heated to 45° to 66° overnight with stirring. The mixture was filtered and the filtrate was evaporated to give

acylpyrrole which was purified by flash[7] or TLC-mesh[8] chromatography.

Table 1: Conversion of primary amides into N-acylpyrroles

Primary amides	N-acyl pyrroles	reaction conditions	% yield	Ref.
		1.2 eq. 1, resin CH_3CN/60°C/overnight	85	3
		1.3 eq. 1, resin CH_3CN/50°C/overnight	73	2,4
		1.3 eq. 1, resin CH_3CN/45°C/overnight	55	5
		1.3 eq. 1, resin $CHCl_3$/55°C/overnight	72	mp=62-64°C

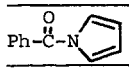
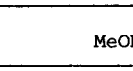
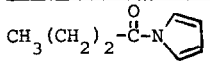
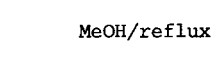
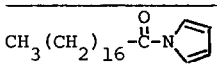
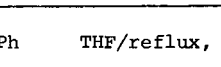
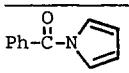
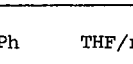
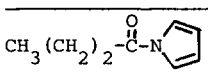
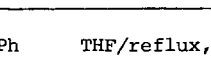
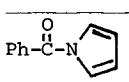
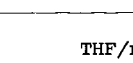
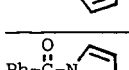
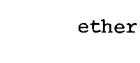
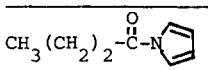
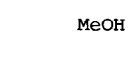
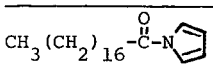
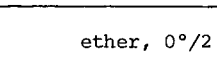
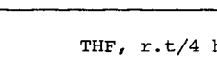
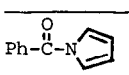
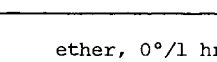
Acylpyrroles can be transformed readily into methyl esters by refluxing sodium methoxide in methanol. Reaction of acylpyrroles with primary amines in refluxing tetrahydrofuran gives secondary amides in good yield. Likewise, reaction with secondary amines gives tertiary amides (Table 2).

Reduction of N-butanoylpyrrole (4) with lithium aluminium hydride had previously been studied by Brown and co-workers[2]. They reported disappointing results in that only 30% butanal was obtained as the reduction product in spite of the expected reactivity of acylpyrroles. We found that reduction of N-butanoylpyrrole with LAH gave indeed only 30% yield of butanal. The major product of the reaction was the pyrrole hemiacetal compound (5, R=$CH_3CH_2CH_2$) in 40% yield. Furthermore, if the reduction of 4 was carried out with sodium borohydride, the pyrrole hemiacetal 5 (R=$CH_3CH_2CH_2$) was obtained as the sole product in 85% yield. Similarly, reduction of benzoylpyrrole (6) with LAH gave benzyl alcohol in 75% yield. Reaction with sodium borohydride in methanol on the other hand gave benzaldehyde in good yield. The same reduction with sodium borohydride in ether gave the hemiacetal 5 (R=Ph) instead. It is clear that the carbonyl group in acylpyrroles can easily be reduced by hydrides in agreement with their expected activation.

Finally, acylpyrroles reacted with either organolithium or Grignard reagents to give the corresponding tertiary alcohols with cleavage of the

TABLE 2

Reactions of Acylpyrroles with Various Nucleophiles

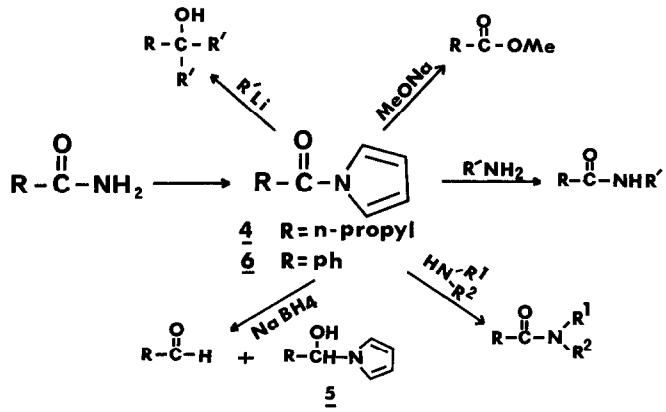
Acyl pyrrole	Nucleophile	Reaction Conditions	Products	% yield (lit)
	MeONa	MeOH/reflux, 14 hrs		quant.
	MeONa	MeOH/reflux, 14 hrs		quant.
	H_2N-CH_2Ph	THF/reflux, 16 hrs		87%, mp=85-88°
	H_2N-CH_2Ph	THF/reflux, 16 hrs		85%, mp=104-106°
	H_2N-CH_2Ph	THF/reflux, 16 hrs		80%
		THF/reflux, 2 days		55%†
	*$LiAlH_4$	ether, 0°/1 hr→ r.t/14 hrs	$PhCH_2OH$	75% (6)
	$NaBH_4$	MeOH, -20°/5 hrs	PhCHO	85%
	$NaBH_4$	ether, r.t/14 hrs		62%†
	$LiAlH_4$	ether, 0°/1 hr→ r.t/14 hrs	$CH_3CH_2CH_2CHO$	30% (2)
				40%†
	$NaBH_4$	MeOH, -20°/5 hrs		85%†
	*n-BuLi	ether, 0°/2 hrs		65%†
	*PhMgCl	THF, r.t/4 hrs		55%†, mp=40-43°
	*n-BuLi	ether, 0°/1 hr→ r.t/14 hrs		72%†

†isolated yield

*more than 2 equivalent of amount were used.

carbon-nitrogen bond (see scheme).

Examples reported in here show clearly that by converting primary amides into acylpyrroles, synthetic transformation leading to the cleavage of the carbon-nitrogen bond can be achieved with relative ease.



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